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NDA 20444

1 OF 8

UDDA 20444

NDAA20-444

AP Ltr

Pharm

Micro

PI

Stat

AE Ltr

Bio

Chem

Cso Review

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Patent Info.

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SEP 20 1995

NDA 20-444

Burroughs Wellcome Company
Attention: Michael J. Dalton, Pharm.D.
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Dr. Dalton:

Please refer to your February 28, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flolan (epoprostenol sodium) for Injection.

We acknowledge receipt of your amendments dated April 28, May 22, June 6 and 9, and July 24, 1995.

This new drug application provides for the long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and Class IV adult patients.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-444. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments that, along with completion dates, are listed below:

1. The commitments agreed to in the April 27, 1995 telephone conversation between representatives of your firm and this Agency, and detailed in an Agency letter dated April 28, 1995 to submit to FDA additional information concerning the sterilization process.
2. The commitments agreed to in your April 10, 1995 submission, and confirmed in an Agency letter dated April 28, 1995, to submit to FDA, within 6 months of approval of the NDA, additional information regarding chemistry, manufacturing, and controls.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Karen Oliver
Consumer Safety Officer
(301) 443-0187

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation 1
Center for Drug Evaluation and
Research

ENCLOSURE

CC:

Original NDA 20-444
HFD-180/Div. files
HFD-180/CSO/K.Oliver
HFD-180/Reviewers
HFD-2/M.Lumpkin
HFD-100 (with labeling)
HFA-100
DISTRICT OFFICE
HF-2/medwatch (with labeling)
HFD-80 (with labeling)
HFD-240/S.Sherman (with labeling)
HFD-500/L.Ripper (with labeling)
HFD-613 (with labeling - Only for applications with labeling.)
HFD-009/J.Tracy (with labeling)

drafted: KO/August 30, 1995

r/d Initials: S.Fredd 09/08/95

r/d Initials: J.Gibbs 09/07/95

r/d Initials: J.Choudary 09/07/95

init: KO/August 30, 1995 *K.Oliver 09/15/95*

final: KO/09/15/95/c:\wpwin\karenfil\nda\20444508.1ko

APPROVAL [with Phase 4 Commitments]

9/15/95
[Signature]
9/15/95
[Signature]
9/15/95

1 **PACKAGE INSERT**

2 **FLOLAN® (epoprostenol sodium) for injection**

3 **DESCRIPTION: FLOLAN (epoprostenol sodium) for**

4 **injection is a sterile sodium salt formulated for**

5 **intravenous administration. Each vial of FLOLAN**

6 **contains epoprostenol sodium equivalent to either**

7 **0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng)**

8 **epoprostenol, 3.76 mg glycine, 2.93 mg sodium**

9 **chloride, and 50 mg mannitol. Sodium hydroxide**

10 **may have been added to adjust pH.**

11 **Epoprostenol (PGI₂, PGX, prostacyclin), a metabolite**

12 **of arachidonic acid, is a naturally occurring**

13 **prostaglandin with potent vasodilatory activity and**

14 **inhibitory activity of platelet aggregation.**

15 **Epoprostenol is (5Z,9,11,13E,15S)-6,9-epoxy-11,15-**

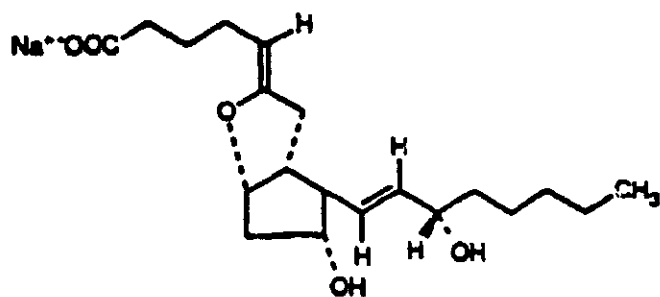
16 **dihydroxyprosta-5,13-dien-1-oic acid.**

17 **Epoprostenol sodium has a molecular weight of**

18 **374.45 and a molecular formula of C₂₀H₃₄NaO₆. The**

19 **structural formula is:**

20



21
 22 FLOLAN is a white to off-white powder that must be
 23 reconstituted with STERILE DILUENT for FLOLAN.
 24 STERILE DILUENT for FLOLAN is supplied in 50 mL
 25 glass vials containing 94 mg glycine, 73.5 mg sodium
 26 chloride, sodium hydroxide (added to adjust pH), and
 27 Water for Injection, USP.

28 The reconstituted solution of FLOLAN has a pH of
 29 10.2 to 10.8 and is increasingly unstable at a lower
 30 pH.

31 **CLINICAL PHARMACOLOGY:**

32 **General:** Epoprostenol has two major
 33 pharmacological actions: (1) direct vasodilation of
 34 pulmonary and systemic arterial vascular beds, and
 35 (2) inhibition of platelet aggregation. In animals, the
 36 vasodilatory effects reduce right and left ventricular
 37 afterload and increase cardiac output and stroke
 38 volume. The effect of epoprostenol on heart rate in
 39 animals varies with dose. At low doses, there is

40 vagally mediated bradycardia, but at higher doses,
41 epoprostenol causes reflex tachycardia in response
42 to direct vasodilation and hypotension. No major
43 effects on cardiac conduction have been observed.
44 Additional pharmacologic effects of epoprostenol in
45 animals include bronchodilation, inhibition of gastric
46 acid secretion, and decreased gastric emptying.

47 **Pharmacokinetics:** Epoprostenol is rapidly
48 hydrolyzed at neutral pH in blood and is also subject
49 to enzymatic degradation. Animal studies using
50 tritium-labelled epoprostenol have indicated a high
51 clearance (93 mL/min/kg), small volume of
52 distribution (357 mL/kg), and a short half-life
53 (2.7 minutes). During infusions in animals, steady-
54 state plasma concentrations of tritium-labelled
55 epoprostenol were reached within 15 minutes and
56 were proportional to infusion rates.

57 No available chemical assay is sufficiently sensitive
58 and specific to assess the in vivo human
59 pharmacokinetics of epoprostenol. The in vitro half-
60 life of epoprostenol in human blood at 37°C and pH
61 7.4 is approximately 6 minutes; the in vivo half-life of
62 epoprostenol in man is therefore expected to be no
63 greater than 6 minutes. The in vitro pharmacologic

64 half-life of epoprostenol in human plasma, based on
65 inhibition of platelet aggregation, was similar for
66 males (n = 954) and females (n = 1024).

67 Tritium-labelled epoprostenol has been administered
68 to humans in order to identify the metabolic products
69 of epoprostenol. Epoprostenol is metabolized to two
70 primary metabolites: 6-keto-PGF_{1α} (formed by
71 spontaneous degradation) and 6,15-diketo-13,14-
72 dihydro-PGF_{1α} (enzymatically formed), both of which
73 have pharmacological activity orders of magnitude
74 less than epoprostenol in animal test systems. The
75 recovery of radioactivity in urine and feces over a
76 one-week period was 82% and 4% of the
77 administered dose, respectively. Fourteen additional
78 minor metabolites have been isolated from urine,
79 indicating that epoprostenol is extensively
80 metabolized in man.

81 Clinical Trials:

← DELETE and REPLACE with:
CLINICAL TRIALS IN PRIMARY
PULMONARY HYPERTENSION (PPH)

82
83 *Hemodynamic Effects:* Acute intravenous infusions
84 of FLOLAN for up to 15 minutes in patients with
85 secondary and primary pulmonary hypertension
86 (PPH) produce dose-related increases in cardiac
87 index (CI) and stroke volume (SV), and dose-related

— CORRECT TYPOGRAPHICAL ERROR:
(Insert space between run-on
words).

88 decreases in pulmonary vascular resistance (PVR),
89 total pulmonary resistance (TPR), and mean
90 systemic arterial pressure (SAPm). The effects of
91 FLOLAN on mean pulmonary artery pressure
92 (PAPm) in patients with PPH were variable and
93 minor.

94 Chronic continuous infusions of FLOLAN in patients
95 with PPH were studied in two prospective, open,
96 randomized trials of 8 and 12 weeks duration
97 comparing FLOLAN plus standard therapy to
98 standard therapy alone. Dosage of FLOLAN was
99 determined as described in DOSAGE AND

100 ADMINISTRATION and averaged 9.2 ng/kg/min

DELETE and REPLACE with: -
at study end.

101 ~~Standard therapy varied~~

102 among patients and included some or all of the
103 following: anticoagulants in essentially all patients;
104 oral vasodilators, diuretics, and digoxin in one-half to
105 two-thirds of patients; and supplemental oxygen in
106 about half the patients. Except for two New York
107 Heart Association (NYHA) functional Class II patients,
108 all patients were either functional Class III or Class IV.

109 As results were similar in the two studies, the pooled
110 results are described. Chronic hemodynamic effects

111 were generally similar to acute effects. CI, SV, and
112 arterial oxygen saturation were increased, and PAPm,

INSERT:
. (period at end of
sentence).

113 right atrial pressure (RAP), TPR, and systemic
114 vascular resistance (SVR) were decreased in patients
115 who received FLOLAN chronically compared to those
116 who did not. Table 1 illustrates the treatment-related
117 hemodynamic changes in these patients after 8 or
118 12 weeks of treatment.

19

120

Table 1

121

Hemodynamics During Chronic Administration of FLOLAN

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Hemodynamic Parameter	Baseline		Mean change from baseline at end of treatment period*	
	FLOLAN (n = 52)	Standard Therapy (n = 54)	FLOLAN (n = 48)	Standard Therapy (n = 41)
CI (L/min/m ²)	2.0	2.0	0.3*	-0.1
PAPm (mm Hg)	60	60	-5*	1
PVR (Wood U)	16	17	-4*	1
SAPm (mm Hg)	89	91	-4	-3
SV (mL/beat)	44	43	6*	-1
TPR (Wood U)	20	21	-5*	1

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* At 8 weeks: FLOLAN n = 10; Standard Therapy n = 11.

At 12 weeks: FLOLAN n = 38; Standard Therapy n = 30.

*Denotes statistically significant change between FLOLAN and Standard Therapy groups.

137

138

CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; SAPm = mean systemic arterial pressure; SV = stroke volume; TPR = total pulmonary resistance.

139

These hemodynamic improvements appeared to

140

persist when FLOLAN was administered for at least

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36 months in an open, non-randomized study.

142

Clinical Effects: Exercise capacity, as measured by

143

the 6-minute walk test, improved significantly in

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patients receiving continuous intravenous FLOLAN

145

plus standard therapy for 8 or 12 weeks compared to

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those receiving standard therapy alone.

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Improvements were apparent as early as the first

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week of therapy.

DELETE

149

increases in

50 exercise capacity were accompanied by significant
151 improvement in dyspnea and fatigue, as measured by
152 the Congestive Heart Failure Questionnaire and the
153 Dyspnea Fatigue Index.

154 Survival was improved in NYHA functional Class III
155 and Class IV PPH patients treated with FLOLAN for
156 12 weeks in a multicenter, open, randomized, parallel
157 study. At the end of the treatment period, 8 of
158 40 patients receiving standard therapy alone died,
159 whereas none of the 41 patients receiving FLOLAN
160 died ($P = 0.003$).

161

162 **INDICATIONS AND USAGE:** FLOLAN is indicated
163 for the long-term intravenous treatment of primary
164 pulmonary hypertension in NYHA Class III and
165 Class IV patients (see CLINICAL PHARMACOLOGY:
166 Clinical Trials).

~~INSERT:
in adults~~

167 **CONTRAINDICATIONS:** A large study evaluating
168 the effect of FLOLAN on survival in NYHA Class III
169 and IV patients with CHF due to severe left ventricular
170 systolic dysfunction was terminated after an interim
171 analysis of 471 patients revealed a higher mortality in
172 patients receiving FLOLAN plus standard therapy
173 than in those receiving standard therapy alone. The

.74 chronic use of FLOLAN in patients with CHF due to
175 severe left ventricular systolic dysfunction is therefore
176 contraindicated

177 FLOLAN is also contraindicated in patients with
178 known hypersensitivity to the drug or to structurally-
179 related compounds.

180 **WARNINGS: FLOLAN must be reconstituted only**
181 **as directed using STERILE DILUENT for FLOLAN.**
182 **FLOLAN must not be reconstituted or mixed with**
183 **any other parenteral medications or solutions**
184 **prior to or during administration.**

185 **Abrupt Withdrawal:** Abrupt withdrawal (including
186 interruptions in drug delivery) or sudden large
187 reductions in dosage of FLOLAN may result in
188 symptoms associated with rebound pulmonary
189 hypertension, including dyspnea, dizziness, and
190 asthenia. In clinical trials, one Class III PPH patient's
191 death was judged attributable to the interruption of
192 FLOLAN. Abrupt withdrawal should be avoided.

193 **Pulmonary Edema:** Some patients with primary
194 pulmonary hypertension have developed pulmonary
195 edema during dose ranging, which may be

96 associated with pulmonary veno-occlusive disease.
197 FLOLAN should not be used chronically in patients
198 who develop pulmonary edema during dose ranging.

199 Sepsis: See ADVERSE REACTIONS: Adverse
200 Events Attributable to the Drug Delivery System.

201 **PRECAUTIONS:**

202 **General:** FLOLAN should be used only by clinicians
203 experienced in the diagnosis and treatment of PPH.

204 The diagnosis of PPH should be carefully established
205 by standard clinical tests to exclude secondary
206 causes of pulmonary hypertension.

207 FLOLAN is a potent pulmonary and systemic
208 vasodilator. Dose ranging with FLOLAN must be
209 performed in a setting with adequate personnel and
210 equipment for physiologic monitoring and emergency
211 care.

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216 During acute dose ranging, asymptomatic increases
217 in pulmonary artery pressure coincident with
218 increases in cardiac output occurred rarely. In such
219 cases, dose reduction should be considered, but

THZZ/94/0030
103/W5

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- DELETE and REPLACE with:

- Although dose ranging in clinical trials was performed during right heart catheterization employing a pulmonary artery catheter, in uncontrolled studies utilizing Flolan, the risk of cardiac catheterization in patients with PPH should be carefully weighed against the potential benefits.

220 such an increase does not imply that chronic
221 treatment is contraindicated.

222 During chronic use, FLOLAN is delivered
223 continuously on an ambulatory basis through a
224 permanent indwelling central venous catheter.

225 Unless contraindicated, anticoagulant therapy should
226 be administered to PPH patients receiving FLOLAN to
227 reduce the risk of pulmonary thromboembolism or
228 systemic embolism through a patent foramen ovale.

229 In order to reduce the risk of infection, aseptic
230 technique must be used in the reconstitution and
231 administration of FLOLAN as well as in routine
232 catheter care. Because FLOLAN is metabolized
233 rapidly, even brief interruptions in the delivery of
234 FLOLAN may result in symptoms associated with
235 rebound pulmonary hypertension including dyspnea,
236 dizziness, and asthenia. The decision to initiate
237 therapy with FLOLAN should be based upon the
238 understanding that there is a high likelihood that
239 intravenous therapy with FLOLAN will be needed for
240 prolonged periods, possibly years, and the patient's
241 ability to accept and care for a permanent
242 intravenous catheter and infusion pump should be
243 carefully considered.

244 Based on clinical trials, the acute hemodynamic

245 response to FLOLAN did not correlate well with
246 improvement in exercise tolerance or survival during
247 chronic use of FLOLAN. Dosage of FLOLAN during
248 chronic use should be adjusted at the first sign of
249 recurrence or worsening of symptoms attributable to
250 PPH or the occurrence of adverse events associated
251 with FLOLAN (see DOSAGE AND
252 ADMINISTRATION). Following dosage adjustments,
253 standing and supine blood pressure and heart rate
254 should be monitored closely for several hours.

255 **Information for Patients:** Patients receiving
256 FLOLAN should receive the following information:
257 FLOLAN must be reconstituted only with **STERILE**
258 **DILUENT** for FLOLAN. FLOLAN is infused
259 continuously through a permanent indwelling central
260 venous catheter via a small, portable infusion pump.
261 Thus, therapy with FLOLAN requires commitment by
262 the patient to drug reconstitution, drug administration,
263 and care of the permanent central venous catheter.
264 Sterile technique must be adhered to in preparing the
265 drug and in the care of the catheter, and even brief
266 interruptions in the delivery of FLOLAN may result in
267 rapid symptomatic deterioration. The decision to
268 receive FLOLAN for PPH should be based upon the
269 understanding that there is a high likelihood that

!70 therapy with FLOLAN will be needed for prolonged
271 periods, possibly years, and the patient's ability to
272 accept and care for a permanent intravenous
273 catheter and infusion pump should be carefully
274 considered.

275 **Drug Interactions:** Additional reductions in blood
276 pressure may occur when FLOLAN is administered
277 with diuretics, antihypertensive agents, or other
278 vasodilators. When other anti-platelet agents or
279 anticoagulants are used concomitantly, there is the
280 potential for FLOLAN to increase the risk of bleeding.
281 However, patients receiving FLOLAN infusions in
282 clinical trials were maintained on anticoagulants
283 without evidence of increased bleeding. In clinical
284 trials, FLOLAN was used with digoxin, diuretics,
285 anticoagulants, oral vasodilators, and supplemental
286 oxygen.

287 **Carcinogenesis, Mutagenesis, Impairment of**
288 **Fertility:** Long-term studies in animals have not
289 been performed to evaluate carcinogenic potential. A
290 micronucleus test in rats revealed no evidence of
291 mutagenicity. The Ames test and DNA elution tests
292 were also negative, although the instability of
293 epoprostenol makes the significance of these tests
294 uncertain. Fertility was not impaired in rats given

295 FLOLAN by subcutaneous injection at doses up to
296 100 µg/kg/day, [600 g/m²/day, 2.5 times the
297 recommended human dose (4.6 ng/kg/min or 245.1
298 g/m²/day, i.v.) based on body surface area].

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299 Pregnancy: Pregnancy Category B. Reproductive
300 studies have been performed in pregnant rats and
301 rabbits at doses up to 100 g/kg/day (600 g/m²/day in

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302 rats, 2.5 times the recommended human dose, and
303 1180 g/m²/day in rabbits, 4.8 times the

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304 recommended human dose based on body surface
305 area) and have revealed no evidence of impaired
306 fertility or harm to the fetus due to FLOLAN. There
307 are, however, no adequate and well-controlled
308 studies in pregnant women. Because animal
309 reproduction studies are not always predictive of
310 human response, this drug should be used during
311 pregnancy only if clearly needed.

312 Labor and Delivery: The use of FLOLAN during
313 labor, vaginal delivery, or caesarean section has not
314 been adequately studied in humans.

315 Nursing Mothers: It is not known whether this drug
316 is excreted in human milk. Because many drugs are
317 excreted in human milk, caution should be exercised
318 when FLOLAN is administered to a nursing woman.

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DELETE and replace
with
Pediatric Use: Safety and
effectiveness in pediatric
patients have not been
established.

X

338 Geriatric Use: Clinical studies of FLOLAN did not
339 include sufficient numbers of patients aged 65 and
340 over to determine whether they respond differently
341 from younger patients. In general, dose selection for
342 an elderly patient should be cautious, reflecting the
343 greater frequency of decreased hepatic, renal, or

344 cardiac function and of concomitant disease or other
345 drug therapy.

346 **ADVERSE REACTIONS:** During clinical trials,

347 adverse events were classified as follows:

348 (1) adverse events during acute dose ranging,

349 (2) adverse events during chronic dosing, and

350 (3) adverse events associated with the drug delivery

351 system.

352 **Adverse Events During Acute Dose Ranging:**

353 During acute dose ranging, FLOLAN was

354 administered in 2 ng/kg/min increments until the

355 patients developed symptomatic intolerance. The

356 most common adverse events and the adverse

357 events that limited further increases in dose were

358 generally related to the major pharmacologic effect

359 of FLOLAN, vasodilation. The most common dose-

360 limiting adverse events were nausea and vomiting,

361 headache, hypotension, chest pain, dizziness, and

362 bradycardia. Table 2 lists the adverse events

363 reported during acute dose ranging in decreasing

364 order of frequency.

Table 2

366 Adverse Events During Acute Dose Ranging

	Adverse Events Occurring in $\geq 1\%$ of Patients	FLOLAN (% of patients) (n = 301)
367	Flushing	58
368	Headache	40
369	Nausea/Vomiting	32
370	Hypotension	16
371	Anxiety, nervousness, agitation	11
372	Chest pain	11
373	Dizziness	8
374	Bradycardia	5
375	Abdominal pain	5
376	Musculoskeletal pain	3
377	Dyspnea	2
378	Back pain	2
379	Sweating	1
380	Dyspepsia	1
381	Hypesthesia/Paresthesia	1
382	Tachycardia	1

385 Adverse Events During Chronic Administration:

386 Interpretation of adverse events is complicated by the
387 clinical features of PPH, which are similar to some of
388 the pharmacologic effects of FLOLAN (e.g.,
389 dizziness, syncope). Adverse events probably related
390 to the underlying disease include dyspnea, fatigue,
391 chest pain, right ventricular failure, and pallor.
392 Several adverse events, on the other hand, can
393 clearly be attributed to FLOLAN. These include
394 headache, jaw pain, flushing, diarrhea, nausea and
395 vomiting, flu-like symptoms, and anxiety/nervousness.
396 In an effort to separate the adverse effects of the
397 drug from the adverse effects of the underlying
398

39 disease, table 3 lists adverse events that occurred at
 400 a rate at least 10% different in the two groups in
 401 controls

402 **Table 3** INSERT:
≥
 403 **Adverse Events Regardless of Attribution Occurring with 10% Difference Between**
 404 **FLOLAN and Standard Therapy Alone**

Adverse Event	FLOLAN (% of patients) (n = 52)	Standard therapy (% of patients) (n = 54)
Occurrence More Common with FLOLAN		
GENERAL		
Chills/Fever/Sepsis/Flu-like symptoms	25	11
CARDIOVASCULAR		
Tachycardia	35	24
Flushing	42	2
GASTROINTESTINAL		
Diarrhea	37	6
Nausea/Vomiting	67	48
MUSCULOSKELETAL		
Jaw Pain	54	0
Myalgia	44	31
Non-specific musculoskeletal pain	35	15
NEUROLOGICAL		
Anxiety/nervousness/tremor	21	9
Dizziness	83	70
Headache	83	33
Hypesthesia, Hyperesthesia, Paresthesia	12	2
Occurrence More Common With Standard Therapy		
CARDIOVASCULAR		
Heart failure	31	52
Syncope	13	24
Shock	0	13
RESPIRATORY		
Hypoxia	25	37

434 Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving FLOLAN.

435 Table 4 lists additional adverse events reported in PPH patients receiving FLOLAN plus standard

therapy or standard therapy alone during controlled clinical trials.

437

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Table 4

439

Adverse Events Regardless of Attribution Occurring with <10% Difference Between FLOLAN
and Standard Therapy Alone

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GENERAL		
Asthenia	87 →	← 81
CARDIOVASCULAR		
Angina Pectoris	19	20
Arrhythmia	27	20
Bradycardia	15	9
Supraventricular tachycardia	8	0
Pallor	21	30
Cyanosis	31	38
Palpitation	63	61
Cerebrovascular accident	4	0
Hemorrhage	19	11
Hypotension	27	31
Myocardial ischemia	2	6
GASTROINTESTINAL		
Abdominal pain	27 →	← 31
Anorexia	25	30
Ascites	12 →	← 17
Constipation	6	2
METABOLIC		
Edema	80	63
Hypotalemia	6	4
Weight reduction	27	24
Weight gain	6	4
MUSCULOSKELETAL		
Arthralgia	6	0
Bone pain	0	4
Chest pain	67	65
NEUROLOGICAL		
Confusion	6	11
Convulsion	4	0
Depression	37	44
Insomnia	4	4
RESPIRATORY		
Cough increase	38	46
Dyspnea	80	85
Epistaxis	4	2
Pleural effusion	4	2
DERMATOLOGIC		
Pruritus	4	0
Rash	10	13

485	Sweating	15	20
486	SPECIAL SENSES		
487	Amblyopia	8	4
488	Vision abnormality	4	0

489 **Adverse Events Attributable to the Drug Delivery**

490 **System:** Chronic infusions of FLOLAN are delivered
491 using a small, portable infusion pump through an
492 indwelling central venous catheter. During controlled
493 trials of up to 12 weeks duration, 21% of patients
494 reported a local infection and 13% of patients
495 reported pain at the injection site. During long-term
496 follow-up, sepsis was reported at least once in 14%
497 of patients and occurred at a rate of 0.32 infections
498 per patient per year in patients treated with FLOLAN.
499 This rate was higher than reported in patients using
500 chronic indwelling central venous catheters to
501 administer parenteral nutrition, but lower than
502 reported in oncology patients using these catheters.
503 Malfunctions in the delivery system resulting in an
504 inadvertent bolus of or a reduction in FLOLAN were
505 associated with symptoms related to excess or
506 insufficient FLOLAN, respectively (see ADVERSE
507 REACTIONS: Adverse Events During Chronic
508 Administration and OVERDOSAGE).

509 **OVERDOSAGE:** Signs and symptoms of excessive
510 doses of FLOLAN during clinical trials are the
511 expected dose-limiting pharmacologic effects of

If the words "and OVERDOSAGE" are to be retained, the events described in the second paragraph of the OVERDOSAGE section should include its relationship to the delivery system.

512 FLOLAN, including flushing, headache, hypotension,
513 tachycardia, nausea, vomiting, and diarrhea.
514 Treatment will ordinarily require dose reduction of
515 FLOLAN.

516 One patient with secondary pulmonary hypertension
517 accidentally received 50 mL of an unspecified
518 concentration of FLOLAN. The patient vomited and
519 became unconscious with an initially unrecordable
520 blood pressure. FLOLAN was discontinued and the
521 patient regained consciousness within seconds. No
522 fatal events have been reported following overdosage
523 of FLOLAN.

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DELETE and REPLACE with:
Single intravenous doses
of FLOLAN at 10 and 50 mg/kg
(2703 and 27027 times the
- recommended acute phase
human dose based on body
surface area) were lethal to
mice and rats, respectively.
Symptoms of acute toxicity
were hypoactivity, ataxia,
loss of righting reflex,
deep slow breathing, and
hypothermia.

530 **DOSAGE AND ADMINISTRATION:**

531 **Important Note: FLOLAN must be reconstituted**

532 **only with STERILE DILUENT for FLOLAN.**

533 **Reconstituted solutions of FLOLAN must not be**

534 **diluted or administered with other parenteral solutions**

535 **or modifications (see WARNINGS).**

536 **Dosage:**

537 **Acute Dose Ranging:**

538 **The initial chronic infusion rate of FLOLAN is**

~~INSERT:
Adults:~~

539 **determined by an acute dose-ranging procedure.**

540 **During controlled clinical trials, this procedure was**

541 **performed during cardiac catheterization (see**

542 **PRECAUTIONS), but in subsequent uncontrolled**

543 **clinical trials, acute doseranging was performed**

544 **without cardiac catheterization. In either case, the**

545 **infusion rate is initiated at 2 ng/kg/min and increased**

546 **in increments of 2 ng/kg/min every 15 minutes or**

547 **longer until dose-limiting pharmacologic effects are**

548 **elicited. The most common dose-limiting**

549 **pharmacologic effects during dose ranging are**

550 **nausea, vomiting, headache, hypotension,**

INSERT:
but also include
(list ALL)

551 **During acute dose**

552 **ranging in clinical trials, the mean maximum dose**

553 **which did not elicit dose-limiting pharmacologic**

554 effects was 8.6 ± 0.3 ng/kg/min.

555 **Continuous Chronic Infusion:**

556 ~~Chronic continuous infusion of FLOLAN should be~~
557 administered through a central venous catheter.
558 Temporary peripheral intravenous infusions may be
559 used until central access is established. Chronic
560 infusions of FLOLAN should be initiated at
561 4 ng/kg/min less than the maximum-tolerated infusion
562 rate determined during acute dose ranging. If the
563 maximum-tolerated infusion rate is less than
564 5 ng/kg/min, the chronic infusion should be started at
565 one-half the maximum-tolerated infusion rate. During
566 clinical trials, the mean initial chronic infusion rate
567 was 5 ng/kg/min.

~~INSERT:
Adults:~~

568 **Dosage Adjustments:** Changes in the chronic
569 infusion rate should be based on persistence,
570 recurrence, or worsening of the patient's symptoms of
571 PPH and the occurrence of adverse events due to
572 excessive doses of FLOLAN. In general, increases in
573 dose from the initial chronic dose should be
574 expected. In the controlled 12-week trial, for
575 example, the dose increased from a mean starting
576 dose of 5.2 g/kg/min (4 g/kg/min less than the new
577 tolerated dose) to 9.2 g/kg/min by the end of
578 week 12, just 1.6 g/kg/min less than the mean non-
579 tolerated dose.

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580 Increments in dose should be considered if
581 symptoms of PPH persist or recur after improving.
582 The infusion should be increased by 1 to 2 ng/kg/min
583 increments at intervals sufficient to allow assessment
584 of clinical response; these intervals should be at least
585 15 minutes. Following establishment of a new
586 chronic infusion rate, the patient should be observed
587 and standing and supine blood pressure and heart
588 rate monitored for several hours to ensure that the
589 new dose is tolerated.

INSERT:
, (comma)

590 During chronic infusion, the occurrence of dose-
591 related pharmacological events similar to those

592 observed during acute dose ranging may necessitate
593 a decrease in infusion rate, but the adverse event
594 may occasionally resolve without dosage adjustment.
595 Dosage decreases should be made gradually in
596 2 ng/kg/min decrements every 15 minutes or longer
597 until the dose-limiting effects resolve. Abrupt
598 withdrawal of FLOLAN or sudden large reductions in
599 infusion rates should be avoided. Except in life-
600 threatening situations (e.g., unconsciousness,
601 collapse, etc.), infusion rates of FLOLAN should be
602 adjusted only under the direction of a physician.

603 In patients receiving lung transplants, doses of
604 FLOLAN were tapered after the initiation of
605 cardiopulmonary bypass.

606 Administration: FLOLAN is administered by
607 continuous intravenous infusion via a central venous
608 catheter using an ambulatory infusion pump. During
609 dose-ranging, FLOLAN may be administered
610 peripherally.

611 The ambulatory infusion pump used to administer
612 FLOLAN should: (1) be small and lightweight, (2) be
613 able to adjust infusion rates in 2 ng/kg/min
614 increments, (3) have occlusion, end of infusion, and
615 low battery alarms, (4) be accurate to $\pm 6\%$ of the

616 programmed rate, and (5) be positive pressure driven
617 (continuous or pulsatile) with intervals between
618 pulses not exceeding 3 minutes at infusion rates used
619 to deliver FLOLAN. The reservoir should be made of
620 polyvinyl chloride, polypropylene, or glass. Infusion
621 pumps used in clinical trials were the CADD-1
622 HFX 5100 (Pharmacia Deltec), Walk-Med 410 C
623 (Medfusion, Inc.), and the Auto Syringe AS2F (Baxter
624 Health Care).

625 To avoid potential interruptions in drug delivery, the
626 patient should have access to a backup infusion
627 pump and intravenous infusion sets. A multi-lumen
628 catheter should be considered if other intravenous
629 therapies are routinely administered.

630 To facilitate extended use at temperatures exceeding
631 25°C (77°F), a cold pouch with frozen gel packs was
632 used in clinical trials (see DOSAGE AND
633 ADMINISTRATION: Storage and Stability). The cold
634 pouches and gel packs used in clinical trials were
635 obtained from Palco Labs, Palo Alto, California.

INSERT:
ambient

← ADD:
Any cold pouch used
must be capable of
maintaining the
temperature of
reconstituted FLOLAN
between 2° and 8°C
for 12 hours.

636 **Reconstitution: FLOLAN is only stable when**
637 **reconstituted with STERILE DILUENT for FLOLAN.**
638 **FLOLAN must not be reconstituted or mixed with**
639 **any other parenteral medications or solutions**
640 **prior to or during administration.**

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646 **A concentration for the solution of FLOLAN for acute**
647 **dose ranging or chronic therapy should be selected**
648 **which is compatible with the infusion pump being used**
649 **with respect to minimum and maximum flow rates,**
650 **reservoir capacity, and the infusion pump criteria listed**
651 **above. FLOLAN, when administered chronically,**
652 **should be prepared in a drug delivery reservoir**
653 **appropriate for the infusion pump with a total reservoir**
654 **volume of at least 100 mL. FLOLAN should be**
655 **prepared using 2 vials of STERILE DILUENT for FLOLAN**
656 **for use during a 24-hour period. Table 5 gives**
657 **directions for preparing several different**
658 **concentrations of FLOLAN:**



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Table 5

661 662 663	To make 100 mL of solution with final Concentration (ng/mL) of:	Directions:
664	3,000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw 3 mL and add to sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
665	5,000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
666	10,000 ng/mL	Dissolve contents of two 0.5 mg vials each with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
667	15,000 ng/mL	Dissolve contents of one 1.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.

668 Higher concentrations may be required for patients who receive

669 FLOLAN long-term.

670 More than one solution strength may be required to
 671 accommodate the range of infusions anticipated
 672 during acute dose-ranging. Generally, 3,000 ng/mL
 673 and 10,000 ng/mL are satisfactory concentrations to
 674 deliver between 2 to 16 ng/kg/min in adults. Infusion
 675 rates may be calculated using the following formula:

$$676 \text{ Infusion Rate (mL/hr) = } \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 60 \text{ min/hr}}{\text{Concentration (ng/mL)}} \quad \text{Final}$$

680 Tables 6 through 9 provide infusion delivery rates for
 681 doses up to 16 ng/kg/min based upon patient weight,

682 drug delivery rate, and concentration of the solution of
 683 FLOLAN to be used. These tables may be used to
 684 select the most appropriate concentration of FLOLAN
 685 that will result in an infusion rate between the
 686 minimum and maximum flow rates of the infusion
 687 pump and which will allow the desired duration of
 688 infusion from a given reservoir volume. Higher
 689 infusion rates, and therefore, more concentrated
 690 solutions may be necessary with long-term
 691 administration of FLOLAN.

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Table 6

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Infusion Rates for FLOLAN at a Concentration of 3,000 ng/mL								
Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)							
10	—	—	1.2	1.6	2.0	2.4	2.8	3.2
20	—	1.6	2.4	3.2	4.0	4.8	5.6	6.4
30	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
40	1.6	3.2	4.8	6.4	8.0	9.6	11.2	12.8
50	2.0	4.0	6.0	8.0	10.0	12.0	14.0	16.0
60	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2
70	2.8	5.6	8.4	11.2	14.0	16.8	19.6	22.4
80	3.2	6.4	9.6	12.8	16.0	19.2	22.4	25.6
90	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8
100	4.0	8.0	12.0	16.0	20.0	24.0	28.0	32.0

Table 7

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Infusion Rates for FLOLAN at a Concentration of 5,000 ng/mL								
Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)							
	2	4	6	8	10	12	14	16
Infusion Delivery Rate (mL/hr)								
10	—	—	—	1.0	1.2	1.4	1.7	1.9
20	—	1.0	1.4	1.9	2.4	2.9	3.4	3.8
30	—	1.4	2.2	2.9	3.6	4.3	5.0	5.8
40	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7
50	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
60	1.4	2.9	4.3	5.8	7.2	8.8	10.1	11.5
70	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4
80	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4
90	2.2	4.3	6.5	8.6	10.8	13.0	15.1	17.3
100	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2

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Table 8

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Infusion Rates for FLOLAN at a Concentration of 10,000 ng/mL							
Patient Weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
Infusion Delivery Rate (mL/hr)							
20	—	—	1.0	1.2	1.4	1.7	1.9
30	—	1.1	1.4	1.8	2.2	2.5	2.9
40	1.0	1.4	1.9	2.4	2.9	3.4	3.8
50	1.2	1.8	2.4	3.0	3.6	4.2	4.8
60	1.4	2.2	2.9	3.6	4.3	5.0	5.8
70	1.7	2.5	3.4	4.2	5.0	5.9	6.7
80	1.9	2.9	3.8	4.8	5.8	6.7	7.7
90	2.2	3.2	4.3	5.4	6.5	7.6	8.6
100	2.4	3.6	4.8	6.0	7.2	8.4	9.6

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Table 9

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Infusion Rates for FLOLAN at a Concentration of 15,000 ng/mL							
Patient	Dose or Drug Delivery Rate (ng/kg/min)						
Weight (kg)	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
30	—	—	1.0	1.2	1.4	1.7	1.9
40	—	1.0	1.3	1.6	1.9	2.2	2.6
50	—	1.2	1.6	2.0	2.4	2.8	3.2
60	1.0	1.4	1.9	2.4	2.9	3.4	3.8
70	1.1	1.7	2.2	2.8	3.4	3.9	4.5
80	1.3	1.9	2.6	3.2	3.8	4.5	5.1
90	1.4	2.2	2.9	3.6	4.3	5.0	5.8
100	1.5	2.4	3.2	4.0	4.8	5.6	6.4

768 **Storage and Stability:** Unopened vials of FLOLAN
 769 are stable until the date indicated on the package
 770 when stored at 15° to 25°C (59° to 77°F) and
 771 protected from light in the carton. Unopened vials of
 772 STERILE DILUENT for FLOLAN are stable until the
 773 date indicated on the package when stored at 15° to
 774 25°C (59° to 77°F).

775 Prior to use, reconstituted solutions of FLOLAN must
776 be protected from light and must be refrigerated at
777 2° to 8°C (36° to 46°F) if not used immediately. Do
778 not freeze reconstituted solutions of FLOLAN.
779 Discard any reconstituted solution that has been
780 frozen.

ADD:

Discard any reconstituted solution if it has been refrigerated for more than 48 hours.

781 During use, a single reservoir of reconstituted solution
782 of FLOLAN can be administered at room temperature
783 for a total duration of 8 hours, or it can be
784 administered up to 24 hours with the use of two
785 frozen 6-oz gel packs in a cold pouch. When stored
786 or in use, reconstituted FLOLAN must be insulated
787 from temperatures greater than 25°C (77°F) and less
788 than 0°C (32°F), and must not be exposed to direct
789 sunlight.

INSERT:

used with a cold pouch and

790 *Use at Room Temperature:* Prior to use at room
791 temperature, 15° to 25°C (59° to 77°F), reconstituted
792 solutions of FLOLAN may be stored refrigerated at 2°
793 to 8°C (36° to 46°F) for no longer than 40 hours.
794 When administered at room temperature,
795 reconstituted solutions may be used for no longer
796 than 8 hours. This 48-hour period allows the patient
797 to reconstitute a 2-day supply (200 mL) of FLOLAN.
798 Each 100 mL daily supply may be divided into three

39 equal portions. Two of the portions are stored
800 refrigerated at 2° to 8°C (36° to 46°F) until they are
801 used.

802 *Use with a Cold Pouch:* Prior to infusion with the
803 use of a cold pouch, solutions may be stored
804 refrigerated at 2° to 8°C (36° to 46°F) for up to
805 24 hours. When a cold pouch is employed during the
806 infusion, reconstituted solutions of FLOLAN may be
807 used for no longer than 24 hours. The gel packs
808 should be changed every 12 hours.

ADD:

Reconstituted solutions may be kept at 2°C to 8°C (36° to 46°F), either in refrigerated storage or in a cold pouch or a combination of the two, for no more than 48 hours.

809 **HOW SUPPLIED:** FLOLAN for Injection is supplied
810 as a sterile freeze-dried powder in 17 mL flint glass
11 vials with gray butyl rubber closures, individually
812 packaged in a carton.

ADD NEW PARAGRAPH:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, reconstituted FLOLAN should not be administered.

813 17 mL vial containing epoprostenol sodium equivalent
814 to 0.5 mg (500,000 ng), carton of 1, (NDC 0081-
815 0460-01).

816 17 mL vial containing epoprostenol sodium equivalent
817 to 1.5 mg (1,500,000 ng), carton of 1, (NDC 0081-
818 0464-01).

819 Store the vials of FLOLAN at 15° to 25°C (59° to
820 77°F). Protect from light.

821 The STERILE DILUENT for FLOLAN is supplied in 50
822 mL flint glass vials with fluororesin faced butyl rubber
823 closures.

824 50 mL vial of STERILE DILUENT for FLOLAN, tray of 4
825 (NDC 0081-0462-01).

826 Store the vials of STERILE DILUENT for FLOLAN at
827 15° to 25°C (59° to 77°F). DO NOT FREEZE.

828 Caution: Federal law prohibits dispensing without
829 prescription.

830

831 U.S. Patent Nos. 4335139, 4539333, and 4883812 (Use Patent)
832 Licensed Under U.S. Patent No. 4338325

833
834

835 Manufactured by
836 THE WELLCOME FOUNDATION LTD.
837 London, England NW1 2BP for
838 BURROUGHS WELLCOME CO.
839 Research Triangle Park, NC 27709

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842 Printed in U.S.A.

(Date of issue)

(Item No.)

843

FINAL PRINTED LABELING
FLOLAN[®] (epoprostenol sodium) for Injection
Package Insert

Table 2
Adverse Events During Acute Dose Ranging

Adverse Events Occurring in ≥1% of Patients	FLOLANP (% of patients) (n=391)
Flushing	58
Headache	48
Nausea/vomiting	32
Hypotension	16
Anxiety, nervousness, agitation	11
Chest pain	11
Dizziness	8
Bradycardia	5
Abdominal pain	5
Musculoskeletal pain	3
Dyspnea	2
Back pain	2
Sweating	1
Dyspepsia	1
Hypoaesthesia/Paresthesia	1
Tachycardia	1

Adverse Events During Chronic Administration: Interpretation of adverse events is complicated by the clinical features of PPH, which are similar to some of the pharmacologic effects of FLOLAN (e.g., dizziness, syncope). Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, right ventricular failure, and pallor. Several adverse events, on the other hand, can clearly be attributed to FLOLAN. These include headache, jaw pain, flushing, darrms, nausea and vomiting, flu-like symptoms, and anasthenousness. In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, table 3 lists adverse events that occurred at a rate of least 10% different in the two groups in controlled trials.

Table 3
Adverse Events Regardless of Attribution Occurring with ≥10% Difference Between FLOLAN and Standard Therapy Alone

Adverse Event	FLOLANP (% of patients) (n=52)	Standard therapy (% of patients) (n=54)
Occurrence More Common with FLOLAN		
GENERAL		
Chills/Fever/Septic/Flu-like symptoms	25	11
CARDIOVASCULAR		
Tachycardia	35	24
Flushing	42	2
GASTROINTESTINAL		
Darrms	37	6
Nausea/vomiting	67	48
MUSCULOSKELETAL		
Jaw Pain	54	0
Myalgia	44	31
Non-specific musculoskeletal pain	35	15
NEUROLOGICAL		
Anxiety/nervousness/tremor	21	9
Dizziness	83	70
Headache	83	33
Hypoaesthesia, Paresthesia	12	2
Occurrence More Common with Standard Therapy		
CARDIOVASCULAR		
Heart failure	31	52
Syncope	13	24
Shock	0	13
RESPIRATORY		
Hypoxia	25	37

Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving FLOLAN.

Table 4 lists additional adverse events reported in PPH patients receiving FLOLAN plus standard therapy or standard therapy alone during controlled clinical trials.

Table 4
Adverse Events Regardless of Attribution Occurring with <10% Difference Between FLOLAN and Standard Therapy

Adverse Event	FLOLANP (% of patients) (n=52)	Standard therapy (% of patients) (n=54)
GENERAL		
Asymptomatic	87	81
CARDIOVASCULAR		
Angina pectoris	19	20
Arrhythmia	27	20
Bradycardia	15	9
Supraventricular tachycardia	8	0
Pallor	21	30
Cyanosis	31	39
Palpitation	63	61
Cerebrovascular accident	4	0
Hemorrhage	19	11
Hypotension	27	31
Myocardial ischemia	2	6
GASTROINTESTINAL		
Abdominal pain	27	31
Anorexia	25	30
Ascites	12	17
Constipation	6	2
METABOLIC		
Edema	60	60
Hypokalemia	6	4
Weight reduction	27	24
Weight gain	6	4
MUSCULOSKELETAL		
Arthralgia	6	0
Bone pain	0	4
Chest pain	67	65
NEUROLOGICAL		
Confusion	6	11
Convulsion	4	0
Depression	37	44
Insomnia	4	4

(continued)

Adverse Events Regardless of Attribution Occurring with <10% Difference Between FLOLAN and Standard Therapy (cont'd)

Adverse Event	FLOLANP (% of patients) (n=52)	Standard therapy (% of patients) (n=54)
RESPIRATORY		
Cough increase	38	46
Dyspnea	90	65
Eupnea	4	2
Pleural effusion	4	2
DERMATOLOGIC		
Pruritus	4	0
Rash	10	13
Sweating	15	20
SPECIAL SENSES		
Amblyopia	8	4
Vision abnormality	4	0

Adverse Events Attributable to the Drug Delivery System: Chronic infusions of FLOLAN are delivered using a small, portable infusion pump through an indwelling central venous catheter. During controlled trials of up to 12 weeks duration, 21% of patients reported a local infection and 13% of patients reported pain at the injection site. During long-term follow-up, sepsis was reported at least once in 14% of patients and occurred at a rate of 0.32 infections per patient per year in patients treated with FLOLAN. This rate was higher than reported in patients using chronic indwelling central venous catheters to administer parenteral nutrition, but lower than reported in oncology patients using these catheters. Malfunctions in the delivery system resulting in an inadvertent bolus of or a reduction in FLOLAN were associated with symptoms related to excess or insufficient FLOLAN, respectively (see ADVERSE REACTIONS, Adverse Events During Chronic Administration).

OVERDOSAGE: Signs and symptoms of excessive doses of FLOLAN during clinical trials are the expected dose-limiting pharmacologic effects of FLOLAN, including flushing, headache, hypotension, tachycardia, nausea, vomiting, and darrms. Treatment will ordinarily require dose reduction of FLOLAN.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unspecified concentration of FLOLAN. The patient vomited and became unconscious with an initially unrecordable blood pressure. FLOLAN was discontinued and the patient regained consciousness within seconds. No fatal events have been reported following overdosage of FLOLAN.

Single intravenous doses of FLOLAN at 10 and 50 mg/kg (2703 and 27,027 times the recommended acute phase human dose based on body surface area) were lethal to mice and rats, respectively. Symptoms of acute toxicity were hyporeactivity, ataxia, loss of righting reflex, deep slow breathing, and hypothermia.

DOSAGE AND ADMINISTRATION:

Important Note: FLOLAN must be reconstituted only with STERILE DILUENT for FLOLAN. Reconstituted solutions of FLOLAN must not be diluted or administered with other parenteral solutions or medications (see WARNINGS).

Dosage:

Acute Dose Ranging:

The initial chronic infusion rate of FLOLAN is determined by an acute dose-ranging procedure. During controlled clinical trials, this procedure was performed during cardiac catheterization (see PRECAUTIONS), but in subsequent uncontrolled clinical trials, acute dose ranging was performed without cardiac catheterization. In either case, the infusion rate is initiated at 2 ng/kg/min and increased in increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting pharmacologic effects are elicited. The most common dose-limiting pharmacologic effects (occurring in ≥1% of patients) during dose ranging are nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia. During acute dose ranging in clinical trials, the mean maximum dose which did not elicit dose-limiting pharmacologic effects was 8.6 ± 0.3 ng/kg/min.

Continuous Chronic Infusion:

Chronic continuous infusion of FLOLAN should be administered through a central venous catheter. Temporary peripheral intravenous infusions may be used until central access is established. Chronic infusions of FLOLAN should be initiated at 4 ng/kg/min less than the maximum-tolerated infusion rate determined during acute dose ranging. If the maximum-tolerated infusion rate is less than 5 ng/kg/min, the chronic infusion should be started at one-half the maximum-tolerated infusion rate. During clinical trials, the mean initial chronic infusion rate was 5 ng/kg/min.

Dosage Adjustments: Changes in the chronic infusion rate should be based on persistence, recurrence, or worsening of the patient's symptoms of PPH and the occurrence of adverse events due to excessive doses of FLOLAN. In general, increases in dose from the initial chronic dose should be expected. In the controlled 12-week trial, for example, the dose increased from a mean starting dose of 5.2 μg/kg/min (4 μg/kg/min less than the new tolerated dose) to 9.2 μg/kg/min by the end of week 12, just 1.6 μg/kg/min less than the mean non-tolerated dose.

Increases in dose should be considered if symptoms of PPH persist or recur after improving. The infusion should be increased by 1 to 2 ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. Following establishment of a new chronic infusion rate, the patient should be observed, and standing and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During chronic infusion, the occurrence of dose-related pharmacological events similar to those observed during acute dose ranging may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2 ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of FLOLAN or sudden large reductions in infusion rates should be avoided. Except in life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of FLOLAN should be adjusted only under the direction of a physician.

In patients receiving lung transplants, doses of FLOLAN were tapered after the insertion of cardiopulmonary bypass.

Administration: FLOLAN is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. During dose-ranging, FLOLAN may be administered peripherally.

The ambulatory infusion pump used to administer FLOLAN should (1) be small and lightweight, (2) be able to adjust infusion rates in 2 ng/kg/min increments, (3) have occlusion, end of infusion, and low battery alarms, (4) be accurate to ± 6% of the programmed rate, and (5) be positive pressure driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver FLOLAN. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. Infusion pumps used in clinical trials were the CADD-1 HFX 5100 (Pharmacia Datascan), Walk-Infed 410 C (Medtronic, Inc.), and the Auto Syringe AS2F (Baxter Health Care).

To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets. A multi-lumen catheter should be considered if other intravenous therapies are routinely administered.

To facilitate extended use at ambient temperatures exceeding 25°C (77°F), a cold pouch with frozen gel packs was used in clinical trials (see DOSAGE AND ADMINISTRATION, Storage and Stability). The cold pouches and gel packs used in clinical trials were obtained from Palco Labs, Palo Alto, California. Any cold pouch used must be capable of maintaining the temperature of reconstituted FLOLAN between 2° and 8°C for 12 hours.

Reconstitution: FLOLAN is only stable when reconstituted with STERILE DILUENT for FLOLAN. FLOLAN must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.

A concentration for the solution of FLOLAN for acute dose ranging or chronic therapy should be selected which is compatible with the infusion pump being used with respect to maximum and minimum flow rates, reservoir capacity, and the infusion pump criteria listed above. FLOLAN, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump, with a total reservoir volume of at least 100 mL. FLOLAN should be prepared using 2 vials of STERILE DILUENT for FLOLAN for use during a 24-hour period. Table 5 gives directions for preparing several different concentrations of FLOLAN.

Table 5

To make 100 mL of solution with final concentration (ng/mL) of	Directions
3,000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN®. Withdraw 3 mL and add to sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
5,000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
10,000 ng/mL	Dissolve contents of two 0.5 mg vials each with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
15,000 ng/mL	Dissolve contents of one 1.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw entire vial contents and add sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.

*Higher concentrations may be required for patients who receive FLOLAN long-term. More than one solution strength may be required to accommodate the range of infusions anticipated during acute dose-ranging. Generally, 3,000 ng/mL and 10,000 ng/mL are satisfactory concentrations to deliver between 2 to 16 ng/kg/min in adults. Infusion rates may be calculated using the following formula:

$$\text{Infusion Rate (mL/hr)} = \frac{[\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 60 \text{ min/hr}]}{\text{Final Concentration (ng/mL)}}$$

Tables 6 through 9 provide infusion delivery rates for doses up to 16 ng/kg/min based upon patient weight, drug delivery rate, and concentration of the solution of FLOLAN to be used. These tables may be used to select the most appropriate concentration of FLOLAN that will result in an infusion rate between the minimum and maximum flow rates of the infusion pump and which will allow the desired duration of infusion from a given reservoir volume. Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of FLOLAN.

Table 6

Patient Weight (kg)	Infusion Rates for FLOLAN® at a Concentration of 3,000 ng/mL							
	Dose or Drug Delivery Rate (ng/kg/min)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)							
10	—	—	1.2	1.6	2.0	2.4	2.8	3.2
20	—	1.6	2.4	3.2	4.0	4.8	5.6	6.4
30	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
40	1.6	3.2	4.8	6.4	8.0	9.6	11.2	12.8
50	2.0	4.0	6.0	8.0	10.0	12.0	14.0	16.0
60	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2
70	2.8	5.6	8.4	11.2	14.0	16.8	19.6	22.4
80	3.2	6.4	9.6	12.8	16.0	19.2	22.4	25.6
90	3.6	7.2	10.8	14.4	18.0	21.6	25.2	28.8
100	4.0	8.0	12.0	16.0	20.0	24.0	28.0	32.0

Table 7

Patient Weight (kg)	Infusion Rates for FLOLAN® at a Concentration of 5,000 ng/mL							
	Dose or Drug Delivery Rate (ng/kg/min)							
	2	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)							
10	—	—	—	1.0	1.2	1.4	1.7	1.9
20	—	1.0	1.4	1.9	2.4	2.9	3.4	3.8
30	—	1.4	2.2	2.9	3.6	4.3	5.0	5.8
40	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7
50	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
60	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5
70	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4
80	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4
90	2.2	4.3	6.5	8.6	10.8	13.0	15.1	17.3
100	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2

Table 8

Patient Weight (kg)	Infusion Rates for FLOLAN® at a Concentration of 10,000 ng/mL						
	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
20	—	—	1.0	1.2	1.4	1.7	1.9
30	—	1.1	1.4	1.8	2.2	2.5	2.9
40	1.0	1.4	1.9	2.4	2.9	3.4	3.8
50	1.2	1.8	2.4	3.0	3.6	4.2	4.8
60	1.4	2.2	2.9	3.6	4.3	5.0	5.8
70	1.7	2.5	3.4	4.2	5.0	5.9	6.7
80	1.9	2.9	3.8	4.8	5.8	6.7	7.7
90	2.2	3.2	4.3	5.4	6.5	7.6	8.6
100	2.4	3.6	4.8	6.0	7.2	8.4	9.6

Table 9

Patient Weight (kg)	Infusion Rates for FLOLAN® at a Concentration of 15,000 ng/mL						
	Dose or Drug Delivery Rate (ng/kg/min)						
	4	6	8	10	12	14	16
	Infusion Delivery Rate (mL/hr)						
30	—	—	1.0	1.2	1.4	1.7	1.9
40	—	1.0	1.3	1.6	1.9	2.2	2.6
50	—	1.2	1.6	2.0	2.4	2.8	3.2
60	1.0	1.4	1.9	2.4	2.9	3.4	3.8
70	1.1	1.7	2.2	2.8	3.4	3.9	4.5
80	1.3	1.9	2.6	3.2	3.8	4.5	5.1
90	1.4	2.2	2.9	3.6	4.3	5.0	5.8
100	1.6	2.4	3.2	4.0	4.8	5.6	6.4

Storage and Stability: Unopened vials of FLOLAN are stable until the date indicated on the package when stored at 15° to 25°C (59° to 77°F) and protected from light in the carton. Unopened vials of STERILE DILUENT for FLOLAN are stable until the date indicated on the package when stored at 15° to 25°C (59° to 77°F).

Prior to use, reconstituted solutions of FLOLAN must be protected from light and must be refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. Do not freeze reconstituted solutions of FLOLAN. Discard any reconstituted solution that has been frozen. Discard any reconstituted solution if it has been refrigerated for more than 48 hours.

During use, a single reservoir of reconstituted solution of FLOLAN can be administered at room temperature for a total duration of 8 hours, or it can be used with a cold pouch and administered up to 24 hours with the use of two frozen 6-oz gel packs in a cold pouch. When stored or in use, reconstituted FLOLAN must be insulated from temperatures greater than 25°C (77°F) and less than 0°C (32°F), and must not be exposed to direct sunlight.

Use at Room Temperature: Prior to use at room temperature, 15° to 25°C (59° to 77°F), reconstituted solutions of FLOLAN may be stored refrigerated at 2° to 8°C (36° to 46°F) for no longer than 40 hours. When administered at room temperature, reconstituted solutions may be used for no longer than 8 hours. The 48-hour period allows the patient to reconstitute a 2-day supply (200 mL) of FLOLAN. Each 100 mL daily supply may be divided into three equal portions. Two of the portions are stored refrigerated at 2° to 8°C (36° to 46°F) until they are used.

Use with a Cold Pouch: Prior to infusion with the use of a cold pouch, solutions may be stored refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours. When a cold pouch is employed during the infusion, reconstituted solutions of FLOLAN may be used for no longer than 24 hours. The gel packs should be changed every 12 hours. Reconstituted solutions may be kept at 2° to 8°C (36° to 46°F), either in refrigerated storage or in a cold pouch or a combination of the two, for no more than 48 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, FLOLAN should not be administered.

HOW SUPPLIED: FLOLAN for injection is supplied as a sterile freeze-dried powder in 17 mL, tint glass vials with gray butyl rubber closures, individually packaged in a carton.

17 mL vial containing epoprostenol sodium equivalent to 0.5 mg (500,000 ng), carton of 1, (NDC 0081-0460-01).

17 mL vial containing epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng), carton of 1, (NDC 0081-0464-01).

Store the vials of FLOLAN at 15° to 25°C (59° to 77°F). Protect from light.

The STERILE DILUENT for FLOLAN is supplied in 50 mL, tint glass vials with fluorocarbon faced butyl rubber closures.

50 mL vial of STERILE DILUENT for FLOLAN, tray of 4 (NDC 0081-0462-01).

Store the vials of STERILE DILUENT for FLOLAN at 15° to 25°C (59° to 77°F). DO NOT FREEZE.

Caution: Federal law prohibits dispensing without prescription.

U.S. Patent Nos. 4335139, 4539333, and 4683812 (Use Patent)
Licensed Under U.S. Patent No. 4338325

Manufactured by
THE WELLCOME FOUNDATION LTD.
London, England NW1 2BP for
BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709
Printed in U.S.A.

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THZZ/94/0030
103/WS

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August 29, 1995

STERILE DILUENT for FLOLAN

Contains drug diluent for use only
with FLOLAN® (epoprostenol sodi-
um) for injection.

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Research Triangle Park, NC 27709
Wellcome Made in U.S.A. 500200

019832

NDA 20-444
FINAL PRINTED I.A.R.F.I. INC

4 Vials 50 mL each

NDC 0081-0462-01

STERILE DILUENT for FLOLAN

Contains drug diluent for use only
with FLOLAN® (epoprostenol sodium)
for injection.

Each vial contains 94 mg glycine, 73.5 mg sodium chloride, sodi-
um hydroxide (added to adjust pH), and Water for Injection, USP.
For reconstitution information see package insert for FLOLAN®
(epoprostenol sodium) for injection.
Store at 15° to 25°C (59° to 77°F). DO NOT FREEZE.
CAUTION: Federal law prohibits dispensing without prescription.



3 0081-0462-01 3



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Research Triangle Park, NC 27709
Wellcome Made in U.S.A. 500200

Contains drug diluent for use only
with FLOLAN® (epoprostenol sodi-
um) for injection.

STERILE DILUENT for FLOLAN

STERILE DILUENT for FLOLAN

4 Vials 50 mL each

NDC 0081-0462-01

Contains drug diluent for use only
with FLOLAN® (epoprostenol sodium)
for injection.

Each vial contains 94 mg glycine, 73.5 mg sodium chloride, sodi-
um hydroxide (added to adjust pH), and Water for Injection, USP.
For reconstitution information see package insert for FLOLAN®
(epoprostenol sodium) for injection.
Store at 15° to 25°C (59° to 77°F). DO NOT FREEZE.
CAUTION: Federal law prohibits dispensing without prescription.

NDA 20-444

FINAL PRINTED LABELING
FLOLAN® (epoprostenol sodium) for Injection
Vial Label x 50 mL - Sterile Diluent

50 mL

NDC 0081-0462-01

STERILE DILUENT
for FLOLAN

Contains drug diluent for use only with FLOLAN® (epoprostenol sodium) for injection.

Each vial contains 94 mg glycine, 73.5 mg sodium chloride, sodium hydroxide (added to adjust pH), and Water for Injection, USP.

For reconstitution information see package insert for FLOLAN® (epoprostenol sodium) for injection.

Store at 15° to 25° C (59° to 77° F).
DO NOT FREEZE.

CAUTION: Federal law prohibits dispensing without prescription.



BURROUGHS WELLCOME CO.
Research Triangle Park, NC 27709
Made in U.S.A. 330211

330211

NDA 20-444

FINAL PRINTED LABELING
FLOLAN® (epoprostenol sodium) for Injection
Carton x 1.5 mg

NDC 0081-0464-01

For intravenous infusion only.
Not for mixture with other
drugs.
Use only STERILE DILUENT
for FLOLAN® for reconstitu-
tion.

See package insert for indica-
tions, dosage, and precautions
information.

Store at 15° to 25° C (59° to
77°F). Protect from light.

FLOLAN
(epoprostenol
sodium)
for Injection




Wellcome
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BURROUGHS WELLCOME (U.S.)
INC. 12000 Wilshire Boulevard
Los Angeles, CA 90025
BURROUGHS WELLCOME (UK)
LTD. 100 Brook Hill Drive
Beverly Hills, CA 91608
Made in England 33 2714

Each vial contains epoprostenol
sodium equivalent to 1.5 mg
(1,500,000 ng) epoprostenol,
3.76 mg glycine, 2.93 mg sodium
chloride, and 50 mg mannitol.
Sodium hydroxide may have
been added to adjust pH.

CAUTION: Federal law prohibits
dispensing without prescription.

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NDA 20-444

FINAL PRINTED LABELING
FLOLAN[®] (epoprostenol sodium) for Injection
Vial Label x 1.5 mg

FLOLAN
(epoprostenol sodium)
for Injection

NDC 0091-0464-01

For intravenous infusion only.
Not for mixture with other drugs.
Use only STERILE DILUENT for FLOLAN[®]
for reconstitution.

See package insert for indications, dosage,
and precautions information.

Store at 15 to 25°C (59 to 77°F). Protect
from light.

Each vial contains epoprostenol sodium
equivalent to 1.5 mg (1,500,000 i.u.)
epoprostenol, 3.75 mg glucose, 2.50 mg
sodium chloride, and 50 mg mannitol.
Sodium hydroxide may have been added
to adjust pH.
CAUTION: Federal law prohibits dispensing
without prescription.

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4,222,224; Brit. Patent
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FINAL PRINTED LABELING
FLOLAN® (epoprostenol sodium) for Injection
Vial Label x 0.5 mg

FLOLAN
(epoprostenol sodium)
for Injection

MEC 001-040-01

0.5 mg (500.000 µg)

Each vial contains epoprostenol sodium
equivalent to 0.5 mg (500.000 µg)
epoprostenol, 1.75 mg pyruvate, 2.50 mg
sodium chloride, and 1 mg mesorolol.
Sodium hydroxide may have been added
to adjust pH.

CAUTION: Federal law prohibits dispensing
without prescription.

For intravenous infusion only.
Not for mixture with other drugs.
Use only STERILE ELUENT for FLOLAN®
for reconstitution.

See package insert for indications, dosage,
and preservative information.
Store at 15° to 25° C (59° to 77°F). Protect
from light.

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Made in England 200712
U.S. Patent Nos. 4,581,130; 4,582,822; and
4,582,812 Also Patent
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NDA 20-444

FINAL PRINTED LABELING
FLOLAN® (epoprostenol sodium) for Injection
Carton x 0.5 mg

NDC 0081-0460-01

For intravenous infusion only.
Not for mixture with other
drugs.
Use only STERILE DILUENT
for FLOLAN® for reconstitu-
tion.

See package insert for indica-
tions, dosage, and procedure
information.

Store at 15° to 25°C (59° to
77°F). Protect from light.


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SUNOVION WILLOUGH CO
Research Triangle Park, NC 27709
Made in England 30013

FLOLAN
(epoprostenol
sodium)
for Injection



019831



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EXP

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 10, 1995

FROM: Arthur B. Shaw, Ph.D., Review Chemist, Division of
Gastrointestinal and Coagulation Drug Products, HFD-180

ABS
8/14/95

THROUGH: John Gibbs, Ph.D., Supervisory Chemist, Division of
Gastrointestinal and Coagulation Drug Products, HFD-160

3/17/95

SUBJECT: Package Insert for Flolan, NDA 20-444

TO: Karen Oliver, CSO

Burroughs-Wellcome submitted a draft package insert on May 22, 1995. There are a number of amendments which the sponsor should be asked to make in order to clarify the limits on storage after reconstitution. Patients and physicians should be alerted to the necessity for maintaining the reconstituted FLOLAN at refrigerated temperatures if it is going to be used for more than 8 hours, as well as the necessity for discarding refrigerated Flolan after 48 hours. The suggested additions are redlined. Note that the following phrase from the original has been amended and moved to be just above the "How supplied" section, in keeping with common practice.

"369 Parenteral drug products should be inspected visually for particulate matter and discoloration
370 prior to administration whenever solution and container permit. If either occurs, FLOLAN
371 should not be administered."

1. Page 19, Beginning on Line 362

362 To facilitate extended use at ambient temperatures exceeding 25°C (77°F), a cold pouch with frozen gel
363 packs was used in clinical trials (see DOSAGE AND ADMINISTRATION: Storage and Stability).
364 The cold pouches and gel packs used in clinical trials were obtained from Palco Labs, Palo Alto,
365 California. Any cold pouch used must be capable of maintaining the temperature of reconstituted
FLOLAN between 2°C and 8°C for 2 hours.

366 Reconstitution: FLOLAN is only stable when reconstituted with STERILE DILUENT for
367 FLOLAN. FLOLAN must not be reconstituted or mixed with any other parenteral
368 medications or solutions prior to or during administration.

2. Page 23, Line 403

403 Prior to use, reconstituted solutions of FLOLAN must be protected from light and must be
404 refrigerated at 2° to 8°C (36° to 46°F) if not used immediately. Do not freeze reconstituted solutions
405 of FLOLAN. Discard any reconstituted solution that has been frozen. Discard any reconstituted
solution if it has been refrigerated for more than 48 hours.

406 During use, a single reservoir of reconstituted solution of FLOLAN can be administered at room
407 temperature for a total duration of 8 hours, or it can be used with a cold pouch and administered up to
408 24 hours with the use of two frozen 6-oz gel packs in a cold pouch. When stored or in use,
409 reconstituted FLOLAN must be insulated from temperatures greater than 25°C (77°F) and less than 0°C
410 (32°F), and must not be exposed to direct sunlight.

411 **Use at Room Temperature:** Prior to use at room temperature, (15° to 25°C (59° to 77°F)),
412 reconstituted solutions of FLOLAN may be stored refrigerated at 2° to 8°C (36° to 46°F) for no
413 longer than 40 hours. When administered at room temperature, reconstituted solutions may be
414 used for no longer than 8 hours. This 48-hour period allows the patient to reconstitute a
415 2-day supply (200 mL) of FLOLAN. Each 100 mL daily supply may be divided into three equal
416 portions. Two of the portions are stored refrigerated at 2° to 8°C (36° to 46°F) until they are
417 used.

418 **Use with a Cold Pouch:** Prior to infusion with the use of a cold pouch, solutions may be stored
419 refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours. When a cold pouch is employed during
420 the infusion, reconstituted solutions of FLOLAN may be used for no longer than 24 hours.
421 The gel packs should be changed every 12 hours. Reconstituted solutions may be kept at 2°C to 8°C
(36° to 46°F), either in refrigerated storage or in a cold pouch or a combination of the two, for no more than 48
hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration
prior to administration whenever solution and container permit. If either occurs, reconstituted FLOLAN
should not be administered.

422 **HOW SUPPLIED:** FLOLAN for Injection is supplied as a sterile freeze-dried powder in 17 mL
423 flint glass vials with gray butyl rubber closures, individually packaged in a carton.

cc:

HFD 20-044

HFD-180/Div File

HFD-180/SFredd

R/D Init. by:JGibbs/8-14-95

abs/dob F/T 8-14-95\WP:c:\wpfiles\chem\N\20444508.as5

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MAY - 9 1995

NDA 20-444

Burroughs Wellcome Company
Attention: Ms. Mary Lou Schenck
3030 Cornwallis Road
Research Triangle Park, North Carolina 27709

Dear Ms. Schenck:

Please refer to your February 28, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Flolan (epoprostenol sodium) for Injection.

We acknowledge receipt of your amendments dated April 6, 7, 20, 22, and 29; May 6 and 27; July 7; August 23; September 14 and 16; October 4, 6, and 28; December 9, 12, 19, and 23, 1994; January 9, 12, 24, 25, and 27; February 2, 7, and 22; March 20 and 21; and April 10, 12, 13, and 20 1995.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit a satisfactory response to the April 28, 1995 letter requesting additional chemistry information.

In addition, we request that you submit final printed labeling (FPL). The package insert should be identical in content to the enclosed marked-up draft labeling. The labels and cartons, submitted April 12, 1995, should be revised as follows:

1. All immediate container and carton labels (Active Drug and Diluent)
 - a. The "O" in the tradename "Flolan" is an obscure design which is different from the type set of the other letters in the name. The letter "O" should be the same type set and size as the other letters in the tradename to minimize the potential problem of misreading the drug name as required under 21 CFR 201.15 (a) (6).
 - b. The entire proprietary drug name, "Flolan for Injection", must be prominently displayed as required under 21 CFR 201.15(a) (6).

- c. The location of the expiration date and lot number location must be identified as required under 21 CFR 201.17.
2. For Flolan carton and vial labels: in the statement "For indications, dosage, precautions, etc., see accompanying package insert." it is unclear to what "etc" refers. We recommend the statement be revised to: "See package insert for indications, dosage, and precautions information."
 3. Sterile Diluent for Flolan (vial and tray)
 - a. The proposed name of the diluent "Sterile Diluent for Flolan (epoprostenol sodium)" is misleading in terms of the name itself and the manner in which it is presented. The diluent may be mistakenly identified as Flolan, since the word Flolan is printed in the largest sized letters and is further highlighted by green print. The proposed name also includes "epoprostenol sodium". However, this is the established name (active ingredient) for Flolan, not the diluent. Thus, it should not be included as part of the diluent name. The name of the diluent should be revised to: "Sterile Diluent for Flolan" and should be prominently and conspicuously displayed together in the same type size, style, and color.
 - b. The warning on the diluent label and carton, "For Drug Diluent Use Only" is not clearly nor prominently displayed. We recommend the following wording, using bolded letters, prominently displayed: "Contains drug diluent for use only with Flolan (epoprostenol sodium) for Injection."

Please submit fifteen copies of the printed labeling, ten of which are individually mounted on heavy weight paper or similar material. If additional information relating to the safety or effectiveness of this drug becomes available, revision of that FPL may be required.

We also remind you of your post approval commitments made in the April 27, 1995 telephone conversation between representatives of your firm and this Agency, and detailed in our April 28, 1995 letter.

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

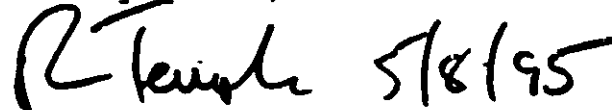
Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Karen Oliver
Consumer Safety Officer
Telephone: (301) 443-0487

Sincerely yours,



Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and
Research

ENCLOSURE

cc:

Original NDA 20-444
HFD-180/Div. Files
HFD-2/M.Lumpkin
HFD-80
HFD-100
HFD-180/K.Oliver
DISTRICT OFFICE
HFD-240/S.Sherman (with draft labeling)
HFD-638 (with draft labeling)

drafted: KO/March 31, 1995/
r/d Initials:B.Collier 04/05/95
r/d Initials:K.Johnson 04/28/95
r/d Initials:A.Shaw 04/28/95
r/d Initials:J.Gibbs 04/28/95
r/d Initials:S.Fredd 04/28/95 *K.Oliver 07/01/95*
Final: KO/05/01/95/c:\wpwin\karenfil\20444503.2ko

APPROVABLE (AE)

8F 5/1/95

CSO Review

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER ADMINISTRATIVE REVIEW OF NDA 20-444

Application Number: NDA 20-444

Name of Drug: Flolan (epoprostenol sodium) Injection

MAR 18 1994

Sponsor: Burroughs Wellcome Company

Material Reviewed

Submission Date(s): February 28, 1994

Receipt Date(s): February 28, 1994

Background and Summary Description: Original NDA for Flolan for the treatment of primary pulmonary hypertension. Flolan is designated Subpart E and Orphan Drug for this indication.

Review

1. **Indexing:** An overall index has been provided in the 1.1 and the first volume for each technical review section. Each technical review section is additionally provided with a detailed index for that section. Study reports and summaries contain individual detailed indexes. These latter indexes generally refer to study report page numbers, and, in some cases both the study report and NDA pages numbers are listed.
2. **Annotated Labeling:** Annotations are to specific (page number) locations in the NDA. Annotations to summaries sections were not noted.
3. **Required elements within the technical review sections, summary volume, Integrated Summary of Efficacy, and Integrated Summary of Safety are addressed.**
4. **Additional Comments:**
 - a. Information regarding the specific batches of drug used in clinical trials is found in both the CMC section (Vol 1.2, page 140) and the Biopharm section (Vol 1.19, page 40 of the summary).
 - b. The drug is approved in 16 foreign countries. The approved foreign labeling has been provided under the section for Foreign Marketing History.
 - c. Subset analyses for age, race, gender, and body weight can be found in the Integrated Summary of Efficacy (Vol 1.53, page 11084)
 - d. Statistical data (stability and clinical) have not been provided in electronic format.

NDA 20-444

Page 2

Conclusions

Administratively, this NDA appears to meet the regulations for format. Indexing and pagination are adequate.

Bronwyn Collier 3/17/94
Consumer Safety Officer

Karen Case 3/18/94

cc:

Orig NDA 20-444

HFD-180

HFD-180/SFredd

HFD-180/CSO/KOliver

BC/3/17/94/C:\wp51\cao\ln\20444403.RBC

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-444

Name of Drug: Flolan (epoprostenol sodium) for Injection

Sponsor: Glaxo Wellcome Inc.

Material Reviewed

NOV 14 1995

Submission Date(s): October 20, 1995

Receipt Date(s): October 23, 1995

Background and Summary Description: The Burroughs Wellcome Company (name changed to Glaxo Wellcome Inc. in a correspondence dated 10/31/95, received 11/01/95) submitted NDA 20-444 for Flolan (epoprostenol sodium) for Injection on February 28, 1994, for the treatment of primary pulmonary hypertension (PPH) NYHA Class III and Class IV. Flolan is designated Subpart E and Orphan Drug for this indication. In response to an Agency September 20, 1995 approval letter, final printed labeling was submitted for the package insert and container labeling for Flolan and Sterile Diluent for Flolan.

Review

Vials and Cartons

The submitted final printed labels (vial label 0.5 mg, carton 0.5 mg, vial label 1.5 mg, carton 1.5 mg, vial label 50 mL-Sterile Diluent, and Tray 4-Sterile Diluent) were compared to mock-up labels submitted June 6, 1995 (CSO Review 09/05/95) and they are identical.

Package Insert

The submitted final printed package insert was compared to the marked-up draft labeling in the September 20, 1995 approval (AP) letter. The package insert labeling differs to that which accompanied the AP letter as follows:

1. Identification code added: 554106 September 1995.

This editorial change is ACCEPTABLE.

2. The words "FLOLAN (epoprostenol sodium) for Injection" were added to top of each of the package insert columns.

This editorial change is ACCEPTABLE.

3. In the DESCRIPTION section, the chemical structure was changed:

from:

to: "Epoprostenol is (5Z, 9 α , 11 α , 13E, 15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid".

This change correctly identifies the chemical formula and is ACCEPTABLE.

4. In the PRECAUTIONS section, the "General" subsection, the sentence was changed

from:

to: "Although dose ranging in clinical trials was performed during right heart catheterization employing a pulmonary artery catheter, in uncontrolled studies utilizing FLOLAN, acute dose ranging was performed without cardiac catheterization. The risk of cardiac catheterization in patients with PPH should be carefully weighed against the potential benefits."

This editorial change is ACCEPTABLE.

5. In the ADVERSE REACTIONS section:

- a. The "Adverse Events During Acute Dose Ranging" subsection, the sentence was changed

from:

to: "The most common dose-limiting adverse events (occurring in ≥1% of patients) were nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia."

This change is ACCEPTABLE.

- b. The "Adverse Events During Chronic Administration" subsection, the word "Alone" in the title of the table was deleted. The title was changed

from:

to: "Adverse Events Regardless of Attribution Occurring with <10% Difference Between FLOLAN and Standard Therapy".

The firm should be requested to reinstate the word "Alone" in the title of Table 4 at the next package insert printing.

- c. In the "Adverse Events Attributable to the Drug Delivery System" subsection, the phrase was changed

from:

to: "(see ADVERSE REACTIONS: Adverse Events During Chronic Administration)".

This change, discussed in the September 20, 1995 AP letter, is ACCEPTABLE.

6. In the OVERDOSAGE section, commas were added to the following numbers to read: 2,703 and 27,027.

This change is ACCEPTABLE.

7. In the DOSAGE AND ADMINISTRATION section, the "Dosage: Acute Dose Ranging subsection", the sentence was changed

from:

to "The most common dose-limiting pharmacologic effects (occurring in $\geq 1\%$ of patients) during dose ranging are nausea, vomiting, headache, hypotension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, abdominal pain, musculoskeletal pain, and tachycardia."

This change is ACCEPTABLE.

Conclusions

The changes identified in the labeling review are acceptable. An acknowledge and retain letter should be issued to the firm. The firm should be requested to add the word "Alone" in the title of Table 4 to read, "Adverse Events Regardless of Attribution Occurring with $<10\%$ Difference between FLOLAN and Standard Therapy Alone" at the next printing. Further, the firm should be requested to submit labeling to show the changes in the name and address of the manufacturer, packer or distributor of the drug in the next annual report under 21 CFR 314.72.

Karen Oliver, CSO 11/14/95
Karen Oliver
Consumer Safety Officer

11/15/95
Karen
JO

cc:

Original 20-444
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/E.Triantas
HFD-180/A.Shaw
HFD-180/J.Choudary
HFD-180/S.Fredd

draft: KO/November 7, 1995

r/d Initials: M.Walsh 11/13/95

r/d Initials: S.Fredd 11/13/95

final: KO/11/14/95/c:\wpwin\karenfil\rev\20444511.0ko
K.Oliver 11/14/95

CSO REVIEW

01-27

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

MAY - 1 1995

Application Number: 20-444

Name of Drug: Flolan (epoprostenol sodium) for Injection

Sponsor: Burroughs Wellcome Company

Material Reviewed

Submission Date(s): April 12, 1995

Receipt Date(s): April 13, 1995

Background and Summary Description: The Burroughs Wellcome Company submitted NDA 20-444 for Flolan (epoprostenol sodium) for Injection on February 28, 1994, for the treatment of primary pulmonary hypertension (PHH) NYHA Class III and Class IV in adults and children. Flolan is designated Subpart E and Orphan Drug for this indication. The April 12, 1995 submission provides draft, color mock-up labeling for the immediate container and carton labels.

Review

The labels (vial label x 0.5mg, carton x 0.5mg, vial label x 1.5mg, carton x 1.5mg, vial label x 50 mL-Sterile Diluent, and Tray x 4-Sterile Diluent) were reviewed. The following were noted as deviations from the labeling regulations:

1. All immediate container and carton labels (Active Drug and Diluent)
 - a. The "O" in the tradename "Flolan" is an obscure design which is different from the type set of the other letters in the name. The letter "O" should be the same type set and size as the other letters in the tradename to minimize the potential problem of misreading the drug name as required under 21 CFR 201.15 (a) (6).
 - b. The proprietary drug name, "Flolan for Injection", must be prominently displayed as required under 21 CFR 201.15(a) (6).

c. The location of the expiration date and lot number location must be identified as required under 21 CFR 201.17.

2. For Flolan carton and vial labels: in the statement "For indications, dosage, precautions, etc., see accompanying package insert." it is unclear to what "etc" refers. Recommend the statement be revised to: "See package insert for indications, dosage, and precautions information."

3. Sterile Diluent for Flolan (vial and tray)

a. The proposed name of the diluent "Sterile Diluent for Flolan (epoprostenol sodium)" is misleading in terms of the name itself and the manner in which it is presented. The diluent may be mistakenly identified as Flolan, since the word Flolan is printed in the largest sized letters and is further highlighted by green print. The proposed name also includes "epoprostenol sodium". However, this is the established name (active ingredient) for Flolan, not the diluent. Thus, it should not be included as part of the diluent name. The name of the diluent should be revised to: "Sterile Diluent for Flolan" and should be prominently and conspicuously displayed together in the same type size, style, and color.

b. The firm intends to market the drug components, Flolan and diluent, in separate packages because the volume of diluent used in a 24 hour period remains constant while the amount of active ingredient is dependent on the prescribed dose. Since Flolan must be reconstituted only with the specified diluent, instructions to the pharmacist to dispense both Flolan and diluent together must be explicit. The warning on the diluent label and carton, "For Drug Diluent Use Only" is not clear nor prominently displayed. Recommended wording, using bolded letters, prominently displayed: "Contains drug diluent for use only with Flolan (epoprostenol sodium) for Injection."

Conclusions

1. Recommendations 1-3 will bring the labeling into conformity with labeling regulations (21 CFR 201.15, 201.17, .201.50, 201.55, and 201.57).
2. The ingredients and storage statement sections: to be reviewed by the chemist.

Karen Oliver CSO 04/28/95
Consumer Safety Officer

cc:

Original 20-444
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/A.Shaw
HFD-180/S.Fredd

5/1/95 Karen
SP

draft: KO/April 14, 1995
r/d Initials: B. Collier 04/27/95
r/d Initials: A. Shaw 04/28/95

final: KO/04/28/95/c:\wpwin\karenfil\rev\20444504.0ko

CSO REVIEW

SEP 5 1995

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: 20-444

Name of Drug: Flolan (epoprostenol sodium) for Injection

Sponsor: Burroughs Wellcome Company

Material Reviewed

Submission Date(s): May 22, 1995 Package Insert
June 6, 1995 Carton and Immediate Container Labels

Receipt Date(s): May 23 and June 7, 1995

Background and Summary Description: The Burroughs Wellcome Company submitted NDA 20-444 for Flolan (epoprostenol sodium) for Injection on February 28, 1994, for the treatment of primary pulmonary hypertension (PPH) NYHA Class III and Class IV in adults and children. Flolan is designated Subpart E and Orphan Drug for this indication. In response to the May 9, 1995 approvable letter, the May 22, 1995 submission provides an annotated draft package insert and the June 6, 1995 submission provides draft, color mock-up labeling for the immediate container and carton labels.

Review

Package Insert

The submitted draft labeling was compared to the marked-up draft labeling in the May 9, 1995 approvable (AE) letter. The labeling differs from that which accompanied the AE letter as follows:

1. In the **CLINICAL TRIALS** section,
 - a. The "Hemodynamic Effects" subsection:
 - 1) The words "for up to 15 minutes" were added to "describe how long" the acute intravenous infusions of FLOLAN lasted and the words "9.2 mg/kg/min at the end of the 12-week trial" were added to identify the average dosage of Flolan "at study end". These revisions respond to requests in the AE labeling and should be evaluated by the medical officer. It should be noted that one

pivotal was for a 12-week duration while the other was for an 8-week duration. Therefore, the words "at study end" should be retained for accuracy, and "at the end of the 12-week trial" should be deleted.

- 2) The initials "PPH" were added after the words "primary pulmonary hypertension" in the first sentence of that section. This is an acceptable editorial revision.
 - 3) Table 1, "Hemodynamics During Chronic Administration of FLOLAN" has not been adjusted. The AE labeling requested correction of the data from the April 20, 1995 submission "if different". The sponsor provided no comments regarding the table. The medical officer should review the accuracy of the table, which was not revised.
- b. In the "Clinical Effects" subsection: In the sentence: "Improvements were apparent as early as the first week of therapy, [and in long-term follow-up appeared to be maintained beyond 2 years]." the bracketed information was retained. The AE labeling requested that a reference be provided or the bracketed phrase deleted. The firm provided the reference: Clinical Data Section, Volume 1.53, Page 11107. The Medical Officer should evaluate the reference provided.
2. In the **INDICATIONS AND USAGE** section, the words "in adults" were deleted. The AE letter included the words "in adults" and deleted only the words "and children". The words "in adults" should be retained. In effect, the firm is proposing use in both adults and children, while we have proposed limiting the recommendation to use in adults. Note: Although we have requested that the "Pediatric Use" subsection be deleted, the medical officer should consider whether a statement such as "Safety and efficacy in children has not been established." should be included.
 3. In the **CONTRAINDICATIONS** section:
 - a. The "WARNING" statement was bolded. This is an acceptable editorial revision.
 - b. In the "Pulmonary Edema" subsection, the word "not" in the second sentence was underlined for emphasis:

"FLOLAN should not be used chronically in patients who develop pulmonary edema during dose-ranging." This is an acceptable editorial revision.

4. In the **PRECAUTIONS** section:

- a. The words "uncontrolled studies utilized Flolan" were not included in the third sentence as requested in the AE labeling. The sentence should read: "Although dose ranging in clinical trials was performed during right heart catheterization employing a pulmonary artery catheter, in uncontrolled studies utilizing Flolan, the risk of cardiac catheterization in patients with PPH should be carefully weighed against the potential benefits." The request should be reiterated.
- b. In the "Information for Patients" subsection, the words FLOLAN must be reconstituted only with STERILE DILUENT for FLOLAN" were bolded. This is an acceptable editorial revision.
- c. Although "Pediatric Use" subsection was deleted in the approvable labeling, the firm has retained it, with minor revisions. The request should be reiterated. (See comment under 2. above.)

5. In the **ADVERSE REACTIONS** section:

- a. In the "Adverse Events During Chronic Administration subsection, the words "an insufficient dose of FLOLAN reflect recurrent" were eliminated from the second sentence. The AE labeling included these words, however, it appears that the phrase was maintained inadvertently. Therefore, the firm's revision is acceptable.
- b. In the "Adverse Events Attributable to the Drug Delivery System", the words "and OVERDOSAGE" were added to the last sentence to read "(see ADVERSE REACTIONS: Adverse Events During Chronic Administration and OVERDOSAGE)." If the words "and OVERDOSAGE" are to be retained, the events described in the second paragraph of the OVERDOSAGE section should include its relationship to the delivery system.

6. In the **OVERDOSAGE** section, the words were added to the first sentence of the third paragraph.

The accuracy of this revision, requested in the AE labeling, should be reviewed by the pharmacologist.

7. In the **DOSAGE AND ADMINISTRATION** section

- a. The "Important Note: FLOLAN must be reconstituted only with STERILE DILUENT for FLOLAN." sentence was bolded. This is an acceptable editorial change.
- b. In the "Dosage: Acute Dose Ranging:" subsection:
 - 1) The first word in that subsection, "Adults", was deleted. The word "Adults" should be retained.
 - 2) Only three additional dose-limiting pharmacologic effects were added, although the AE labeling requested that all 15 be listed.
- c. In the "Dosage: Continuous Chronic Infusion:" subsection, the first word in that subsection, "Adults", was deleted. The word should be retained.
- d. In the "Administration" subsection:
 - 1) The "Reconstitution" sentence was bolded. This is an acceptable editorial change.
 - 2) The sixth and seventh paragraphs were combined. The paragraphs should be separately retained as in the AE labeling.
- e. In the "Storage and Stability" subsection, the words "Do not freeze reconstituted solutions of FLOLAN. Discard any reconstituted solution that has been frozen." have been bolded. This is an acceptable editorial change.

8. In the **HOW SUPPLIED** section, the phrase "Caution: Federal law prohibits dispensing without prescription." the word "Caution" was bolded. This is an acceptable editorial change.

Vials and Cartons

The submitted mock-up labels (vial label 0.5 mg, carton 0.5 mg, vial label 1.5 mg, carton 1.5 mg, vial label 50 mL-Sterile

Diluent, and Tray 4-Sterile Diluent) were compared to the requested changes in approval letter. They differ as follows: The location of the expiration date and lot number could not be located. The AE letter requested that the locations be identified as required under 21 CFR 201.17. In a June 9, 1995 submission, the firm stated that, during production, the lot number and expiration date will be stamped on the both the vial labels for Flolan and the vial label and tray for the Sterile Diluent for Flolan. This is acceptable.

Conclusions

Package Insert

1. The revised content in the **CLINICAL TRIALS** section, the "Hemodynamic Effects" and the "Clinical Effects" subsection, should be evaluated by the medical officer.
2. The revised content in the **OVERDOSAGE** section should be evaluated by the pharmacology reviewer.
3. The firm should be requested to:
 - a. In the **ADVERSE REACTIONS** section, the "Adverse Events Attributable to the Drug Delivery system" subsection, the words "and OVERDOSAGE" were added to the last sentence to read "(see Adverse Reactions: Adverse Events During Chronic Administration and OVERDOSAGE)." If the words "and OVERDOSAGE" are to be retained, the events described in the second paragraph of the **OVERDOSAGE** section must include an explanation of its relationship to the delivery system.
 - a. In the **INDICATIONS AND USAGE** section, retain the words "in adults" as indicated in the AE labeling.
 - b. In the **PRECAUTIONS** section:
 - (1) The third sentence should be corrected as requested in the AE labeling.
 - (2) The "Pediatric Use" subsection should be deleted as requested in the AE labeling. The medical officer should determine whether a statement such as "Safety and efficacy in children has not been established." should be included.

- c. In the **DOSAGE AND ADMINISTRATION** section:
- (1) In the "Dosage: Acute Dose Ranging:" subsection:
 - (a) The first work in that subsection, "Adults", should be retained as requested in the AE labeling.
 - (b) All dose-limiting pharmacology effects should be added as requested in the AE labeling.
 - (2) In the "Dosage: Continucus Chronic Infusion:" subsection, the word "Adults" should be retained as requested in AE letter.
 - (3) In the "Administration" subsection, the sixth and seventh paragraphs should be retained as separate paragraphs as in the AE labeling.
5. The section heading "**Clinical Trials**" should be capitalized, "**CLINICAL TRIALS:**", to be consistent with other section headings.

Vials and Cartons: The changes are acceptable.

Karen Oliver 08/30/95
Karen Oliver
Consumer Safety Officer

cc:

Original NDA 20-444
HFD-180/Div. Files
HFD-180/K.Oliver
HFD-180/S.Fredd
HFD-180/A.Shaw
HFD-180/S.Fredd

9/5/95
Concur
JP

draft: KO/July 14, 1995
r/d Initials:K.Johnson 08/07/95
r/d Initials:A.Shaw 08/14/95
r/d Initials:J.Choudary 08/15/95
r/d Initials:S.Fredd 08/15/95
init: KO/July 14, 1995
final:KO/08/30/95/c:\wpwin\karenfil\rev\20444507.0ko

CSO REVIEW

mor

OW
Oliver

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 20-444
DRUG: Flolan
SPONSOR: Burroughs Wellcome

MAR 30 1995

DATE OF SUBMISSION: 3/21/95
CONTENTS: Clinical case history of patient from study #46.

The history of patient 46 as described in this submission, is quite different from the information that we had received in the original NDA submission, Vol. 1.70.

In the original submission it is stated that on admission patient had active chronic hepatitis C and also a history of bleeding (please see attached copies of relevant information from the original record). There was no mention in that record that she had been treated previously with interferon and that she had been cured from her hepatitis. Also there was no mention that she was already on warfarin for about 1 1/2 year before entering study 46. The original record indicated that she had been started on warfarin on 5/14/92, the date of her admission to study 46. Furthermore, there was no mention of prothrombin time or aPTT values in the original record. The only information that both the original record and the submission of 3/21/95 agree on is that patient had suffered bleeding in the past (which should have made the treating physicians more careful with her anticoagulation during study 46).

I do not understand why we were given the wrong information originally.

There is also another question. Patient a class III patient, was first seen at the Columbia-Presbyterian Medical Center in November 1990. Study #46 was initiated in September 1991. I wonder why this patient had not been entered into this study earlier than 5/14/92 before her pulmonary disease had progressed further. Hepatitis, as they said, was not an exclusion criterion.

E. Triantas 3/30/95
E. Triantas, M.D., Ph.D.

CC:
NDA 20-444
HFD-180
HFD-180/SFredd
HFD-180/ETriantas
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
f/t 3/30/95 jgw
MED\N\20444503.0ET

3/30/95
Green
JT

FEB - 8 1995

NDA 20-444
Drug: Flolan, PGI₂

SPONSOR: Burroughs-Wellcome

MEDICAL REVIEW
February 8, 1995

REVIEWER: Eugenie Triantas, M.D., Ph.D.

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

FEB - 8 1995

NDA: 20-444

SPONSOR: Burroughs-Wellcome

NAME OF DRUG: Flolan, Prostacyclin, PGI₂

PROPOSED INDICATION: Treatment of primary pulmonary hypertension (PPH). Classified as a priority and orphan indication.

DATE OF SUBMISSION: Dec. 11, 1994

PURPOSE OF SUBMISSION: Response to the questions/comments raised in the FDA Medical Review of NDA 20-444. This response was presented by the sponsor at the Dec 5 meeting with them.

DATE SUBMISSION RECEIVED: Dec. 13, 1994

DATE RECEIVED BY MEDICAL OFFICER: Dec. 23, 1994

DATE REVIEW COMPLETED: Dec 21, 1994 ?

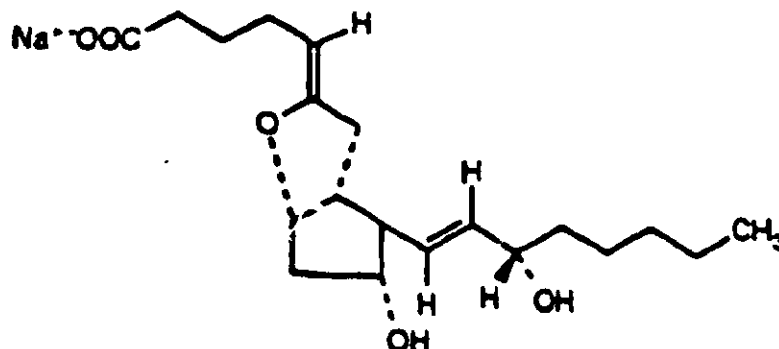
ADDITIONAL DATA:

In this review I have also incorporated and reevaluated data from the original NDA, the 4-month Safety Update of July 17, 1994, the October 28, 1994 submission and from the DSI inspection of study 46 in order to focus attention to the controlled studies by including all the information that we have received so far.

DATE FINAL REVIEW COMPLETED: February 3, 1995

THE DRUG:

Prostacyclin (epoprostenol, PGI₂, cycloprostin, flolan) is the most potent naturally occurring vasodilatory and platelet inhibitory prostaglandin.



Molecular Weight 374.45

Flolan is supplied by the sponsor in the form of sterile lyophilized powder in vials containing the equivalent of 0.5 mg or 1.5 mg of epoprostenol. Before administration the powder is dissolved into a sterile diluent, which is also provided. This diluent contains glycine, sodium chloride, water for injection, and NaOH to adjust the pH to 10.2 to 10.8. The solution is increasingly unstable at lower pHs. Epoprostenol is rapidly hydrolysed at neutral pH in the blood. It is also broken down enzymatically. For treatment flolan is infused i.v. through a central venous catheter.

PRIMARY PULMONARY HYPERTENSION (PPH) is a very rare but progressive, intractable and usually fatal disease, although spontaneous improvement and disease regression have been reported. According to the results of the NIH Registry the median survival time from baseline catheterization was estimated to be 2.8 years. The risk of death was higher among patients classified in functional NYHA class III or IV than among those classified in functional class I or II. Median survival time for patients of class I or II was 59 months, for functional class III it was 32 months and for patients who were in functional class IV the median survival time was 6 months. It has been claimed that the best indicators for survival are the mean pulmonary arterial pressure (PAPm), the mean right atrial pressure (RAPm), and the cardiac index (CI) (Alonzo et al., *Annales of Intern. Med.* 115, 343, 1991).

The disease is identified by 1) clinical, radiographic and electrocardiographic manifestations of pulmonary hypertension; 2) demonstration of mean pulmonary arterial pressure ≥ 25 mm Hg, pulmonary vascular resistance >67 dynes/sec/cm⁵ (or $>0.05R$ units; 1 R unit = 1328 dynes) in association with normal pulmonary wedge pressure and a nearly normal or low cardiac output; and 3) by the inability to find a cause for the pulmonary hypertension in a disorder of the heart, lungs or systemic circulation.

CLINICAL STUDIES:

Burroughs-Wellcome has supported 9 clinical studies in order to provide evidence that flolan (prostacyclin) is safe and effective for the treatment of PPH. Two of these studies (#35/36 and #46) were controlled and the remaining 5 (#37, #47, #49, #50, #5/10, #20, and #21) were uncontrolled.

The Controlled Studies:

Chronic intravenous infusions of placebo were considered inappropriate due to the known risks associated with a central venous catheter and the absence of expected benefit from placebo. As a result none of the controlled studies on flolan was double-blind.

STUDY #35/33:

Title: Multicenter evaluation of Long-Term Flolan Infusions in Patients with Primary Pulmonary Hypertension (PPH)

Study Period: April 10, 1987 - February 28, 1990

Investigators and No. of Patients:

Study 35/36 was carried out by:

	<u>No of Pts</u>
Lewis Rubin, MD, U of Maryland Hospital, Baltimore, MD	16
Robyn Barst, MD, Columbia Presbyterian Hosp., N.Y.	6
Michael McGoon, Mayo Clinic, Rochester, MN.	4

Patients with NYHA Class I and II were entered into study #35 and those of Class III and IV were entered into study #36. Study 35 was terminated prematurely because of the occurrence of embolism and one death in 2 flolan patients in study #36 and of another death in the continuation study #37. It was reasoned that the potential benefits of flolan infusion might not outweigh the risks associated with the flolan delivery system in less ill patients with NYHA Class I and II. Thus only two patients were recruited for study 35. The results of these patients were combined with those of study #36.

Study Design: open, parallel, randomized, multicenter. The study included essentially 3 phases:

1. Screening (Days 0 and 1)
2. Baseline (Day 1. Compliance with the inclusion and exclusion criteria; Dose-ranging with flolan; randomization)
3. Long term infusion segment (Day 1 to 57)

The original protocol included 3 additional phases: a post-treatment phase of 7 days without flolan and two additional dose-ranging segments. However, when flolan was discontinued the patients exhibited significant deterioration of hemodynamic parameters and/or worsening of PPH symptoms and these phases were not implemented.

Dose-ranging: All patients including the control patients before randomization were infused with flolan starting at 2 ng/kg/min for 10 to 20 minutes. The dose increased by 2 ng/kg/min up to 12 ng/kg/min. Doses greater than 12 ng/kg/min could be administered only whe. the 12 ng/kg/min dose was well tolerated and the investigator was of the opinion that higher doses could provide further hemodynamic improvement without posing undue hazard to the

patient. The dose-ranging procedure could be cut short if: a) a serious side effect appeared, b) a change in the mean systemic arterial pressure (SAPm) of more than 40% of baseline value occurred, c) the heart rate changed to <60 or to >130 bpm or to greater than 40% of the baseline value, or c) an ST change of 0.1 mv or greater at the J-point of the ECG occurred or if myocardial ischemia was suspected.

Randomization: Upon completion of the dose-ranging segment the investigator contacted Burroughs-Wellcome personnel who provided the patient number and the treatment assignment. Numbers were assigned consecutively across all study sites. The code was predetermined. Random numbers were generated using procedure PLAN of SAS. Five blocks of four random numbers were used. The patients were stratified according to whether they were using oral vasodilators for at least 60 days or not at baseline. Patients being treated with oral vasodilators were assigned a treatment beginning with the first number in the randomization list and proceeding in an ascending order with each new patient. Patients not being treated with oral vasodilators were assigned a treatment beginning with the 20th number of the randomization list and proceeding in a descending order with each new patient (Exhibit #1).

A total of 26 patients were recruited for this study, 2 for study 35 and 24 for study 36. The first patient was not randomized. He was assigned to flolan to work out the logistics of the administration of flolan. Of the remaining 25 patients 11 were randomized to flolan and 14 to the control group.

Treatments:

Patients randomized to the control group were treated with what is considered as standard (conventional) treatment for PPH: oral vasodilators, inotropes, oxygen, diuretics, electrolytes, and anticoagulants. Patients randomized to flolan received infusions of flolan in addition to the conventional treatment. Patients randomized to flolan were instructed how to prepare the flolan solution aseptically and how to care about the pump and the catheter.

Patients completing study 35/36 were allowed to enroll in the continuation study 37, if they wished.

RESULTS:

Flolan Dosage: During the dose-ranging phase the infusion rate of flolan increased from 2 to 22 ng/kg/min. During the long term phase the rate varied from 2 to 12 ng/kg/min. The dose increased from a

mean rate of 4.6 ng/kg/min at baseline to 7.3 ng/kg/min at the end of the first week. After that it remained more or less constant for the 8 week period of the study.

There were several interruptions of the infusion during the Long-Term infusion Period due mainly to pump malfunction (5 times, all in one patient) accidents (3 cases), incorrect position of the catheter, or to the formation of clots (2 cases each).

Efficacy:

The primary Efficacy Parameter in study 35/36 were changes in exercise capacity i.e. changes in the distance walked by a patient back and forth along a level, measured corridor in 6 minutes on Days 2, 29 and 56 compared to the distance walked at baseline. The test was administered by the investigator, who encouraged the patients to walk.

The sponsor has analyzed the data in various ways. In the original NDA submission the following 2 ways were reported:

a) Patients with missing data were assigned the lowest rank (Table 1, sponsor's Table 36). Using this analysis the exercise capacity of the flolan patients improved by 173 meters, while the capacity of the control patients decreased by 6 meters ($p=0.045$).

b) The last observation was carried forward for patients with missing data. This analysis showed that the mean exercise capacity of the flolan patients improved by 139 meters, while the capacity of the control patients improved by only 28 meters (Table 2, sponsor's Table 37, $p=0.043$).

c) In the most recent submission (Dec. 12, 1994) we received a third kind of analysis (Table 3, sponsor's Table 5). According to this analysis (method not explained but it seems that there were no substitutions for missing data) the baseline walk values are the same as in Table 2 (sponsor's Table 37), i.e. the flolan group walked for 225 meters and the control group for 213 meters ($p=0.85$). However, the Day 56 values are different: 378 meters for the flolan and 279 meters for the control group. This new set of values indicates that at the end of the study the flolan group had walked for an additional 153 meters compared to the baseline walk, while the control group had walked for 66 more meters i.e. the flolan group had walked 87 more meters than the control group had. Statistical analysis of this difference was not reported by the sponsor. Analysis by Dr. Al Osh, FDA statistician, showed that the difference was not significant ($p=0.1016$).

The secondary Efficacy Parameters were:

1. Differences in hemodynamic measurements between the baseline and the end of the 8 week period. It was found that flolan had significantly reduced the:

total pulmonary resistance (TPR) by 5.92 Wood units,
total systemic resistance (TSR) by 5.42 W units,
systemic vascular resistance (SVR) by 5.69 W. units,
systolic pulmonary arterial pressure (PAPs) by 14.5 mm·Hg,

At the same time flolan had significantly increased the:

Cardiac index (CI) by 0.31 L/min/m² and the
Cardiac output (CO) by 0.52 L/min.

2. Differences in hemodynamic measurements between the flolan and the control group. The only significant differences were:

a) flolan reduced the median PAPs value by 12.50 mmHg while the control treatment reduced this parameter by 5.0 mm Hg only.

b) Flolan reduced the median value of the total pulmonary resistance (TPR) by 2.93 W units while the TPR of the control patients increased by 0.90 W units.

P values for these differences were not reported.

The Tertiary Efficacy Parameters were:

a) **Blood Gas measurements.** No significant changes were found.

b) **The evaluation of the Nottingham Health Profile.** The patients completed a Questionnaire of whether they had problems with various aspects of life: energy, pain, emotional reactions, sleep, social isolation, physical mobility, work, looking after the home, social life, home life, sex life, interests and hobbies. The sponsor reported that at the end of the study the patients who were treated with flolan had significantly fewer problems with physical mobility, while the control patients had experienced essentially no change or had more problems with physical mobility on weeks 4 (p=0.044) and 8 (p=0.0197) compared to baseline. No significant differences between the two groups were found regarding problems with the other aspects of life.

c) Survival/Deaths:

Two of the 12 (17%) flolan and 3/14 (21%) control patients died during the study. I have summarized their cases below:

Flolan Patients:

Pt.

Pt. was a 21 y.o. NYHA Class IV, WM. By protocol arrangement he was assigned to flolan in order to work out the logistics of flolan infusion. At baseline his PAPm was 46 mm Hg, his RAPm 2 mm Hg, and his CO 2.9 L/min. He was on oxygen, 6 L/min. After dose-ranging (he reached 22 ng/kg/min) he received continuous prostacyclin infusion at 9 ng/kg/min. Two weeks later he developed diarrhea, hot flushes, SOB, diaphoresis, a seizure and went into cardiopulmonary arrest. Resuscitation was unsuccessful. An autopsy revealed veno-occlusive disease and a patent foramen ovale.

Pt. (allegedly not randomized)

She was a 27 y.o., NYHA Class IV, WF. At baseline her PAPm was 84 mm Hg, her RAPm 11 mm Hg, and her CO 3.4 L/min. She was dose-ranged with flolan but at 6 ng/kg/min she developed progressive dyspnea, tachypnea, frequent cough, and anxiety. She was found to have developed pulmonary rales bilaterally and was diagnosed as having severe "PROSTACYCLIN-INDUCED PULMONARY EDEMA." Flolan was discontinued. She died one month later.

The sponsor claims this pt. was not randomized, however, the records show (exhibit 1) that she was randomized.

Control Patients:

Pt.

A 21 year old, WF, with Class IV PPH was admitted to study 36 on 10/9/89 with symptoms of right heart failure progressing "quickly and precipitously." She had severe SOB, fatigue, syncopal episodes, ascites, edema, severe tricuspid regurgitation and an LDH of 695 U/L. Her PAPm was 46 mm Hg, her CO 2.23 L/min, and her RAPm 12 mm Hg. She was unable to stand or walk and for this reason the Day-2 walk was done on Day-8 (Exhibit 2). She was randomized to the control group and received the conventional treatment.

She died on 11/28/89, 49 days after randomization. A flolan solution was prepared for her on the day of her death. It is not stated whether the solution was administered to her for the determination of Dose-Ranging Segment #2 or not. An Adverse Experiences report (Exhibit #3, from vol. 1.69, p. 264) indicates that on 11/29/89, a day after her death, the patient complained of fatigue, dizziness, presyncope, etc.!

Pt.

This 33 y.o., NYHA Class IV, BF had a history of left arm sarcoma (1968) and of a spinal tumor (1974). She was in severe heart failure when she was admitted to study #36. She was on O₂, 3-5 L/min; she had ascites, peripheral edema, pericardial effusion, ST segment depression, pulmonary insufficiency, tricuspid regurgitation, LDH 657 U/L, SGOT 273 U/L, and BUN 26 mg/dl. Her PAPm was 75 mm Hg, her CO 1.65 L/min, and her RAPm was 17 mm Hg. She could not walk on Day-2 the day of randomization (exhibit #5). The physician, who treated this patient, wrote to the sponsor on April 7, 1988 that this patient "was extremely ill at the time of entry into the study and was having frequent syncopal attacks and hypotensive episodes prior to her cardiac catheterization".

The patient was dose-ranged with flolan on 3/22/88 from 2 ng/kg/min to 14 ng/kg/min very quickly within 46 minutes. One hour after flolan was discontinued the patient was given sublingual nifedipine, which was tolerated hemodynamically. The day after dose-ranging the patient was randomized to receive conventional therapy alone and was started on mifedipine. She developed hypotension, AV dissociation and finally respiratory arrest. Two blood cultures grew streptococcus viridans. She died one day later, two days after randomization. The investigator considers her death as "secondary to hypotension and a junctional rhythm following an oral dose of nifedipine." The autopsy revealed "extensive acute bronchopneumonia", which was considered the immediate cause of death by the pathologist. The patient was afebrile with normal WBC counts before the cardiac catheterization. The bronchopneumonia seems to have developed after the catheterization.

Pt.

This was a 15 y.o., NYHA Class III, WF with a history of familial PPH. At baseline this patient was on O₂, her PAPm was 88 mm Hg (higher than her SAPm, which was 83 mm Hg), her CI was 1.5 L/min/m² (CO 2.1 L/min), and her RAPm 2.0 mm Hg (she had a patent foramen ovale and a R to L shunt). She had pulmonary insufficiency and tricuspid regurgitation. She was randomized to receive the conventional treatment alone.

After dose-ranging with flolan she was restless and "felt awful". She was diagnosed as having developed pneumothorax as a complication of right heart catheterization. She became progressively hypoxemic and died 5 days later following a vasovagal reaction.

EVALUATION OF STUDY 35/36 by the REVIEWER:

In my original review of study 35/36 I had misunderstood one of the exclusion criteria and I had stated that pts were ineligible to enter study 35/36 because of high laboratory values (LDH, SGOT, and BUN). I was wrong. Both of these patients were very ill patients with confirmed PPH and were qualified to enter the study.

However, study 35/36 had the following deficiencies:

1. Unreliable Data:

Pt. The sponsor claims that pt. walked for 120 meters on the second day of her study. However, exhibit #3 from her CRF, vol 1.69, p. 277, shows that her "Day 2 walk test was done on day 8 since the pt. was unable to stand or walk until this time without feeling dizzy and nauseated."

The sponsor further claims that pt. did not have syncopal episodes in her history or at baseline (submission of Dec. 12, 1994, p. 35/36-21). Page 211 of her CRF, vol. 1.69, Exhibit #4, (written on 10/9/89, her screening day), shows that this pt. was syncopal with recent increases in s/s of PPH (severe DOE, syncope, severe fatigue) which were "quickly and precipitously progressing."

Pt. died on 11/28/89. Yet there is an adverse reaction report, which shows that this patient was examined on 11/29/89 (Exhibit #3), and she complained of fatigue, presyncope, dizziness etc. How could that be one day after her death. It has also been recorded that she performed a walk test on Day 56 i.e. 7 days after her death.

We have received the CRFs of the patients who died only we do not know whether similar discrepancies have been recorded for other patients as well.

2. Bias in the Exclusion of Patients:

Flolan patient who developed prostacyclin-induced pulmonary edema during Dose-Ranging with flolan was dismissed from the study and allegedly had not been randomized. Due to the development of the pulmonary edema, the participation of this patient in the study was cut short. She would have died quickly for sure, if she were readministered flolan. The fact remains, however, that this patient was randomized to flolan (exhibit 1) and her pulmonary edema was induced by the infusion of flolan. She cannot be dismissed as if nothing had happened. Both the Intent-to-treat and the evaluable analyses require that her death be counted in the flolan group.

On the other hand, control patients who developed extensive acute bronchopneumonia and pneumothorax respectively as a result of cardiac catheterization were not dismissed from the study. These patients should have been excluded from the evaluable analysis.

3. Bias in the administration of the walk test.

The investigators themselves administered the walk test and were free to encourage the patients during their walk. The study was open. Bias cannot be excluded in the degree of encouragement.

There is also the possibility of patient bias. The patients believed that they were getting a new and effective drug and a placebo effect cannot be excluded. The difference between the groups regarding improvement of walking ability was small: 87 meters.

Evaluation of Survival:

Study 35 had only 2 patients, who were classified as NYHA class II. Their results should not be combined with the results of study 36 which included only patients of class III and IV.

Study 36

Study 36 had 24 patients, 11 were randomized to flolan and 13 to standard treatment.

The results of study 36 should be analyzed as follows:

	Intent to Treat Analysis		Evaluable Analysis	
	Number of Patients	Deaths	Number of Patients	Deaths
Flolan	11	2	11	2
Control	13	3	11	1
p	>0.75		>0.50	

Conclusion: There were no significant differences regarding survival between the two groups.

Evaluation of the Hemodynamic Measurements:

MM Study 35/36 showed that flolan reduced the median value of PAPs by 7.5 mm Hg more than the standard therapy did i.e. flolan reduced this parameter from a mean value of 90 to a mean value of 78 mm Hg while the standard treatment reduced it from 102 to 98 mm Hg. How significant is this reduction clinically? A PAP of 78 mm Hg is still a very high pressure. Incidentally, the

results show that at baseline the control patients as a group had a higher mean PAPs than the flolan patients did, 102 vs 90 mm Hg. This difference was not statistically significant but was close ($p=0.118$; the standard errors were large). However, the difference between the groups was as high as the reduction affected by flolan. Flolan also decreased the median value of the total pulmonary resistance (TPR) from 16 to 13 Wood units, which was a beneficial effect, while the TPR of the control group increased from 21 to 22 units. There were no other significant differences between the treatment groups (27 comparisons). It should be noted again that the control patients were in a worse condition than the flolan patients. In addition to their higher mean PAP, their TPR at baseline was 21 Wood units compared to 16 Wood units for the flolan group.

STUDY 46:

Title: A Multicenter, Open-Label, Randomized, Parallel Comparison of the Safety and Efficacy of Chronic Flolan Infusions plus Conventional Therapy to Conventional Therapy Alone in Patients with Severe Primary Pulmonary Hypertension: A twelve Week Study.

Study Period: Sept. 12, 1991 - August 13, 1992

This trial was conducted in order to confirm the results of study 35/36. Eighteen investigators indicated willingness to participate and 17 were able to recruit patients (Table 4).

Study Design: This was essentially similar to the design of study 35/36. The study included 3 phases:

1. Screening,
2. Baseline (2 days),
3. Treatment: a) Dose-Ranging Segment (1-2 hours; all patients including the control patients were dosed with flolan).
b) 12-Week Treatment Segment (conventional therapy alone or conventional therapy plus flolan).

Randomization: There was no predetermined code of random numbers. The randomization was done through the use of an adaptive randomization computer program established by the sponsor. After the patients had been screened and thoroughly assessed for two days by the investigators, they were dose-ranged with flolan. After dose-ranging was completed the investigator called the Medical Division of the sponsor to get the randomization assignment for his(her) patient. The stratification criteria were: study center, NYHA class (III or IV), and use or no use of vasodilators at

baseline. However, the investigators were asked to provide additional information as well: the distance that the patient had walked in 6 minutes, the maximum tolerated dose of flolan, the

intolerated dose, the PAPm, CO, PCWpm, and PVR values and also the sex, weight and date of birth of the patient to be randomized (Exhibit 5).

A total of 82 (one patient was withdrawn because she developed pneumothorax as a result of catheterization) patients were recruited; 42 were randomized to receive flolan plus conventional therapy and 40 to receive conventional therapy alone. All patients who completed the study had the option to enter study 47, where they received continuous infusions of flolan in addition to conventional therapy.

Flolan Dosages: During Dose-Ranging the dose was titrated to intolerance and varied from 2 to 20 ng/kg/min. Most patients peaked at 6-12 ng/kg/min. During the 12 week treatment period flolan was started at a dose of 4 ng/kg/min lower than the highest tolerated dose. Thereafter the dose was increased or decreased according to the presence of clinical symptoms of PPH or the appearance of side effects. Generally the dose was increased from a mean of 5.3 ng/kg/min at the end of the first week to 9.2 ng/kg/min at the end of Week 12. The highest tolerated dose was 1.6 ng/kg/min less than the non-tolerated dose. During the dose-ranging segment flolan was administered either peripherally or through the proximal port of the Swan-Ganz catheter.

Conventional Therapy: Both groups used mostly anticoagulants (98%). Other medications were (flolan vs control): analgesics (83% vs 70%), diuretics (68% vs 78%), anxiolytics (61% vs 55%), vasodilators (61% vs 60%), digoxin (56% vs 50%), and oxygen (39% vs 53%). The prothrombin time was maintained between 1.3 to 1.5 of control in all patients.

Results:

1. Primary Efficacy Parameter/Exercise Capacity: The 6-minute walk.

The patients were instructed to walk indoors on a level surface at least 65 feet long and 4-6 feet wide. The temperature was kept at 20-23°C. The tests were administered by a tester trained by personnel from _____ The tester was not involved in the patients' daily care and was unaware of their assignment. During the test all patients were wearing an infusion pump and a loose hospital gown over their cloths to ensure that the tester could not see whether a patient was fitted with an indwelling catheter or not. The tester was not allowed to encourage the patients to walk. After the walk ended the tester showed the Borg

Dyspnea scale to the patient and asked him(her) to grade the degree of the dyspnea that he(she) had felt during the walk.

The walk test was repeated on Day 2, and Weeks 1, 6, and 12. The walk on Day-1 was considered training. The walk on Day-2 was considered the Baseline.

The sponsor reported that at baseline (Day-2) the flolan group walked a median distance of 315 m and the control group walked a median distance of 266 m (Table 5, sponsor's Table 32, p=NS). At the end of the 12th week the flolan group was able to walk 350 m. i.e. 35 m longer than at baseline, while the control group had walked for 284 m. i.e. 18 m. longer than at baseline. The flolan group had walked 17 meters more than the control group.

The sponsor analyzed the data in two ways: non-parametrically (Table 6, sponsor's Table 34; patients who died or did not perform the walk due to their health were assigned the lowest rank for the calculation of the median and test statistic) and parametrically (Table 7, sponsor's Table 35; last observation carried forward for missing values or results after a transplant). They found highly significant differences in favor of flolan with both methods of analysis (p=0.0103-0.0029).

2. Secondary Efficacy Parameter: Survival:

The sponsor reported that 8 of the 40 control patients died during the study 0 to 68 days after randomization. None of the 41 flolan patients died during the study (p=0.0027). The reported cause of death was progressive right heart failure for 6 patients, pulmonary hemorrhage for one patient and cardiac arrest for another

Two control and one flolan patient were transplanted and two flolan patients withdrew from the study.

3. Tertiary Efficacy Parameters:

a) Hemodynamic Parameters and Blood Gas Measurements:

Table 8 (Table 43 of the original NDA submission) shows the hemodynamic and gas values that were obtained at baseline and on Day 88 (end of the 12 week Treatment Period). It also shows the differences between respective values obtained at baseline and on Day 88. It appears that flolan increased the CO, CI, the stroke volume and the % arterial and mixed venous saturations and at the same time it decreased somewhat the pulmonary and the mean right atrial pressures (RAPm) and the resistances. Significant differences between the flolan and the control group were found by

the sponsor regarding:

	Flolan	Control
CO (L/min)	increased by 0.54	decreased by 0.43
CI (L/min/m ²)	0.33	0.23
SV (ml/beat)	6.65	3.48
‡ Art. Satur.	2.00	0.63
‡ Mixed Ven. Sat.	1.16	2.62
PAPs (mmHg)	decreased by 7.21	increased by 3.17
PAPd (mmHg)	3.66	1.17
PAPm (mmHg)	4.82	1.87
RAPm (mmHg)	2.17	0.09
PVR (Wood Units)	3.42	1.52
TPR (Wood Units)	4.14	2.04
SAPd (mmHg)	4.92	0.14
SVR (Wood Units)	4.04	2.13
TSR (Wood Units)	5.58	2.43
SAPm (mmHg)	4.84	decreased by 0.89

P values were not provided for any of these comparisons.

Of these changes only the cardiac output and the cardiac index reached the low values of the normal range. They were increased from a mean of 3.52 to 4.05 L/min and from a mean of 2.04 to 2.37 L/min/m², respectively. The pulmonary arterial pressures remained very high. The PAPm was reduced from 60 to 55 mm Hg only, which is still very high. The mean systemic arterial pressures were normal to start with and remained normal during the study in both groups.

The pulmonary vascular resistance (PVR) was reduced from 16 to 12 Wood units, which is still significantly higher than normal.

b) Chronic Heart Failure Index Questionnaire (CHFIIQ):

The patients were handed a questionnaire which included various questions regarding activities which were divided into 4 areas or dimensions: dyspnea, fatigue, emotional function, and mastery (of eating, hurrying, mopping or scrubbing the floor and shopping). The patients were expected to grade these questions on a 7-point scale every two weeks. The better that the patient coped with each of these activities, the higher was his(hers) evaluation grade. This test was administered in an interview format. The investigator checked the answers with the patient by repeating each question to make sure that the answers were correct. A change of a 0.5 grade/question/dimension represented a significant difference.

Table 9 (sponsor's Table 44) shows the mean and median scores of the two groups at baseline and at week 6 and Day 87. The scores generally increased during the study for both groups indicating improvement except for fatigue for the standard group. The increases were greater in the flolan group. The sponsor found that the improvement was significantly better for flolan than for the standard treatment regarding all dimensions (dyspnea, fatigue, emotional function and mastery) at all evaluation times (8 out of 8 comparisons). No p values have been reported.

c) Nottingham Health Profile:

This profile is composed of two parts. Part I includes 38 questions and part II seven. Most of the questions are similar in meaning with the questions of the CHFIQ. In part I the questions referred to emotional reactions, energy, pain, physical mobility, sleep, and social isolation. In part II they involved "home life", "looking after the home", "interests and hobbies", "sex life", "social life", "vacations", and "work". The patient was supposed to answer each question by checking a "yes" or a "no" box.

Table 10 (sponsor's Table 47) shows the scores for part I, which were obtained on Day 1 (baseline), Week 6 and Day 87. The greater the score, the greater was the number and the severity of the problems that were experienced by the respondents.

The majority of the scores decreased during the study indicating improvement, especially for the flolan group. Statistical analysis of the differences from baseline (median values) by the sponsor indicated that the improvements of the flolan group regarding emotional reactions, energy, and sleep were significantly greater than those of the standard group (Hodges-Lehmann estimate for the true treatment effect). There were 3 significant differences out of 12 comparisons.

Table 11 (sponsor's Table 50) shows the results of Part II. The baseline scores show that the flolan group had considerably fewer problems regarding home life (33% vs 55%), social life (58% vs 70%), vacations (53% vs 68%) and especially work (paid employment; 37% vs 60%). The scores of the flolan group improved (decreased) during the study except for work. Essentially no improvement was observed for the group on standard therapy especially regarding "looking after the home", and "vacations". Comparison of the scores of the two groups indicated that the differences regarding "looking after the home" at week 6 and Day 87, and "vacations" at Day 87 were significant in favor of flolan (3 significant differences out of 14 comparisons).

d) Dyspnea-Fatigue Rating:

Dyspnea-fatigue was also evaluated by the patients independently of the chronic Heart Failure Index. The scores varied from zero (worse condition) to 12 (best condition). The results indicated that at baseline the patients had light to moderate dyspnea-fatigue. The flolan group had a mean score of 4.2 while the control group had a mean score of 3.5. During the study the score of the control group essentially did not change but the score of the flolan group increased by 1.3 - 1.6 degrees to 5.8 at 6 weeks and to 5.5 on the last day of the study. This increase in scores indicated improvement. The between groups differences were found to be statistically significant by the sponsor at weeks 6, 9, and 12 (in 3 out of the 5 comparisons; the p values were not reported).

e) PPH Symptoms:

The physician recorded the frequency of the PPH symptoms (dyspnea at rest, dyspnea on exertion, fatigue, dizziness, syncope, chest pain, palpitations, paroxysmal nocturnal dyspnea, and orthopnea) based upon the patient's response. Statistical analysis of the results by the sponsor indicated that a greater proportion of flolan patients than patients on conventional treatment alone had less frequent symptoms during the study regarding chest pain (40% vs 18% at week 1), dizziness (34% vs 10% on Day 87), dyspnea on exertion at all evaluation periods, fatigue at weeks 3, 6, and 9, and orthopnea at week 9 (43% vs 16%). There were eleven significant differences out of 50 comparisons.

f) PPH Signs:

The sponsor reported that the flolan group improved significantly more than the control group regarding edema, and the distention of the jugular vein during week 6, and also regarding the murmur of pulmonary insufficiency and NYHA class during Week 6 and Day 87 (6 significant differences among 30 comparisons). No significant differences at all were found regarding hepatomegaly, right ventricular S₃, and S₄ sounds, murmur of tricuspid insufficiency, loud P₂ sound, or the right ventricular heave.

EVALUATION OF STUDY 46 BY THE REVIEWER:

Study 46 had the following deficiencies:

1. The randomisation of the patients:

As I mentioned earlier, while the stratification criteria were only "study center", "use or no use of vasodilators at baseline", and

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"NYHA Class", the computer program in order to randomize a patient required to be provided, in addition to these criteria, with the distance walked by the patient, the PAP, the CO, the PCWP, the PVR, the maximum dose of flolan that was tolerated by the patient, and the intolerated dose (Exhibit #5). These additional parameters were not part of the stratification criteria and yet the program did not work, if all this information was not provided. The sponsor claims that the additional information was not used for the randomization of the patients.

When the Division of Scientific Investigations of FDA inspected Burroughs-Wellcome they found that the program had never been validated. The sponsor was unable to provide a "virgin" copy of the original adaptive program as it existed prior to the addition of patient data to the data files. Back-up copies of the data files going back to 5 generations (patients) were said to have been kept on the hard drive of the laptop computer used for the randomization, but the hard disk was said to have been crashed after the completion of the study.

Knowing all the essential information about each patient the randomizers could "randomize" the most severely sick patients to the control and those in relatively better condition to the flolan group.

The sponsor presented an analysis showing that there were no statistically significant differences between the groups regarding the baseline values of the factors which are considered predictors of survival in patients with severe PPH: cardiac index, mean arterial pulmonary pressure, right atrial pressure and % mixed venous saturation (Table 2 of the December 12, 1994 submission).

Ability to Walk and Survival:

Although ability to walk has not been included among the predictors of survival for patients with PPH, the results of study 46 show that this parameter is very important. The baseline walk data of study 46 show that 5 of the patients who died during the study were either unable to walk at all or walked for less than 120 m. Significantly more of these poor walkers, 9 vs 2 $p < 0.025$, were randomized to the control group (Table 12) i.e. the control group was significantly handicapped regarding poor walkers compared to the flolan group. The existence of this handicap did not show in the mean values for the groups because both groups included also patients who could walk for more than 300 and 500 meters in 6 minutes and their results reduced the difference of the means to an insignificant level ($p = 0.134$).

The significance of the walk test in predicting survival can be underlined by the fact that the degree of physical activity and its limitations has been the basis for the classification of the patients with heart disease into classes according to the recommendations of the NYHA and other professional societies: the Canadian Cardiovascular Society, the Harvard Group (Goldman et al., Circulation 64, 1227, 1981). The greater the limitation of the physical activity of a patient, the higher is the functional class that he/she is classified to. Furthermore, the NIH Registry of patients with PPH has shown that survival of these patients is closely related to their NYHA class. They found that patients of class IV have a mean survival of 6 months, while the mean survival of patients of class III is 2.6 years, i.e. the greater the limitation of a patient's physical activity, the shorter his/her survival is.

The patients who died in study 46 had also additional conditions, which could reduce survival (moribund condition, morbid obesity, ineligibility for transplantation, chronic arrhythmias, recurrent hospitalizations, multiple electrolyte abnormalities, active hepatitis C and bleeding tendency, and marked polycythemia. Their treatment was apparently difficult and several of them developed electrolyte abnormalities and/or digitalis toxicity during the study as can be seen from the description of their cases below:

Patients Who Died:

A. The following 5 patients who died could not walk more than 117 meters at baseline.

1. Pt.

At baseline this 44 y.o. WF was in cardiovascular collapse due to right heart failure. She had hypotension, hypoxia, nausea, palpitations, shortness of breath at rest, and loss of consciousness. Her FAPm was 78 mm Hg, her RAPm was 13 mm Hg, and her CO 2.3 L/min. SHE WAS UNABLE TO WALK. She had multiple syncopal episodes before she was admitted to the study and also during her hospitalization.

According to her cardiac catheterization record dose-ranging with flolan was performed with the patient receiving 100% oxygen via a face mask in addition to 7L via nasal cannula. Dose-ranging was cut short. The dose of prostacyclin was not increased beyond 8 ng/kg/min due to intermittent hypotension with systolic pressures falling to the high 80's. Under "General comments" of her record it is explained that "During the procedure, every time the patient changed her position, her oxygen saturation fell and she became hypotensive. At the end of the procedure when she was moved onto the stretcher she again became short of breath and her oxygen increased. She then rolled onto her left side, dropped her saturation and lost consciousness. She began to seize and her heart rate fell to the

20's. She had no spontaneous cardiac rhythm." She never regain consciousness. She was pronounced dead at 3:35 PM." of the same day.

The cardiac catheterization was started at 12:30 and was terminated at 2:23 PM. The sponsor has stated (Dec 5 meeting, p. R-16) that according to the randomization program the patient was randomized at 2:01 PM,. It appears therefore that this patient was randomized before the cardiac catheterization was completed while the patient had the syncopal episodes.

In a recent letter, dated Nov 23, 1994, her physician, confirms that the patient had recurrent syncopal episodes prior to cardiac catheterization." and explains that "patients similar to this patient carry a very high risk of mortality associated with cardiac catheterization." "We rarely perform cardiac catheterization for acute drug testing to initiate oral vasodilator therapy with patients as ill as this patient was ..."

The sponsor claims that pt. "was equally critically ill (as patient and was randomized to flolan."

Copies of patient's hospital record have not been submitted. The submission contains only a copy of a letter dated Dec. 1, 1994 from the physician, who had treated this patient. He states that this NYHA Class IV patient was critically ill with severely advanced disease. At baseline her CO was 2.2 L/min (CI 1.1 L/min/m²), her PAP was 129/69, PAPm 89 mm Hg, and her RAPm 23 mm Hg. She walked only 2 feet at baseline. (She was one of the two flolan patients who walked less than 120 m.).

During dose-ranging her hemodynamics improved, cardiac output increased to 4.1 L/min (CI 2.1 L/min/m²), and her pulmonary arterial pressure fell to 82 mm Hg, and her RAPm to 17 mm Hg. Her calculated total pulmonary resistance fell from 40.3 Wood units at baseline to 20 Wood units on 6 ng/kg/min. "Had this critically ill patient not been offered flolan, she would surely have died despite being on conventional therapy ..."

Reviewer's Comments: Pt. was the most severely sick patient of the flolan group. She had the lowest CI, the highest PAPm and one of the highest RAPms. However, this patient was not as critically ill as control pt. was. She had not suffered syncopal episodes and loss of consciousness either at baseline or during dose-ranging with flolan. On the contrary, this patient had improved tremendously during dose-ranging. Most importantly this patient was not moribund when she was randomized.

Incidentally, patient died 3 months later in spite of the fact that she was receiving flolan continuously.

2.

Patient was a 63 year old WM with a history of hypertension, peptic ulcer disease, smoking for 36 years, familial history of PPH, procainamide-induced SLE, chronic atrial and ventricular arrhythmias, right heart failure and cardiovascular collapse. He also had a history for recurrent hospitalizations for CHF in the last few months before admission. On admission he was confined in

a wheel chair, unable to do any minimal physical exertion yet he is reported to have walked for 46 m at baseline. His heart rate was 113 bpm, his PAPm 50 mm Hg, his RAPm 18, and his CO 3.2 L/min. He had infiltrates in his lungs and multiple electrolyte abnormalities (Na 132, K 2.0, Cl 78, CO₂ 35), BUN 36, and creatinine 1.4. mg/dl. He was classified as having "severe PPH and cor pulmonale, NYHA Class IV, having less than 6 months to live and was "randomized" to receive standard therapy alone.

He was treated with digoxin, aggressive diuresis and potassium supplements. On 6/2/92 symptoms of digoxin toxicity appeared. He died in hypotension, hypokalemia, and hyponatremia.

The physician who treated this patient, asserts in a letter to Burroughs-Wellcome, dated November 30, 1994, that:

"The patient was assessed by both his referring physicians and the admitting physician as having severe end-stage New York Heart Association Class IV cardiac dysfunction." "He was noted on admission to the hospital to be both hypokalemic and hyponatremic with signs of prerenal azotemia. This is consistent with end stage cardiac disease..." "Such hyponatremia is characteristic of end stage cardiac disease and is one of the worst prognostic factors for outcome in patients with cardiac dysfunction." "His admission EKG revealed atrial fibrillation." "Right atrial pressure was 18 mm Hg (highly predictive of death in the next six months)" "Dose-ranging with flolan was aborted early as this patient was relatively hypotensive with a drop in his systemic blood pressure by approximately 12 mm Hg from his baseline mean".

3. Pt

According to her hospital record, which we received after the Division of Scientific investigations visited Center 6, patient was admitted to study #46 with worsening cor pulmonale. She was on oxygen 6L since 9/26/91 (about 2 months before recruitment). "On presentation she had congestive heart failure, massive pitting edema 4+ up to her abdomen. The liver was palpable 12 cm. below the right costal margin. She had nausea (even the smell of food caused her nausea) and vomiting, syncopal attacks, palpitations, hypotension. She had been considered too unstable for transplantation, etc. Her cardiac output was 2.2 L/min, her PAPm 58 mmHg and her RAP 18 mmHg. HER BASELINE WALK DISTANCE WAS 62 M ON DAY-1 AND 101 ON DAY 2 OR THE OTHER WAY AROUND BECAUSE THE DATA HAVE BEEN SWITCHED. She was "randomized" to the control group and received the standard treatment (digitalis, diuretics etc). She developed bradycardia and ventricular tachycardia in the course of the study and multiple electrolyte abnormalities (decreases in Cl, Na, CO₂ and Ca⁺⁺, increase in phosphate) She died 19 days after randomization.

4. Pt.

A 38 year old NYHA Class IV WM was admitted to study #46 with symptoms of right heart failure. His PAPm was 61 mm Hg, his RAPm 21 mm Hg and his CO very low (2.19 L/min). HE ONLY WALKED FOR 91 M AT BASELINE. This patient had been exposed to flolan before. After

dose-ranging he was "randomized" to receive conventional therapy alone. Two months later he developed a junctional rhythm and was diagnosed as having digitalis toxicity and was administered digoxin antibodies. He died the same day.

5. Pt.

A 42 year old, NYHA Class III, Spanish female was admitted to study #46 with all the symptoms of right heart failure including shortness of breath at rest, ascites, pericardial effusion, cough, and peripheral edema. Her cardiac output was 2.3 L/min., her PAPm 68 mm Hg, her RAPm 18 mm Hg, and her heart rate 103 bpm. SHE WALKED ONLY FOR 117 M. AT BASELINE. She was also suffering from hypothyroidism, vertigo, and depression (suicidal tendency).

This patient had been rejected for transplantation by two transplantation centers because of "morbid obesity". She was "randomized" to standard therapy alone. She was treated with digitalis, diuretics, and potassium supplements. She developed hyperkalemia, increases in BUN and creatinine during her course and died 43 days later.

B. The following control patient who died had a history of bleeding = contraindication to anticoagulation = exclusion criterion.

Pt.

Pt. was a 16 y.o., NYHA Class III WP suffering from chronic active hepatitis C in addition to PPH. She also had a history of bleeding, familial PPH and right heart failure. At baseline her PAPm was 80 mm Hg, her RAPm 3 mm Hg (she had an atrial septostomy), and her CO 4.3 L/min. She was randomized to the control group and was treated with the standard therapy for PPH including warfarin. She died 68 days later in cardiovascular collapse with bleeding, hemoptysis and hypotension.

The physician who treated her explained in her November 23, 1994 letter to the sponsor that hemoptysis is a known cause of death in PPH patients and has been reported to be the terminal event in patients with PPH regardless of whether or not they were anticoagulated with warfarin. She further states that hepatitis C is not a contraindication for anticoagulation in patients with PPH. "Anticoagulation with warfarin has been shown both retrospectively and prospectively to increase survival in primary pulmonary hypertension and is therefore considered a component of standard medical therapy for primary pulmonary hypertension."

We are well aware that anticoagulation is part of the medical treatment of PPH. However, patient had CHRONIC ACTIVE HEPATITIS C and a HISTORY OF BLEEDING. History of bleeding is a contraindication to anticoagulation and contraindication to anticoagulant therapy was one of the exclusion criteria of protocol #46. The autopsy report of patient 01012 states that on arrival at Kent General Hospital, where she died, she was vomiting large

amounts of blood. Her trachea and bronchi were full of blood. She also had free blood in the pleural cavities, the mediastinum and the abdomen. Patient could probably have survived for several more months or possibly years, if she were not anticoagulated (She died 68 days into the study).

C. The following patient who died had an operation during the study.

Pt.

Pt. was a 43 y.o., WM originally classified as NYHA Class IV which was corrected to Class III. His presenting symptoms at baseline were chest pain, edema, SOB at rest, exercise intolerance, orthopnea, weakness, loss of consciousness, syncope, depression, etc. His PAP was 100/45 mmHg (PAPm was 64 mm Hg), his RAPm 9 mm Hg and his CO 4.9 L/min. He was "randomized" to the control group and received the standard therapy. Two months later he developed right heart failure and was admitted to the University of Illinois Hospital. He was subjected to atrial septostomy and died 6 hours after the procedure. The added stress of the surgical procedure might have precipitated his death. Without it, he might have survived a few weeks or months more. An autopsy was performed but we received only a copy of the first page.

In a letter to the sponsor, dated Nov 28, 1994, the physician who had treated pt. states that "Based on a previous experience on performing an atrial septostomy in this setting....we made another attempt to do this. "The patient died six hours following the atrial septostomy procedure.....one cannot state conclusively that the septostomy was either beneficial or detrimental to him."

The physician has attached a reprint from the Amer. J. of Cardiol., where he had described his previous experience, a case of septostomy he had performed on a patient with PPH in 1982. That patient died one day after the procedure. I do not see how this previous experience could have provided hope for a good outcome following atrial septostomy in the setting of pat.

D. The following pt. who died had marked polycythemia in addition to PPH.

Pt

Patient a 36 y.o., NYHA Class III, WF, was diagnosed at baseline as having right heart failure: she had dyspnea, cyanosis, hypoxia, peripheral edema, nausea, orthopnea, weakness, dizziness, depression, hypotension, etc. Her PAPm was 51 mm Hg, her CO 2.6 L/min, and her RAPm 6 mm Hg, she also had a patent foramen ovale. In addition, she had marked polycythemia. HER HEMOGLOBIN WAS 19 G/DL, AND HER HEMATOCRIT 60%. She was randomized to the control group and received the conventional treatment including continuous oxygen. She later developed a urinary tract and an upper respiratory infection and died 2 months later in cardiac arrest. No details have been provided.

2. Inconsistency in the Classification of Patients into Functional Classes:

The classification of patients with heart disease into functional classes is based on the evaluation of their limitations to perform ordinary physical activities (go up or down a flight of stairs, take a shower, carry weights, make the bed, clean windows, play golf, getting dressed without stopping, etc.). The limitations in these activities are difficult to quantitate. Thus differences in the classification of patients with heart disease by different cardiologists have been observed. On the other hand, the ability to walk can be easily quantitated and could be used to classify heart disease patients into functional classes or to compare the results of other methods (Goldman et al., Circulation 64, 1227, 1981).

The records of study 46 show that there is not a good correlation between the classification of the patients in NYHA classes and the walk test. Flolan patients and control patients who were able to walk for more than 250 meters at baseline were classified as class IV patients, while flolan patients and control patients who walked for less than 200 meters at baseline were classified as class III patients. If we consider the ability to walk as a more reliable indicator of functional ability of the patients, these results show that the control patients as a group were in a considerably weaker condition than the flolan patients to start with (18 control patients vs 9 flolan patients walked less than 250 meters in 6 minutes at baseline, $p=0.027$).

3. Bias regarding the discontinuation of patients.

Flolan Pt.

Pt # the first patient of center 15, developed pneumothorax on 2/27/92 during cardiac catheterization. According to the physician's hospital notes this patient for the next 4 days (3/1/94) was hemodynamically stable and essentially unchanged with respect to admission blood pressure and heart rate. She was not dyspneic, she was comfortable. Repeat CXR showed nearly complete re-expansion of Rt-lung after chest tube placement. The chest tube was later removed and at 11 PM on 3/1/92 the pneumothorax increased and the patient died the next day. This patient allegedly was not randomized. Her original ID number, however, was a flolan number which was changed after her death from A new patient who was recruited the next day, was assigned the number and was randomized to flolan.

Pt.

Pt. suffered a dissection of the left subclavian artery during the attempt to place a Swan-Ganz catheter. The dissection was identified by injection of radioscopic contrast and although the patient (in addition to the dissection) developed a reaction to the contrast injection, she was entered into the study and was randomized to the control.

4. Unreliable Data (From vol. 1.32 of the original NDA):

Control pt. was transplanted on 3/14/92 (p. 920), 68 days into the study. However, on p. 889 this same patient is reported to have been transplanted on 3/31/92 (last day of the study).

Flolan pt. withdrew from study 46 on 5/14/92 (3 days after randomization p. 882), however, she has been listed on p. 890 that she completed the study normally. She has been further listed on p. 999 that she walked for 429 meters on 8/3/92 (Day 88), 81 days after her withdrawal.

Control pt. was transplanted on 4/7/92 (62 days into the study, p. 921) but he is listed on p. 999 that he walked for 549 meters on 5/5/92 (Day 88), 28 days after transplantation.

Flolan pt. withdrew from study 46 on 6/25/92 (44 days into the study, p. 885) because of adverse reactions. This patient, however, is reported on p. 891 that she completed the study normally, and on p. 1004 that she walked on 8/12/92, 48 days after her withdrawal, for 362 meters. She had no ECHO data for Day 87.

Flolan pt. was transplanted on 5/22/92, i.e. 11 days into the study, p. 925) but she has been listed on p. 892 that she was transplanted on 7/29/92 (80 days into the study). She has further been listed on p. 1006 that she walked on 7/29/92 (Day 88), 68 days after her transplantation, for 218 meters. She had no ECHO data for Day 87.

Pts. who died during study 46 are listed in Appendix B3.3 that they continued to take all or some of their medications till the end of the study.

None of these patients had Day-88 data for hemodynamic measurements or for the flolan delivery system Questionnaire, which confirms that these patients were transplanted or withdrawn before Day-88. It is not clear whether the irregular data were used in the efficacy analyses.

The Division of Scientific Investigations in their inspection of study 46 found several irregularities:

1. Non-fatal adverse reactions from hospital records were not recorded in the "Non-Fatal Adverse Experiences" section of the CRF or they were crossed out from this section without explanation:

Flolan pt had suffered a CVA (not recorded)

Control pt suffered syncope, seizure, dizziness, hypotension during dose-ranging with flolan (not recorded),

Flolan pt suffered atrial fibrillation, hypoxemia, hypocalcemia, hyponatremia and renal insufficiency (not recorded) and severe nausea and dry heaves (crossed out without explanation),

Flolan pt had suffered edema (not recorded) and severe headaches (crossed out without explanation),

Flolan pt had depression (not recorded)

Flolan pt experienced two vasovagal responses as the catheter was inserted into the vein (not listed anywhere). The same patient developed right subclavian-jugular-axillary venous thrombosis on the 22d day of flolan infusion.

All these omissions were in favor of flolan.

The sponsor claims that the reactions which were crossed out from the "Non-Fatal Adverse Experiences" were expected reactions attributable to flolan and were correctly transferred to "Complications of PPH".

2. At least 16 patients did not meet either protocol inclusion/exclusion criteria. Yet they were allowed to participate in the study.

3. The inspection also revealed that the investigators had noticed that the continuous infusion of prostacyclin may have exacerbated or caused ascites/fluid retention in patients.

5. Lack of Clinical Laboratory and ECG Data.

The sponsor did not provide any clinical chemistry or ECG data even when they were specifically requested to provide these data. The limited information we have about electrolyte abnormalities of individual patients was obtained indirectly from concomitant

medication reports and from the inspection of one of the centers by the Division of Scientific Investigations. The patients who had participated in study 46 were very sick cardiac patients, many of them had renal and liver insufficiencies as well. These patients were treated with diuretics and digitalis and balance of their electrolytes was essential. Patients and possibly pt. had developed such abnormalities and died during the study.

6. Dose-Ranging of Control Patients with Flolan:

Judging from the CRFs of the patients who died, it appears that the infusion of flolan was stopped more or less abruptly in most of the patients after dose-ranging. For the flolan patients this did not matter because these patients were subsequently infused with their optimal dose of flolan for the long-term phase of the study. For the control patients, however, abrupt discontinuation could be a severe stress. Abrupt discontinuation of flolan has been shown to cause rebound hypertension, hyper aggregability of platelets and adverse events, even death in severely sick patients.

BENEFIT/RISK RATIO:

THE BENEFITS

1. Survival (Secondary endpoint):

Study 36 did not show any significant difference in favor of flolan regarding survival:

I-T-T analysis: Flolan 2/11 patients died
Control 3/13 patients died
p>0.75

Evaluable Analysis: Flolan: 2/11 patients died
Control: 1/11 patients died
p>0.50

Study 46: The sponsor claims that 8 of the 40 control patients and none of the 41 flolan patients died during study 46, p=0.0027.

Comments: The experimental groups in study 46 were not comparable to start with.

At baseline there was a significant difference between the groups regarding their ability to walk. Significantly more control than flolan patients, 9 vs 2 (p<0.025) could not walk for more than 117 meters. Five of these poor walkers died during the study (Table 12).

A 6th control patient died from extensive hemorrhage. This patient had a history of bleeding and she should have been excluded from entering the study. A 7th control patient who died during study 46 was subjected to an operation (septostomy) during the study, which may have precipitated his death. The eighth patient who died had marked polycythemia in addition to PPH. Her hematocrit was 60%.

It is relevant to mention here that the extraordinary results regarding survival that the sponsor claims that study 46 has demonstrated, 0 flolan vs 8 control deaths, have not been confirmed by study 49. Study 49 was uncontrolled but the patients who entered this study were class III and class IV PPH patients, just as the patients in study 46 and were all treated with flolan from the very beginning as the flolan patients in study 46 were.

According to the IND Annual Report submitted on July 11, 1994, 127 patients had entered study 49 by the cut-off date of 3/31/94. Of these patients 22 had died, 14 of them (11%) had died within 78 days after entering the study. If flolan were as effective to prolong survival as study 46 has been claimed to have shown, none of the patients of study 49 would have died during the first 3 months. The results of study 49 are far apart from the results of study 46.

Note: The 14 patients, who died within 3 months in study 49 had been treated with the old formulation, except of pt. who was switched to the new formulation 2 days before he died. He was on the old formulation for 64 days.

Two other patients, who died 3½ and 4 months after they had entered study 49, had been started with the new formulation and were switched to the old one after 3 months and 4 days respectively.

2. The 6-Minute Walk. (Primary Endpoint):

	<u>Study 35/36</u>	<u>Study 46</u>
No. of meters that the flolan group actually walked more than the control group in 6 minutes at the end of the study. (see p 7 and 14)	87 p=0.102	17 0.0103-0.0029*
	Patients encouraged to walk	

Conclusion: *The actual data did not show any significant difference

in favor of flolan. A benefit was claimed when in the analysis missing data were assigned the lowest rank or the last observation was carried forward.

3. Hemodynamic and Blood Gas Measurements (Tertiary Endpoint):

Flolan decreased significantly the pulmonary and right atrial pressures by 2-8 mm Hg and the pulmonary and systemic resistances by 4-5 Wood units. On the other hand, it increased the CO and CI by 0.6 L/min. and 0.4 L/min/m², respectively.

Conclusion: These results indicate that flolan exerted some beneficial effect on the hemodynamic measurements but the changes were small and the PAP and PVR remained well above the normal ranges.

4. Quality of Life (Tertiary Endpoint):

a) Nottingham Health Profile (NHP):

A total of 62 comparisons were made. Nine of these comparisons (15%) showed significant differences in favor of flolan. Some consistency was noted regarding improvement of physical mobility and "looking after the home". Other significant differences regarding energy, vacations, emotional reactions and sleep represented isolated benefits which could have been the result of chance.

b) Chronic Heart Failure Index Questionnaire:

The CHF IQ was not used in study 35/36. It was used only in study 46 and was evaluated at baseline and on weeks 6 and 12.

This Questionnaire was administered in an interview format. The interviewer asked the questions and was allowed to "probe" if an answer was not clear to him(her).

Significant differences in favor of flolan were found regarding all the parameters [dyspnea, fatigue, emotional functions, mastery (of eating, hurrying, mopping, scrubbing, shopping)] at all the evaluation periods.

Conclusion: Flolan was found to be beneficial consistently in this test. However, we should take into consideration that this test was carried out in the form of an interview between the investigator and the patient and the investigator recorded the answers.

Investigator bias cannot be excluded especially if we compare the results of this test with the results of the Nottingham Profile.

c) Dyspnea-Fatigue Rating:

Dyspnea-fatigue was also evaluated independently of the CHFIQ in study 46.

The results showed that Flolan was consistently effective in improving dyspnea-fatigue during the later half of the study. The rating was completed by the physician based upon the patient's report of symptoms. Investigator bias cannot be excluded.

d) PPH Symptoms:

Results regarding the evaluation of the symptoms of PPH have been submitted only from study 46. The physician recorded the frequency of the PPH symptoms based upon the patient's response. Significant differences in favor of flolan were found regarding dyspnea on exertion and fatigue during weeks 3-9.

e) PPH Signs:

Results regarding the evolution of the PPH signs during the study period were reported only from study 46.

Significant differences in favor of flolan were found in 6 out of 30 comparisons. It seems that flolan improved somewhat the pulmonary insufficiency and the functional ability (NYHA class) of the patients.

THE RISKS AND OTHER DISADVANTAGES:

A. Adverse Events:

1. Reactions observed in both the control and the flolan patients:

Table 13 (Table 68 of the sponsor from study 46) shows that asthenia, dyspnea, dizziness, palpitations, chest pain, and edema were the most frequent adverse events which were observed during the study and were equally frequent in both groups in spite of the fact that several significant differences in favor of flolan were found regarding dyspnea, fatigue, dizziness and edema among the results of the Chronic Heart Failure Index Questionnaire, the independent evaluation of dyspnea-fatigue and among the PPH symptoms and signs.

Sepsis not associated with the flolan delivery system occurred in one flolan and one control patient.

Headache, myalgia, diarrhea, pain in general, fever, and nervousness were generally more frequent in the flolan group. The investigators also noted that the continuous infusion of flolan may have exacerbated or caused ascites/fluid retention.

Pain in the jaw, flushing, arthralgia, and supraventricular tachycardia were exclusively observed in the flolan group. Flolan was found to decrease the incidence of cough, cyanosis, hypoxia, and heart failure. The decrease in heart failure is debatable considering that 7 of the 8 patients who died during the study were in right heart failure when they were randomized.

2. Reactions Observed Exclusively in Patients Receiving Flolan:

a) Dose-Limiting Adverse Reactions:

Hypotension:	37%
Persistent severe headache:	31%
Extreme flushing:	28%
Severe nausea:	25%
Severe restlessness/anxiety:	14%

b) Reactions Due to Delivery System Malfunction:

	Cases
Catheter Occlusion (Thrombosis):	3
Perforation:	6
Dislodgement:	4
Infection (sepsis)	4
Infection (Catheter area)	7
Detachment of extension tubing	6
Blood in tubing	2
Air in Line	1
Incorrect position of catheter	2
Pump Mechanical:	
Stoppage and malfunction	12
Accidents	3
Other	2
Human, Programming Error	3
Other	11
	66

c) Reactions due to discontinuation of flolan.

When flolan was discontinued abruptly, significant deterioration and/or worsening of PPH symptoms was observed. Study 35/36 was amended to avoid such events. [However accidents have occurred in other studies and patients have died.]

3. Adverse Reactions Due to Catheterization Itself:

	<u>Cases</u>
Pneumothorax followed by death	2
Acute bronchopneumonia and death	1
Subclavian artery dissection	1
Supraventricular tachycardia	1
Vasovagal response	2

CONCLUSIONS:

The benefits were not substantial:

1. There was no real effect on survival.
2. There were small significant reductions in pulmonary pressures (2-12 mm Hg) and resistances (4-5 Wood units) and small significant increases in CO (0.6 L/min) and CI (0.4 L/min/m²). However, the pulmonary pressures and the resistances remained very high, far above the normal levels (PAP_m: 55-78 mm Hg, PVR_m: 12 and TPR: 21 Wood units, respectively).
3. A very small increase in the ability to walk.
4. A few improvements in the quality of life, which, however, were disproved by the frequency of side effects.

We must take into consideration that both study 35/36 and 46 were open and bias on the part of the patients and on the part of the investigators cannot be excluded. The placebo effect must have been substantial (there is a firm belief among the investigators that flolan is very effective for the treatment of PPH). Most importantly, we must consider the fact that the control patients in study 46 were severely handicapped from the beginning because they included significantly more (9 vs 2) patients who could hardly walk. Five of the 8 patients who died belonged to this group. There must have been a negative effect due to the presence of these patients on the hemodynamic parameters and the walk test of the control group.

The risks are certainly higher than those involved with the conventional therapy for PPH. The patients will still have to use the conventional drugs for the treatment of PPH and on top of them they will have to carry a permanent venous catheter subject to all sorts of complications (infection, clotting, perforation, pneumothorax formation, etc.). They will also have to prepare the solution of flolan aseptically every day, perhaps more than once a day, and take care of the pump to prevent accidents. All these tasks will be additional great burdens for a patient with PPH.

The risks seem to outweigh the benefits.

RECOMMENDATION: I recommend that the drug not be approved based on my conclusions from what I have seen thus far that the risks outweigh the benefits.

E. Triantas, M.D.
E. Triantas, M.D.

CC:
NDA 20-444
HFD-180
HFD-180/SFredd
HFD-180/ETriantas
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
r/d 1/30/95 jgw
f/t 2/8/95 jgw
MED\N\20444501.OET

2/8/95
Noted. Advisory Com.
to discuss 2/23/95.
JP

TABLE I

Table 38. Preferred Analysis of the Between-Treatment Comparison of Six-Minute Walk Test: Adjusted for Baseline Walk and Vasodilator Use at Baseline

Parameter	Fiolen (N=11) Standard (N=14)						Nonparametric Analysis ¹ of Covariance (two sided p-value)
	Fiolen			Standard			
	N	Baseline Median	Day 56 Median	N	Baseline Median	Day 56 Median	
6 Min. Walk	11	213.3	386.0	14	254.3	248.2	0.045

NOTE: Patients were missing on 6 minute walk tests. Their six minute walk results were used for this analysis. In addition, some patients walked longer than 6 minutes. For these patients, a fraction of the total distance proportional to 6 minutes was used for the summary statistics.
¹All 25 randomized patients were included in the analysis. Patients who died or could not walk were assigned the lowest rank for the calculation of the median and test statistic.

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TABLE 2

Table 37. Protocol-Specified Analysis for Six-Minute Walk (Analysis of Variance Using the "Last Observation Carried Forward" Method)

		Fleien (N=11)			Standard (N=14)			Parametric Analysis ¹ of Variance (two-sided p-value)
		Fleien		Standard				
N	Baseline Mean	Day 56 Mean	Mean Change from Baseline	N	Baseline Mean	Day 56 Mean	Mean Change from Baseline	
11	225.2	363.7	138.5	14	213.4	241.5	28.0	0.043

NOTE: Patients were missing on 6 minute walk tests. Their six minute walk results were used for this analysis. In addition, some patients walked longer than 6 minutes. For these patients, a fraction of the total distance proportional to 6 minutes was used for the summary statistics.

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TABLE 3

Burroughs Wellcome Co.
 110-33/36
 FLOTAB (oxprenolol sodium)

Appendix D.4.2
 Summary of the Exercise Tolerance Test
 (80m-Minute Walk)

Ploten (N=33)
 Standard (N=14)

Study Day	Treatment	N	Mean	S.E.	Min	25-th Z-tile	Median	75-th Z-tile	Max	P-value
0	Ploten	11	275.2	43.7	0.0	107.0	213.3	314.0	402.0	0.05
	Standard	14	272.4	39.7	0.0	70.0	259.3	342.0	420.0	
2	Ploten	11	307.0	41.3	129.7	220.8	289.2	430.0	517.0	
	Standard	9	282.2	30.7	120.0	165.0	247.0	341.0	410.0	
29	Ploten	0	221.2	40.6	140.0	245.5	310.0	340.2	540.0	
	Standard	0	263.9	43.9	0.0	210.3	278.0	341.0	360.0	
56	Ploten	10	370.0	19.9	200.0	322.0	393.0	420.0	462.0	
	Standard	11	279.4	43.6	1.0	120.0	300.0	400.0	480.0	

p = 0.1016 (calculated by Dr. Al Osh, FDA Statistician)

Patients were missing the 6 minute walk test for Study Day 0. Their 60 walk results were used for this analysis. In addition, some patients walked longer than 6 minutes. For these patients, a fraction of the total distance proportional to 6 minutes was used in computing the summary statistics.

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TABLE 4

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TABLE 5

Table 32. Summary of the 6-Minute Walk Exercise Test Results

Period	Treatment	N ¹	Mean	S.E.	Min	Flolan (N=41)		Standard (N=40)	
						25-th X-ile	Median	75-th X-ile	Max
Day 1	Flolan	41	306.0	10.9	2.1	244.5	307.0	365.0	559.4
	Standard	38	245.7	21.1	0.0	155.4	240.0	304.2	534.9
Day 2	Flolan	40	315.3	10.6	0.6	261.0	312.0	389.1	521.2
	Standard	39	265.5	22.0	0.0	137.2	260.7	390.1	487.4
Wk 1	Flolan	40	330.0	16.0	0.0	206.5	332.4	396.7	510.2
	Standard	39	254.9	20.2	43.9	166.4	257.3	347.0	511.2
Wk 6	Flolan	40	375.0	17.4	39.6	300.9	385.3	453.4	556.5
	Standard	37	280.0	24.6	0.0	151.0	302.1	404.2	572.1
Day 80	Flolan	41	349.9	17.0	24.4	313.2	362.4	426.7	543.2
	Standard	32	283.0	27.5	0.0	154.5	265.5	403.3	550.7

TABLE 6

Table 34. Summary of the Between-Treatment Comparisons of the 6-Minute Walk Exercise Test Adjusting for Baseline Walk and Vasodilator Use at Baseline (Nonparametric Analysis of Covariance - Using Analysis 2)

Week	N	Fleiss		Standard (N=40)		Nonparametric Analysis of Covariance (two-sided test)	
		Baseline median (meters)	Median (meters)	Baseline median (meters)	Median (meters)		
1	40	312.0	332.4	40	269.6	254.4	0.0039
6	40	312.0	305.3	40	269.6	260.1	0.0010
12	41	314.6	362.4	40	269.6	203.5	0.0020

NOTE: Patients who did not perform the walk on Day 2 due to their health were assigned the lowest rank for the calculation of the median and test statistic. If a patient did not perform a baseline walk (study day 2) for reasons other than the patient's health, the results from study day 1 were used. For subsequent visits, patients who died or did not perform the walk due to their health were assigned the lowest rank for the calculation of the median and test statistic.

¹This method uses a Cochran-Mantel-Haenszel correlation statistic based on the residuals from an ordinary least squares regression. The regression is based on the ranks of the results from the 6-min walk.

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TABLE 7

Table 35. Summary of the Between-Treatment Comparisons of the 6-Minute Walk Exercise Test (Analysis of Variance, Carrying forward results for missing values or results after a transplant)

Week	N	Flelen		Standard (N=40)		Analysis of Variance (two-sided test)	
		Baseline mean (meters)	Mean (meters)	Baseline mean (meters)	Mean (meters)		
1	41	318.7	331.1	40	272.2	248.8	0.0103
6	41	318.7	370.9	40	272.2	263.9	0.0005
12	41	318.7	348.1	40	272.2	257.2	0.0029

NOTE: Patients who did not perform the walk on Day 2 due to their health were assigned a walk of zero. If a patient did not perform a baseline walk (study day 2) for reasons other than the patient's health, the results from study day 1 were used.

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TABLE 8

Table 43. Summary of Baseline, Day 88, and changes from Baseline of Hemodynamic and Blood Gas Measurements, Between-Treatment Comparison

Parameter	Treatment	Fleolan (N=41)		Standard (N=40)			% change in means	Difference in mean change (Fle.- Stand.)	95% Confidence interval ² for the diff. in mean change (Fle.- Stand.)
		N ¹	Baseline mean	Day 88 mean	Mean change	S.E. mean change			
Heart Rate (bpm)	Fleolan	38	79.97	79.11	-0.87	2.48	-1.1	0.96	(-2.18, 4.03)
	Standard	38	82.88	80.97	-1.83	1.58	-2.2		
Cardiac Output (L/min)	Fleolan	38	5.52	4.85	-0.64	0.17	-15.3	0.96	(0.65, 1.27) n
	Standard	38	3.98	3.47	-0.43	0.28	-10.9		
Cardiac Index (L/min/m ²)	Fleolan	38	2.04	2.37	0.33	0.10	16.1	0.56	(0.38, -0.74) n
	Standard	38	2.20	1.97	-0.23	0.16	-10.5		
PAPs (mm Hg)	Fleolan	38	97.58	98.37	-7.21	2.78	-7.4	-18.38	(-14.81, -6.75) n
	Standard	38	92.47	95.63	3.17	2.29	3.4		
PAPd (mm Hg)	Fleolan	38	41.16	37.56	-3.46	1.38	-8.9	-4.82	(-6.84, -2.81) n
	Standard	38	48.17	41.33	1.17	1.49	2.9		
PAPw (mm Hg)	Fleolan	38	59.95	55.13	-4.82	1.32	-8.0	-6.68	(-8.69, -4.67) n
	Standard	38	57.68	59.47	1.87	1.55	3.2		
RAPs (mm Hg)	Fleolan	36	13.11	18.94	-2.17	1.89	-16.5	-2.25	(-3.71, -0.88) n
	Standard	29	11.68	11.69	0.09	0.92	0.7		
PCWPs (mm Hg)	Fleolan	27	9.47	10.87	0.41	1.18	4.2	1.41	(-0.88, 3.32)
	Standard	17	10.82	9.82	-1.00	1.59	-9.2		
PVR (Wood u)	Fleolan	27	15.62	12.28	-3.42	0.72	-21.9	-4.95	(-6.25, -3.64) n
	Standard	17	15.53	17.85	1.52	1.23	9.8		
TPR (Wood u)	Fleolan	38	19.88	15.66	-4.14	0.96	-20.9	-6.18	(-7.56, -4.88) n
	Standard	38	18.16	20.28	2.04	0.99	11.2		

¹The number of patients with results from both the baseline and the Day 88 evaluations.

²A confidence interval that does not contain 0 implies statistical significance.

TABLE 8 (Con't)

Table 43. Summary of Baseline, Day 88, and changes from Baseline of Hemodynamic and Blood Gas Measurements, Between-Treatment Comparison (continued)

Parameter	Fleolan (N=41)		Standard (N=40)					95% Conf. Interval for the difference in mean change in mean change (Fl.- Stand.)
	Treatment	N ¹	Baseline mean	Day 88 mean	Mean change	S.E. mean change	% change in mean	
SAPs (mm Hg)	Fleolan	38	120.32	115.76	-4.55	3.15	-3.8	-1.29 (-5.40, 2.83)
	Standard	38	122.85	119.57	-3.27	2.42	-2.7	
SAPd (mm Hg)	Fleolan	38	74.68	69.76	-4.92	1.81	-6.6	-5.86 (-7.53, -2.60) *
	Standard	28	74.07	74.21	0.14	1.54	0.2	
SAPm (mm Hg)	Fleolan	38	89.92	85.08	-4.84	2.07	-5.4	-3.95 (-6.72, -1.18) *
	Standard	28	98.57	89.68	-8.89	1.68	-1.8	
SVR (Wood u)	Fleolan	36	24.86	28.82	4.04	0.98	16.3	-6.17 (-7.84, -4.51) *
	Standard	27	23.25	25.38	2.13	1.44	9.2	
TSR (Wood u)	Fleolan	38	29.37	23.79	-5.58	1.14	-19.8	-8.81 (-9.95, -6.88) *
	Standard	28	27.86	29.58	2.43	1.68	9.8	
SV (ml/beat)	Fleolan	38	45.68	52.33	6.65	2.25	14.6	10.13 (6.31, 13.94) *
	Standard	38	47.88	44.41	-3.48	3.26	-7.3	
Arterial Saturation (%)	Fleolan	29	98.29	92.29	-6.00	1.58	-6.1	-6.43 (-8.44, -4.82) *
	Standard	22	91.39	90.75	-0.63	1.43	-0.7	
Mixed Venous Saturation (%)	Fleolan	33	61.85	63.81	1.96	1.78	3.2	3.78 (1.88, 6.47) *
	Standard	27	61.16	58.54	-2.62	2.05	-4.3	
PaCO ₂ (mm Hg)	Fleolan	29	35.88	33.28	-2.60	0.81	-7.3	-2.60 (-4.14, -1.06) *
	Standard	23	31.81	38.98	7.17	0.84	8.5	
PaO ₂ (mm Hg)	Fleolan	29	68.49	72.13	3.64	3.76	5.3	5.66 (-0.75, 12.04)
	Standard	23	78.15	68.13	-10.02	5.41	-13.2	

¹The number of patients with results from both the baseline and the Day 88 evaluations.

²A confidence interval that does not contain 0 implies statistical significance.

TABLE 8 (Con't)

Table 43. Summary of Baseline, Day 88, and changes from Baseline of Hemodynamic and Blood Gas measurements, Between-Treatment Comparison (continued)

Parameter	Fleian (N=61)		Standard (N=60)		S.E. mean change	Z change in means	Difference in mean change (Flc.- Stand.)	95% Confidence Interval ² for the diff. in mean change (Flc.- Stand.)
	Treatment	N ¹	Baseline mean	Day 88 mean				
pH _a	Fleian	25	7.44	7.44	-0.00	0.01	-0.0	(-0.02, -0.00) *
	Standard	23	7.44	7.46	0.01	0.01	0.1	
Transcut. blood O ₂ Sat. (%)	Fleian	37	92.49	93.22	0.73	0.53	0.0	(0.09, 2.64) *
	Standard	29	92.72	91.69	-1.03	0.74	-1.1	

¹The number of patients with results from both the baseline and the Day 88 evaluations.

²A confidence interval that does not contain 0 implies statistical significance.

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TABLE 10 (Con't)

Table 47. Summary of the Scores of the Nottingham Health Profile (Part 1), All Patients (continued)

		Fiolan (N=41) Standard (N=40)								
	Period	Treatment	N ²	Mean	S.E.	Min	25-th X-ile	Median	75-th X-ile	Max
Physical mobility	Day 07	Fiolan	40	24.0	3.0	0.0	10.0	22.0	33.0	66.1
		Standard	31	36.5	3.4	0.0	22.0	41.9	47.3	70.7
Sleep	Day 1	Fiolan	41	37.3	4.6	0.0	12.6	34.9	56.0	100
		Standard	40	35.7	5.0	0.0	6.3	31.5	65.1	100
	Wk 6	Fiolan	38	23.4	4.2	0.0	0.0	12.6	34.9	87.4
		Standard	37	30.5	3.9	0.0	0.0	12.6	65.1	100
	Day 07	Fiolan	41	19.0	3.9	0.0	0.0	12.6	20.7	100
		Standard	31	40.3	5.9	0.0	12.6	34.3	65.1	100
Social isolation	Day 1	Fiolan	41	10.9	3.7	0.0	0.0	20.1	22.5	100
		Standard	40	20.2	4.5	0.0	0.0	9.0	22.5	100
	Wk 6	Fiolan	38	14.4	3.9	0.0	0.0	0.0	22.5	100
		Standard	37	10.9	4.4	0.0	0.0	0.0	22.5	100
	Day 07	Fiolan	40	12.4	3.2	0.0	0.0	0.0	22.5	64.7
		Standard	31	14.8	3.8	0.0	0.0	0.0	22.5	64.7

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TABLE 9

Table 44. Summary of the Scores of the Chronic Heart Failure Questionnaire, All Patients

Dimension	Treatment	Period	N	Mean	S.E.	Min.	Summary statistics			
							25th X-tile	Median	75th X-tile	Max.
Dyspnea	Flelan	Day 1	36	14.1	0.6	7.0	12.5	14.0	19.5	20.0
		Wk 6	32	26.0	1.1	10.0	22.5	26.0	29.0	34.5
		Day 07	35	24.6	1.1	10.0	20.0	24.0	30.0	35.0
	Standard	Day 1	36	14.0	0.7	0.0	12.0	14.0	17.0	25.0
		Wk 6	32	15.0	1.0	5.0	11.5	14.4	20.0	27.0
		Day 07	26	17.3	1.0	5.0	14.0	16.5	20.0	34.0
Fatigue	Flelan	Day 1	40	13.5	0.6	4.0	9.5	13.0	17.0	24.0
		Wk 6	30	17.9	0.7	7.0	15.0	18.0	21.0	28.0
		Day 07	39	17.9	0.7	9.0	15.0	18.0	21.0	28.0
	Standard	Day 1	40	13.0	0.9	4.0	9.0	12.0	16.0	24.0
		Wk 6	36	13.6	0.9	0.0	10.0	12.0	16.0	27.0
		Day 07	31	12.0	0.6	5.0	10.0	12.0	15.0	25.0
Emotional function	Flelan	Day 1	39	27.0	1.3	13.0	20.0	26.0	35.0	43.0
		Wk 6	30	32.2	1.3	11.0	27.0	33.0	40.0	46.0
		Day 07	39	33.7	1.3	12.0	29.0	34.0	40.0	49.0
	Standard	Day 1	39	20.6	1.3	11.0	23.0	26.0	35.0	45.0
		Wk 6	36	29.9	1.5	7.0	25.5	30.5	34.0	46.0
		Day 07	31	30.0	1.5	14.0	23.0	30.0	36.0	48.0
Nostalgia	Flelan	Day 1	40	17.9	0.6	6.0	14.5	18.0	22.0	27.0
		Wk 6	30	20.4	0.9	6.0	10.0	21.5	25.0	28.0
		Day 07	39	21.0	0.7	10.0	10.0	22.0	25.0	28.0
	Standard	Day 1	39	16.0	0.7	6.0	13.0	17.0	20.0	24.0
		Wk 6	36	17.0	0.6	4.0	15.0	18.0	21.0	27.0
		Day 07	31	10.7	0.6	10.0	14.0	18.0	22.0	27.0

TABLE 10

Table 47. Summary of the Scores of the Nottingham Health Profile (Part 1), All Patients

	Period	Treatment	N ²	Mean	S.E.	Min	25-th X-ile	Median	75-th X-ile	Max	Fleiss (N=41)	
											Standard	(N=40)
Emotional Reactions	Day 1	Fleiss Standard	36 46	26.6 26.4	3.7 4.2	0.0 0.0	9.0 7.2	22.5 17.7	42.9 42.8	63.8 100		
	Wk 6	Fleiss Standard	36 36	18.8 20.3	4.2 4.5	0.0 0.0	0.0 0.0	9.3 11.9	29.9 28.3	76.7 100		
	Day 87	Fleiss Standard	39 31	14.7 22.4	3.1 4.1	0.0 0.0	0.0 0.0	9.8 14.0	23.7 40.3	66.6 64.7		
Energy	Day 1	Fleiss Standard	41 46	53.7 62.3	5.7 6.3	0.0 0.0	24.0 24.0	60.0 63.2	100 100	100 100		
	Wk 6	Fleiss Standard	39 37	28.2 53.5	5.1 6.2	0.0 0.0	0.0 24.0	24.0 60.0	24.0 100	100 100		
	Day 87	Fleiss Standard	39 31	21.8 50.3	4.9 7.1	0.0 0.0	0.0 24.0	0.0 60.0	24.0 100	100 100		
Pain	Day 1	Fleiss Standard	39 46	17.3 14.3	4.4 4.1	0.0 0.0	0.0 0.0	0.0 5.8	22.9 18.6	100 100		
	Wk 6	Fleiss Standard	37 37	12.0 12.0	3.9 3.9	0.0 0.0	0.0 0.0	0.0 0.0	12.9 15.8	79.1 100		
	Day 87	Fleiss Standard	41 31	7.8 8.7	2.8 3.4	0.0 0.0	0.0 0.0	0.0 0.0	5.8 10.5	61.3 100		
Physical ability	Day 1	Fleiss Standard	46 39	36.4 44.1	3.0 3.7	0.0 0.0	21.4 22.0	52.6 43.3	84.7 56.8	96.7 100		
	Wk 6	Fleiss Standard	38 37	21.9 37.2	2.9 3.5	0.0 0.0	9.3 22.0	21.4 41.9	32.6 54.5	66.1 88.5		

TABLE 11

Table 50. Summary of the Responses to the Nottingham Health Profile (Part II)

Parameter	Period	Treatment	Total N	Yes		No	
				(%)	N	(%)	N
Home life	Day 1	Flolan	40	13	(33)	27	(68)
		Standard	40	22	(55)	18	(45)
	Wk 6	Flolan	30	0	(21)	30	(79)
		Standard	37	17	(46)	20	(54)
Looking after the home	Day 07	Flolan	39	9	(23)	30	(77)
		Standard	31	13	(42)	18	(58)
	Day 1	Flolan	30	34	(89)	4	(11)
		Standard	40	30	(75)	10	(25)
Interests & Hobbies	Day 1	Flolan	40	24	(60)	16	(40)
		Standard	40	24	(60)	16	(40)
	Wk 6	Flolan	37	21	(57)	16	(43)
		Standard	37	20	(54)	17	(46)
Sex life	Day 07	Flolan	39	19	(49)	20	(51)
		Standard	31	19	(61)	12	(39)
	Day 1	Flolan	37	21	(57)	16	(43)
		Standard	40	24	(60)	16	(40)

TABLE 11 (Con't)

Table 50. Summary of the Responses to the Nottingham Health Profile (Part II) (continued)

Parameter	Period	Fiolan (N=41)		Standard (N=40)		Yes		No	
		Treatment	Total	N	(%)	N	(%)	N	(%)
Sex life	Wk 6	Fiolan	34	13	(38)	21	(62)		
		Standard	36	19	(53)	17	(47)		
	Day 87	Fiolan	38	14	(42)	22	(58)		
		Standard	31	16	(52)	15	(48)		
Social life	Day 1	Fiolan	40	23	(58)	17	(43)		
		Standard	40	20	(70)	12	(30)		
	Wk 6	Fiolan	38	16	(42)	22	(58)		
		Standard	37	29	(78)	8	(22)		
Day 87	Fiolan	40	18	(45)	22	(55)			
	Standard	31	19	(61)	12	(39)			
Vacations	Day 1	Fiolan	40	21	(53)	19	(48)		
		Standard	40	27	(68)	13	(33)		
	Wk 6	Fiolan	37	21	(57)	16	(43)		
		Standard	37	24	(65)	13	(35)		
Day 87	Fiolan	39	18	(46)	21	(54)			
	Standard	31	21	(68)	10	(32)			
Work	Day 1	Fiolan	38	14	(37)	24	(63)		
		Standard	40	24	(60)	16	(40)		
	Wk 6	Fiolan	36	10	(28)	26	(72)		
		Standard	36	19	(53)	17	(47)		

TABLE 11 (Con't)

Table 50. Summary of the Responses to the Nottingham Health Profile (Part II) (continued)

Parameter	Period	Flolan (N=41)		Standard (N=40)	
		Treatment	Total	Yes	No
		N	N	(%)	(%)
Work	Flolan	38	35	(59)	(25)
	Standard	31	17	(55)	(14)

TABLE 12

6-Minute Walk; Baseline Values

<u>Flolan + Standard T.</u>		<u>Standard Treatment Alone</u>		<u>Death After Randomization (Days)</u>	<u>Additional Morbidity</u>
<u>Pt. ID #</u>	<u>NYHA Class</u> <u>Distance Walked (meters)</u>	<u>Pt. ID #</u>	<u>NYHA Class</u> <u>Distance Walked (meters)</u>		
	314.6		427.9		
	511.2		534.9		
	487.4		487.4		
IV	332.8	IV	0.0	0	Moribund
	332.8		475.5		
	404.2		427.9	68	Hepatitis C Hx of bleeding
	352.3		427.9		
	309.4	IV	237.4		
	279.8		422.5		
	291.7		410.6		
IV	394.4		374.0		
IV	359.4		438.0	58	Septostomy
	394.1		336.5 T		
	516.3	IV	310.9		
IV	253.6		390.1		
	351.1 W	IV	253.6		
	161.5	IV	198.1		
IV	131.7		272.5 T		
	183.8	IV	100.6	19	Multiple electr. abnormal, Dig. Tox.
IV	68.3	IV	266.7		
	358.4		158.5		
IV	270.1		336.8	56	Marked Polycythemia
	384.0		60.0		
	306.3		117.3	43	Hyperkalemia, hypothyroidism.
	291.1		192.6		
	331.9		385.6		
	379.2	IV	220.7		
	217.9	IV	91.4		
	237.7		156.4		
	285.0		114.3		
	434.3		275.2		
	279.8 W		340.5		
IV	276.8		248.1		
	455.7		352.0		
	384.0		443.5		
	429.8	IV	91.4	59	Digitalis Toxicity
	226.5		118.9		
IV	0.6		137.2		
IV	148.4 T		208.5		
	296.3	IV	45.7	48	Multiple electrol. abnormalities, dig. tox.
	521.2				

T = Transplanted

W = Withdrew consent

* = Patients without NYHA class designation were classified as class III

TABLE 13

Table 68. Expected and Unexpected Adverse Experiences that Occurred in at Least 3 Patients in Either Treatment Group, 12-Week Treatment Segment

Adverse Experience	FLOLAN®		Standard	
	N	(%)	N	(%)
Asthenia	41	(100%)	39	(98%)
Dyspnea	41	(100%)	39	(98%)
Dizziness	37	(90%)	34	(85%)
Headache	35	(85%)	15	(38%)
Palpitations	33	(80%)	30	(75%)
Pain, chest	31	(76%)	33	(83%)
Edema	30	(73%)	30	(75%)
Nausea	28	(68%)	23	(58%)
Pain, jaw	27	(66%)	0	(0%)
Myalgia	23	(56%)	16	(40%)
Cough, increase	19	(46%)	25	(63%)
Depression	19	(46%)	23	(58%)
Vascular disorder, peripheral	19	(46%)	20	(50%)
Tachycardia	16	(39%)	13	(33%)
Diarrhea	16	(39%)	3	(8%)
Cyanosis	14	(34%)	21	(53%)
Pain, abdominal	14	(34%)	15	(38%)
Weight decrease	14	(34%)	13	(33%)
Arrhythmia	14	(34%)	11	(28%)
Hypoxia	13	(32%)	19	(48%)
Heart failure, right	13	(32%)	19	(48%)
Hypotension	13	(32%)	16	(40%)
Anorexia	13	(32%)	15	(38%)
Pain, general	13	(32%)	7	(18%)
Heart failure (Low cardiac output)	12	(29%)	21	(53%)
Flushing	11	(27%)	0	(0%)
Pallor	10	(24%)	16	(40%)
Angina pectoris	10	(24%)	11	(28%)
Fever	10	(24%)	3	(8%)
Vomit	8	(20%)	4	(10%)
Sweat	7	(17%)	9	(23%)
Bradycardia	7	(17%)	5	(13%)
Syncope	6	(15%)	11	(28%)
Ascites	6	(15%)	8	(20%)
Hemorrhage	6	(15%)	5	(13%)

TALLE 13 (Con't)

Table 68. Expected and Unexpected Adverse Experiences that Occurred in at Least 3 Patients in Either Treatment Group, 12-Week Treatment Segment (continued)

Adverse Experience	FLOLAN®		Standard	
	N	(%)	N	(%)
Anxiety	5	(12%)	3	(8%)
Amblyopia	4	(10%)	2	(5%)
Nervousness	4	(10%)	1	(3%)
Confusion	3	(7%)	6	(15%)
Rash	3	(7%)	5	(13%)
Infection, general	3	(7%)	3	(8%)
Pain, back	3	(7%)	2	(5%)
Weight increase	3	(7%)	2	(5%)
Constipation	3	(7%)	1	(3%)
Hypokalemia	3	(7%)	1	(3%)
Hypesthesia	3	(7%)	1	(3%)
Arthralgia	3	(7%)	0	(0%)
Tachycardia, supraventricular	3	(7%)	0	(0%)
Rhinitis	2	(5%)	4	(10%)
Infection, urinary tract	2	(5%)	3	(8%)
Liver function abnormality	1	(2%)	4	(10%)
Ischemia, myocardial	1	(2%)	3	(8%)
Shock	0	(0%)	7	(18%)

[Table excerpted from Table 67]

PGI, PROTOCOL 36--NYHA CLASSES III AND IV

INSTRUCTIONS:

Patients currently being treated* for PPH are assigned a number in an ascending order beginning with one (i.e., 1, 2, 3, . . .) with each new patient.

Patients not being treated* for PPH are assigned a number in descending order beginning with twenty (i.e., 20, 19, 18, . . .) with each new patient.

Back-up codes: These patients are numbered 21-28 and will be employed in the manner outlined above.

PLEASE COMPLETE THE FOLLOWING INFORMATION.

*with vasodilator

Patient No.	Treated	Treatment	Site No.	Investigator	Monitor
	YES	NO FLOLAN	01	Rubin	Watson
	YES	FLOLAN	01	Rubin	Watson
	YES	FLOLAN	01	Rubin	Dieltz
	YES	FLOLAN	06	McGoons	C. P. Greenstein
	YES	NO FLOLAN	06	McGoons	Greenstein
	YES	NO FLOLAN	01	Rubin	Dieltz
	YES	FLOLAN	01	Rubin	Greenstein
	YES	FLOLAN	05	BARST	WATSON
	YES	NO FLOLAN	01	Rubin	GREENSTEIN
	NO	FLOLAN	01	RUBIN	Greenstein
	NO	NO FLOLAN	01	RUBIN	D. EHL
	NO	FLOLAN	06	McGoons	GREENSTEIN
	NO	NO FLOLAN	01	RUBIN	Dieltz
	NO	NO FLOLAN	01	RUBIN	Dieltz
	NO	FLOLAN	01	Rubin	Dieltz Greenstein
	NO	FLOLAN	06	McGoons	Greenstein
	NO	NO FLOLAN	05	BARST	DIETZ
	NO	FLOLAN	01	Rubin	Koller
	NO	FLOLAN	01	Rubin	Watson
	NO	NO FLOLAN	01	Rubin	Watson

Back-up Codes:

21	YES	NO FLOLAN	05	Barst	Greenstein
22					
23					
24					
25					
26					
27	NO	NO FLOLAN	05	Barst	Greenstein
28	NO	NO FLOLAN	05	Barst	Greenstein
	NO	PGI	05	Barst	Dieltz

Dieltz

EXHIBIT 11

1111

Properties (1)

Operations (2)

10

10

U. 11. 1994

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 20-444

NOV 23 1994

DRUG: Flolan (PGI₂)

SPONSOR: Burroughs-Wellcome

PROPOSED INDICATION: Long-term i.v, treatment of NYHA Class III and IV patients with primary pulmonary hypertension (PPH)

DATE OF DOCUMENT: October 28, 1994

DATE RECEIVED: October 28, 1994

DATE RECEIVED BY MEDICAL OFFICER: October 31, 1994

DATE REVIEW COMPLETED: November 9, 1994

CONTENTS: This submission is a response to FDA letter of September 23, 1994 (copy attached to this review) requesting missing information regarding the flolan studies. It contains 8 volumes of material.

Response to:

Request A: The sponsor states that the autopsy reports of patients were only one page in length. Consequently we cannot get additional information about these patients. (We had already received copies of these pages with the original NDA.)

Request B: Tabulation and analysis of the results of the Borg Dyspnea Score in study 46 is being provided. The data were analyzed by the sponsor using 3 methods.

1. The data were adjusted for baseline score and oral vasodilator use at baseline and then analyzed by an intent-to-treat method. Scores for patients who died or did not perform the test were assigned the highest rank (worst dyspnea). The analysis showed that dyspnea was significantly improved in patients who received flolan, while dyspnea became worse in the control group. The differences between the groups were significant ($p=0.029$) at Week 1 and highly significant ($p=0.001$, 0.0001) at Weeks 6 and 12 respectively.

2. For the second type of analysis the last observation was carried forward for the patients who died, withdrew, were transplanted or missed a test for any reason. The results were similar to those obtained with the first method of analysis but the differences were less significant at Week 6 ($p=0.046$) and not significant at week 12 ($p=0.11$).

3. For the third method of analysis the data of the patients who did not have a walk test were excluded. With this analysis the differences were highly significant at Weeks 1 ($p=0.009$) and 6 ($p=0.006$) and barely significant at Week 12 ($p=0.052$).

Request C: The sponsor explains that each question in Part I of the Nottingham Health Profile (copy attached at the end of this review) has been assigned a weight which was determined using Thurstone's Method of Paired Comparisons, where members of the public were asked to make judgements about the relative seriousness of each question. The weights of the questions which were marked with a "yes" were added to obtain the scores that were reported for study 46.

Request D and E: The case histories of the patients who died in studies 37, 47, 49, and 50 and the missing CRFs of some of these patients are finally submitted. I have summarized the essential information for each patient of each study in Tables 1, 2, 3, and 4 (respectively). All these studies were uncontrolled and multicenter.

Deaths in Study 37:

Study 37 is a continuation of study 35/36. Study 35/36 was one of the pivotal studies of flolan. It was multicenter, controlled and open-labeled. It lasted for 8 weeks and had 11 flolan and 14 control patients. Ten of the flolan and 8 of the control patients entered study 37 after the completion of study 35/36. All received flolan during study 37. The sponsor reported that by the cut-off date, March 22, 1994, 8 of these patients had been transplanted and 6 had died. We have received only the CRFs of the patients who died. I have summarized the essential data about each patient in Table 1.

TABLE 1

Patients Who Died in Study #37

Study 37 is the continuation of study 35/36, which was initiated on April 10, 1987. Study 37 itself was initiated on August 25, 1987 and is still ongoing. All patients are receiving flolan. The total number of patients in study 37 was 18. It has been reported that 6 of these patients had died by March 22, 1994

Pt # and NYHA Class	Date Entered	Date of Death	Period in Study	Cause of Death	Side Effects
C* IV	1/23/89	3/29/93	4 years, 2 months	Not stated	Diarrhea, pneumonia, fluid retention
F* III	9/15/87	2/16/90	2 years, 5 months	Cardiopulmonary Decompensation	Pump stoppage, sepsis, hyponatremia, catheter clotted
F* III	12/16/87	10/23/88	10 months	Progression of PPH	Interruption of flolan flow associated with heparin flushing, Death
C* III	10/10/88	5/21/90	1 year 8 months	Sudden Death	Thromboembolism, arrhythmia
F* IV	2/13/89	11/7/93	4 yrs, 11 mos	PRHF	Catheter infection, persistent PGI ₂ syndrome**, sepsis, hepatorenal failure
F* III	5/3/89	7/9/92	3 years 2 months	Progression of PPH	Cardiovascular collapse

*C=the pt. was a control pt. in Study 35/36; F=the pt. was a flolan pt. in Study 35/36.

** = Jaw/taste bud pain, muscle aches, diarrhea.

These data indicate that by the cut-off date of March 22, 1994 (6 years and 7 months into the study), the mean length of survival in study 37 was 34 ± 18 months (range 10-59 months). This represents a survival rate of a selected population. I must point out here that study 37 included the survivors of study 35/36. Five patients had died during the parent study and 3 control patients had refused to enter study 37.

The mortality rate in study 37 was $6/18 = 33\%$.

Deaths in Study 47:

Study 47 is the continuation of study 46. Study 46 was the second pivotal study of flolan. It had 41 flolan and 40 control patients and lasted for 3 months. Thirty-eight (38) of the former and 26 of the latter entered study 47 after the completion of study 46. All received chronic infusions of flolan. The sponsor reported that by March 22, 1994, 27 months into the study, 11 of these patients had died, 15 had been transplanted and 2 had been withdrawn. We have received only the CRFs of the 11 patients who have been reported that they had died in study 47 (Table 2). We have not received any CRFs of the patients who withdrew. Six of the patients who died had received flolan in study 46 and 6 had received only the

standard treatment.

The mortality rate in study 47 was $11/64 = 17\%$. The patients in this study had survived for 3-16 (mean 8 ± 4) months. In evaluating the survival of these patients we must remember that the severely ill patients of the study population (8 of them) had died in study 46.

Deaths in Study 49:

Study 49 is an independent study. Unlike study 37, and 47, it is recruiting new patients who had not participated in another study. It is uncontrolled and still ongoing. Its objective is to provide chronic infusions of flolan to patients with severe PPH (NYHA Class III and IV) until they are transplanted or die. It was initiated on August 24, 1992. By March 22, 1994, 128 patients had been recruited. The sponsor has reported that by the cut-off date, 19 months into the study, 20 of these patients had died, 11 had been transplanted and 7 were withdrawn. We have received case histories/CRFs from 21 patients who died (Table 3) and the CRFs of 3 of the patients who withdrew (Table 3a).

The mean length of survival of the 21 patients in study 49 was 3.3 ± 3.3 months.

TABLE 2
Patients who Died In STUDY # 47
Study 47 is the continuation of study 46. Study 46 was initiated on September 12, 1991 and study 47 on December 1991 and is still ongoing. All patients are receiving flolan.
The total number of patients in study 47 was 64.

Pt#	Date Entered Study	Onset of Event which Lead to Death	Date of Death	Cause of Death	Period in Study	NYHA Class	Side Effects
C*	12/5/91	11/21/92	12/24/92	Hepatic Encephalopathy	1 year, 19 days Autop.	III	Cirrhosis, G.I. bleeding IHSS*, CAD
F*	4/9/92	8/31/92	10/9/92	Massive GI Bleeding	6 mos Autop.	II then III and IV	Thrombocytopen. Hx of Epistaxis Cath infect., Sepsis
C*	12/18/91	9/11/92	10/8/92	Compl of PPH	8 mos 21 days	III	Ascites, 1 urine output
F*	1/24/92	12/10/92	12/11/92	PRHF	10 mos 18 days Autop.	III	diarrhea photosensitivy, vomiting, pleural effusion
C*	4/6/92	8/8/93	8/8/93	PRHF	1 year, 4 mos	III, IV	palpitations, cyanosis, dyspnea
F*	5/11/92	5/19/93	5/19/93	sudden death	1 year, 8 days	III	diarrhea, rash, vomiting, ascites, CVA
C*	6/3/92	11/13/92	11/14/92	septicemia	5 mos, 11 days	IV	diarrhea, Elevated liver enzymes
F*	4/30/92	11/20/92	11/22/92	PRHF	6 mos, 22 days Autop	III	nausea, 1 digoxin level
F*	3/5/92	5/13/92	5/31/92	PRHF,	2 mos, 26 days Autop.	IV	pleural effusion Throbocytopenia , severe ascites dig tox
C*	3/10/92	7/16/92	7/16/92	PRHF	4 mos 6 days	III	Allergy, Thrombocytopenia ascites, hypona, hyperK., renal insufficiency
F*	7/2/92	10/10/92	10/10/92	Staph Aureus Septicemia	3 mos, 8 days Autop	IV	UTI, diarrhea, cath. dislodged

C* patient had received standard treatment in Study 46; F* patient had received flolan in study 46.
*IHSS=Idiopathic Hypertrophic Subaortic Stenosis.
PRHF=progressive right heart failure

TABLE 3

Data from the Patients Who Died in STUDY #49.
Study 49 Was Initiated on August 24, 1992 and is still ongoing.
By March 22, 1994 the Total Number of Patients in Study 49 was 128. All patients are receiving flolan.

Pt #	Date Entered Study	NYHA Class	Date of Death	Cause of Death or Discontinuation	Side Effects	Length of Survival in Study
	11/10/92	IV	11/21/92	sudden death	persist. nausea, vom., recurr. SVT	11 days
	2/3/93	III	4/10/93	arrhythmia	Ventricular tachycardia	2 months 6 days (66 days)
	6/16/93	III	7/25/93	PRHF		39 days
	12/14/92	IV	1/5/93	unknown		22 days
	8/24/92	IV	9/1/92	PRHF		8 days
	2/12/93	IV	2/17/93	CNS INJURY		5 days
	3/13/93	IV	6/29/93	SUDDEN DEATH	hypotension	3 1/2 mos (108 days)
	8/9/93	IV	8/12/93	RESP. FAILURE		3 days
	10/22/92	IV	12/17/92	FAILED TRANSPLANT	DVT, depression	56 days
	1/20/93	IV	1/20/93	CARDIAC ARREST,	Renal failure, hepatomegaly	0 days
	4/12/93	III	5/14/93	PRHF		32 days
	4/5/93	IV	8/11/93	PRHF	Hypotension, severe SOB	4 months 6 days (128 days)
	6/16/93	IV	7/1/93	PRHF	Pulmonary edema	15 days
	8/12/93	IV	10/29/93	PRHF		78 days
	9/8/93	IV	1/25/94	PRHF	diarrhea	139 days
	6/9/93	IV	2/18/94	PRHF	ascites, sepsis, bilateral knee infection	8 mos
	7/30/93	IV	9/13/93	Cardiogenic shock	red macular rash	45 days
	12/17/92	IV	9/11/93	Resp. Failure		7 1/2 mos
	5/10/93	III	3/18/94	massive hemoptysis	pneumonia	10 mos
	5/12/93	IV	2/16/94	arrhythmia	cath. infection nausea, vomiting	9 mos
	6/28/93	III	3/7/94	Multi-organ failure	sepsis, resp. failure	8 mos

PRHF=Progressive right heart failure.

TABLE 3a
Patients who Withdrew from study 49
Seven patients withdrew from study 49. We have received only the CRFs of 3 of these patients.

Pt #	Date Entered Study	NYHA Class	Date of Discontinuation	Reason of Discontinuation	Length of Participation in the Study	Side Effects
	1/20/93	III	3/9/93	Lack of Efficacy	48 days	SOB, jaw pain
	3/8/93	III	5/18/93	Adverse Reactions	71 days	Ascites, diarrhea, thrombocyt. leukocytosis
	6/22/93	III	6/23/93	Acute pulmonary congestion during dose-ranging	1 day	

* After flolan was discontinued the nurse noted in the CRF of patient 13104 that "Ascites disappeared, SOB decreased, weakness resolved, clinically felt better; 6/19/93 patient reports feeling great."

Deaths in Study 50:

Study 50 is similar to study 49. It is multicenter, uncontrolled, and still ongoing. Its objective is to provide compassionate treatment with flolan to patients with severe PPH (NYHA Class III or IV) until they are transplanted or die. The sponsor reported that by March 22, 1994, 8 months into the study, 66 patients had been recruited. Of these 4 had died and 4 had withdrawn. We have received the CRFs/case histories of 7 patients who died (3 more than the sponsor has reported; Table 4) and none of the patients who withdrew. It is reported that pts had originally been entered in study 47 and 49, respectively, but both died in study 50 (information from the first page of the CRFs of these patients).

TABLE 4
Study 50
Study 50 was initiated on July 23, 1993
By March 22, 1994 Study 50 had 66 patients.
Four of these patients were reported that they had died.
We received the CRFs on 7 patients who died in study 50.

Pt #	Date Entered Study	NYHA Class	Date of Death	Length of Survival	Cause of Death	Side - Effects
	12/20/93	IV	12/20/93	0 days	PRHF	Hypotension; nausea, SOB
	8/31/93	IV	12/13/93	104 days	cardiac arrest	Hypotension
	2/19/94	IV	2/21/94	2 days	pneumonia,	
	3/15/94	IV	3/22/94	6 days	pulmonary hemorrhage	
	2/11/94	III	3/16/94	33 days	hemorrhage	pneumothorax, sepsis, cath. compl. thrombosis
	2/11/94	III	3/19/94	38 days	Cardiac arrest	Battery disconnected
17201	2/1/94	IV	2/15/94	14 days	PRHF	

PRHF=Progressive right heart failure.
** Originally reported in study 47.
***Originally reported in study 49.

The mean length of survival in study 50 was 28 ± 37 days.

Requests F and G refer to statistical information.

CONCLUSIONS:

1. Survival/Mortality Rates

The most important aspect of this submission is that we have finally received enough information to be able to estimate the mortality rate of PPH patients treated with flolan.

Studies 49 and 50 included only patients of NYHA Class III and IV. These patients had entered their respective study directly i.e. they were not survivors of another study as they were the patients in studies 37 and 47. Their mortality rate must

represent the true early mortality rate of class III or IV PPH patients being treated with iv infusions of flolan.

The mortality rate in study 49 during the first 19 months was $21/128=16\%$ (Table 3). These patients died within 0 days and 10 months after they had entered their study. Most of them (13) had died within 3 months after they had entered the study, exhibiting a 3-month mortality rate of $13/128=10\%$.

The mortality rate during the first 8 months of study 50 was $7/66=11\%$ (Table 4). Six of these patients had died within a month exhibiting a one-month mortality rate of $6/66=9\%$.

If we combine the results of both of these studies together in a meta-analysis, the total mortality rate will be $28/194=14\%$, which represents the early mortality rate of PPH patients of Class III and IV when they are treated with flolan. Ten percent of them ($19/194$) died within 3 months. This finding is in contrast with the results of the pivotal studies of flolan, as reported by the sponsor.

The sponsor reported that 1 of the 11 flolan patients and 3 of the 14 control patients of study 35/36 had died during the 8 week duration of the study. The respective rates in study 46 were: control: $8/40$, flolan: $0/41$ during the 12 week duration of the study, i.e. the combined mortality rate as reported by the sponsor was $11/54=20\%$ for the control and $1/52=2\%$ for flolan.

As I explained in my review of the original NDA submission the results of the pivotal studies 35/36 and 46 are not reliable. In study 35/36, 3 patients who should have been excluded from the study had been entered into the control group and had died during the study. In study 46 the randomization was done by the sponsor, apparently unblinded, after they had received information about all the important characteristics of each patient. All the severely sick patients were "randomized" to the control. Eight of these patients died during the 3 months of the study, while none of the flolan patients did so.

The patients in the pivotal studies of flolan, studies 35/36, and 46, were similar to the patients of studies 49 and 50. These patients were also of Class III and IV PPH patients who had entered their studies directly i.e, they were not

survivors of other studies like the patients of studies 37 and 47. The difference between studies 49 and 50 on the one hand and studies 35/36 and 46 on the other, was that all the patients in the former studies are receiving flolan from the beginning, while only about one-half of the patients in the pivotal studies had received flolan. The other half had been "randomized" to receive only standard treatment. These patients had received no flolan.

Considering the irregularities of the randomizations, it is more reasonable to assume that the patients of the pivotal studies were not randomized at all but they all belonged to one undivided group. The combined mortality rate then of the patients in studies 35/36, and 46 would be: $4+8=12$ deaths among $(25+81)=106$ patients = 11%. This rate is almost identical to the 3-month mortality rate of the combined studies 49 and 50 where all the patients had received flolan, in spite of the fact that in the pivotal studies only one-half of the patients had received flolan.

To Summarize:

	Total Mortality Rate	2-Month Mortality Rate	3-Month Mortality Rate	
Study 49	16%		10%	All patients had Received Flolan
Study 50	11%	9%		
Both studies Combined	14%		10%	
Study 35/36	16%	16%		Only 1/2 of the patients had received flolan
Study 46	10%		10%	
Both Pivotal Studies Together	11%		11%	

The number of patients who participated in these studies was small and solid conclusions cannot be drawn. However, the available data indicate that flolan does not provide any significant benefit for survival to patients with PPH Class III and IV.

Regarding studies 37 and 47, as I mentioned earlier, these studies included the survivors of studies 35/36 and 46. The severely sick patients among the respective populations had already died in the parent studies. The survival rates of studies 37 and 47 represent the survival of moderately and mildly sick PPH patients only. They do not represent the survival of an intact population. The duration of each study is also important as shown below:

<u>Study #</u>	<u>Duration Til</u> <u>March 22, 1994</u>	<u>Mortality</u> <u>Rate</u>	<u>Mean Length</u> <u>of Survival</u> months
37	6 yrs. 7 mos	33%	34 ± 18
47	2 yrs. 3 mos	17%	8 ± 4
49	19 mos	16%	3 ± 3
50	8 mos	11%	0.9 ± 1.2

All the patients had received flolan in all 4 of these studies.

The longer a study lasts the more patients die. On the other hand, the mean length of survival increases because the patients who started the study in better condition die last.

2. The result of the Borg Dyspnea Score and the Nottingham Health Profile may not be interpretable considering that the randomization of the patients in study 46 was biased in favor of flolan.

3. **Withdrawals:**

Unfortunately, we have received very few (3/13) of the CRFs of the patients who withdrew from the flolan studies. We do not know why most of them withdrew their consent. One of the patients, felt much better when the flolan infusion was discontinued.

4. **Side Effects:**

From the CRFs of the patients who died, it appears that during the long-term flolan studies the patients had suffered from nausea, diarrhea, hypotension, SOB, pneumonia, sepsis, hyponatremia, hypokalemia, arrhythmia, thromboembolism,

ascites, bleeding, thrombocytopenia, jaw pain, muscle pain, pump stoppage and death, interruption of flolan flow after heparin flushing and death, renal failure, pulmonary edema, rash, pneumothorax, hemothorax, etc. (Tables 1-4).

It is difficult to distinguish how many of these effects were due to the underlying disease or to the other medications that the patients were receiving or to flolan itself. It is, however, sure that catheter infection and sepsis, pump stoppage and sudden death, and the so-called PGI₂ syndrome (jaw pain, taste bud pain, muscle aches and diarrhea) are caused by flolan and its delivery system.

As study 46 (Table 68 of the original NDA) has shown the use of flolan did not significantly reduce the incidence of PPH symptoms of dyspnea, asthenia, dizziness, palpitations, chest pain or edema and actually increased the incidence of headache, myalgia, and diarrhea. As I noted in my review of the Safety Update of 7/27/94, the longer a patient was treated with flolan, the higher was the incidence of the side effects that he/she suffered. In addition, the dosage of flolan had to be increased as the treatment continued (tachyphylaxis, tolerance). It appears, that as the treatment continues, flolan becomes ineffective (if it ever were effective), and there is always the danger of an accident: abrupt discontinuation of the infusion, severe hypotension and death.

Final Conclusion:

NDA 20-444 has not provided reliable evidence that flolan prolongs the survival of Class III and IV PPH patients or that it significantly reduces the incidence of PPH symptoms.

RECOMMENDATIONS:

Request that the sponsor provide information regarding the patients who were transplanted or withdrew from study 49 and 50:

- a) The date each of them entered the respective study,
- b) the date they were transplanted or withdrawn.

E. Triantas
Elgenie Triantas, M.D., Ph.D.

CC:
NDA 20-444
~~HFD-180~~
HFD-180/SFredd
HFD-180/ETriantas
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
r/d 11/14/94 jgw
f/t 11/22/94 jgw
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SEP 14 1994

NDA: 20-444
DRUG: Flolan, PGI₂

SPONSOR: Burroughs-Wellcome

MEDICAL REVIEW

REVIEWER: E. Triantas, MD, Ph.D.

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

SEP 14 1994

NDA: 20-444

DRUG: Flolan (Epoprostenol, prostacyclin, PGI₂, Cyclo-prostin)

CLASS: Inhibitor of platelet aggregation, vasodilator

PROPOSED INDICATION: Treatment of primary pulmonary hypertension (PPH). Flolan has been classified as a priority and orphan drug for this indication.

SPONSOR: Burroughs-Wellcome

DATES OF DOCUMENTS: 2/28/94, 4/7/94, 5/6/94, 5/27/94. The first document represents the original NDA submission and the others are responses of the sponsor to my requests for information about the randomization method of Study #46.

DATES RECEIVED: 2/28/94, 4/8/94, 5/9/94 and 5/31/94, respectively

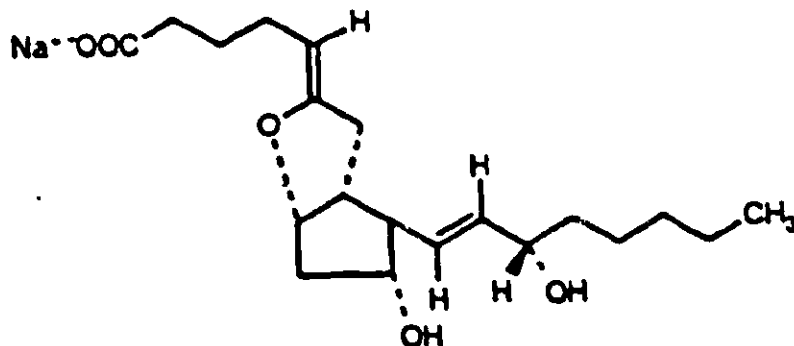
DATES RECEIVED BY MEDICAL OFFICER: 3/3/94, 4/15/94, 5/10/94, 6/2/94, respectively

DATE REVIEW COMPLETED: May 31, 1994 for document of 2/28/94 and April 15, 1994 for doc. of 4/7/94
May 25, 1994 for doc. of 5/6/94
June 2, 1994 for doc. of 5/27/94

DATE REVIEW REVISED: September 9, 1994

CHEMISTRY:

Epoprostenol is a metabolite of arachidonic acid. It is the most potent naturally occurring vasodilatory and platelet aggregation inhibitory prostaglandin. Its structural formula is:



C₂₀ H₃₁ NaO₅; Molecular Weight: 374.45

Flolan is supplied as a sterile lyophilized powder to be used for iv administration. It is provided in vials containing the equivalent of 0.5 mg or 1.5 mg of epoprostenol. The vials contain in addition _____ mg of glycine, _____ mg of sodium chloride and _____ Sodium hydroxide is used to adjust the pH, if needed.

Before administration the powder must be reconstituted to 50 ml with sterile diluent especially provided. This diluent contains 94 mg glycine, 73.5 mg sodium chloride, NaOH to adjust the pH and water for injection. The reconstituted solution of flolan has a pH of 10.2 to 10.8 and is increasingly unstable at a lower pH. Epoprostenol is rapidly hydrolysed at neutral pH in the blood and is also broken down enzymatically.

Flolan is synthesized by the

TOXICOLOGY:

The I.V. LD₅₀ has been found to be:

Mice: >100 mg/kg
Rats: 66.3 mg/kg

Subchronic I.V. Toxicity:

Rats (5M, 5F): Infusions of flolan at 0, 56, 180, and 560 ng/kg/min for 14 days induced hyperemia of the extremities, temporary body weight loss in males at the middle and high dose and a decrease in platelet counts at all dosages in both sexes.

Dogs (2M, 2F): Infusions of flolan at 12.5, 40, and 125 ng/kg/min into beagle dogs for one month caused transient emesis, and soft feces at the high dosages and intussusception of the ileum in one high dose male and one high dose female. The 12.5 ng/kg/min dose was a no effect dose. The G.I. symptoms abated after 6 (males) and 9 (females) days. The 40 and 125 ng/kg/min doses caused, in addition, marked decreases in circulating platelets and minor decreases in leukocyte counts. Large immature platelets were also seen in the circulation by electron microscopy. ADP-induced platelet aggregation at the end of the study was markedly increased in a dose related manner. All changes were reversible.

Rhesus Monkeys (2M, 2F): I.V. infusions of flolan at 0, 0.01, 0.1, and 1 µg/kg/min for 1 hour every other day for 2 weeks indicated that the 0.01 dose was the no effect dose. The highest dosage induced hypotension, emesis, defecation, tachycardia, increased bleeding time, marked inhibition of platelet aggregation, hyperglycemia, and glycosuria. In one high-dose monkey a small

focal area of degenerate and necrotic tissue was noted in one papillary muscle. The hearts were normal in the other 3 monkeys of this group.

Subchronic S.C. Toxicity:

Rats (2F): Doses of 1, 10, 30, and 60 mg/kg/min for 7 days induced hypotention, myocardial ischemia (ST segment depression, increased amplitude of S wave), and subendocardial myonecrosis in the left ventricle; they also caused prostration and marked reddening of the ears and feet.

A male Patas Monkey was given single S.C. injections of epoprostenol at 1, 10, 30, 60 and 60 mg/kg in consecutive days. Each dose produced inactivity, facial flushing, facial perspiration, hypothermia, hypotention, tachycardia, and decreased bleeding time. Several focal areas of necrosis were found in the papillary muscles of the left ventricle.

Fertility, Teratogenicity:

No effect was found at doses of 0, 10, 30, and 100 µg/kg/day s.c. in rats.

Mutagenicity:

The Ames test, the mouse micronucleus assay, and the alkaline elution DNA damage assay were negative.

Effect of 6-Keto-PGF_{1α}:

This hydrolysis product of prostacyclin was administered i.v. into Patas Monkeys at 1µg/kg/min for 60 minutes, 3 times/week, for 2 weeks. No adverse effects were noted.

PHARMACOKINETICS IN ANIMALS:

Metabolism: PGI₂ is rapidly hydrolysed and extensively metabolized. It is most stable at pH 10 or greater. It becomes rapidly hydrolysed at physiological pH to 6-keto-PGF_{1α}, which is 1000 times less potent than PGI₂. The 6-keto-PGF_{1α} is further metabolized to 2,3-Dinor-6-keto-PGF_{1α} and 13,14-dihydro-6,15-diketo PGF_{1α} glucuronide and other compounds. A total of 12 metabolites have been identified in the urine of monkeys. Because of the extreme instability of PGI₂, it is very difficult to develop a biological assay for it.

The plasma $T_{1/2}$ in rabbits has been found to be <3 min;
in cats 1.29-1.52 min;
in dogs 14 min;

Clearance: rabbit: 93 - 256 ml/min/kg
Vd: rabbit: 357-1015 ml/kg

Steady State: Rabbits: within 15 minutes
Cats: <60 min
Dogs: <10 min.

Tissue Distribution in rats: Fifteen minutes after I.V. or S.C. administration of ^3H -epoprostenol sodium at $\mu\text{g}/\text{kg}$, tritium concentrations in the tissues declined rapidly. The highest levels of tritium were found in the liver (31%), kidney (4%), and small intestine (9%). The lowest concentrations were found in the brain and adipose tissue. Ten days after dosing only 0.21% of the administered radiolabel remained in the body. This label was uniformly distributed among the tissues indicating no accumulation in any particular tissue.

HUMAN PHARMACOLOGY:

Pharmacokinetics:

Due to the lack of a sensitive, specific, and precise analytical method for the determination of PGI_2 in the plasma, conventional pharmacokinetic studies have not been done. The sponsor maintains that the use of radiolabelled PGI_2 is not appropriate due to the size of the required dose and the possibility of tissue incorporation of radioactivity into the endogenous PGI_2 . Tritium labelled Cyclo-prostin was administered into 3 male volunteers by continuous infusion for 24 hours at the rate of 4 ng/kg/min. Over 90% of the radioactivity was recovered in the urine within 24 hours. HPLC and mass spectrometry revealed the presence of at least 16 metabolites. Ten of these were characterized. All these metabolites had been previously found in dogs, rats and monkeys.

The hemodynamic effects of flolan end within minutes of terminating the infusion indicating that PGI_2 has a very short $T_{1/2}$ life and a rapid clearance. Continuous infusion is required in order to maintain an effective concentration of flolan in human patients. Based on in vitro studies with human blood and plasma, the mean in-vivo $T_{1/2}$ in man cannot be longer than 6 minutes and it may be as short as 2-3 minutes.

Pharmacodynamics:

has conducted 4 Phase I trials in 41 normal

volunteers. Burrows-Wellcome has conducted one Phase I study in 6 uremic patients (see Table below). In addition, about 60 Phase I studies have been performed by independent investigators in various countries.

The studies showed that infusions of 0.1 to 4 ng/kg/min of flolan had little or no effect on the blood pressure and heart rate in normal volunteers. At rates of 5 to 15 ng/kg/min flolan increased the HR and decreased the diastolic blood pressure. The effect on

PHARMACODYNAMIC STUDIES

Study #	Year	Objective	Design	Performed by _____ and Burroughs-Wellcome		
				Number of Pts.	Infusion Rate (ng/kg/min)	Duration
1059*	1979	Min. Eff. Dose Max. Toler. Dose	Uncontrolled	27	0.15-15 0.5-6	30, 60m 6, 24h
1066*	1983	Metabolism	Uncontrolled	3	4	24h
1067*	1981	Blood Levels	open contr. randomized	5	0, 0.1	6h
1099*	1982	Effect on Platelets	Double-Bl contr., cross-over	6	0.2, 5	72h
BW 01**	1981	Effects in uremic pts.	Open, contr.	6	2, 4, 8	60m

*Studies performed by
**Study performed by Burroughs-Wellcome
m=minutes
h=hours

the systolic pressure was variable. Peak effects occurred within a few minutes of the start of the infusion and were maintained for the duration of the infusion. Cardiac output was increased at dosages >5 ng/kg/min. Similar results were observed in patients with chronic renal failure. The cardiovascular parameters returned to the preinfusion levels within 30 minutes of the discontinuation of the infusion.

Platelet Effects: Infusions of flolan at 3-5 ng/kg/min in normal volunteers shifted the ADP-induced platelet aggregation dose-response curve 1.6 to 1.8 fold to the right i.e. the platelets became less sensitive to the aggregatory action of ADP. The effect was dose related. The threshold dose was 3-5 ng/kg/min. Consistently significant elevations in intracellular AMP were found at infusions of 8 ng/kg/min. Platelet counts were found to be elevated during several infusions of 4 to 10 ng/kg/min.

The response of cyclic AMP to flolan diminished as the duration of the infusion continued. After 72 hours at 5 ng/kg/min platelet AMP lost approximately 50% of its responsiveness to PGI₂. Paralleling the effect on cyclic AMP, platelet aggregation response to ADP was found to have been reduced after 24 and 48 hours of continuous infusion. This response was found to have returned to the baseline after 48 to 72 hours of infusion. Platelet hyperaggregability to ADP was observed 6-24 hours after discontinuation of infusions of PGI₂. Platelet sensitivity to ADP returned to control levels 48 to 72 hours after the discontinuation of the infusions. In 3 volunteers in whom 5 ng/kg/min PGI₂ infusions were decreased gradually over a 12 hour period, hyper-aggregability of the platelets was not observed.

Side Effects: Flushing, headache, jaw pain, arthralgias, fatigue, irritability, anorexia, tachycardia, nausea, abdominal pain, hypotension, restlessness. The effects were dose-related. All disappeared within 30 minutes after discontinuation of the infusion.

Infusion of flolan at 5 ng/kg/min and higher increased plasma renin activity in normal volunteers and uremic patients.

CLINICAL TRIALS ON PRIMARY PULMONARY HYPERTENSION (PPH):

Primary pulmonary hypertension is a very rare disease. It accounts for about 1% of all cases of cor pulmonale identified at autopsy. An extensive study on the natural history of the disease was carried out at the Mayo Clinic. One hundred and twenty (120) patients were diagnosed by strict clinical and homodynamic criteria between January 1955 - April 1977 and were followed up to 1983 (Circulation, 70:580, 1984). In another, prospective, multicenter, observational study sponsored by NIH (National Registry), 194 patients with PPH were enrolled at 32 centers in the USA from July 1981 to September 1985 and were followed through 1988.

An accurate number is not known, but it is estimated that approximately 400 cases of PPH are identified each year in the USA. Most cases are sporadic but during the past few years about 25 families have been reported in which the disease seems to be hereditary (autosomal dominant).

The disease is identified by 1) clinical, radiographic, and electrocardiographic manifestations of pulmonary hypertension; 2) demonstration of mean pulmonary arterial pressure ≥ 25 mm Hg, pulmonary vascular resistance >67 dynes/sec/cm⁵ (or $>0.05R$ units; 1 R unit=1328 dynes) in association with normal pulmonary wedge pressure and a nearly normal or low cardiac output; and 3) by the inability to find a cause for the pulmonary hypertension in a disorder of the heart, lungs or systemic circulation.

In its early stages the disease is difficult to recognize. It usually takes about 1.9-2.0 years until a diagnosis of PPH is made because the first symptoms (dyspnea on exertion, easy fatigability, and chest discomfort) are often discounted. Prognosis is poor. The disease is fatal due to progressive right heart failure. On the average death occurs approximately 3 years after the onset of symptoms. However survival varies significantly by NYHA functional class with 4.9 yrs as the median survival time for classes I and II, 2.6 yrs for class III and 0.5 yrs for class IV. A few patients have been reported to have lived for as long as 30 years. In at least one reported case PPH appeared to regress (Brit. Heart J., 38:264, 1976). At the present there is no specific treatment for PPH.

Burroughs-Wellcome has supported 7 studies on PPH, 2 Phase II (#5/10, #20) and 5 Phase III (#21, #35/36, #37, #46, #47). Two of the studies were controlled (#35/36, #46) but all the others were uncontrolled (Tables Cl₁ and Cl₂).

All the studies were open-labelled. None of them was double-blind. The sponsor decided that chronic intravenous infusions of placebo would be inappropriate given the known risks associated with a central venous catheter and the absence of expected benefit from placebo. An effort was made in one of the controlled studies (#46) to keep the persons administering the "walk" test unaware of whether the evaluated patient was receiving flolan or standard therapy alone.

TABLE Cl,
CLINICAL STUDIES ON PPH
Supported by Burroughs-Wellcome

Controlled Studies

Study #	Investigator	Stratification Criteria	Design	Stress	Duration	NYHA Class	#Pts		Flolan Dose (ng/kg/min)
							F	C	
35	Rubin	Use of oral Vasodilator	Controlled open Parallel random.	1. Dose- Rang. 2. Long- Term	1-2 h 8 wk	II	1	1	2-12 4, 6
36	Rubin Barst McGoon	Use of oral Vasodilator	as above	as above	1-2 h 8 wk	III IV	8 2	7 6	2-22 2-12
46	17 centers incl. those of investig. listed above	Use of oral vasodilator, NYHA class, Study center	as above	as above	1-2 h 12 wk	III	31	29	22-20

TABLE Cl, (continued)

Study #	Distance Walked, Difference from Baseline (meters)		Hemodynamic Effects of Flolan		Hemod. Effects Sign. Diff. Between Groups	Nottingham Profile Sign. Diff. Bet. Groups	Deaths F C
	F	C					
35/36	73	-5	TPR TSR SVR PAPs	CI CO	PAPs TPR favoring flolan	Physical Mobility	2 ^a 3
46	30	-50	TPR TSR SVR PVR SAPd PAP RAP	CI CO S V AS MVS Tc ₂	CI, CO, SV, PAP, PVR, TPR SAP, SVR, TSR, Arter. satur. in favor of flolan.	emotions energy, sleep home care, vacations	0 8

Deficiencies

35	Open, bias in rand. & discontin. of pts. favoring flolan, ineligible patients, deaths due to cardiac catheterization. Investigator interference with walk test.	F=flolan
46	Open, bias in random. & discontin favoring flolan. Deaths due to electrolyte imbalance, dig. toxicity. Investigator interfer. with questionnaires. Lack of clin. chem. hematology and ECG data.	C=control

TABLE C1,
CLINICAL STUDIES ON PPH
Supported by Burroughs-Wellcome

Uncontrolled Studies:

Study #	Investigators	# Pts.	Duration	Study Period	Flolan Dose ng/kg/m)	Hemod. Effects	Outcome
37 ¹	Rubin, Barst, McGoon, Caldwell	(10F+8C)*	til transpl. or death	8/87- ongoing	9-52	↑ CI CO SV PAP PaO ₂ SOT ↓ PVR SVR TSR	4-D 8-T -
47 ²	The same 17 investigators as in study 46	(38F+26C)*	as above	ongoing			8-D 7-T
5/10	Rubin, Groves, Montenegro		2-41h	10/80 - 1/82	2-12	↑ CI CO HR ↓ PVR TSR TPR SAP	
20	Rubin, Groves		1-5h	6/82 - 11/86	2-12	↑ CI CO SV PCUR SUI HR ↓ PVR TSR TPR SAP SVR PAP	
21	9 invest.		1-96h 15, 58d	7/82 - ongoing	2-170	↑ CI CO SV PaO ₂ HR ↓ PVR TSR TPR SAP PAP Respir. RAPM	6-D

¹ = Uncontrolled extension of Study 35-36

² = Uncontrolled extension of Study 46

F = Flolan

C = Control

D = Died

T = Transplanted

*Former flolan or control patients

3

A. Controlled Studies

1. BW Study 35/36, (Phase III; Table Cl.)

Title: Multicenter Evaluation of Long-Term Flolan Infusions in Patients with Primary Pulmonary Hypertension (PPH)

Investigators/Affiliation and Number of Patients:

	# pts.	
	<u>Flolan</u>	<u>Stand.</u>
Lewis Rubin, MD, U. of Maryland Hosp., Baltimore	7	9
Robyn Barst, MD, Columbia Presbyterian Hosp. New York	2	4
Michael McGoon, MD, Mayo Clinic, Rochester	3*	1
Total	12	14

*includes non-randomized pt

Patients: Patients with PPH, NYHA Class I and II, were screened and entered into study 35 and those of Class III and IV were entered into study 36. It was expected to recruit 20 patients into each of these studies. Patients completing these studies had the option to enter Study 37 and be treated with continuous infusions of flolan until they received a lung transplant or they died.

Period of Study: April 10 1987 - February 28, 1990

Termination of Study #35: Study #35 was prematurely discontinued on April 27, 1988 due to the occurrence of serious life-threatening (embolism) and/or fatal events in two flolan patients in study #36 and one flolan patient in study #37 (the uncontrolled study which was run concurrently with Study #35/36). The sponsor and the investigators decided that the potential benefits of flolan infusion might not outweigh the risks of the serious adverse experiences which are associated with the flolan delivery system, in less ill patients with PPH NYHA Class I and II disease. Study #35 was discontinued after two patients were recruited. The results of these two patients were combined with the results of the patients in Study #36.

Inclusion Criteria:

Age: 6 months to 70 yrs

Confirmation of diagnosis of PPH:

PAPm ≥ 25 mm Hg
Total pulmonary resistance (TPR) ≥ 5 or pulmonary vascular resistance (PVR) ≥ 3 mm Hg/liter/min.
At least a 10 mm Hg gradient between PAPm and PCWPm
Right ventricular hypertrophy with ECG and ECHO revealing a normal mitral valve and normal left ventricular function.

Exclusion Criteria:

Pregnancy or breast feeding.
Supine systemic blood pressure outside of 80-150 mm Hg systolic or 50-100 mm Hg diastolic.
Resting HR outside 60-120 beats/min
Arrhythmias
Abnormal Lab values
Significant other illness
Pulmonary embolism verified by ventilation/perfusion scan or angiogram.
Use of Flolan within 60 days preceding the study.

Efficacy Parameters:

1. Primary: Exercise capacity (6-minute walk = the distance a patient could walk back and forth along a level measured corridor in 6 minutes).
2. Secondary: Hemodynamics (measurements of heart rate, pulmonary and systemic blood pressures including capillary wedge pressure, vascular resistance and cardiac output).
3. Tertiary: Blood Gas Measurements [pulmonary arterial CO₂ tension (PaCO₂), pulmonary arterial oxygen tension (PaO₂), arterial pHa, & arterial oxygen saturation, mixed venous blood gases (PvCO₂, PvO₂), pHv, & mixed venous oxygen saturation].
4. Derived Parameters (total pulmonary resistance, total systemic resistance, pulmonary vascular resistance, systemic vascular resistance, arteriovenous oxygen difference, stroke volume, systemic oxygen transport, stroke work index).
5. Subjective well-being was assessed using the Nottingham Health Profile (Copy of Questionnaire attached. Table 35/36).
6. Survival.

Safety Parameters:

Physical examination, ECG, clinical chemistry, hematology and coagulation tests, platelet aggregation at selected sites,

hemodynamic values and adverse events.
(Schedules of Events attached, Table 35/36₂).

Study Design: Open, controlled, parallel, randomized, multicenter. According to the protocol the study included 4 phases:

1. Screening (Days 0 and 1)
2. Baseline (Day 1; compliance with inclusion and exclusion criteria and Dose-Ranging segment #1).
3. Treatment: long-term infusion segment (Day 1-57) and Dose-Ranging Segment #2 (Day 57)
4. Post-treatment (Days 57-64: no flolan; Dose-Ranging Segment #3 on Day 64).

Patients completing Study 35/36 were allowed to enroll in the continuation study #37, if they wished.

Flolan Administration:

Flolan was administered continuously by a portable, positive pressure infusion pump through an indwelling intravenous catheter placed either centrally (in most patients) or peripherally.

Dose Ranging Segment #1:

During the dose-ranging segment #1 all patients received 10-20 minute infusions of flolan doses as follows: 2, 4, 6, 8, 10, and 12 ng/kg/min. Doses greater than 12 ng/kg/min were administered only when the 12 ng/kg/min dose was well tolerated and the investigator was of the opinion that higher doses could provide further hemodynamic improvement without posing undue hazard to the patient. The dose-ranging procedure could be cut short if: a) a serious side effect appeared, b) a change in the mean SAP of more than 40 % of baseline value occurred, c) mean SAP fell to <55 mmHg, d) heart rate changed to <60 or >130 beats/min or to greater than 40% of baseline value, or e) ECG changes (0.1 mv depression or greater, downward sloping or horizontal ST segment, etc) were observed.

Randomization:

Upon completion of Dose-Ranging Segment #1, the investigator contacted Burroughs Wellcome personnel who provided the patient number and the treatment assignment. Numbers were assigned consecutively across all study sites. Patients were stratified according to the use of oral vasodilators at baseline using a code (in blocks of 4) generated by the Department of Statistics

of Burroughs Wellcome. Patients who had used oral vasodilators for at least the past 60 days were assigned ascending numbers (1, 2, 3, ...). Patients who had not used vasodilators were assigned numbers in descending order (20, 19, etc.).

Long-Term Infusion Segment: flolan was infused continuously during the 8-week Treatment Phase to the patients who were randomized to flolan at the maximum effective dose, the dose which elicited the greatest reduction in pulmonary resistance during dose-ranging, while maintaining systemic oxygen transport at or above baseline. Dose decreases or increases were implemented when serious side effects appeared or when less than the maximum effect was obtained, respectively. The patients were instructed how to prepare the flolan solution aseptically and how to care about the pump and the catheter. Then, they were sent home with instructions to call the investigator whenever there was a problem. The patient's local physician was advised about the protocol. The patients were also contacted independently every week by the investigator to assess the occurrence of adverse events and obtain information about concomitant medication. These patients received, in addition, the standard treatment for PPH (digitalis, anticoagulants, diuretics, oral vasodilators, oxygen, electrolytes). The patients who were randomized to "no flolan" received only the standard treatment.

During Dose-Ranging Segment #2, patients randomized to flolan had their dose increased from the last long-term infusion rate in increments of 2 ng/kg/min until a new maximum tolerated dose was reached. After reaching the maximum tolerated dose, the infusion rate was decreased every 10-20 min in decrements of 2 ng/kg/min. According to the protocol the aim was to decrease the dose to 0 ng/kg/min. However, patients exhibited significant deterioration of hemodynamic parameters and/or worsening of PPH symptoms when flolan was discontinued and Phase #4 was not implemented.

Protocol Amendments:

1. Protocol #36 was amended in April 1987 to forgo randomization of the first patient. This patient was given flolan in order to establish the logistics of administering flolan continuously.
2. Both the 35 and the 36 protocols were amended in June 1987 to
 - a) include women of childbearing potential only, if they were practicing a method of birth control acceptable to the investigator
 - b) clarify dosing terminologies.

RESULTS:

Twenty-six patients suffering from PPH were recruited for these studies (35/36). All 26 patients received flolan in dose ranging Segment #1 according to the protocol. After completing this segment the patients were randomized. One of the 26 patients developed pulmonary edema during Segment #1 and was considered ineligible to enter the study. As mentioned earlier, the first patient was not randomized but was assigned to flolan in order to establish the logistics of the continuous administration of flolan. The remaining 24 patients were randomized according to the code. Eleven received flolan (plus standard treatment) and 14 received standard treatment alone.

Demographic Characteristics at Baseline:

The baseline characteristics of the patients are shown in Table 35/36. The patients were mostly females (64% flolan, 79% standard), relatively young (flolan 37 yrs, standard 33 yrs) and predominantly white (100% flolan, 79% standard). Most of them (73% flolan, 50% standard) belonged to NYHA Class III. Eighteen percent of the patients who received flolan and 43% of those who received standard treatment belonged to Class IV; 46% and 43% respectively were using oral vasodilators at baseline. Statistical analysis of these data is not provided.

Premature Discontinuations:

Only 17 of the 21 patients who completed the Long-Term Segment (8 on flolan and 9 patients on standard therapy), were entered into the Dose-Ranging Segment #2. Two flolan patients did not complete this segment because of technical problems with the Swan-Ganz catheter; two patients on standard therapy did not complete this segment either: one had problems with the catheter and the other withdrew his consent.

Patient . . . who was randomized to standard treatment, died on Day-57 following the 6-minute walk but before the right heart catheterization.

Patients excluded from Efficacy Analysis:**6-minute Walk**

No patient was excluded from the initial analysis. One patient was excluded from a secondary analysis. This patient (standard therapy) could not walk at baseline, Day 2 or Day 29 due to severe symptoms of PPH. On Day-56 this patient could not walk because of symptoms of severe gout rather than symptoms of PPH.

Hemodynamics:

Dose ranging #1: Data were missing from several patients
Long-term Segment: data from 6 patients were excluded:
3 pts had problems with the Swan-Ganz catheter
1 withdrew consent
2 pts received unknown doses of flolan due to pump malfunction

Dose-ranging #2: data from 6 pts were not included in the analysis because of incorrect flolan doses;
1 pt died before entering this segment.

Nottingham Health Profile:

No data were excluded.

Protocol Deviations:

Inclusion Criteria: Three flolan patients and 3 patients on standard therapy alone were assessed outside of scheduled time. In addition, for 1 flolan pt rt. ventricular hypertrophy was not assessed at the study site.

6-minute Walk: 14 pts were tested only once instead of twice during the screening phase. A practice walk was supposed to be conducted on the same day at least one hour before the test on screening day and Days 2, 29, and 56. Practice walks were not performed in 23 patients. Seven pts on standard therapy and 3 pts on flolan were receiving oxygen during the walk.

Baseline walking exercise was not performed in one pt. on standard therapy inadvertently. The first exercise test for this pt was done on Day 8 and this value was used as baseline.

Exercise capacity at Day 56 was evaluated in 21 patients, 10 on flolan and 11 on standard therapy. One on flolan and 2 pts on standard therapy had died before Day 56, and one pt. on standard therapy was unable to walk on Day 56.

Hemodynamics: As mentioned earlier, according to the protocol flolan should have been withdrawn from all patients after completion of the long-term treatment segment. However, withdrawal of flolan from the first 5 patients resulted in deterioration of hemodynamics and/or PPH symptoms (increases in PAP, RAP, decrease in mixed venous O₂ saturation), and appearance of side effects (agitation, syncope, dyspnea, chest

pain) and was not attempted for the remaining pts. Dose-Ranging Segment #2 was completed for 15 of the patients only but not according to the protocol (infusion rate was not tapered to 0; the rate was not increased before being tapered off).

Dose-Ranging Segment #3 was not performed in any of the patients.

Flolan Dosage:

Acute Dose-Ranging Segments:

The infusion rate increased from 2 to 22 ng/kg/min (in some patients). The mean value of the maximum Tolerated Dose (MTD) for the flolan group was 9.8 ng/kg/min during Segment #1 and 10.3 ng/kg/min for Segment #2. The respective values for the standard group were 8.0 and 9.7 ng/kg/min. The differences were not statistically significant.

Long-Term Infusion Segment:

The infusion rate during this period varied from 2 to 12 ng/kg/min in individual patients. The mean and median values for the last day of every week are shown in Table 35/36₄. These values were fairly stable. They varied from 7.2 to 7.4 except for the first week when they were lower (4.6 ng/kg/min). The reasons for changing the infusion rate were adverse experiences (decreasing the rate) and to improve the hemodynamic parameters and PPH symptoms (increasing the rate). Adjustments of flolan infusion rates were common during the first week. Adjustments were made in 9/11 patients.

There were several interruptions of the infusion during the Long-Term Infusion Segment due mainly to pump malfunction (5 times, all in one patient), accident (3 cases), incorrect position of catheter, or formation of clot in catheter (2 cases each).

Concomitant medications (Table 35/36₅):

The patients continued to receive their standard treatment for PPH. The investigators were advised to maintain each patient in either group on the same standard therapy throughout the long-term period. However, doses were adjusted and therapies added or discontinued as clinical necessity required.

Most flolan patients received anxiolytic drugs (7), oxygen (7), oral anticoagulants (6), diuretics (6), analgesics (5), electrolytes (5), antacids (5), and vasodilators (5). Most

patients on standard therapy received anticoagulants (11), oxygen (9), analgesics (8), anxiolytics (8), diuretics (8), vasodilators (8), antitussives (5) and electrolytes (5). Generally, more patients (83%) on standard therapy than on flolan (67%) used concomitant medications during the study and more of them used analgesics, anticoagulants, antitussives, digoxin and Ca⁺⁺ channel blockers.

The medications which were used at least 75% of the time by most of the patients were the anticoagulants, the diuretics, and the electrolytes. Oral vasodilators were discontinued shortly after initiation of long-term flolan infusions in 4 out of 5 patients. Oral vasodilators were added to the therapy of 2 standard therapy patients for at least 75% of the period. Oxygen was administered to 36% of the flolan and to 64% of the standard patients.

Antibiotics were given to 27% of flolan patients and to 21% of patients on standard therapy. Four courses of therapy were given to 3 patients from each group.

Efficacy Results:

Exercise Capacity:

The 6-minute walking test was conducted 4 times during the study: once during the Baseline Phase and 3 times during the treatment period on Days 2, 29, and 56. The patients walked on a level, uncrowded, enclosed hospital corridor. A physician was present, who gave encouragement and measured the distance walked. Practice walks were not conducted by the majority (23) of the patients.

Distance Walked in 6 minutes

	<u>N</u>	<u>at Baseline</u>	<u>Day 56</u>	<u>p</u>
Flolan Patients	11	213	386*	0.045
Standard Therapy Pts	14	253	248*	
Pts Receiv. Vasodilat.	11	221		
Not Receiv. Vasodil.	14	217		

*Adjusted for vasodilator use at baseline.

For the analysis of the exercise capacity patients with missing data were assigned the lowest rank. The results showed that the exercise capacity of the flolan patients improved while the capacity of the patients on standard therapy decreased slightly. The difference was statistically significant (p=0.045). When the patient who could not walk on Day 56 was excluded from the

analysis, the exercise capacity of the patients on standard therapy improved slightly, and the between treatment difference was not statistically significant ($p=0.07$). When the data were analyzed using analysis of variance with the last observation carried forward for patients with missing data, mean exercise capacity improved by 139 meters in the patients who received flolan and only by 28 meters in the patients who were treated with standard therapy alone ($p=0.043$, Table 35/36_g). The values were adjusted for baseline walk and baseline vasodilator use.

In another analysis patients with missing data were excluded and comparisons of the change from baseline to Days 2, 29, and 56 were performed with paired observations. Consequently the number of observations was different at each evaluation time. Table 35/36_g shows that the exercise capacity of the flolan patients improved significantly from baseline on Days 2 and 56 by a mean of 83 and 141 m, respectively. No significant improvement was shown by the patients on standard therapy. The exercise capacity of these patients increased only by 3 and 36 m on the respective days.

Hemodynamic and Gas Values:

Baseline

The hemodynamic and gas values of the patients at baseline are shown in Table 35/36_g. The groups seem to have been comparable regarding percent arterial and mixed venous saturation, arteriovenous oxygen difference, cardiac index, cardiac output, arterial and venous CO₂ pressure, mean and diastolic arterial pressures, wedge pressure, venous oxygen pressure, pulmonary vascular resistance, right atrial pressure, and stroke work. However, the between groups differences were rather large regarding the systolic pulmonary arterial pressure (12%), the mean systemic arterial pressure (11%), the systolic systemic arterial pressure (14%), the systemic vascular resistance (21%), and total systemic (21%) resistance.

Statistical analysis of these differences has not been provided.

Dose-Ranging Segment #1:

There was considerable variation regarding the effect of flolan dosage on the hemodynamic parameters. Generally, the following significant changes were observed at the maximum tolerated dose in both groups (from Table 35/36_g):

<u>Increases</u> (amount)	<u>Decreases</u> (amount)
cardiac output (1.1-1.2 L/min)	AVO ₂ D (2.1-2.9 ml/dl)
cardiac index (0.65 L/min/m ²)	PVCO ₂ (2.0-4.7 mm Hg)
Heart Rate (8-9 bpm)	PVR (2.3-4.7 Wood U)
Mixed venous satur. (10-16%)	SAPm (7.3-14.1 mm Hg) Hg)
PVO ₂ (4.6-12.9 mm Hg)	SAPd (7.0-14.5 mm Hg)
SOT (224 ml/O ₂ /min)	SVR (8.6-13.1 Wood U)
SV (stroke volume; 8.2-8.7 ml/beat)	TPR (4.3-7.7 Wood U)
	TSR (9.2-14.1 Wood U)

In addition, flolan decreased the systolic systemic arterial pressure (SAPs) by 13.4 mm Hg in the standard group.

Flolan did not significantly affect the pulmonary blood pressures during the Dose-ranging Segment.

Similar results were obtained during Dose-Ranging Segment #2.

Long-Term Treatment:

Differences from Baseline: Table 35/36₁₀ shows the mean and median values of the hemodynamic and blood gas measurements of the two groups during baseline and during Day 57. Table 35/36₁₁ shows the differences between these two sets of measurements.

Statistical analysis of these results indicated that by the end of the 8th week flolan had significantly:

<u>Reduced</u>	<u>Increased</u>
TPR (-5.92 W U),	Cardiac index (0.31 L/min/m ²)
TSR (-5.42 W U),	Cardiac output (0.51 L/min)
SVR (-5.69 W U),	
PAPs (-14.50 mmHg)	

relative to baseline. During the same period the patients on standard treatment experienced a significant decrease in:

SAPd (-7.18 mm Hg), and
SAPm (-8.55 mm Hg)

Differences between Groups: Table 35/36₁₂ shows the comparison of the differences from baseline to Day 57 between the two groups. The only significant differences between the two treatments were:

a) a greater reduction (-12.50 mm Hg) in PAPs induced by flolan compared to the reduction induced by the standard treatment (-5.0 mm Hg)

and b) a reduction in total pulmonary resistance (TPR) by 2.93 Wood units caused by flolan, while the patients on standard treatment experienced an increase of 0.90 Wood units from baseline.

Nottingham Health Profile:

The sponsor reported that physical mobility was improved more in the patients treated with flolan than in the patients treated with standard therapy ($p=0.0197$). No significant differences between the groups were found regarding the other dimensions of the Nottingham Health Profile (energy, pain, emotional reaction, sleep, work, social life, or hobbies). It is not explained, however, how the sponsor arrived at the scores that are shown on Tables 46 and 47 from the "yes" or "no" answers of the patients on the Questionnaire.

Survival:

The sponsor has reported that during the 8-week treatment period one patient on flolan therapy and 3 patients on standard treatment died. The difference is not statistically significant ($p=0.39$ long-rank test).

Adverse Reactions:

Dose-Ranging Segments:

The most frequent adverse reactions which occurred during the dose-ranging segments are shown in the next page:

	Number of Patients	% of Total Number of Patients
Flushing	21	81
Headache	19	73
Nausea	8	31
Dizziness	6	23
Abdominal Pain	3	12
Anxiety	3	12
Jaw Pain	3	12
Dyspnea	3	12

The most serious of these events were as follows::

<u>Adverse Event</u>	<u>Number of Patients</u>	<u>% of Total Number of Patients</u>
Dizziness	3	12
Nausea	2	8
Agitation	1	4
Asthenia	1	4
Chest Pain	1	4
Headache	1	4
Malaise	1	4
Pneumothorax	1	4
Supraventricular tachycardia	1	4
Tachycardia	1	4
Vomit	1	4
A. Pulmonary Edema	1	4

The pneumothorax and the acute pulmonary edema required hospitalization. Both patients died.

The following adverse events required limitation of dosage:

<u>Adverse Event</u>	<u>Number of Patients</u>	<u>% of Total Number of Patients</u>
Headache	14	54
Flushing	14	54
Nausea	7	27
Dizziness	5	19
Dyspnea	3	12

Long-Term Infusion Segment:

The adverse reactions which were observed during the Long-term Infusion Segment are shown in Table 35/36₁₃. For flolan, the most frequent of these events were flushing (84%), and headache (73%), dizziness (54%) and nausea (63%), dyspnea (54%), asthenia (36%), diarrhea (27%), and pain at the injection side (27%). Some of these cases were life threatening (Table 35/35₁₄).

For the patients on standard treatment the most frequent adverse reactions were dyspnea (50%), asthenia (36%), peripheral edema (28%), dizziness (28%), headache (21%), palpitations (21%), nausea (14%), chest pain (14%).

The most serious and life threatening event was dyspnea which was equally frequent in both groups (36%), asthenia (29% in the standard and 9% in the flolan group), nausea (18% in flolan and 7% for the standard treatment), chest pain (18% in the flolan and 7% in the standard). Flushing was life threatening in 18% of the flolan cases. Flushing was not observed in the standard group.

Adverse Experiences associated with Adjustment of Flolan Dose:

Tachycardia, flushing, dizziness, dyspnea and two episodes of nausea.

Adverse Effects Associated with the Flolan Delivery System:

These included:

1. Experiences resulting from the inadvertent administration of a bolus during changing of syringes which caused severe hypotension and bradycardia or tachycardia, flushing and dizziness, dyspnea, nausea, sweating and/or tinnitus.
2. Experiences associated with the infusion pump malfunction: dyspnea, syncope, headache, and nausea.
3. Experiences associated with catheter placement: clotting, infection, bleeding. Eight patients had 27 experiences associated with catheter and tubing. One patient had 8 serious adverse effects (fever, pain and irritation at the insertion site twice, chest pain, increased cough and dyspnea) and another patient had a CVA (clot from the catheter).

Catheter infections included systemic infection (only one patient on standard therapy developed sepsis due to catheterization during dose-ranging), local infection and irritation at the catheter site (3 flolan patients).

**Treatment Emergent
ECG Abnormalities:**

	Flolan	Standard
Junctional tachycardia	1 (10%)	0
Right atrial enlargement	1 (10%)	0
First degree AV block	1 (10%)	0
Nonspecific ST-T wave changes	2 (20%)	1 (8%)
Other	1 (10%)	

Deaths:

One flolan pt., a 21 y.o., Class IV WM, has been reported to have died from cardiac arrest two weeks after entering the study. This pt. was assigned to flolan per protocol (to work out the logistics of flolan infusion). Post-mortem examination revealed pulmonary occlusive disease.

It appears that another flolan patient, a 27 y.o., NYHA Class IV, WF died because of the study. This patient was diagnosed as having developed "prostacyclin-induced severe pulmonary edema" during the 1st Dose-Ranging segment on 10/18/88 and was discontinued from the study because of the complication. She died on 11/18/88, one month later (Vol. 1.76, p. 2130). Her death was directly related to the administration of flolan.

The death of this patient is not reported in the sponsor's description of Study 36. It is reported that she "improved clinically" (Vol. 1.25, p. 45). She had been listed in the data tabulations as "not randomized", her number, however, is a flolan code number and her initial data till the discontinuation date are included in all tabulations.

Three patients on standard therapy also died during the study:

Pt. A 33 y.o., Class IV BF was already in heart failure when she was admitted to the study on 3/22/88. She had enlargement of the RA, RV and of the liver. She had ascites, peripheral edema, pericardial effusion, ST segment depression, LDH 657 U/L, SGOT 273 U/L and BUN 26 mg/dl. She was on O₂ 4-5 L/min, and her PaO₂ was 145 mmHg. Her PAP was 125/50 mmHg and her SAP 125/80 mmHg. The investigator noted in this patient's CRF that "she was extremely ill at the time of entry into the study and was having frequent syncopal attacks and hypotensive episodes". On the second day (3/23/88) she could not walk at all. She was randomized to "no flolan". She deteriorated quickly: she developed hypotension, AV dissociation and finally respiratory arrest. She died on 3/24/88, two days after randomization. The autopsy report identified the immediate cause of death as "extensive acute bronchopneumonia". Considering that on admission her WBC count was 4,900 and that she

had no fever, it appears that she developed her bronchopneumonia in the hospital perhaps as a result of the cardiac catheterization. The investigator attributed this complication to resuscitation efforts. The list of concomitant medications did not include any antibiotics. The bronchopneumonia was apparently unrecognized during life. This patient was ineligible to be entered into the study because of her high LDH, SGOT and BUN levels.

Pt. A 15 y.o., Class III, WF with a history of familial PPH was screened on 10/31/89. On 11/1/89 she developed pneumothorax as a complication of right heart catheterization. Yet she was entered into the study and was randomized to "no flolan". She became progressively hypoxemic and died 5 days later on 11/6/89 following a vasovagal reaction in spite of cardiopulmonary resuscitative measures.

Pt. A 21 y.o., Class IV, WF was admitted to the study on 10/9/89 with severe dyspnea on exertion, severe fatigue, dizziness, syncopal episodes, ascites, edema, severe tricuspid regurgitation and an LDH level of 695 U/L. According to the nurse's notes she was unable to stand or walk. According to the protocol she should have been excluded because of her high LDH level. On 11/27/89 she was readmitted to the hospital in order to complete the study a week earlier than specified by the protocol. She died the next day (11/28/89). A flolan solution was prepared for her on that day at 8 AM. It is not stated whether the solution was administered to the patient or not. An adverse reaction report indicates that on 11/29/89 the patient complained of fatigue, dizziness, presyncope, etc. How could that be, if she had died one day earlier? The records of this patient were not kept properly.

EVALUATION OF STUDY 35/36 BY THE REVIEWER:

Study 35/36 was open and bias cannot be excluded from any phase of the study.

1. Bias was clearly shown during the randomization of the patients:

Flolan patient developed what was characterized in her CRF as "prostacyclin-induced pulmonary edema" during dose-ranging with flolan. She died one month later. The sponsor claims that she was not randomized and has not reported her death. Her ID number, however, is a flolan number.

Two of the control patients who died, patients were extremely sick at baseline, unable to stand or walk having frequent hypotensive and/or syncopal attacks. They were also ineligible to enter the study because they had high SGOT, BUN and/or LDH values. Patient in addition, had developed acute

bronchopneumonia as a result of cardiac catheterization or resuscitation efforts, which occurred before randomization, yet both patients were considered eligible and were randomized to the control group.

The third control patient who died, developed pneumothorax as a complication of cardiac catheterization. In spite of this complication she was also entered into the study and was randomized to the control group.

Fair clinical Trial Methodology would have excluded all 3 control patients who died but it would have included flolan patient because her pulmonary edema was the result of the infusion of flolan. The net results of survival in study #36 were then:

2 flolan deaths
0 control deaths.

2. There was an imbalance regarding the proportion of NYHA class IV patients among the groups. The flolan group had only 2 patients of class IV compared to 6 patients in the control group. The p value is >0.1 , which is not statistically significant but if we consider the fact that 4 of the 5 patients who died during the study belonged to class IV and only one to class III, the difference in the number of patients of class IV between the groups becomes clinically very significant ($p < 0.025$). This conclusion is also supported by the results of the National Registry, which showed that the median survival time of patients of class III is 2.6 years and that of patients of class IV is only 0.5 years.

3. 6-Minute Walk: As mentioned above, the control group included some very sick patients who could not walk at all. The groups were not comparable to start with. The investigators who evaluated the patients during the study, supervised them during the walk and "encouraged" them to walk. Considering that the study was open the possibility of applying bias was considerable. The results are also confounded by the fact that a significant proportion of patients (56%) were exercised only once during the screening phase instead of twice and a large number of them did not have a practice walk on any day.

Hemodynamic Measurements:

Statistical analyses of the values of the baseline hemodynamic and gas measurements have not been provided and we do not know whether there were significant differences between the groups regarding any of these measurements rendering the groups not comparable to start with. The standard group had higher pulmonary pressures and resistances. I ran a plain t test and found that the between groups differences in SAPs, SAPs, SVR and TSR were very close to

being significant ($p > 0.05$). Also the PAPs and SAPd differences had values of $p > 0.1$. All these differences were in favor of flolan. Although each of these differences by itself is not statistically significant, considered all together, indicate that the patients who were randomized to standard therapy alone, were sicker than those who were randomized to flolan. This conclusion is supported by the fact that the mean PaO_2 value of the patients on standard therapy was 120 (vs 64.5) mmHg, which is excessive and indicates that the control group included more patients who were under oxygen treatment i.e., they were very sick. The value of PaO_2 in normal people is 83-100 mm Hg. In PPH there is hypoxia and hypokapnia and one would expect low PaO_2 mean values.

It can be argued that when there are multiple comparisons between two groups, 27 in this case, some of the comparisons will appear significant or close to be significant by mere chance. In that case, however, some of them would turn in favor of one group and some in favor of the other. In study 35/36, all the trends, 7 of them, were in favor of flolan ($p < 0.01$).

In Summary:

Study 35/36 had the following deficiencies:

1. It was open.
2. There was bias in the randomization of the patients. The control group included some severely ill patients.
3. Ineligible, severely sick patients with abnormal lab values were not excluded but were randomized to the control.
4. Two control deaths were caused by complications of cardiac catheterization.
5. There was bias in discontinuation policy. A flolan patient was discontinued after she developed pulmonary edema during dose-ranging, but the control patients who developed pneumothorax and pneumonia due to cardiac catheterization were not discontinued.
6. The investigators "encouraged" the patients to walk during the walk test.

4

2. Study # 46 (Phase III, Table Cl₁).

A Multicenter, Open-label, Randomized, Parallel Comparison of the Safety and Efficacy of Chronic Flolan Infusions plus Conventional Therapy Alone in Patients with Severe Primary Pulmonary Hypertension: A Twelve Week Study.

Study Period: Sept. 12, 1991 - August 13, 1992.

This trial was conducted in order to confirm the results of study 35/36. Eighteen investigators indicated willingness to participate and 17 were able to recruit patients (Table 46₁).

Study Design: This was similar to the design of study 35/36 with some differences:

There was only one dose-ranging segment.
The treatment period lasted for 12 weeks instead of 8 weeks.
Flolan dose during the dose-ranging segment was titrated to intolerance (instead of up to 12 ng/kg/min or to the greatest hemodynamic benefit).

Patients/Randomization: The inclusion and exclusion criteria are shown in Tables 46₂ and 46₃. Eighty-one patients were entered into the study. The patients were randomized chronologically to receive standard therapy alone or standard therapy plus flolan after completing the dose-ranging segment. Randomization was stratified by study center, NYHA Class and vasodilator use at baseline. The randomization was done by Burroughs-Wellcome using an adaptive randomization computer program. Forty-one patients were randomized to flolan and 40 to standard therapy alone.

One patient developed pneumothorax during cardiac catheterization and allegedly was not randomized.

All patients who completed the study had the option to receive flolan in a continuation study (#47).

Objectives/Efficacy/Safety Parameters:

Same as in study 36. The primary efficacy endpoint was the improvement of the exercise capacity (6-minute walk). The secondary endpoint was survival, while the tertiary objectives included improvement in the hemodynamic parameters, improvement in clinical signs and symptoms of PPH, and improvement in the quality of life. Additional objectives were to evaluate the effect of flolan on the right ventricular structure and function and on "health economics".

Safety was evaluated by monitoring side effects. The patients were visited by study personnel weekly and their adverse effects were recorded.

Demographic Characteristics:

The Demographic characteristics of the patients are shown in Table 46. The groups seem to have been comparable. The mean age was 40y in both groups. The majority of the patients were female (76% Fl. vs 70% St.), white (81% Fl. vs 85% St.) and belonged to NYHA Class III. The flolan group had a mean weight of 68 kg vs 72 kg for the standard group. The mean duration of PPH was 32 months for the flolan group and 25 for the standard group.

Flolan Dosages:

During the Dose-Ranging Segment the dose was titrated to intolerance and varied from 2 to 20 ng/kg/min. Most patients peaked at 6-12 ng/kg/min. During the 12 Week Treatment Period flolan was started at a dose 4 ng/kg/min lower than the highest tolerated dose. Thereafter the dose was increased or decreased according to the presence of clinical symptoms of PPH or the appearance of side effects. Generally the dose increased from a mean of 5.3 ng/kg/min at the end of the first week to 9.2 ng/kg/min at the end of Week 12. The highest tolerated dose was 1.6 ng/kg/min less than the non-tolerated dose.

pump met the necessary specifications and was used to administer flolan during the 12-week treatment period via a dedicated central venous catheter. During the dose ranging segment flolan was administered either peripherally or through a proximal port of the Swan-Ganz catheter.

Concomitant Medications: Both groups used mostly anticoagulants (98%), and flolan vs standard: analgesics (83% vs 70%), diuretics (68 vs 78%), anxiolytics (61% vs 55%), vasodilators (61% vs 60%), digoxin (56 vs 50%) and oxygen (39 vs 53%). The prothrombin time was maintained between 1.3-1.5 of control in all patients.

RESULTS:

Two flolan patients withdrew their consent and discontinued the study.

Efficacy:

Primary Efficacy Parameter: The 6 minute Walk:

During the first Day the patients were instructed to walk on a level surface for 6 minutes and the distance was measured. They were allowed to stand or sit briefly during the test. However, the clock was not stopped during the walk interruptions. In contradistinction to study 35/36 the patients were not encouraged to walk during the testing. The tests were administered by a trained tester, who was not involved in the patients' daily care and was unaware of their assignment. He was specifically trained by personnel from . The walk area was indoors at least 65 feet long and 4-6 feet wide. The temperature was kept at 20-23°C. The walk test was repeated on Day 2, and Weeks 1, 6 and 12. The first walk was considered training and its results were not taken into consideration. The walk on Day 2 represented the baseline value.

During the test all patients were wearing an infusion pump and a loose hospital gown over their cloths to ensure that the tester could not see whether a patient was fitted with an indwelling catheter and thus he remained unaware of treatment assignment. After the walk ended the tester showed the Borg Dyspnea Scale (copy attached to this review, Table 46₅) to the patient and asked him(her) to grade the degree of the dyspnea that he(she) felt during the test.

Patients who could not walk due to the severity of their disease or because of death were assigned a value of 0 meters. Patients who could not walk for reasons other than the severity of their disease (lost to follow-up) were excluded from the analysis. The results are tabulated in Table 46₆. Table 46₇ shows the differences from baseline at Weeks 1, 6, and 12. This Table shows that at the end of the first week the flolan group walked 16 m. longer than on Day 2, while the standard treatment group walked 24 m less than on Day 2; and on Day 88 the respective distances were 34 and -8 meters. After adjusting for differences in Baseline Walk and Vasodilator use the values at the end of the 12th week became flolan: 30 m, control - 50 m.

Two analyses were carried out by the sponsor. For the first analysis only the baseline walk was used as a covariate. In the second analysis both baseline walk and vasodilator use at baseline were used as covariates. In the latter analysis instead of using the actual values walked at week 12 in the linear regression, ranks of the 12 Week distances were used and the Cochran-Mantel-Haenszel correlation statistic was calculated on the actual residuals. The results of the latter analysis showed highly significant differences between the two groups in favor of flolan (Table 46₈); $p=0.0010-0.0030$).

Survival:

All 41 patients, who belonged to the flolan group survived but 8 of the 40 patients, who belonged to the standard group died during the 12 week period of the study ($p=0.0027$) within 0 and 68 days after randomization. The reported cause of death was progressive right heart failure in 6 cases and pulmonary hemorrhage and cardiac arrest for patients _____ respectively. In addition, three patients, two from the standard group (pts _____ and one from the flolan group _____) were transplanted. The baseline characteristics of the patients who died are shown in Table 46₉. Summaries of the course of the patients who died have not been submitted.

Table 46₁₀ shows a comparison of baseline characteristics of the patients who died to those who survived. The only differences which may be significant were: NYHA class, the length of the baseline walk and the mixed venous saturation. A greater proportion of Class IV patients died than Class III. Also as a group, the patients who did not die walked a longer distance and had a higher percentage of mixed venous saturation at baseline than the patients who died:

	<u>Surviving Pts</u>	<u>Dead Patients</u>
NYHA Class III	Standard 86%	14%
IV	64%	36%
Mixed venous Saturation:	Flolan 62%	
	Standard 61%	52%
Baseline Walk	Flolan 316 m	
	Standard 292 m	195 m

Statistical comparison of these results is not provided by the sponsor. My calculations show a p value of >0.1 for NYHA Class and of >0.4 for the other two comparisons, i.e. none of these differences by itself appears to have been significant.

Hemodynamic Parameters and Blood Gas Measurements:

Table 46₁₁ shows the baseline hemodynamic and blood gas measurements of the patients by treatment group. These measurements show that indeed the patients had pulmonary hypertension (the mean pulmonary arterial pressures were 59 and 61 mm Hg, the pulmonary vascular resistance was 16 Wood units, etc), while the cardiac index, the cardiac output, the stroke volume, the arterial saturation and the PaO_2 and $PaCO_2$ were decreased.

Table 46₁₂ shows the hemodynamic and gas measurements which were recorded during the infusion of the maximum tolerated doses of flolan for each of the groups separately during the Dose-Ranging Segment and the differences of these measurements from the baseline values. This table shows that generally, flolan induced similar changes in both groups, except regarding PaCO₂, arterial saturation and transcutaneous O₂ saturation, where the changes went the opposite way. However, these changes were small and insignificant. Generally, the changes were greater in the flolan group especially for cardiac output, cardiac index, stroke volume, PVR, TPR, SVR, and TSR, except for RAPm, and mixed venous saturation the changes were greater in the standard group.

Regarding the flolan group the changes included:

Decreases in	Increases in
PVR by 35%	CO by 46%
SVR 42%	CI 46%
SAPm 15%	PCWpm 16%
TPR 33%	SV 32%
TSR 41%	Mixed v. sat. 9%
PaO ₂ 4%	PaCO ₂ 4%
	HR 9%

Table 46₁₃ shows the means of the hemodynamic values at baseline and during the highest tolerated dose of both groups combined and the differences between each set of measurements including the results of their statistical analysis. All changes from baseline were statistically significant, except of the changes in PAPs, arterial saturation, PaCO₂, PaO₂ and transcutaneous blood O₂ saturation.

Table 46₁₄ shows the hemodynamic parameters and blood gas measurements that each group experienced during baseline and on Day-88 (end of the treatment period) and the respective differences between these measurements. This Table shows that the changes induced by flolan during the 12 week period were similar to those observed during the maximum tolerated dose and in addition flolan reduced the pulmonary arterial pressures both systolic and diastolic and also increased the arterial saturation. The changes during this period were 1.5 to 4 times smaller than they were during dose ranging. Specifically the significant changes (compared to the changes in the standard group) were:

Decreases in:

Pulmonary systolic arterial pressure by 7%
Pulmonary diastolic arterial pressure by 9%
Mean right atrial pressure by 17%
Pulmonary vascular resistance by 22%
Total pulmonary resistance by 21%
Systemic arterial pressure (diastolic) by 7%
Systemic vascular resistance by 16%
Total systemic resistance by 19%

and Increases in:

Cardiac output by 15%
Cardiac Index by 16%
Stroke volume by 15%
Arterial saturation 2%
Mixed venous saturation by 2%
Transcutaneous blood oxygen saturation by 1%.

During the same period the group on standard treatment experienced:

increases in:

pulmonary pressures (3%)
pulmonary vascular resistance (10%)
total pulmonary resistance (11%)
systemic vascular resistance (9%), and
total systemic resistance (9%)

decreases in:

cardiac output (11%),
cardiac index (11%),
PCWPM (9%),
stroke volume (7%),
mixed venous saturation (4%),
PaO₂ (3%), and
PaCO₂ (3%).

i.e. it appears that the patients on standard therapy became worse during the study.

Most of these data were provided by 38 flolan and 30 patients on standard treatment. For some parameters (PCWPM, PVR) only 27 flolan and 17 patients on standard treatment provided data. Comparison of the differences of the two groups indicated that the changes in cardiac output, cardiac index, the pulmonary arterial pressures,

right atrial pressure, PVR, TPR, SAPd, SAPm, SVR, TSR, SV, % arterial saturation, % mixed venous saturation and transcutaneous blood O₂ saturation were statistically significant.

Chronic Heart Failure Index Questionnaire (CHF IQ):

The patients were handed a questionnaire which included various questions regarding activities which were divided into 4 areas or dimensions: dyspnea, fatigue, emotional function, and mastery (of eating, hurrying, mopping or scrubbing the floor, shopping). The patients were expected to grade these questions on a 7-point scale every two weeks. The better the patient coped with each of these activities, the higher was his(hers) evaluation grade. The investigator checked the answers with the patient by repeating each question to make sure that the answers were correct. A change of a 0.5 grade/question/dimension represented a significant difference.

Table 46₁₅ shows the mean and median scores of the two groups at baseline and at week 6 and Day 87. The scores generally increased during the study for both groups indicating improvement except for fatigue for the standard group. The increases were greater in the flolan group. Table 46₁₆ shows the comparison of the median scores of the two groups for week 6 and Day 87. The sponsor found that the improvement was significantly better for flolan than for the standard treatment regarding all dimensions (dyspnea, fatigue, emotional function and mastery).

Nottingham Health Profile (Copy of the Questionnaire is enclosed with study 35/36, Table 35/36₁):

This profile is composed of two parts. Part I includes 38 questions and part II seven. Most of the questions are similar in meaning with the questions of the CHF IQ. In part I the questions referred to emotional reactions, energy, pain, physical mobility, sleep, and social isolation. In part II they involved "home life", "looking after the home", "interests and hobbies", "sex life", "social life", "vacations", and "work". The patient was supposed to answer each question by checking a "yes" or a "no" box. The investigator was supposed to help the patient to answer the questions correctly "without biasing him or her".

Table 46₁₇ shows the scores for part I, which were obtained on Day 1 (baseline), Week 6 and Day 87. It is not clear how these scores were obtained considering that the patients were expected to answer each question with a "yes" or a "no" check. The scores indicate that the greater the score, the greater was the number and the severity of the problems that were experienced by the respondents. Statistical analysis of the baseline values has not been provided and we do not know whether the groups were comparable in these characteristics to start with.

The majority of the scores decreased during the study indicating improvement, especially for the flolan group. Statistical analysis of the differences from baseline (median values) by the sponsor indicated that the improvements of the flolan group regarding emotional reactions, energy, and sleep were significantly greater than those of the standard group (Hodges-Lehmann estimate for the true treatment effect).

Table 46₁₈ shows the results of Part II. The baseline scores show that the flolan group had considerably fewer problems regarding home life (33% vs 55%), social life (58% vs 70%), vacations (53% vs 68%) and especially work (paid employment; 37% vs 60%). The scores of the flolan group improved (decreased) during the study except for work. Essentially no improvement was observed for the group on standard therapy especially regarding "looking after the home", and "vacations". Comparison of the scores of the two groups indicated that the differences regarding looking after the home at week 6 and Day 87, and 'vacations' at Day 87 were significant in favor of flolan.

Dyspnea-Fatigue Rating:

The scale used to rate the Dyspnea-Fatigue Index included 3 components (Table 46₁₉). Each component (Magnitude of Task, Magnitude of Pace, Functional Impairment) was rated on a scale of 0 to 4. The aggregate score of the Index varied from 0 (worse condition) to 12 (best condition). The results are tabulated in Table 46₂₀. The mean scores indicate that at the baseline the patients had light to moderate dyspnea. The flolan group had a mean score of 4.2 while the group on standard therapy had a mean score of 3.5. During the study the score of the group on standard therapy essentially did not change but the score of the flolan group increased by 1.3 - 1.6 degrees to 5.8 at 6 weeks and to 5.5 on Day 87. This increase in score indicates improvement. The between groups differences were found to be significant at Weeks 6 and 9 and on Day 87 (Table 46₂₁).

PPH Symptoms:

The physician recorded the frequency of the PPH symptoms (Dyspnea at rest, dyspnea on exertion, fatigue, dizziness, syncope, chest pain, palpitations, paroxysmal nocturnal dyspnea, and orthopnea) based upon the patient's response. The number of patients who had each of the symptoms "none of the time", "some of the time", "most of the time", or "all of the time" are shown in Table 46₂₂. This table, in addition, shows the severity of orthopnea by indicating the number of pillows and other means (sleeping in a chair, keeping the bed on blocks) that the patients were using during sleep.

Statistical analysis of these results by the sponsor (Table 46₂₃) indicated that a greater proportion of flolan patients than patients on standard treatment had less frequent symptoms during the study: chest pain 40% vs 18% at Week 1, dizziness 34% vs 10% on Day 87, dyspnea on exertion at all evaluation periods, fatigue at weeks 3, 6, and 9, and orthopnea at Week 9 (43% vs 16%).

PPH Signs:

Comparison of the changes in PPH signs from baseline during the various periods of the study (Table 46₂₄) showed that the flolan group improved significantly more than the standard group regarding edema and the distention of the jugular vein during week 6, and also regarding the murmur of pulmonary insufficiency and NYHA class during Week 6 and Day 87.

Tabulations and analyses of the data regarding the effect of flolan on the right ventricular structure and function and also on Health Economics have not been presented.

Adverse Reactions:

The adverse reactions which occurred in at least 3 patients during the study are shown in Table 46₂₅. The most frequent of them were asthenia, dyspnea, dizziness, chest pain, palpitations, and edema, which were more or less equally frequent in both groups. Headache, myalgia, diarrhea, pain in general, fever, and nervousness were generally more frequent in the flolan group, while pain in the jaw, flushing, arthralgia, and supraventricular tachycardia were observed exclusively in the flolan group. The patients on standard treatment experienced more frequent increases in cough, depression, cyanosis, hypoxia, heart failure, pallor, confusion, and rash. Shock was observed exclusively in the standard group (7 pts vs 0).

Two patients, one on flolan and one on standard treatment (pt) developed sepsis not associated with the flolan delivery system. The flolan patient had a history of endocarditis and the standard patient had a history of urinary tract infection.

One flolan patient has been reported that she discontinued the study prematurely (vol 1.32 p 885) because of adverse reactions (fever, headache, hypotension, pallor, musculoskeletal pain, nausea, palpitations, etc). This patient, however, is reported on p 891 of the same volume as having had completed the study normally. This patient has no D-88 data for ECHO, hemodynamic measurements or the delivery system questionnaire. She has been, however, reported as having walked 362 m on Day-88.

Dose-Limiting Adverse Reactions:

Hypotension:	37%
persistent severe headache:	31%
extreme flushing:	28%
Severe nausea:	25%
Severe restlessness/anxiety:	14%

Delivery System Malfunction:

	Cases
Catheter Occlusion:	1
Perforation:	6
Dislodgement:	4
Infection (sepsis)	4
Infection (Catheter area)	7
Detachment of extension tubing	6
Blood in tubing	2
Air in Line	1
Pump Mechanical:	
Stoppage	7
Other	2
Human, Programming Error	3
Other	<u>11</u>
Total	54

Adverse Reactions Due to Catheterization Itself:

Pneumothorax developed in a patient during the Swan-Ganz catheter placement followed by death 6 days later. This patient was not randomized. Subclavian artery dissection (occurred in standard pt and Supraventricular tachycardia in flolan pt. (Hx of supraventricular tachycardia)).

EVALUATION OF STUDY #46 BY THE REVIEWER:

A. Deficiencies:

Study #46 was open all the way through from randomisation to completion, bias therefore cannot be excluded from any part of the study.

I. Randomisation: There was no predetermined code of random numbers. As mentioned earlier, the randomization was done by an

adaptive randomization computer program established by the sponsor. After the patients were screened and thoroughly assessed for 2 days by the investigators, they were dose-ranged with flolan. Then the investigators called the medical division of Burrows-Wellcome to get the randomization assignment for each patient. The stratification criteria were: study center, NYHA class (III or IV), and use or no use of vasodilators at baseline. However, the investigators were asked to provide additional information as well: the distance that the patient walked in 6 minutes, the maximum tolerated dose, the intolerated dose, and the PAPm, CO, PCWpm, and PVR values of the patient to be randomized. Knowing all this information one could randomize the patients in such a way that patients with relatively worse symptoms and parameters would receive standard treatment alone and those in relatively better condition would receive flolan.

This conclusion is supported by the following facts:

a) Significantly more patients who could not walk more than 200 meters at baseline were randomized to the standard treatment (14 vs 6; $p < 0.05$; see Table 46c). Five of these patients died during the study. Ability to walk is one of the best prognostic criteria for the survival of patients with cardiovascular disease and this parameter was selected as the primary endpoint in the PPH studies, apparently because of its significance.

b) The patients who died were either very sick at baseline or had additional conditions, known to reduce survival. Their treatment was apparently difficult to control and several of them developed electrolyte abnormalities and/or digitalis toxicity during the study.

1. The first patient to die, patient _____ was randomized to standard treatment while she was dying or perhaps after her death. This patient lost consciousness right after dose-ranging with flolan and despite attempts to resuscitate her she died one hour after discontinuation of flolan.

2. Patient _____ was on oxygen, 6L/min, for 2 months already when she was recruited. She developed bradycardia, ventricular tachycardia (dig. tox.?) and acute renal failure during the study. She died 19 days later.

3. Patient _____ was very fat. She had been rejected for transplantation by two transplatation centers because of "morbid obesity". She also had hypothyroidism. She was placed on digoxin, diuretics and potassium supplements. She

developed hyperkalemia, high levels of creatinine and BUN and died 43 days after randomization.

Table 46₂₇

6-Minute Walk; Baseline Values

<u>Flolan + Standard T.</u>		<u>Standard Treatment Alone</u>		<u>Death After Randomization (Days)</u>	<u>Additional Morbidity</u>
<u>Pt. ID #</u>	<u>Distance Walked (meters)</u>	<u>Pt. ID #</u>	<u>Distance Walked (meters)</u>		
	314.6		427.9		
	511.2		534.9		
	487.4		487.4		
	332.8		0.0	0	Moribund
	332.8		475.5		
	404.2		427.9	68	Hemorrhage
	352.3		427.9		
	309.4		237.4		
	279.8		422.5		
	291.7		410.6		
	394.4		374.0		
	359.4		438.0	58	Septostomy
	394.1		336.5 T		
	516.3		310.9		
	253.6		390.1		
	351.1 W		253.6		
	161.5		198.1		
	131.7		272.5 T		
	183.8		100.6	19	Digitalis Toxicity?
	68.3		266.7		
	358.4		158.5		
	270.1		336.8	56	URI
	384.0		60.0		
	306.3		117.3	43	Hyperkalemia, hypothyroidism. Digitalis Toxicity
	291.1		192.6		
	331.9		385.6		
	379.2		220.7		
	217.9		91.4		
	237.7		156.4		
	285.0		114.3		
	434.3		275.2		
	279.8 W		340.5		
	276.8		248.1		
	455.7		352.0		
	384.0		443.5		
	429.8		91.4	59	Digitalis Toxicity
	226.5 T		118.9		
	0.6		137.2		
	148.4		208.5		
	296.3		45.7	48	Hypokalemia, dig. tox.
	521.2				

T = Transplanted
W = Withdrew consent

4. Patient was in right heart failure at baseline and very orthopneic. He could not sleep on a bed. He was sleeping on a chair. He developed digitalis toxicity during the study and died.

5. Patient had a history of prokainamide-induced SLE. He also developed digitalis toxicity and was hypokalemic during most of the study. He died in hypokalemia.

6. Patient had hepatitis C in addition to PPH. She also had a history of bleeding. Yet she was placed on warfarin during the study. She died from hemorrhage.

7. Patient was subjected to atrial septostomy during the day he died. The surgical procedure might have caused or at least precipitated his death.

8. Patient had right heart failure at baseline and was on oxygen, 6 L/min, when she was randomized to the control group.

II. Alteration of a Patient's ID:

It has been reported that Patient developed pneumothorax during cardiac catheterization and was not randomized. She died 5 days after the development of the pneumothorax. The records show that this patient was the first patient to be recruited by center 15. The first 20 pages of her CRF show that her original number was 15001, which is the correct number for her, considering that she was the first patient recruited by this center. This number, however, was changed over to and pages 21-79 are missing from her record. The patients were numbered sequentially as they were recruited. Center 15 had only 6 patients. Number is an improbable number for this center (and for any other center). A new patient with ID number was randomized to flolan in the same center one day after patient had died. I do not know what to make out from this ID alteration, except perhaps that the first patient died after she had been randomized to flolan and was replaced by another patient after her death.

III. Complete lack of Summaries of the Patients who died. I summarized these data myself collecting information from various parts of the NDA (the summaries are appended to the end of this Evaluation).

IV. Complete Lack of Clinical Chemistry, Hematology, and ECG Data.

Clinical chemistry, hematology or ECG data for study #46 were not included in the original NDA. I specifically asked for these data later on. The sponsor replied that these data were not required for study #46 because "no significant, relevant abnormalities were observed in clinical chemistry or hematology when flolan was administered in animals, normal volunteers, uremic patients or patients with PPH" .. and no clinically important, consistent treatment emergent abnormalities in ECGs were reported..." (submission of August 23, 1994).

The sponsor seems to be oblivious to the fact that many of the patients who entered study #46 were very sick cardiovascular patients treated with digitalis and diuretics and their electrolytes and digitalis dosages had to be controlled very carefully. Eight of these patients died during the 12 week study. It is hard to believe that the treating physicians did not order any tests for electrolyte and digoxin levels or did not get any ECGs when a patient became worse or developed an arrhythmia during treatment. This would have amounted to malpractice. I found some electrolyte data myself among the concomitant medications data. It appears that the sponsor does not want to submit these data.

We cannot consider study #46 as adequate and well controlled without the appropriate laboratory data.

V. Dose-ranging of control Patients with flolan:

The control patients in both study #35/36, and #46 were dose-ranged with flolan before randomization. The sponsor explains that this was done in order to evaluate each patient's baseline residual pulmonary vasoreactivity and also to increase the amount of data available to demonstrate flolan dose versus hemodynamic response in these patients. Considering that flolan was not expected to be used for the treatment of the control patients, evaluation of their vasoreactivity to flolan was irrelevant and an extra burden for them.

Judging from the CRFs of the patients who died, it appears that the infusion of flolan was stopped abruptly after dose-ranging. For the flolan patients this did not matter because these patients were subsequently infused with their optimal dose of flolan for the long-term phase of the study. For the control patients, however, abrupt discontinuation could be a severe stress. Abrupt discontinuation of flolan has been shown to cause rebound hypertension, hyperaggregability of platelets and adverse events, even death in severely sick patients. The death of patient _____ who died immediately after the dose-ranging procedure was stopped, may have been precipitated because of the abrupt discontinuation of flolan.

B. Effectiveness:

I. Hemodynamic and Blood gas measurements:

Study #46 showed that flolan significantly reduced the pulmonary arterial pressures, the vascular and total pulmonary and systemic resistances and increased cardiac index and cardiac output, stroke volume, arterial saturation, mixed venous saturation and transcutaneous oxygen saturation compared to the baseline values. These results were all favorable for the patients. Study #46 further showed that the differences between the results of the flolan and the control group were significant favoring flolan.

These results can be accepted as reliable because regarding the differences from the baseline values, they represent comparisons of data from the same patients. Regarding the comparison of the results of the flolan patients to the results of the control patients at the end of the study, these results also are reliable, because the results of the patients, who died were excluded both from the baseline and from the final data during the analyses (Table 46₁₄). Thus these data represent comparisons between more or less similar populations.

II. The 6-Minute Walk:

The sponsor showed that the flolan patients walked a longer distance in 6 minutes than the control patients did and the difference was highly significant ($p=0.010-0.003$). The sponsor in this case compared two populations, which were considerably different. The control group included more severely ill patients.

Dr. M. Al Osh, Mathematical Statistician of FDA, did several reanalyses of the walk data. He found that even when the patients who died and those who were transplated were excluded from the analysis, even then the results showed that the flolan patients had walked longer distances than the control patients: 353 vs 284 meters, with a difference from baseline of 32 vs -6 meters, respectively ($p=0.0253$). In this analysis, at baseline, the flolan patients had walked for 320 meters, while the control patients had walked for only 291 meters. This difference was not found to be statistically significant ($p=0.299$). Two explanations can account for the better results for flolan: either flolan truly increased the ability of the PPH patients to walk during the study or there was a placebo effect. The study was open. The flolan patients knew that they were being treated with a new "effective" drug, while the control patients knew that

they were not getting the new "effective" drug (see case of patient p. 43).

III. Survival:

Control patients: as explained under randomization (p. 38), the first control patient who died was moribund when she was randomized. Five other control patients died from treatment toxicity (4 from digitalis toxicity and one from exacerbation of a bleeding tendency after being dosed with anticoagulants). An additional control patient had surgery (septostomy) on the day he died. Only one control patient may have died due to a complication (URI) or progression of his disease.

Flolan Patients: There are indications that patient who died during study #46, was a flolan patient. The sponsor has not been candid regarding this patient.

The net result on survival probably was:

1 control dead vs 1 flolan dead

If we consider the death of patient as a complication of cardiac catheterization, the net result becomes:

1 control death vs 0 flolan deaths

i.e. there was no significant difference on survival between the groups during Study #46.

IV. Self-Evaluation of the Chronic Heart Failure Index and the Nottingham Health Profile:

The scores (Tables 46₁₅₋₁₈) are supposed to represent each patient's self perception of the quality of his life. However, according to the protocol, in all the cases it was recommended that the physician should discuss the questions with the patient to make sure that he(she) had understood them correctly. Such a procedure can introduce significant bias consciously or unconsciously.

It is not clear how the scores regarding Part I of the Nottingham Health Profile, reported in Table 46₁₇, were obtained. The patients were supposed to check a "yes" or "no" box in the case reports. Scores were not used.

V. Dyspnea:

Dyspnea was evaluated as a component of the Chronic Heart Failure Index, as a PPH symptom under various categories (dyspnea at rest, dyspnea on exertion etc), and as dyspnea-fatigue. According to the protocol dyspnea should have also been evaluated by the patients according to the Borg Dyspnea Score immediately after the 6-minute walk. These results have not been included in the NDA submission.

DEATHS Summarized by the reviewer.

The sponsor reported that no flolan patient died during the 12 week study period while 8 control patients did. The sponsor did not provide any summaries of the death cases.

Patient

A 44 y.o., NYHA class IV, WF with a Hx of hypertension, was screened on 11/18/91. The patient was in the ICU in cardiovascular collapse due to rt heart failure (dyspnea at rest, cyanosis, peripheral edema, syncope, HR 122 bpm, PAP 122/41 mm Hg, mixed venous saturation 45%, arterial saturation 90%, etc.). She did not have any baseline walk test. "In the clinical judgement of the investigator, the patient was too critically ill to be taken out of bed and exercised (i.e., patient is confined to bed, bathroom and shower privileges are denied, and attempting to exercise the patient would be hazardous to her health)." This patient lost consciousness right after dose-ranging with flolan and despite attempts to resuscitate her she died one hour later. Apparently, she was randomized to the control group while she was dying or may be after death.

Patient

A 16 y.o. WF, NYHA Class III, suffering also from hepatitis C in addition to PPH, with a Hx of atrial septostomy (11/91), right heart failure, bleeding, and a family history of PPH, was randomized to receive standard therapy on 5/14/92. At baseline she complained of dizziness, dyspnea on exertion, cyanosis, exercise intolerance, fatigue, dizziness, orthopnea, palpitations, lightheadedness, and cold extremities. Her PAP was 115/50 mm Hg, i.e. higher than her SAPs, which was 106/64. She was on digoxin since 11/12/91 and on heparin since 5/4/92. On the day of randomization (5/14/92) she was placed on ferrous sulfate, warfarin and multivitamins. On 5/15/92 it was noted in her CRF that "patient was very depressed during 6-minute walk and did very poorly compared to baseline walks. She was disappointed that she did not get randomized to flolan". On 6/5/92 she developed an U.R.I. for which she was hospitalized and treated with antibiotics. This infection lasted for 10 days. On 7/19/92 she went into

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cardiovascular collapse with bleeding, hemoptysis, hypotention, chest pain, cough, cyanosis, disorientation, dizziness, fever, abdominal pain, pallor, and weakness. Vitamin K was prescribed on 7/20/92. She died on 7/21/92; the cause of death has been recorded as pulmonary hemorrhage.

The autopsy showed diffuse pulmonary hemorrhage with subpleural extension into the posterior mediastinum, bilateral bloody pleural effusions, pericardial serous effusion, and massive right ventricular hypertrophy with marked dilatation of the main pulmonary artery and its branches.

This patient had hepatitis C which was associated with a tendency for bleeding (she had a history of bleeding), yet she was placed on anticoagulant therapy.

Patient

A 43 y.o., NYHA class III, WM, with low cardiac output, lightheadedness, nausea, orthopnea, shortness of breath at rest, syncope, weakness, arm pain, chest pain, cough, fatigue, exercise intolerance etc. was randomized to standard therapy on 12/16/91. His PAP then was 100/45 mm Hg, RAPm 9 mm Hg, mixed venous saturation 64% and his arterial saturation 95%. On 2/4/92 he was found to have increased pro-time and coumadin administration was discontinued. On 2/10/92 the patient developed right heart failure with edema, angina, bradycardia, dizziness, hypotension, syncope, vomiting, and complete cardiovascular collapse. He died on 2/12/92. The patient was intubated, and subjected to atrial septostomy apparently on his last day. However, the recording of the procedures was crossed out from the dated record and was added to the last page of his CRF without indicating when these procedures were done. The cause of death has been recorded as progressive right heart failure.

Patient :

A 44 y.o., NYHA class IV, WF, was screened on 11/14/91 and was randomized to standard treatment on 11/15/91. She was on oxygen, 6 liters/min, since 9/26/91. Her presenting symptoms were those of right heart failure: chest pain, abdominal pain, ascites, cough, coldness of the extremities, dizziness, fatigue, hypotension, hepatomegaly, nausea, orthopnea, palpitations, shortness of breath at rest, syncope, weakness, peripheral edema, hepatomegaly, etc.. Her PAP was 85/35 mm Hg, her RAPm 18 mm Hg, her mixed venous saturation 39.2%, and her arterial saturation 88.6%. On 11/28/91 the patient was rehospitalized in cardiovascular collapse and died on 12/4/91. The cause of death was originally recorded as acute renal failure but was later crossed out and substituted by progressive right heart failure. This patient was on digoxin

(0.25 mg QD from 9/27/91-12/3/91 when she developed bradycardia and digoxin was discontinued) and was loaded with diuretics (furosemide, chlorothiazide, spironolactone, ethacrynic acid, metolazone). She has also been reported to have had developed ventricular tachycardia on 12/1/91 for which she was treated with lidocaine. I cannot find any clinical chemistry data for her.

Patient :

This patient was a 36 y.o., NYHA class III, WF with a patent foramen ovale, increased hematocrit and irregular menses. On 1/21/92, (Baseline), the patient was complaining of lightheadedness, muskuloskeletal pain, nausea, orthopnea, peripheral edema, cyanosis, hepatomegaly, (supraventricular) tachycardia, weakness, weight loss, clubbing, anorexia, cool extremities, cough, cyanosis, depression, dizziness, dyspnea, and headache, and was diagnosed as having right heart failure. Her PAP was 84/31, her RAPm 6, her mixed venous saturation 68.8% and her arterial saturation 91.3%. The PaO₂ was 61 mm Hg. She was randomized to standard treatment on 1/23/92. On 2/7/92 she developed a urinary tract infection and was treated with antibiotics. The infection lasted for 7 days, till 2/14/92. On 3/9/92 she was rehospitalized for unrecorded reasons. On 3/14/92, while still at the hospital she developed an URI for which she was treated with antibiotics until her death. She died on 3/19/92. The cause of death is recorded as "cardiac arrest". No more information is provided.

Patient

A 42 y.o. F, of spanish descent, NYHA class III, with a Hx of cholecystectomy, vertigo, pericardial effusion, and smoking for 20 years, was admitted on 2/24/92 with symptoms of right heart failure: chest pain, cool extremities, dyspnea on exertion, shortness of breath at rest, ascites, pericardial effusion, cough, dizziness, peripheral edema, exercise intolerance etc. Her HR was 103 bpm, her PAP was 100/50 mm Hg, her RAPm 18 mm Hg, her mixed venous saturation 31%, and her arterial saturation 88%. She was randomized on 2/25/92 to conventional therapy alone. This patient had been rejected for transplantation by the Washington University and the Stanford Lung Transplantation Program because of "morbid obesity". On 3/18/92 she became suicidal and was hospitalized in a psychiatric unit. She was diagnosed as suffering from hypothyroidism and was started on synthroid. On 4/8/92 while still at the hospital she developed diarrhea, rash, her liver function tests became elevated while her right heart failure symptoms became worse. She developed pleural effusion in addition to her pericardial effusion. She was also found to have hyperkalemia, increased levels of BUN and creatinine (She was on digoxin, diuretics and potassium supplements). She died on 4/8/92. The cause

of death is listed as progressive heart failure.

Patient:

A 38 y.o., NYHA class IV, WM with a Hx of right heart failure, was admitted on 3/31/92 and was randomized to standard therapy on 4/1/92. On admission he had symptoms of right heart failure: shortness of breath at rest, cyanosis, hepatomegaly, peripheral edema, and orthopnea. His PAP was 87/47, RAPm 21, mixed venous saturation 54% and arterial saturation 88%, PaO₂ 49 mm Hg and PaCO₂ 25 mm Hg. On 4/9/92 he was rehospitalized; reason not stated. On 5/29/92 he was diagnosed as having digitalis toxicity (junctional rhythm) while still at the hospital and was administered digoxin antibodies. He died the same day (In addition to digitalis he was receiving several diuretics). The cause of death has been reported as progressive right heart failure.

Patient

A 63 y.o., NYHA Class IV, WM with a Hx of hypertension, peptic ulcer disease, smoking for 36 years, right heart failure and cardiovascular collapse, family Hx of PPH, and procainamide-induced lupus was screened on 5/14/92. On admission he complained of cough, cyanosis, diaphoresis, dizziness, dyspnea on exertion, exercise intolerance, fatigue, shortness of breath at rest, weakness, and weight loss. He also had hepatomegaly. On 5/15/92 he was randomized to conventional therapy alone. His HR was 113 bpm, SAP was 98/68, PAP 67/40 mm Hg, RAPm 18 mm Hg, mixed venous saturation 46%, arterial saturation 92%, PaO₂ 53 mm Hg, PaCO₂ 34 mm Hg. From the notes regarding concomitant medications it appears that on 5/14/92 (admission day) the patient was placed on digoxin, diuretics and KCl. On 5/21/92 the diuretic dosage was increased ("aggressive diuresis") because the edema was increased. On 5/23/92 the dosage of the potassium was also increased. On 6/2/92 symptoms of digoxin toxicity appeared and digoxin was discontinued. Digoxin was restarted on 6/7/92. The digoxin, the diuretics and the KCl were continued until 7/2/92 when the patient died. He died with symptoms of hypotension and hypokalemia. The cause of death has been reported as progressive right heart failure.

A Patient who Died but her Death has not been Counted:

Patient a 52 y.o. WF developed pneumothorax during cardiac catheterization and was allegedly not entered into the study nor was she randomized. She died on 3/3/92, 5 days after the development of the pneumothorax. Pages 21-79 are missing from her record and her ID number has been changed on the first 20 pages. It seems that her original number was _____ and then it was changed over to _____. There is no explanation for the change. Center 15

had only 6 patients. Patients were numbered chronologically as they were screened. No. 999 is clearly an improbable number. A new patient, , a flolan patient, was randomized on 3/4/92, one day after the mysterious patient had died.

5

UNCONTROLLED STUDIES:

The sponsor supported 5 uncontrolled studies (Table Cl₂). Studies #37 (the extension of study #35/36) and study #47 (the extension of study #46) are long-term studies and are on-going. Studies 5/10, 20, and 21 were short-term studies. The first two of them have been completed. Study #21, although of short-term, is still ongoing.

1. Study 37: Open Multicenter Evaluation of the Effects of Chronic Flolan Infusions in Patients with Primary Pulmonary Hypertension.

Objective: to assess the safety and efficacy of long-term (one year) infusions of flolan in patients with PPH.

This study was uncontrolled and multicenter (4 investigators). Patients who had completed study #35/36 and who met all the inclusion and exclusion criteria (same as in study #35/36) were recruited for study #37.

Investigators:

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Study Design: This was similar to the design of studies #35/36 and #46. According to the protocol the study included 4 phases:

Screening (1-7 days),

Baseline: 1 day,

Treatment Phase: It included two dose-ranging segments and a long-term infusion segment. It was scheduled to last for 1 year.

Post-treatment Phase: flolan was supposed to be discontinued after the one year treatment. However, the patients could not be weaned off flolan (their PPH symptoms worsened) and the chronic infusion was continued till the patient received a transplant or died.

Patient enrollment started on August 25, 1987 and ended on February 28, 1990 (2 years and 6 months). Eighteen patients in all (12F + 6M, all white, 12-66 yrs of age) entered. One belonged to Class II, 14 to Class III and 3 to Class IV. Ten had received flolan during study 35/36 while the remaining 8 had received standard treatment during the same study. After entering the Treatment Phase the patients were evaluated every 6 months (physical examination, 12-lead ECG, 6-minute walking test, Nottingham Health Profile, employment questionnaire, lab

tests, right heart catheterization).

Study #37 is ongoing. The cutoff date for efficacy was August 13, 1992 and for survival December 1, 1992 (total period of 5 years and 3 months).

Maximum Tolerated Dose (MTD) of Flolan: At baseline the mean of the MTD was 9.4 ng/Kg/min but it increased progressively to 52 ng/Kg/min at 30 months. At 42 and 48 months only one patient was tested. He had an MTD of 30 and 36 ng/Kg/min respectively.

Exercise Capacity

The exercise capacity of the patients increased during the first 36 months from a mean of 360 meters to 456 meters. After that it decreased to 239 at 42 months and to 341 after 48 months (Table 37,).

Two patients died shortly after their last walk and another was transplanted.

Hemodynamic and Blood Gas Measurements:

Most of these parameters remained constant with small or large variations. The mean values of some parameters, however, clearly increased or decreased although these too exhibited variations:

Increases	Decreases
CI from 2.0 to 3.3 L/min/m ²	PVR from 13.4 to 4.7 Wood U.
CO from 3.6 to 7.2 L/min	SVR from 25 to 16 Wood U.
SV from 43 to 85 ml/beat	TSR from 28 to 13 Wood U.
PaO ₂ from 61 to 77 mmHg	
PAP, from 89 to 107 mmHg	
SOT from 637 to 1317 ml O ₂ /min	

Nottingham Health Profile:

Only the first part of this profile was evaluated. The scores for most of the components decreased with some variations during the study indicating improvement: The scores for energy decreased from 43 to 24, while the scores for pain fluctuated from 0.0 to 33.3. The scores for emotional reaction decreased from 16.1 to 0, for sleep from 24 to 0.0; for social isolation from 13 to 0.0; and for physical mobility from 25.5 to 0.

Survival:

By December 1, 1992 4 patients had died, 8 were transplanted and 6 continue in the study (Fig 37,). The mortality in the 5-year period from the beginning of recruitment was 22% plus those who would have died had they not been transplanted.

Adverse Effects:

Life threatening adverse reactions included: sepsis in 4 patients, syncope in 5 patients, hypotension in 2, DIC, and dyspnea in one patient each. There were also 6 embolic events and 49 episodes of infection due to the drug delivery system and 57 events due to excess flolan associated with pump malfunction (chest pain, headache, muscle ache and seizures).

2. Study 47: A Multicenter, Open Evaluation of the Safety of Chronic Flolan Infusions plus Conventional Therapy in Patients with Severe Primary Pulmonary Hypertension: A continuation Study.

Patients who completed study 46 were given the option to continue flolan treatment in this study.

Only the protocol has been submitted in the Clinical Data Section (vol. 1.29). In the general summary (Vol. 1.1, p. 150) it is stated that 64 patients entered study #47. Thirty-eight of these patients had received flolan in study #46 and 26 had received standard therapy alone. By December 1, 1992, the data collection date:

49 patients were still alive receiving flolan
7 had been transplanted and
8 had died.

Copies of the records of the patients who died have not been submitted.

3. Study 5/10 (Phase II).

Title: Pilot Study of Prostacyclin Sodium in the Treatment of Primary Pulmonary Hypertension in Adults.

Objective: evaluation of the acute and short term effects of flolan on the pulmonary vascular resistance, other cardiopulmonary parameters, and platelet aggregation in adult patients with PPH.

Investigators

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Durham, NC

Berton Groves
University of Colorado HSC
Denver, CO

Hugo Montenegro
Cleveland VA Medical Center
Cleveland, OH

Study Period: October 27, 1980 - January 21, 1982 (15 months)

Design: Open, multicenter, uncontrolled. It included 4 phases: Screening, Baseline, Treatment and a Post-Treatment Phase. The Treatment Phase included a short Dose-Ranging segment and an Extended Infusion Segment for a maximum of 48 hours for patients for whom there was a clear indication of benefit during the dose ranging segment. According to the protocol the infusion rate could not exceed 12 ng/kg/min without joint approval of the investigator and the Burroughs-Wellcome Co clinical monitor.

Efficacy Parameters:

Cardiopulmonary measurements and inhibition of ADP-induced platelet aggregation.

RESULTS

Eleven patients, 18-60 years old, participated in this study. All patients received flolan during the dose-ranging segment. Seven patients received the optional extended infusion for 1 to 41 hours.

Baseline Characteristics:

Eighty-two percent of the patients were white, and 64% were female. The PAFm ranged from (mean 59.7) mm Hg, the cardiac index from (mean 2.2) L/min/m², the PVR from (mean 15.4) Wood units and the total peripheral resistance from (mean 17.3) Wood U (table 5/10₁). The changes in hemodynamic parameters from baseline are shown below:

Parameter	N	Median Change	Median % Change	Mean Change	Mean % Change
CO (L/min)	9	+1.1	+27%	+1.8	+44%
CI (L/min/m ²)	9	+0.7	+31%	+1.0	+45%
HR (bpm)	9	-12	+15%	+11	+14%
PAPs (mm Hg)	9	-5	-5%	-3	-3%
PAPm (mm Hg)	9	-3	-5%	-5	-5%
PCWP (mm Hg)	4	0	0%	0	0%
SAPm (mm Hg)	9	-11	-13%	-13	-15%
PVR (Wood U)	3	-2	-12%	-4	-25%
TPR (Wood U)	8	-6	-32%	-7	-40%
TSR (Wood U)	8	-13	-55%	-14	-54%

The results show that flolan decreased the resistances (PVR, TPR and TSR) and the pulmonary arterial pressures and increased CI, CO and heart rate.

Adverse Events:

Severe and/or Dose-Limiting Effects Occurring During Acute Dose Ranging with FLOLAN®:

Adverse Event	Severe		Any Dose Limiting	
	Number of Patients	% of Patients	Number of Patients	% of Patients
Flushing	2	20%	2	20%
Headache	1	10%	2	20%
Malaise	1	10%	1	10%
Pain chest	0	0%	1	10%
Nausea	0	0%	1	10%
Anxiety	0	0%	1	10%
Nervousness	0	0%	1	10%

Fatal Adverse Events: None.

Severe Adverse Experiences During the Extended Infusion:

Event	No. of Patients	%
Headache	2	29%
Nausea	2	29%
Anxiety	1	14%
Diplopia	1	14%
Photosensitivity	1	14%
vomit	1	14%

Withdrawals:

Three patients (27%) experienced $\geq 20\%$ increases in PAPm and/or in PVR compared to baseline during post-treatment.

Results from the platelet studies have not been reported. The investigators had technical difficulties with the determinations.

4. Study 20:

Evaluation of Flolan and Subsequent Therapy in the Treatment of Primary Pulmonary Hypertension in Adults.

This was also a phase II study.

Investigators:

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Baltimore

Berton Groves, M.D.
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Denver

Period of Study: June 22, 1982 - November 11, 1986

Objective: To evaluate the cardiopulmonary and platelet inhibitory effects of flolan in adult PPH patients.

Study Design: acute, open-labelled, uncontrolled. Like the other studies it included 4 phases. a:

Screening phase of 7 days (History, Physical examination, chest x-ray, echocardiography, Tc^{99m} lung scan, clinical chemistry, hematology, urinalysis, and ECG to assure diagnosis of PPH).

Baseline: Heart catheterization. A balloon-tipped Swan-Ganz catheter was inserted. The distal port was used to monitor pulmonary arterial pressures. One proximal port was located in the right atrium and was used to infuse iced injectate for the determination of cardiac output by thermodilution. The other proximal port was used to infuse flolan. Patients remained supine throughout this phase.

Treatment Phase: Only patients who met the additional invasive hemodynamic criteria (PAPm ≥ 30 mm Hg, TPR ≥ 8 mm Hg or PVR ≥ 5 mm Hg/L/min and PCWP ≤ 15 mm Hg) were admitted to this phase. Dose ranging with flolan was started immediately.

Post-treatment Phase: HR, blood pressure and ECG were under continuous surveillance for at least one hour or longer, if it was necessary. Patients received appropriate care to combat adverse events, if they were present. Vital signs and 6-second ECG strip were determined at 15, 30, 45, and 60 minutes. Other cardiopulmonary parameters (CO, TPR, SVR, SV, SWI) were determined only at 60 minutes.

During the treatment phase flolan was infused at increasing concentrations of 0, 1, 2, 4, 6, 8, 10, and 12 ng/kg/min. Doses greater than 12 ng/kg/min could

be administered only upon the joint approval of the investigator and the Wellcome monitor. The total infusion time did not exceed 5 hours.

The maximum tolerated dose (not causing ST depression of 0.1 mV or greater with horizontal or downward sloping ST segment, onset of nausea and/or emesis, change in SAP >30% from baseline or SAP <65 mmHg, severe headache) and the maximum effective dose (the dose which elicited the greatest reduction in total PVR and/or the maximum increase in CO and SV (stroke volume) were determined for each patient.

No concomitant medications were administered.

Inclusion and Exclusion Criteria: signs and symptoms of PPH, and absence of: supine systolic blood pressure outside the range of 150-90 mm Hg diastolic blood pressure outside of 100-60 mm Hg resting heart rate outside the range of 110-60 beats/min, clinically significant arrhythmia, coronary disease, mitral valvular disease, clinically significant abnormal lab values.

RESULTS

Thirty-nine patients participated in this study. Table 20, shows the baseline characteristics of these patients. They were 80% white and 69% female; they had a mean diastolic pressure of 78 mm Hg and a mean systolic pressure of 113 mm Hg.

The maximum dosage of flolan which was used in this study was 12 ng/kg/min while the mean dosage was 8.36 ng/kg/min. During the infusion of flolan the following changes in the hemodynamic parameters were recorded.

Increases

HR by 1 to 16 beats/min
 CO 0.3 to 2.0 L/min
 CI 0.2 to 1.2 L/min/m²
 SV 1.3 to 15.4 ml/beat
 PCWP 0.1 to 1.3 mm Hg
 SWI (stroke work index): 0.7 to 9.9 g.m/m²
 O₂ consumed: 1.25 to 11.4 ml/min/m²
 PaO₂ 1.7 to 20.5 mm Hg
 PvO₂ 0.9 to 6.8 mm Hg
 PvCO₂ at low concentrations of flolan (up to 4 ng/kg/min) increased, at higher concentrations it decreased (-1.9 to -4.7 mm Hg).

Decreases

PAPs by -2.3 to -7.3 mm Hg
 PAPd -1.1 to -5.4 mm Hg
 PVR -2.7 to -8.3 Wood units
 TPR -2.1 to -8.4 Wood units
 SAPs 2 to -14.9 mm Hg
 SAPd 1.9 to -16.1 mm Hg
 SVR -2.6 to -18.0 Wood units
 TSR -2.8 to -15.9 Wood units
 AvO₂D 0.2 to -2.6 ml/dl
 PaCO₂ 1.8 to -4.4 mm Hg

Adverse Effects:

Most patients complained of flushing (72%), headache (62%), and nausea (41%); 13% complained of chest pain. Eight percent of the headaches and nausea were severe (Table 20,).

5. Study 21 (Phase III).

Title: Multicenter Emergency Evaluation of Flolan in the Assessment of Pulmonary Vasoactivity in Patients with Pulmonary Hypertension.

Study Period: The study started on July 20, 1982 and is still ongoing. The cutoff date for the interim report was August 13, 1982. On May 4, 1983 patients with secondary hypertension were allowed to enter this study. These patients are not identified in the report.

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Study Design: This was similar to the design of study 20. It included the same 4 phases:

Screening

Baseline

Treatment: Dose-Ranging Segment

Extended Infusion Segment (up to 96 hours)

Post-Treatment: Patient monitoring for at least 1 hour.

The study formally ended for each patient with the post-treatment period. However, patients could enter a post-flolan phase and receive acutely other vasodilators or other treatment deemed appropriate for each individual.

Flolan was administered via a right heart catheter. However, in some patients it was given by peripheral IV line.

The inclusion and Exclusion Criteria were similar to those of Study 20.

Efficacy Parameters: Cardiopulmonary measurements

Safety Parameters: Clinical Laboratory Assessments, ECGs, and adverse experiences.

RESULTS

Two hundred and 97 patients have been treated so far. Thirteen of these patients received in addition to the Dose-Ranging Segment, the optional extended infusion of flolan for 12 hours to 58 days.

The Baseline Characteristics of these patients are shown in Table 21. Seventy-seven percent of them were White, 11% Black and 66% female. Their mean diastolic blood pressure was 73 mm Hg, and mean systolic pressure 114 mm Hg. The Baseline Hemodynamic Parameters are shown in Table 21, and confirm the diagnosis of pulmonary hypertension (increased pulmonary pressures and resistances, normal pulmonary capillary wedge pressure, decreased cardiac output and stroke volume).

Twenty-six patients entered the study more than once; 5 entered it 3 times and 2 entered it 4 times. The maximum dose of flolan used in this study was 170 ng/kg/min (one patient only) and the minimum 2 ng/kg/min. The mean dose was 12.9 ng/kg/min. Two patients received flolan on a compassionate reason and were infused for more than 96 hours: for 15, and 58 days, respectively.

The most frequent reasons of discontinuing the administration of flolan were:

<u>Reason</u>	<u>No. of Patients</u>	<u>%</u>
Changes in signs and/or symptoms	140	48
Sufficient hemodyn. response	50	17
Change in systemic art press. >30%	42	15
Anticipated next dose not tolerated	41	14
Systemic art. press. <65 mm Hg	27	9
12 ng/kg/min dose reached	25	9
Significant nausea	24	8
Adverse invasive hemodyn. response	14	5
Persistent severe headache	11	4
Emesis	11	4

Hemodynamic Changes from Baseline During Dose-Ranging:

Increases:

HR from 1.3 to 10.0 bps
 CO 0.1 to 1.3 L/min
 CI 0.1 to 0.9 L/min/m²
 SV 0.9 to 10.2 ml/beat
 SWI -0.23 to 7.1 g-m/m²
 PaO₂ -0.21 to 13.1 mm Hg
 PvO₂ -1.17 to 6.4 mm Hg
 Resp. Rate: 0.26 to 1.9 breaths/min.

Decreases:

PAPs -0.94 to -4.7 mm Hg
 PAPd -0.2 to -4.9 mm Hg
 PCWP -0.4 to -1.3 mm Hg
 PVR -0.96 to -4.6 Wood U
 TPR -1.08 to -6.3 Wood U
 RAPm -0.1 to -0.9 mm Hg
 SAPs -2.3 to -16.1 mm Hg
 SAPd -0.9 to -14.1 mm Hg
 SVR -1.7 to -10.7 Wood U
 TSR -1.4 to -11.4 Wood U
 O₂ cons. 11.5 to -29.4 ml/min/m²
 AvO₂D -0.5 to -2.3 ml/dl
 PaCO₂ -0.1 to 2.0 mm Hg
 PvCO₂ -0.6 to -3.9 mm Hg

Changes in Hemodynamic Parameters During the Extended Infusion Segment:

Mostly Increases:

HR -1.22 to 16.9 beats/min
 CO -0.2 to 2.0 L/min
 CI -0.1 to 0.9 L/min/m²
 SV -7.4 to 20.9 ml/beat
 PaCO₂ -4.5 to 15.0 mm Hg (ups and downs)
 Resp Rate: 3.20 to -1.9 breaths/min (ups and downs)

Mostly Decreases:

PAPs 2.0 to -18.0 mm Hg
 PAPd 3.5 to -5.3 mm Hg (ups and downs)
 PCWP 7.0 to -20.0 mm Hg (ups and downs)
 TPR 3.3 to -8.9 Wood U
 RAPm 6.3 to -11.5 mm Hg (ups and downs)
 SAPs 11.0 to -18.0 mm Hg (mostly downs)
 SAPd 10.1 to -15.8 mm Hg (mostly downs)
 SVR -7.8 to 17.0 Wood U
 TSR -9.6 to 18.2 Wood U
 PaO₂ 55.0 to -92.5 mm Hg (ups and downs, mostly downs)
 PvO₂ 5.0 to -10.5 mm Hg (ups and downs)
 PvCO₂ 5.0 to -18.0 mm Hg (all down except at 24 hours)

Adverse Events:

The most frequent adverse events during the Dose-Ranging Segment were:

Event	n
Flushing	48
Headache	39
Nausea	25
Hypotension	10
Chest pain	9
Vomit	7
Dizziness	5

The most frequent adverse effects during the Extended Infusion Segment were:

<u>Event</u>	<u>No. of Patients</u>	<u>%</u>
Hypotension	5	38
Bradycardia	4	31
Headache	2	15
Heart arrest	2	15
Hypoxia	2	15
Flushing	2	15

Deaths: Four patients died during the study and 2 died shortly after the extended infusion of flolan was discontinued:

1. Six year old BF with a Hx of PPH, maintained on extracorporeal membrane oxygenation received flolan at 12 ng/kg/min one day after a heart transplant. She died 14.5 hours later.
2. One year old WM with PH secondary to pulmonary atresia. The child was placed on flolan 3 days after left pneumonectomy. After Dose-Ranging he was maintained on 18 ng/kg/min. He developed pulmonary edema after 13 hours and died 3 hours later.
3. This patient was a 28 yr old BF with severe hypertension and right heart failure (PAP 99/45 mm Hg, SAP 66/47 mm Hg, HR 116 bpm). At baseline, before flolan administration, she had developed sudden respiratory decompensation requiring vasopressors, intubation and mechanical ventilation. Her PAP decreased and her CO increased during flolan administration. She then developed severe bradycardia and hypotension which required cardiopulmonary resuscitation and pressor therapy. She subsequently developed aspiration pneumonia but her condition improved over the next 2 days while she was receiving flolan. The dose of flolan was subsequently reduced in anticipation to ending the infusion as dictated by the protocol. The patient developed cardiac arrest and died 22 hours after flolan was discontinued.
4. A 42 yr old WF developed pneumonia and possibly pulmonary contusion as a result of a motor vehicle accident. She underwent right heart catheterization for respiratory decompensation and then she was started on flolan. Arterial oxygen saturation increased during flolan dosing and she was placed on the extended infusion. She did well until the dose of flolan began to be reduced. Her condition deteriorated and she developed cardiac arrest and died.
5. A 33 year old BF with a Hx of PH, lupus erythematosus, hilar adenopathy, aortic stenosis and thrombocytopenia entered the study several hours after a cesarian section. At about 48 hours of continuous flolan infusion she had 4 episodes of decreased HR and SAP complicated with tonic/clonic seizures. After 75 hours the dose of flolan was gradually decreased and was stopped one hour later. The patient experienced two additional episodes of seizures, decreased HR and SAP after flolan was discontinued. She died of cardiac arrest 5 hours later.
6. A 52 y.o. WM with a history of scleroderma and PPH entered the study twice. During the first period he underwent dose-ranging with good results. His PVR decreased from 37.5 Wood units to 15.8 Wood u., while his CO increased from 1.36 L/min to 2.8 L/min. He was discharged home but 6 days later he developed deep vein thrombosis in his right arm. He was admitted and placed on thrombolytic therapy. His arm condition

improved but his respiratory condition deteriorated. He was placed on flolan (4 ng/kg/min increased gradually to 12 ng/kg/min). After 2 weeks the patient developed anxiety and the next day dyspnea and chest pain. Sublingual nitroglycerin did not relieve the patient. He became progressively bradycardiac and cyanotic and developed electromechanical dissociation in spite of 100% oxygen, epinephrine, atropine and electroshock. The patient died after having been on flolan for 15 days.

Significant Changes in Laboratory Values:

The mean hematocrit value was reduced by $2.8 \pm 0.3\%$ and the platelet count by $40 \pm 4 \times 10^3/\text{mm}^3$.

No significant ECG changes were found.

Thirty-one patients (11%) had post-treatment PAPm and/or PVR equal to or greater than 20% of their respective baseline values.

National Registry of Patients with PPH. Comparison with the Burroughs-Wellcome studies.

The National Registry of PPH patients was a multicenter prospective observational study sponsored by NIH. A total of 194 patients were enrolled from 1981 to 1985 and were followed through 1988. All these patients were treated with conventional therapy.

The sponsor compared the survival of class III/IV patients from the National Registry (N=138) to the patients of studies 36, 37, 46, and 47 (N=104). They claim that baseline demographics and pulmonary hemodynamics were similar among the two groups. They summarized the results of the survival in the following Table:

Follow-up Time (months)	FLOLAN		Standard Therapy		NIH Registry	
	Number of Patients Followed	Estimated Probability of Survival	Number of Patients Followed	Estimated Probability of Survival	Number of Patients Followed	Estimated Probability of Survival
0	51	1.00	53	1.00	138	1.00
2	49	0.98	40	0.81	114	0.84
3	48	0.98	10	0.71	110	0.81
6	44	0.96	3	0.71	97	0.72
12	16	0.86	1	0.71	85	0.64
18	5	0.90	1	0.71	73	0.56
24	5	0.80	0	-	68	0.52

The sponsor claims that the probability of survival was better for the floLAN patients compared to the patients of the Registry (p=0.0001).

Evaluation by the Reviewer:

It is not possible to follow the calculations of the sponsor because details have not been given. Except for the patients who died or were transplanted during the first 3 months of follow-up we do not know when exactly the remaining patients died or when they were transplanted to check the censoring.

Furthermore, the table of the sponsor is inaccurate regarding the survival of the patients on standard therapy (controls) during the first 3 months. At the end of the second month there were 10 class III/IV control patients from study #36 and 33 others from study #46, i.e., a total of 43 control patients, were alive at the end of two months (see table on next page). The table of the sponsor shows only 40.

Survival of Control Class III/IV Patients:

	<u>At Baseline</u>	<u>At 2 months</u>	<u>At 3 months</u>
<u>Study #36</u>	13	10*	2**
<u>Study #46</u>	40	33+	30++
<u>Total</u>	53	43	30 at least

*8 of these 10 patients entered study 37 and received flolan from then on.

**There is no information of how long these 2 control patients, who declined to enter study 37, survived.

+2 of the 33 patients received transplants after 86 and 92 days, respectively.

++26 of the 30 patients entered study 47 after the 12th week and received flolan from then on.

At the end of 3 months there were 30 control patients alive coming from study #46 and may be there were some survivors from the 2 class III/IV control patients from study #36 who had declined to enter study #37. In any event, at least 30 control patients were alive at the end of the 3 months and two others had received transplants. The table of the sponsor shows only 10 control patients surviving at 3 months.

We should also take into consideration that 8 of the 10 (class III/IV) control patients who had finished study #36 had entered study #37 and had been switched to flolan. Similarly 26 control patients from study #46 had entered study #47 after the completion of their study and were receiving flolan. All these patients were censored from the control group. Furthermore, we have no information of what happened to the 4 control patients from study #46, who declined to enter study #47. Some of them may still have been alive by the time that the sponsor's table, showing the comparison with the NIH Registry, was made. Any comparisons after the second and third months are invalid mainly because of the switch of the overwhelming majority (8/10, 26/30) of the control patients to flolan. The fact that there were fewer control patients after these months does not mean that all the missing patients had died.

In addition:

As mentioned earlier, the better results that were reported for flolan during the first 3 months were due to: a) Both studies

#35/36, and study #46 were open. Bias therefore in favor of flolan during randomization (severely ill patients were randomized to standard treatment and during patient treatment, and an effect on the moral of these patients cannot be excluded (case . b) At least one flolan patient and in all probability another one with the unorthodox number of died during studies 36 and 46 but were not counted as flolan deaths. These patients were reported as not-randomized. c) None of the flolan patients has been reported to have died from complications of catheterization or treatment while officially participating in the study. d) Several control patients died from complications of treatment or catheterization (digitalis toxicity, electrolyte imbalance, pneumothorax etc.).

STUDIES SPONSORED BY INDEPENDENT INVESTIGATORS (from the literature). Twenty-six such studies have been published most of them as abstracts. These studies had small numbers of patients and were uncontrolled. There was also one relatively large study with 38 patients treated with flolan and 27 others treated with standard therapy. This study was also published as an abstract without details. Two other studies were controlled with iloprost or nifedipine but had small numbers of patients.

STUDIES FOR OTHER INDICATIONS

Flolan has been tested for the following indications:

Congestive Heart Failure (2 studies)
Ischemic Heart Disease (8 studies)
Acute MI
Hypertension
Secondary Pulmonary Hypertension
Sepsis
COPD, Cor Pulmonale
Extracorporeal Circulation
Hemodialysis
Acute Renal Failure
Hemolytic Anemia
Thrombotic Thrombocytopenic Purpura
Peripheral Vascular Disease
Acute Stroke
Obstetric & Gynecological Disorders.

FOREIGN MARKETING

Flolan has been approved for use in hemodialysis as a heparin substitute in patients who have an increased risk of bleeding in the following countries: United Kingdom (1981), Spain (1988), Singapore (1988), Netherlands (1992), New Zealand (1992), Italy (1992), Ireland (1992), and Austria (1993).

An application for the same indication was disapproved by FDA in August 1989 (NDA 19-607).

8

SUMMARY

Number of Studies on PPH: The sponsor, Burroughs-Wellcome, has supported 7 clinical studies in order to provide evidence that flolan (prostacyclin) is safe and effective for the treatment of primary pulmonary hypertension (PPH). Two of these studies (#35/36 and #46) were controlled, phase III trials, and have been submitted as this NDA's pivotal studies (Table Cl₁). The others, #5/10, #20, #21, #37, and #47, were uncontrolled (Tables Cl₂).

In all the studies flolan was infused i.v. to patients who were receiving in addition what is considered standard therapy for PPH: oral vasodilators, anticoagulants, digoxin, diuretics, electrolytes, oxygen, anxiolytics, analgesics, etc. In the controlled studies a group receiving standard therapy alone served as controls. The exact composition of the standard therapy was left to the discretion of the investigator. However, there were no significant differences between the groups regarding standard therapy.

Number of Patients and Duration of Treatment: A total of 433 patients received flolan in these studies. Most of them received the drug for a very short period:

347 patients were infused with flolan for 1-5 hours in the uncontrolled studies #5/10, #20, and #21 (Table Cl₂), in a Dose-Ranging fashion where flolan dosage was increased progressively by 2 ng/kg/min every 10-15 minutes until toxic effects were induced. Seven of these patients received flolan for an additional (extended) period of 1-41 hours in study #5/10, and 13 others for a period of 12 hrs to 58 days in study #21; Study #21 is still ongoing.

Flolan was also administered as a continuous i.v. infusion to 11 patients for 8 weeks in the controlled study #35/36 and to 41 others for 12 weeks in the controlled study #46 (Table Cl₁). Fifty-four patients, 14 and 40 respectively, served as controls. Both controlled studies included in addition, an initial dose-ranging period when all patients, including the controls, received flolan. After the patients completed studies 35/36 and 46, they were given the option to enter studies 37 or 47 respectively, where flolan was administered continuously until the patient was transplanted or died. Eighteen patients (10 flolan and 8 controls) entered Study 37 and 64 (38 flolan and 26 control) entered Study 47. When all the long-term studies are considered together, by the cut off dates of August 13, 1992 for study #37, and December 1, 1992 for study 47, flolan had been infused continuously into 104 patients with PPH for a maximum of 59 months and a mean follow-up period of 27 months.

Infusion Rate of Flolan in the Long-Term Studies: The mean infusion rate of flolan was 5 ng/kg/min at the end of the first week and increased to 50 ng/kg/min after 50 months of continuous infusion. It appears that the sensitivity of the patients to flolan decreases as the infusions continue and higher doses are required to obtain the same benefits on the hemodynamic parameters (TACHYPHYLAXIS). There is also great variability among individual patients regarding the maximum tolerated dose (2-170 ng/kg/min).

The maximum tolerated dose was higher for males than for females (mean: 14 vs 10 ng/kg/min) and for younger, <16 years, than for older patients (mean: 25 vs 9 ng/kg/min). Abrupt discontinuation of flolan after a continuous infusion of a few days or longer had deleterious effects: worsening of the PPH symptoms, deterioration of hemodynamics, side effects (agitation, syncope, dyspnea, chest pain), even death. Rebound ADP-induced hyperaggregability of the platelets has also been observed and rebound hypertension has occurred in about 11-27% of the patients after discontinuation. Adverse events and rebound hypertension have also been observed following acute dose-ranging. Flolan must be withdrawn gradually to avoid these effects.

The pivotal studies: (Study 35/36 with 11 flolan and 14 control patients; and Study 46 with 40 flolan and 41 control patients).

Both pivotal studies were open-labeled. Chronic i.v. infusions of placebo were considered inappropriate given the known risks associated with a central venous catheter (clotting, embolism, infection, dislocation, vein dissection, etc.). Bias therefore on the part of the investigators, patients and the analysts cannot be excluded, especially from Study #46.

1. Deficiencies:

a) Randomization:

The randomization code in Study #46 was not predetermined but "adaptive", evolving as the randomization of the patients progressed. The randomizers received, in addition to the stratification criteria (study center, NYHA class, use of vasodilator or not), all other vital information about each patient (baseline walk distance, PAPm, CO, PCWpm, PVR, tolerated dose of flolan, intolerated dose) before randomizing him or her.

Severely ill patients (in cardiovascular collapse, with frequent syncopal attacks and hypotensive episodes, severely orthopneic, unable to walk) and patients having additional conditions besides PPH (Hepatitis C with history of bleeding, morbid obesity, hypothyroidism, history of SLE, peptic ulcer disease, systemic hypertension) were randomized to standard therapy alone.

Clearly, the groups were not comparable at baseline in Study 46.

For Study 35/36 the code was predetermined. The study, however, was wide open and selection of patients seems to have taken place. Patients who were randomized to the control, were very sick at baseline, unable to stand or walk, with frequent hypotensive episodes and/or syncopal attacks. Both were ineligible to enter the study because they had very high SGOT, BUN, and/or LDH values.

b) **Bias in Discontinuation Policy:** Study #36: pt developed severe pulmonary edema during Dose-Ranging Segment #1 and was discontinued from the study because of the complication. She died one month later. Her ID number is a flolan code number, the sponsor, however, claims that this patient had not been randomized and her death has not been reported. On the other hand, patients who developed acute bronchopneumonia and pneumothorax respectively, as a result of cardiac catheterization in the same study, were not discontinued but were randomized to "no flolan" according to the code. Both died during the study.

Study #46: pt. developed subclavian artery dissection during catheterization. In spite of this accident she was entered into the study and was randomized to standard therapy alone. On the other hand, Pt. who developed pneumothorax during catheterization, was allegedly not entered into the study and was not randomized. She died on 3/3/92, 5 days after the formation of the pneumothorax. Her ID number on the first 20 pages of her CRF has been tampered. It looks like her original number was . The patients were numbered sequentially as they were screened for the study and this patient was the first patient for study center 15. Number is an improbable number. Center 15 had only 6 patients. A new patient was randomized to flolan one day after the alleged patient had died.

c) **Treatment Toxicity:** Aggressive treatment with diuretics and digitalis induced electrolyte abnormalities and arrhythmia in 4 very sick control patients, who died. Contraindicated use of anticoagulants in another patient caused her death by bleeding.

d) **Abrupt discontinuation of flolan:** All the control patients in both Study #35/36 and Study #46 were dose-ranged with flolan to start with. Judging from the patients who died (for whom we have copies of CRFs) the infusion was stopped abruptly. Abrupt discontinuation of flolan even in short range cases can cause adverse effects, rebound hypertension and worsening of PPH symptoms, as mentioned earlier. In very sick patients it could even cause death as in the case of patient who died on the day of randomization, shortly after dose-ranging.

e) **Lack of Clinical Chemistry, Hematology, and ECG Data:** Study #46, the larger of the controlled studies, lacks completely clinical chemistry, hematology, and ECG data. The sponsor claims that such data were not required for this study. Considering that the patients who were treated in Study 46 were very sick people, most of them on digitalis and diuretics requiring strict control of electrolytes and digoxin dosage, this deficiency is very serious and by itself alone disqualifies study 46 from the claim of being an adequate and well controlled investigation.

2. Effectiveness:

a) **Hemodynamic Effects:** All the studies showed that flolan decreased the pulmonary pressures, systolic and/or diastolic, and the resistances (pulmonary and systemic, vascular and total) and on the other hand it increased the CO, CI, SV, and HR compared to baseline values. The changes were shown to be significant only in the controlled studies. These changes were also found to be significant when they were compared with the effect of the control (standard treatment alone) mainly in study #46.

The hemodynamic results can be accepted as reliable representing the effect of flolan in PPH patients because the comparisons included only patients who had data both at baseline and at the end of the study i.e. the very sick patients who died, were not included in the analyses (Tables 35/36_{11,12}, 46₁₄).

b) **The 6-Minute Walk:** The controlled studies showed that the patients, who received flolan walked significantly longer distances during the 6-minute period than the patients, who had received only the standard therapy alone.

In these comparisons all patients were included (Tables 35/36₆, 46₆). As explained earlier, the experimental groups were not comparable. The control groups had more severely ill patients. The results cannot be accepted as reliable. In addition, in Study 35/36 the patients were "encouraged" by the investigators to walk during the test. The study was open and bias in the degree of "encouragement" cannot be excluded.

c) **Survival:** Most importantly, the sponsor claims that flolan increased the survival of the patients very significantly: they reported that only one flolan patient died in study 35/36 and none in study #46. The respective numbers for the control patients were 3 and 8 i.e. the total number of patients who died according to the sponsor was 1 flolan patient vs 11 control patients ($p < 0.01$).

The larger number of deaths in the control groups was mainly due to the fact that a) as explained earlier, more severely ill patients or patients with additional morbid conditions, were randomized to the control group in both studies (see randomization). b) The patients were subjected to aggressive treatment with diuretics and digoxin. Due to the severity of their disease some of the control patients developed electrolyte abnormalities and digitalis toxicity, c) some control patients developed complications during cardiac catheterization and died. Flolan patients who developed similar complications were discontinued from the study and their death was not counted.

All in all the number of deaths which can be reasonably attributed to the test treatments in the pivotal studies were:

	<u>Flolan</u>	<u>Control</u>
Study 35/36	2	0
Study 46	0	1
Total	2	vs 1

d) **Quality of Life:** The results of the quality of life cannot be accepted as meaningful. As mentioned earlier, the control groups included more severely ill patients than the flolan groups. In addition, investigator influence on the self evaluation of the patients cannot be excluded (The patients had to discuss the questions with the investigators before evaluating them.)

3. Safety:

a) **Dose-Ranging Period:** The most frequent adverse reactions were:

Flushing	58%
Headache	49%
Nausea, vomiting	32%
Hypotension	16%
Chest Pain	11%
Anxiety/nervousness/agitation	11%
Dizziness	8%
Bradycardia	5%
Abdominal pain	5%

Continuing Adverse Events:

Vomiting	19%
Headache	18%
Hypotension	15%
Flushing	14%

Life-Threatening Events:

	No. of Cases
Pulmonary edema	1
Pneumothorax	2
Bronchopneumonia	1
Subclavical artery dissection	1

b) Chronic infusion: The most frequent adverse events are shown below:

Adverse Experience	% of Patients	
	FLOLAN	Standard Therapy
Headache	83%	33%
Dizziness	83%	70%
Nausea/vomiting	67%	48%
Jaw pain	54%	0%
Myalgia	44%	31%
Flushing	42%	2%
Diarrhea	37%	6%
Pain	35%	15%
Tachycardia	35%	24%
Heart failure/Right heart failure	31%	52%
Hypoxia	25%	37%
Anxiety/Nervous/Tremor	21%	9%
Chills/Fever/Sepsis/Flu syndrome	25%	11%
Injection site reaction/inflammation	21%	0%
Injection site pain	13%	0%
Syncope	13%	24%
Shock	0%	13%

It appears that the flolan group experienced considerably more headaches, nausea/vomiting, flushing, diarrhea, pain, tachycardia, anxiety, and sepsis than the control group. The flolan group in addition, suffered reactions not encountered in the control group: jaw pain (54%), inflammation and pain at the injection site (21%).

In addition to these reactions there were also reactions associated with the flolan delivery system: adjustment of the flolan dose (tachycardia, dizziness, nausea, etc), problems with catheter placement, dislodgement, occlusion (thrombosis, CVA), bleeding, and problems associated with infusion pump malfunction. There was also a case of "prostacyclin induced" pulmonary edema.

CONCLUSIONS:

None of the pivotal studies of NDA 20-444 can be considered adequate or well controlled.

The studies showed that flolan can reduce the pulmonary pressures and resistances of patients with PPH significantly in agreement with its pharmacodynamic properties. However, convincing evidence that flolan can prolong the survival of PPH patients has not been presented. The information about the patients who died is insufficient. The reviewer had to become detective to dig up information regarding the circumstances of death. Unconvincing are also the results of the 6-minute walk and those of the quality of life.

The lack of a flolan effect on survival may be due to the fact that the reductions of the pulmonary pressures were not large enough to bring these pressures down to physiological levels or close to them. In study #46, which the sponsor considers as their best, the pulmonary pressures were reduced from 98/41 mm Hg to 90/37 mm Hg with the mean pulmonary pressure reduced from 60 to 55 mm Hg, which is still much higher than 25 mm Hg, the limit for the diagnosis of pulmonary hypertension. [The normal pulmonary pressures vary from 20/12, mean 15 mm Hg, to 38/14, mean 25 mm Hg (depending on altitude)]. Similarly, the increases in CO (3.5 to 4.1 L/min) and CI (2.0 to 2.4 L/min/m²) induced by flolan were not large enough to bring these parameters to normal (6.0 L/min, 3.1 L/min/m², respectively).

Another very important reason for the inability of flolan to truly increase survival was the increase in adverse events, especially those associated with cardiac catheterization and the flolan delivery system (pneumothorax, infection, sepsis, thrombosis, embolism, etc.).

There is also the problem of tachyphylaxis. The longer a patient is on flolan, the higher the infusion rate must be. It has been shown that the response of the platelets to ADP decreases after 24-48 hours of continuous PGI₂ infusion and returns to baseline values after 48-72 hours of infusion. Platelet studies in the PPH studies were not done, although they were included in some protocols. It would probably have been better if the flolan infusions were discontinuous tapering gradually after 24 hrs and restarting after 1 or 2 days to counteract the effect of tachyphylaxis.

RECOMMENDATIONS:

1. We must verify the circumstances of death of the control patients in study #46 from the hospital records. We have to wait for the report of the Division of Scientific Investigations.
2. Request that the sponsor provide:
 - a) Complete copies of the autopsy reports of pts.
Only the first pages of these reports have been submitted.
 - b) Complete copies of the CRFs of the patients who died in Study #47.
 - c) Tabulations and analysis of the results of the Borg Dyspnea Score from Study #46.
3. Request that the sponsor explain how the scores of Part I of the Nottingham Health Profile were obtained. The patients were supposed to check a "yes" or "no" box on the report forms. There were no scores.

E. Triantas, M.D., Ph.D.
E. Triantas, M.D., Ph.D.

CC:
NDA 20-444
HFD-180
HFD-180/SFredd
HFD-180/ETriantas
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
r/d 7/26/94 jgw
f/t
MED\N\20444406.0ET

9/14/94
Concur
ST

20-444

NDA: 20-444
DRUG: Flolan, PGI₂

SPONSOR: Burroughs-Wellcome

TABLES

REVIEWER: E. Triantas, MD, Ph.D.

LIST OF ABBREVIATIONS/UNITS

Abbreviation	Full Designation	Units
ACE	Angiotensin-converting enzyme	—
ADP	Adenosine diphosphate	—
AE	Adverse experience	—
AP	Alkaline phosphatase	U/L
aPTT	Activated partial thromboplastin time	seconds
AVO ₂ D	Arteriovenous oxygen difference	mL/dL
BIN	Batch identification number	—
BSA	Body surface area	m ²
BUN	Blood urea nitrogen	mg/dL
C	Centigrade	—
CI	Confidence interval	—
CO	Cardiac output	liters/min
COSTART	Coding symbols for thesaurus of adverse reaction terms	—
CRF	Case report form	—
CTM	Clinical trial material	—
D ₅ W	5% dextrose in water	—
dL	Deciliter	—
ECC	Electrocardiogram	—
FDA	Food and Drug Administration	—
F number	Formulation number	—
Hb	Hemoglobin	mg/dL
hr	Hour	—
HR	Heart rate	beats/min
IND	Investigational new drug	—
IRB	Institutional Review Board	—
IV	Intravenous	—
kg	Kilogram	—
L	Liters	—
LDH	Lactate dehydrogenase	U/L
LVEDP	Left ventricular end diastolic pressure	mm Hg
m	Meter	—
mg	Milligram	—
min	Minute	—
mL	Milliliter	—
mm	Millimeter	—

<u>Abbreviation</u>	<u>Full Designation</u>	<u>Units</u>
mM	Millimole	—
mV	Millivolt	—
μ L	Microliter	—
μ M	Micromole	—
μ g	Microgram	—
MTD	Maximum tolerated dose	—
MVO ₂	Mixed venous oxygen saturation	%
ng	Nanogram	—
NIH	National Institutes of Health	—
NHP	Nottingham Health Profile	—
NYHA	New York Heart Association	—
PaCO ₂	Arterial carbon dioxide tension	mm Hg
PaO ₂	Arterial oxygen tension	mm Hg
PAP	Pulmonary arterial pressure	mm Hg
PAPd	Diastolic pulmonary arterial pressure	mm Hg
PAPm	Mean pulmonary arterial pressure	mm Hg
PAPs	Systolic pulmonary arterial pressure	mm Hg
PCWP	Pulmonary capillary wedge pressure	mm Hg
PCWPm	Mean pulmonary capillary wedge pressure	mm Hg
pHa	Arterial pH	pH units
pHv	Venous pH	pH units
PPH	Primary pulmonary hypertension	—
PPP	Platelet poor plasma	—
PRP	Platelet rich plasma	—
PT	Prothrombin time	seconds
PvCO ₂	Mixed venous carbon dioxide tension	mm Hg
PvO ₂	Mixed venous oxygen tension	mm Hg
PVR	Pulmonary vascular resistance	Wood Units (mm Hg/liter/min)
qs	A quantity sufficient	—
RAP	Right atrial pressure	mm Hg
RAPm	Mean right atrial pressure	mm Hg
SaO ₂	Arterial oxygen saturation	%
SAP	Systemic arterial pressure	mm Hg
SAPd	Diastolic systemic arterial pressure	mm Hg
SAPm	Mean systemic arterial pressure	mm Hg
SAPs	Systolic systemic arterial pressure	mm Hg

<u>Abbreviation</u>	<u>Full Designation</u>	<u>Units</u>
SGOT	Serum glutamic-oxaloacetic transaminase (aspartate aminotransferase)	U/L
SOT	Systemic oxygen transport	mL/O ₂ /min
SV	Stroke volume	mL/beat
SVR	Systemic vascular resistance	Wood Units (mm Hg/liter/min)
SWI	Stroke work index	g · m/m ²
TPR	Total pulmonary resistance	Wood Units (mm Hg/liter/min)
TSR	Total systemic resistance	Wood Units (mm Hg/liter/min)
U	Units	—
V/Q	Ventilation perfusion	—

TABLE C1,

CLINICAL STUDIES ON PPM
Supported by Burroughs-Wellcome

Controlled Studies

Study #	Investigator	Stratification Criteria	Design	Stages	Duration	NYHA Class	#Pts		Flolan Dose (ng/kg/min)
							F	C	
35	Rubin	Use of oral Vasodilator	Controlled open Parallel random.	1. Dose- Rang. 2. Long- Term	1-2 h 8 wk	II	1	1	2-12 4, 6
36	Rubin Barst McGoon	Use of oral Vasodilator	as above	as above	1-2 h 8 wk	III IV	8 2	7 6	2-22 2-12
46	17 centers incl. those of investig. listed above	Use of oral vasodilator, NYHA class, Study center	as above	as above	1-2 h 12 wk	III	31	29	22-20

TABLE C1, (continued)

Study #	Distance Walked, Difference from Baseline (meters)		Hemodynamic Effects of Flolan		Hemod. Effects Sign. Diff. Between Groups	Nottingham Profile Sign. Diff. Bet. Groups	Deaths F C
	F	C					
35/36	73	-5	TPR TSR SVR PAPs	CI CO	PAPs TPR favoring flolan	Physical Mobility	2* 3
46	30	-50	TPR TSR SVR PVR SAPd PAP RAP	CI CO S V AS MVS Tc) ₂	CI, CO, SV, PAP, PVR, TPR SAP, SVR, TSR, Arter. satur. in favor of flolan.	emotions energy, sleep home care, vacations	0 8

Deficiencies

- 35 - Open, bias in rand. & discontin. of pts. favoring flolan, ineligible patients, deaths due to cardiac catheterization. Investigator interference with walk test.
- 46 Open, bias in random. & discontin favoring flolan. Deaths due to electrolyte imbalance, dig. toxicity. Investigator interfer. with questionnaires. Lack of clin. chem. hematology and ECG data.

F=flolan
C=control

TABLE 35/36, (Con't)
PART II

In the list below, check YES for each area of your life which is being affected by your state of health; check NO for each area which is not being affected or which does not apply to you.

IS YOUR PRESENT STATE OF HEALTH CAUSING PROBLEMS WITH YOUR...

	YES	NO
WORK (That is, paid employment)	☐	☐
LOOKING AFTER THE HOME? (Examples: cleaning & cooking, repairs, odd jobs around the home, etc.)	☐	☐
SOCIAL LIFE? (Examples: going out, seeing friends, going to the movies, etc.)	☐	☐
HOME LIFE? (That is, relationships with other people in your home)	☐	☐
SEX LIFE?	☐	☐
INTERESTS AND HOBBIES? (Examples: sports, arts and crafts, do-it-yourself, etc.)	☐	☐
VACATIONS? (Examples: summer or winter vacations, weekends away, etc.)	☐	☐

Now please go back to the first page and make sure that you have answered yes or no to every question on all four pages. Thank you.

TABLE 35/36₂

General Time and Events Schedule

Event	Study Phase:		Baseline		Treatment													Posttreatment	
	Study Day:	Screening		Dose-Ranging Segment #1	Long-term Infusion Segment											Dose-Ranging Segment #2	Dose-Ranging Segment #3		
		0	1		1	1	1	2	8	15	22	29	36	43	50		56	57	57
Medical History	X																		
Informed Consent	X																		
Physical Examination	X													X					X ^a
12-Lead ECG ^b	X													X					
Echocardiogram ^b	X													X					
Chest Radiograph ^c	X													X					
Clinical Laboratory Tests ^d																			
Blood Chemistry		X													X				
Hematology		X													X				
Coagulation Times		X													X				
Platelet Aggregation (optional)			X	X ^e											X			X	
Compliance with Inclusion/Exclusion Criteria		X	-----	X															
Place Swan-Ganz Catheter		X		X												X			X
Dose-Ranging Infusion of PLOLAN ^e				X												X			X
Long-term Infusion of PLOLAN						X	-----	X											
Monitor Blood Pressure	X	X	-----	X	X										X	X			X
Continuous ECG		X	-----	X												X			X
Hemodynamic Measurements ^b		X	X	X										X	X				X
Blood Gas Measurements		X	X	X										X	X				X
6 Minute Walk	X ^h					X			X				X					X	
Adverse Experience Reports				X	X	-----	X							X	X				X
Health Profile ⁱ	X					X			X				X					X	

^a Performed after hemodynamic parameters have returned to baseline
^b Obtained within 1 month prior to Screening
^c Obtained within 6 months prior to Screening
^d Obtained within 2 weeks prior to Screening
^e At maximum allowable dose of PLOLAN

^f Long-term infusion segment began immediately after dose-ranging segment #1.
^g Patient fasted for at least 12 hours prior to making hemodynamic measurements.
^h Performed once in the morning and once in the afternoon.
ⁱ Administered to patients 16 years of age and older

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TABLE 35/36₂ (Con't)

Detailed Time and Events Schedule for Dose-Ranging Segments

EVENT	Baseline	Infusion Rate (ng/kg/min)					
		2	4	6	8	10	12
Record time at start and at finish	X	X	X	X	X	X	X
Hemodynamic Data ^a							
Heart Rate	X	X	X	X	X	X	X
SAPs, SAPd, SAPm	X	X	X	X	X	X	X
PAPs, PAPd, PAPm	X	X	X	X	X	X	X
CO ^b	X	X	X	X	X	X	X
PCWPm; RAPm	X	X	X	X	X	X	X
Blood Gas Data							
% Arterial Saturation	X	X	X	X	X	X	X
PaO ₂ , PaCO ₂ , pH _a	X	X	X	X	X	X	X
% Mixed Venous Saturation	X	X	X	X	X	X	X
PvO ₂ , PvCO ₂ , pH _v	X	X	X	X	X	X	X

Except during the screening period, events marked X were performed at the conclusion of the segment identified.

^a Patient fasted for at least 12 hours prior to making hemodynamic measurements.

^b Cardiac output was measured by thermodilution and/or Fick methods.

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TABLE 35/36₃

Summary of Demographic Characteristics

Characteristic	Summary Statistics	Flown	Standard
Age (years)	N	11	14
	Mean	37.45	33.00
	Std.Dev.	12.65	15.45
	Median	34.00	30.00
	Minimum Maximum	21.00 66.00	12.00 60.00
Age Category (years)	< 20		2 (14.3%)
	20-29	2 (18.2%)	5 (35.7%)
	30-39	5 (45.5%)	3 (21.4%)
	40-49	1 (9.1%)	
	50+	2 (18.2%)	4 (28.6%)
Sex	Female	7 (63.6%)	11 (78.6%)
	Male	4 (36.4%)	3 (21.4%)
Race	Black		3 (21.4%)
	White	11 (100.0%)	11 (78.6%)
Weight (kg)	N	11	14
	Mean	64.90	70.29
	Std.Dev.	12.35	16.39
	Median	67.20	69.30
	Minimum Maximum	42.20 82.50	45.00 117.00
Weight Category (kg)	< 50	2 (18.2%)	1 (7.1%)
	50-59		3 (21.4%)
	60-69	5 (45.5%)	3 (21.4%)
	70-79	3 (27.3%)	5 (35.7%)
	80+	1 (9.1%)	2 (14.3%)
NYHA Class	II	1 (9.1%)	1 (7.1%)
	III	8 (72.7%)	7 (50.0%)
	IV	2 (18.2%)	6 (42.9%)
Prior Vasodilator Use	No	6 (54.5%)	8 (57.1%)
	Yes	5 (45.5%)	6 (42.9%)

TABLE 35/364

Summary of FLOLAN® Doses and Dosing Changes During the Long-Term Infusion Segment

FloLAN (N=11)

Week	N	Mean	S.E.	Dose Summary Statistics ^a			Max.	Patients Requiring Dose Adjustments (N)	Mean Number of Days Per Patient where Dose Adjustments were Required	Mean Number of Dose Adjustments per Patient
				25-th	Median	75-th				
Initial dose	11	4.6	0.5	2.0	4.0	6.0	8.0			
1	11	7.2	0.8	4.0	4.2	10.0	10.0	9	1.5	1.9
2	11	7.2	0.8	4.0	4.2	10.0	10.0	0	0.0	0.0
3	11	7.4	0.8	4.0	4.2	10.0	10.0	1	0.1	0.1
4	10	7.2	0.9	4.0	4.2	10.0	10.0	0	0.0	0.0
5	10	7.4	0.9	4.0	4.2	10.0	12.0	1	0.1	0.1
6	10	7.4	0.9	4.0	5.2	10.0	12.0	0	0.0	0.0
7	10	7.4	0.9	4.0	4.2	10.0	12.0	0	0.0	0.0
8	10	7.4	0.9	4.0	4.2	10.0	12.0	0	0.0	0.0
9-1	10	7.4	0.9	4.0	4.2	10.0	12.0	0	0.0	0.0

^aDue to scheduling, some patients remained in the longterm infusion segment for longer than 87 days. All doses are measured in ng/kg/min as of the last day of each week.

TABLE 35/36₅

Summary of Concomitant Medications Used at Baseline

Fleien (N=11)
Standard (N=14)

Drug Class	Fleien N (Z)	Standard N (Z)
Anesthetics	5 (45)	0 (57)
Antiarrhythmics	0 (0)	1 (7)
Antibiotics	1 (9)	0 (0)
Anticholinergics	0 (0)	2 (14)
Anticoagulants	6 (54)	11 (78)
Coagulants	1 (9)	1 (7)
Antihistamines	3 (27)	2 (14)
Antihypertensive	0 (0)	1 (7)
Antitussives/Expectorants/Cold Meds	0 (0)	5 (35)
Bronchodilators	1 (9)	1 (7)
CNS: Anxiolytic/Sedative-hypnotic	7 (63)	0 (57)
CNS: Antidepressants	1 (9)	0 (0)
Diuretics	6 (54)	0 (57)
Electrolytes	5 (45)	5 (35)
Fluids	1 (9)	1 (7)
GI: Antacids	1 (9)	1 (7)
GI: Stool Softeners/Laxatives	2 (18)	3 (21)
GI: Antacids/Antiulcer	5 (45)	1 (7)
Digestin	2 (18)	4 (28)
Other Inotropes/Vasopressors	1 (9)	0 (0)
Ophthalmics	0 (0)	1 (7)
Hypoglycemics	1 (9)	1 (7)
Steroids	1 (9)	0 (0)
All Vasodilators	5 (45)	0 (57)
ACE Inhibitors	0 (0)	1 (7)
Ca + Channel Blockers	2 (18)	0 (57)
Other Vasodilators	3 (27)	2 (14)
Oxygen	7 (63)	9 (64)

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TABLE 35/36₆

Protocol-Specified Analysis for Six-Minute Walk (Analysis of Variance Using the "Last Observation Carried Forward" Method)

		Fioren (N=11)			Standard (N=14)			Parametric Analysis ¹ of Variance (two sided p-value)
		Fioren		Standard				
N	Baseline Mean	Day 56 Mean	Mean Change from Baseline	N	Baseline Mean	Day 56 Mean	Mean Change from Baseline	
11	225.2	363.7	138.5	14	215.4	241.5	26.0	0.043

NOTE: Patients 36018 and 36019 were missing pm 6 minute walk tests. Their am walk results were used for this analysis. In addition, some patients walked longer than 6 minutes. For these patients, a fraction of the total distance proportional to 6 minutes was used for the summary statistics.

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TABLE 35/367

Summary of Changes from Baseline in Exercise Capacity at Days 2, 29 and 56

Flofen (N=11)
Standard (N=14)

Parameter	Treatment Group	Study Day	N ²	Mean	S.E.	Min.	Max.	Change from Baseline Summary Statistics ¹			Nonparametric 95% Confidence Interval	
								Z-tile	Median	Z-tile	Max.	Est.
6 Min. Walk	Flofen	2	11	82.6	39.0	-64.7	0.0	85.0	175.0	230.7	88.8	(19.24, 340.00) *
		29	7	120.3	59.9	-97.0	-10.0	140.9	270.7	200.0	127.6	(-51.05, 278.70) *
		56	10	141.2	43.1	-82.0	40.3	116.0	241.8	346.0	141.0	(44.79, 237.80) *
	Standard	2	6	3.4	42.3	-198	-73.4	3.3	96.7	169.0	0.9	(-90.25, 112.00)
		29	6	56.2	79.0	-315	5.0	134.0	100.4	199.1	97.4	(-318.00, 199.10)
		56	11	35.7	43.4	-314	14.0	20.0	100.0	260.3	27.3	(-26.05, 137.15)

NOTE: Patients 3608 and 3609 were missing on 6 minute walk tests. Their 6 min walk results were used for this analysis. In addition, some patients walked longer than 6 minutes. For these patients, a fraction of the total distance proportional to 6 minutes was used for the summary statistics. Also patients with missing start or end times were excluded.

* A confidence interval that does not contain 0 implies a statistically significant treatment effect. Only walks that had a recorded start and end time were summarized. Number of patients with values at the noted study day and also at baseline (study day 0). Hodges-Lehmann estimate for the true change from baseline.

TABLE 35/36

Baseline Hemodynamic and Blood Gas Measurements for Both Treatment Groups

Flofen (N=11)
Standard (N=14)

Hemodynamics and Blood Gases	Treatment Group	N	Mean	S.E.	Min.	Summary Statistics				
						25-th	Median	75-th	Max.	
Arterial Saturation (%)	Flofen	11	92.45	1.30	86.00	89.00	93.00	96.00	100.00	
	Standard	14	94.71	1.22	86.00	93.00	97.00	98.00	99.00	
AVO2D (ml/dL)	Flofen	11	6.76	0.76	3.59	6.34	7.34	7.96	12.22	
	Standard	14	6.05	0.46	3.91	5.39	6.97	7.05	11.01	
Cardiac Index (L/min/m ²)	Flofen	11	1.07	0.19	1.22	1.29	1.67	2.49	2.91	
	Standard	14	1.66	0.17	0.93	1.33	1.50	3.67	3.22	
Cardiac Output (L/min)	Flofen	11	3.23	0.34	1.74	2.40	3.04	4.46	5.00	
	Standard	14	2.99	0.37	1.65	2.20	2.52	3.00	5.90	
Heart Rate (bpm)	Flofen	11	64.64	3.04	63.00	76.00	80.00	100.00	105.00	
	Standard	14	64.79	4.70	50.00	70.00	81.50	95.00	112.00	
Mixed Venous Saturation (%)	Flofen	11	50.36	3.65	29.00	56.00	59.00	67.00	73.00	
	Standard	14	61.00	2.05	45.00	59.00	61.00	65.00	75.00	
PaCO2 (mm Hg)	Flofen	4	20.00	1.00	25.00	24.50	20.50	29.50	30.00	
	Standard	6	33.50	2.31	24.00	31.00	34.00	39.00	39.00	
PaO2 (mm Hg)	Flofen	4	64.00	0.70	52.00	53.50	50.00	75.00	90.00	
	Standard	6	120.17	32.16	52.00	60.00	96.50	165.00	263.00	
PAPd (mm Hg)	Flofen	11	40.09	3.05	22.00	32.00	30.00	55.00	69.00	
	Standard	14	44.36	3.42	20.00	30.00	45.00	50.00	68.00	

TABLE 35/36_g (Con't)

Baseline Hemodynamic and Blood Gas Measurements for Both Treatment Groups (continued)

Flolan (N=11)
Standard (N=14)

Summary Statistics

Hemodynamics and Blood Gases	Treatment Group	N	Mean	S.E.	Min.	25-th		Median	75-th		Max.
						Z-ile	Z-ile		Z-ile	Z-ile	
PAPm (mm Hg)	Flolan Standard	11	56.64	4.26	40.33	46.00	46.00	51.00	59.33	67.33	87.33
	Flolan Standard	14	63.67	3.77	41.00	53.00	53.00	63.00	75.00	88.67	
PAPs (mm Hg)	Flolan Standard	11	89.73	5.42	65.00	77.00	77.00	86.00	106.00	124.00	
	Flolan Standard	14	102.29	5.38	63.00	93.00	93.00	103.50	113.00	132.00	
PCUPm (mm Hg)	Flolan Standard	10	7.89	1.02	2.00	4.00	4.00	6.00	10.00	22.00	
	Flolan Standard	9	9.00	2.34	0.00	3.00	3.00	10.00	13.00	22.00	
pha	Flolan Standard	3	7.44	0.01	7.41	7.41	7.41	7.44	7.44	7.44	7.44
	Flolan Standard	6	7.44	0.02	7.37	7.40	7.40	7.44	7.44	7.44	7.52
pllv	Flolan Standard	10	7.44	0.01	7.39	7.41	7.41	7.44	7.44	7.44	7.44
	Flolan Standard	9	7.41	0.01	7.30	7.39	7.39	7.40	7.43	7.47	7.47
PVCO2 (mm Hg)	Flolan Standard	9	37.44	1.24	33.00	36.00	36.00	37.00	39.00	45.00	
	Flolan Standard	9	37.09	1.33	33.00	36.00	36.00	38.00	42.00	44.00	
PVO2 (mm Hg)	Flolan Standard	10	31.00	1.30	22.00	30.00	30.00	31.00	34.00	37.00	
	Flolan Standard	10	32.50	1.23	25.00	30.00	30.00	32.00	34.00	40.00	
PVR (Wood u)	Flolan Standard	10	18.79	3.05	9.57	16.76	16.76	14.97	27.22	37.55	
	Flolan Standard	9	19.59	2.95	7.43	16.25	16.25	16.54	25.09	32.55	
MAPm (mm Hg)	Flolan Standard	10	7.00	2.01	-3.00	2.00	2.00	0.50	13.00	16.00	
	Flolan Standard	14	9.07	1.43	0.00	6.00	6.00	7.50	15.00	18.00	

TABLE 35/36₈ (Con't)

Baseline Hemodynamic and Blood Gas Measurements for Both Treatment Groups (continued)

Hemodynamics and Blood Gases	Treatment Group	Flolan (N=11) Standard (N=14)							
		Summary Statistics							
		N	Mean	S.E.	Min.	25-th X-ile	Median	75-th X-ile	Max.
SAPd (mm Hg)	Flolan	11	75.02	4.09	48.00	69.00	70.00	80.00	100.00
	Standard	14	81.71	2.67	62.00	77.00	80.00	85.00	101.00
SAPm (mm Hg)	Flolan	11	87.18	4.10	61.67	79.00	80.00	92.33	112.67
	Standard	14	98.83	4.18	84.00	89.67	93.50	104.67	130.33
SAPs (mm Hg)	Flolan	11	113.91	4.95	95.00	100.00	109.00	130.00	141.00
	Standard	14	133.87	8.94	101.00	117.00	122.00	133.00	231.00
SOT (mL/O2/min)	Flolan	11	874.28	66.04	304.87	394.51	587.02	719.41	982.36
	Standard	14	624.39	75.90	348.47	415.84	500.12	620.72	1219.3
SV (mL/beat)	Flolan	11	39.23	4.73	16.87	30.00	32.43	51.32	78.79
	Standard	14	16.18	4.66	18.00	25.00	30.95	48.10	81.94
SVR (Wood u)	Flolan	10	26.48	2.94	18.16	19.63	32.93	33.86	48.48
	Standard	14	33.53	2.56	14.75	24.67	34.78	40.88	47.27
SWI (g-m/m ²)	Flolan	10	24.27	4.15	12.69	13.48	19.31	42.52	43.55
	Standard	9	26.92	5.29	9.98	17.27	17.54	34.32	54.55
TPR (Wood u)	Flolan	11	28.62	3.39	9.79	11.07	18.88	33.49	39.88
	Standard	14	25.24	3.11	7.43	18.58	28.58	35.38	46.48
TSR (Wood u)	Flolan	11	29.88	3.18	18.61	28.29	24.75	38.47	58.57
	Standard	14	37.53	3.16	18.42	24.17	39.85	47.69	57.58

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TABLE 35/36₉

Summary of Acute Hemodynamic and Blood Gas Effects of FLOLAN[®], Changes from Baseline to Maximum Tolerated Dose in Dose-Ranging Segment #1

Parameters	Treatment Group	Study day	Summary Statistics									Nonparametric 95% Confidence Interval
			N ¹	Mean	S.E.	Min.	25-th X-ile	Median	75-th X-ile	Max.	H-1 ² Est.	
Arterial Saturation (%)	Floian	1	11	1.45	0.55	-1.00	0.00	1.00	3.00	4.00	1.50	(0.00,3.00)
	Standard	1	13	0.30	0.60	-3.00	-1.00	0.00	2.00	6.00	0.00	(-1.00,2.00)
AVO ₂ D (mL/dL)	Floian	1	8	-2.00	0.41	-4.60	-3.50	-3.19	-1.77	-1.20	-2.04	(-4.04,-1.65) *
	Standard	1	11	-2.11	0.26	-3.12	-2.94	-2.13	-1.50	-0.93	-2.07	(-2.06,-1.40) *
Cardiac Index (L/min/m ²)	Floian	1	11	0.67	0.15	0.00	0.23	0.54	1.19	1.61	0.64	(0.32,1.04) *
	Standard	1	14	0.62	0.10	0.14	0.34	0.42	0.97	1.33	0.64	(0.34,0.87) *
Cardiac Output (L/min)	Floian	1	11	1.20	0.20	0.00	0.40	0.90	2.16	2.09	1.15	(0.50,1.09) *
	Standard	1	14	1.09	0.17	0.22	0.60	0.90	1.50	2.20	1.05	(0.65,1.45) *
Heart Rate (bpm)	Floian	1	11	8.02	1.90	2.00	5.00	7.00	12.00	23.00	7.75	(5.00,14.00) *
	Standard	1	14	7.06	2.20	-5.00	0.00	11.00	15.00	17.00	0.00	(5.00,15.00) *
Mixed Venous Saturation (%)	Floian	1	8	15.75	2.05	0.00	11.50	15.00	20.00	24.00	15.75	(11.00,21.00) *
	Standard	1	11	10.09	0.77	7.00	7.00	10.00	12.00	14.00	10.00	(8.50,12.60) *
PaCO ₂ (mm Hg)	Floian	1	4	-0.75	1.31	-3.00	-2.50	-1.50	1.00	3.00	-1.25	N is too small
	Standard	1	6	-1.17	0.40	-3.00	-1.00	-1.00	-1.00	0.00	-1.00	(-3.00,0.00)
PaO ₂ (mm Hg)	Floian	1	4	-1.75	6.94	-21.00	-11.50	1.50	0.00	11.00	-0.25	N is too small
	Standard	1	6	-23.17	17.05	-104.0	-30.00	-12.50	0.00	12.00	-12.50	(-104.00,12.00)
PAPd (mm Hg)	Floian	1	11	2.00	2.00	-5.00	-4.00	1.00	0.00	15.00	1.50	(-2.50,7.00)
	Standard	1	14	-3.21	3.29	-43.00	-4.00	-1.00	1.00	10.00	-1.00	(-4.50,2.00)

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A confidence interval that does not contain 0 implies a statistically significant treatment effect.

¹Number of patients with lab values at dose-ranging and also at baseline.²Hedges-Lehmann estimate for the true change from baseline.

NOTE: One patient reached their maximum tolerated dose more than once in the first dose-ranging segment.

The last measurements were summarized.

SS031(FLSSHEMS) 12/13/93 10:51

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TABLE 35/36, (Con't)

Summary of Acute Hemodynamic and Blood Gas Effects of FLOLAN[®], Changes from Baseline to Maximum Tolerated Dose in Dose-Ranging Segment #1 (continued)

Parameters	Treatment Group	Study day	N ¹	Summary Statistics									Nonparametric 95% Confidence Interval
				Mean	S.E.	Min.	25-th X-11s	Median	75-th X-11s	Max.	H-L ² Est.		
PAPm (mm Hg)	FloLAN	1	11	2.91	2.28	-5.67	-3.67	0.53	6.33	17.33	1.03	(-2.33, 6.67)	
	Standard	1	14	-2.48	3.49	-45.06	-2.33	-0.17	2.00	8.33	0.06	(-2.67, 2.33)	
PAPs (mm Hg)	FloLAN	1	11	4.73	3.13	-7.00	-3.00	3.00	8.00	25.00	2.75	(-2.50, 12.50)	
	Standard	1	14	-1.80	3.02	-49.00	0.00	2.50	4.00	11.00	2.00	(-0.50, 4.50)	
PCHPm (mm Hg)	FloLAN	1	7	-0.14	0.54	-1.00	-1.00	0.00	0.00	1.00	0.00	(-1.00, 1.00)	
	Standard	1	6	-2.33	0.84	-5.00	-4.00	-2.50	0.00	0.00	-2.50	(-5.00, 0.00)	
pha	FloLAN	1	3	0.02	0.01	0.01	0.01	0.02	0.03	0.03	0.02	N is too small	
	Standard	1	6	0.00	0.01	-0.04	-0.01	0.01	0.02	0.04	0.01	(-0.04, 0.04)	
pliv	FloLAN	1	7	0.03	0.01	0.00	0.00	0.03	0.03	0.04	0.03	(0.00, 0.05)	
	Standard	1	6	0.03	0.01	0.01	0.01	0.03	0.03	0.03	0.03	(0.01, 0.05) *	
PVC02 (mm Hg)	FloLAN	1	6	-4.67	1.26	-8.00	-8.00	-4.50	-2.00	-1.00	-4.50	(-8.00, -1.00) *	
	Standard	1	6	-2.00	0.97	-5.00	-3.00	-2.50	-1.00	2.00	-2.00	(-5.00, 2.00)	
PVO2 (mm Hg)	FloLAN	1	7	12.86	6.05	5.00	6.00	6.00	9.00	49.00	7.50	(5.00, 29.00) *	
	Standard	1	7	4.57	0.50	4.00	4.00	4.00	5.00	6.00	4.50	(4.00, 5.50) *	
PVR (Wood U)	FloLAN	1	7	-2.39	0.72	-5.65	-3.04	-2.34	-0.40	0.27	-2.39	(-4.01, -0.40) *	
	Standard	1	6	-4.72	1.14	-8.41	-6.49	-5.27	-1.64	-1.24	-5.03	(-8.41, -1.24) *	
RAPm (mm Hg)	FloLAN	1	9	0.67	0.69	-3.00	0.00	1.00	1.00	4.00	0.50	(-1.00, 2.50)	
	Standard	1	14	-0.64	0.58	-6.00	-1.00	0.00	0.00	2.00	0.00	(-2.00, 0.50)	

* A confidence interval that does not contain 0 implies a statistically significant treatment effect.
¹Number of patients with 1st values at dose-ranging and also at baseline.
²Hodges-Lehmann estimate for the true change from baseline.
 NOTE: One patient reached their maximum tolerated dose more than once in the first dose-ranging segment.
 The last measurements were summarized.
 SSD31(FLSHENS) 12/13/93 10:51

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TABLE 35/36, (Con't)

Summary of Acute Hemodynamic and Blood Gas Effects of FLOLAN[®], Changes from Baseline to Maximum Tolerated Dose in Dose-Ranging Segment #1 (continued)

Parameters	Treatment Group	Study Day	Summary Statistics									
			N ¹	Mean	S.E.	Min.	25-th X-ile	Median	75-th X-ile	Max.	H-L ² Est.	Nonparametric 95% Confidence Interval
SAPd (mm Hg)	Flolan	1	11	-7.00	2.17	-15.00	-13.00	-8.00	-3.00	9.00	-7.75	(-12.00, -2.00) *
	Standard	1	14	-14.50	2.30	-32.00	-10.00	-13.50	-9.00	-2.00	-14.00	(-19.50, -9.50) *
SAPm (mm Hg)	Flolan	1	11	-7.33	2.37	-17.33	-13.33	-8.33	-3.67	12.00	-8.25	(-12.83, -2.67) *
	Standard	1	14	-14.12	3.02	-42.33	-10.00	-13.17	-4.67	-8.67	-13.00	(-19.83, -7.83) *
SAPs (mm Hg)	Flolan	1	11	-8.00	3.97	-36.00	-12.00	-10.00	-3.00	18.00	-8.75	(-16.00, 1.00)
	Standard	1	14	-13.36	4.89	-63.00	-21.00	-12.50	0.00	9.00	-10.50	(-22.00, -3.00) *
SOT (mL/O2/min)	Flolan	1	11	223.79	40.22	29.75	72.51	175.07	403.78	517.62	209.51	(115.61, 341.20) *
	Standard	1	15	225.03	37.54	-13.33	127.50	197.93	310.46	473.55	220.11	(132.63, 310.70) *
SV (mL/beat)	Flolan	1	11	8.71	2.28	-8.98	1.52	7.94	14.67	23.04	8.07	(3.40, 14.21) *
	Standard	1	14	8.24	1.87	-2.18	2.76	5.62	13.50	19.44	8.15	(3.59, 12.40) *
SVR (Wood u)	Flolan	1	9	-8.64	1.88	-17.25	-11.47	-8.56	-7.73	3.00	-9.19	(-12.63, -3.83) *
	Standard	1	14	-13.06	1.86	-22.60	-19.73	-13.62	-8.37	-1.81	-12.21	(-18.02, -2.15) *
SWI (g-m/m ²)	Flolan	1	7	2.41	1.14	-3.00	0.93	2.06	4.33	6.34	2.60	(-0.51, 5.20)
	Standard	1	6	0.34	2.69	-12.42	-0.50	2.70	3.91	5.60	1.95	(-12.42, 5.60)
TPR (Wood u)	Flolan	1	11	-4.34	1.64	-11.94	-7.17	-3.43	-2.36	0.07	-3.84	(-7.17, -1.96) *
	Standard	1	14	-7.67	1.97	-27.80	-8.42	-7.10	-2.00	-1.41	-6.48	(-11.35, -4.23) *
TSR (Wood u)	Flolan	1	11	-9.15	1.61	-18.63	-12.57	-9.23	-6.96	2.40	-9.28	(-12.80, -5.60) *
	Standard	1	14	-14.07	1.93	-23.89	-20.74	-14.90	-7.07	-2.49	-14.23	(-19.49, -9.31) *

* A confidence interval that does not contain 0 implies a statistically significant treatment effect.
¹Number of patients with lab values at dose-ranging and also at baseline.
²Hedges-Lehmann estimate for the true change from baseline.
 NOTE: One patient reached their maximum tolerated dose more than once in the first dose-ranging segment.
 The last measurements were summarized.
 33031(FLSSEHS) 12/13/93 10:51

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TABLE 35/36₁₀

Summary of Long-Term Hemodynamic and Blood Gas Effects by Treatment Groups (Day 1 Versus Day 57)

Flolan (N=11)
Standard (N=14)

Hemodynamics and Blood Gases	Treatment Group	Study Day	Study Phase	N	Mean	S.E.	Summary Statistics				
							Min.	25-th %ile	Median	75-th %ile	Max.
Arterial Saturation (%)	Flolan	1	Baseline	11	92.45	1.30	84.00	89.00	93.00	96.00	100.00
	Standard	57	Longterm	10	93.60	1.45	83.00	92.00	95.00	97.00	98.00
AVO2D (mL/dL)	Flolan	1	Baseline	11	6.76	0.76	3.59	4.34	7.34	7.96	12.22
	Standard	57	Longterm	10	5.96	0.75	3.94	4.19	4.94	6.49	10.91
Cardiac Index (L/min/m ²)	Flolan	1	Baseline	14	6.85	0.68	3.91	5.39	6.97	7.85	11.01
	Standard	57	Longterm	11	6.37	0.53	4.14	5.35	6.26	7.79	9.69
Cardiac Output (L/min)	Flolan	1	Baseline	11	1.67	0.19	1.22	1.29	1.67	2.49	2.91
	Standard	57	Longterm	10	2.20	0.21	1.41	1.49	2.23	2.44	3.25
Heart Rate (bpm)	Flolan	1	Baseline	14	1.54	0.17	0.93	1.33	1.50	1.67	3.22
	Standard	57	Longterm	11	1.92	0.30	0.60	1.16	1.60	2.55	3.90
Mixed Venous Saturation (%)	Flolan	1	Baseline	11	3.23	0.34	1.74	2.40	3.04	4.46	5.00
	Standard	57	Longterm	10	3.77	0.30	2.10	2.50	3.95	4.60	5.40
Heart Rate (bpm)	Flolan	1	Baseline	14	2.99	0.37	1.65	2.20	2.32	3.00	3.90
	Standard	57	Longterm	11	3.56	0.56	1.60	2.10	3.00	5.00	6.90
Mixed Venous Saturation (%)	Flolan	1	Baseline	11	64.64	3.06	63.00	76.00	80.00	100.00	105.00
	Standard	57	Longterm	10	60.50	4.50	50.00	66.00	80.00	93.00	110.00
Mixed Venous Saturation (%)	Flolan	1	Baseline	14	65.79	4.70	50.00	70.00	81.50	95.00	112.00
	Standard	57	Longterm	11	62.55	3.13	60.00	73.00	80.00	91.00	100.00
Mixed Venous Saturation (%)	Flolan	1	Baseline	11	50.36	3.65	29.00	56.00	59.00	67.00	73.00
	Standard	57	Longterm	10	61.40	4.45	20.00	54.00	65.50	72.00	74.00

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TABLE 35/36₁₀ (Con't)

Summary of Long-Term Hemodynamic and Blood Gas Effects by Treatment Groups (Day 1 Versus Day 57)
(continued)

Flolan (N=11)
Standard (N=14)

Hemodynamics and Blood Gases	Treatment Group	Study Day	Study Phase	N	Summary Statistics						
					Mean	S.E.	Min.	25-th %	Median	75-th %	Max.
Mixed Venous Saturation (%)	Standard	1	Baseline	14	61.00	2.05	46.00	50.00	61.50	65.00	75.00
		57	Longterm	11	60.36	3.11	36.00	54.00	62.00	60.00	72.00
PaCO ₂ (mm Hg)	Flolan	1	Baseline	4	20.00	1.00	25.00	26.50	20.50	29.50	30.00
		57	Longterm	3	30.00	0.00	30.00	30.00	30.00	30.00	30.00
	Standard	1	Baseline	6	33.50	2.31	24.00	31.00	34.00	39.00	39.00
		57	Longterm	3	31.33	4.06	24.00	24.00	32.00	30.00	30.00
PaO ₂ (mm Hg)	Flolan	1	Baseline	4	64.50	0.70	52.00	53.50	50.00	75.50	90.00
		57	Longterm	3	66.33	9.21	53.00	53.00	62.00	84.00	84.00
	Standard	1	Baseline	6	120.17	32.16	52.00	60.00	96.50	145.00	243.00
		57	Longterm	3	60.67	10.90	40.00	40.00	65.00	77.00	77.00
PAPd (mm Hg)	Flolan	1	Baseline	11	40.09	3.05	22.00	32.00	30.00	50.00	69.00
		57	Longterm	10	36.80	4.45	16.00	20.00	34.50	51.00	59.00
	Standard	1	Baseline	14	44.36	3.42	20.00	30.00	45.00	50.00	60.00
		57	Longterm	11	44.27	4.37	27.00	29.00	47.00	55.00	70.00
PAPm (mm Hg)	Flolan	1	Baseline	11	56.64	4.26	40.33	46.00	51.00	69.33	87.33
		57	Longterm	10	50.43	4.89	27.67	39.00	46.17	66.67	76.00
	Standard	1	Baseline	14	63.67	3.77	41.00	53.00	63.50	75.00	80.67
		57	Longterm	11	62.24	4.46	39.67	40.00	59.67	74.67	83.33
PAPs (mm Hg)	Flolan	1	Baseline	11	89.73	5.42	65.00	77.00	84.00	106.00	124.00
		57	Longterm	10	77.70	6.04	51.00	69.00	70.50	90.00	110.00
	Standard	1	Baseline	14	102.29	5.30	63.00	93.00	103.50	113.00	132.00
		57	Longterm	11	90.18	5.44	65.00	85.00	102.00	110.00	127.00

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TABLE 35/36₁₀ (Con't)

Summary of Long-Term Hemodynamic and Blood Gas Effects by Treatment Groups (Day 1 Versus Day 57)
(continued)

Fiolan (N=22)
Standard (N=14)

Hemodynamics and Blood Gases	Treatment Group	Study Day	Study Phase	N	Mean	S.E.	Summary Statistics				Max.
							Min.	25-th K-ile	Median	75-th K-ile	
PCMPa (mm Hg)	Fiolan	1	Baseline	10	7.50	1.02	2.00	4.00	6.00	10.00	22.00
	Standard	57	Longterm	3	6.67	2.96	1.00	1.00	6.00	11.00	11.00
		1	Baseline	9	9.00	2.34	0.00	3.00	10.00	22.00	22.00
pHa	Fiolan	1	Baseline	3	7.44	0.01	7.41	7.41	7.44	7.46	7.46
	Standard	57	Longterm	3	7.41	0.01	7.39	7.39	7.42	7.43	7.43
		1	Baseline	6	7.44	0.02	7.37	7.40	7.44	7.49	7.52
pHv	Fiolan	1	Baseline	3	7.47	0.05	7.37	7.37	7.50	7.54	7.54
	Standard	57	Longterm	10	7.44	0.01	7.39	7.41	7.44	7.46	7.46
		1	Baseline	9	7.40	0.01	7.36	7.38	7.41	7.43	7.44
PVC02 (mm Hg)	Fiolan	1	Baseline	9	37.44	1.24	33.00	34.00	37.00	39.00	45.00
	Standard	57	Longterm	9	38.70	1.20	34.00	35.00	39.00	42.00	43.00
		1	Baseline	9	37.09	1.33	33.00	35.00	36.00	42.00	44.00
PVO2 (mm Hg)	Fiolan	1	Baseline	9	35.67	1.75	29.00	31.00	36.00	40.00	43.00
	Standard	57	Longterm	10	31.00	1.30	22.00	30.00	31.00	34.00	37.00
		1	Baseline	10	33.40	7.20	24.00	31.00	32.00	37.00	104.00
PVR (Wood u)	Fiolan	1	Baseline	10	32.56	1.23	26.00	30.00	32.00	34.00	40.00
	Standard	57	Longterm	9	32.56	1.19	26.00	32.00	33.00	38.00	37.00
		1	Baseline	10	10.79	3.05	9.57	10.76	14.97	27.22	37.55
		57	Longterm	3	7.50	0.60	6.31	6.31	7.93	0.26	0.26

TABLE 35/36₁₀ (Con't)

Summary of Long-Term Hemodynamic and Blood Gas Effects by Treatment Groups (Day 1 Versus Day 57)
(continued)

Hemodynamics and Blood Gases	Treatment Group	Study Day	Study Phase	Summary Statistics							
				Flolan (N=11)		Standard (N=14)					
				N	Mean	S.E.	Min.	25-th X-ile	Median	75-th X-ile	Max.
PVR (Wood u)	Standard	1	Baseline	9	19.59	2.95	7.43	15.25	16.54	25.69	32.55
		57	Longterm	6	19.20	3.58	6.50	10.86	21.90	26.97	27.00
RAPm (mm Hg)	Flolan	1	Baseline	10	7.00	2.01	-3.00	2.00	0.50	13.00	16.00
		57	Longterm	0	10.75	2.97	3.00	6.00	0.50	12.00	30.00
	Standard	1	Baseline	14	9.07	1.63	0.00	4.00	7.50	15.00	18.00
		57	Longterm	9	10.56	1.87	2.00	10.00	10.00	11.00	23.00
SAPd (mm Hg)	Flolan	1	Baseline	11	73.82	4.09	45.00	69.00	70.00	80.00	100.00
		57	Longterm	10	75.80	3.43	61.00	67.00	76.00	80.00	94.00
	Standard	1	Baseline	14	81.71	2.67	62.00	77.00	80.00	85.00	101.00
		57	Longterm	11	76.64	3.50	64.00	65.00	73.00	87.00	97.00
SAPm (mm Hg)	Flolan	1	Baseline	11	87.10	4.10	61.67	79.00	80.00	92.33	112.67
		57	Longterm	10	87.33	3.59	71.33	80.00	86.67	91.67	110.33
	Standard	1	Baseline	14	90.83	4.10	84.00	89.67	93.50	104.67	130.33
		57	Longterm	11	92.82	3.93	70.00	82.00	91.67	101.33	115.67
SAPs (mm Hg)	Flolan	1	Baseline	11	113.91	4.95	95.00	100.00	109.00	130.00	141.00
		57	Longterm	10	110.40	4.51	92.00	101.00	111.00	116.00	143.00
	Standard	1	Baseline	14	133.07	8.94	161.00	117.00	122.00	133.00	231.00
		57	Longterm	11	125.18	8.86	106.00	106.00	123.00	139.00	162.00
SOT (mL/O2/min)	Flolan	1	Baseline	11	576.25	56.04	384.87	394.51	457.02	719.41	902.36
		57	Longterm	10	655.29	74.96	320.06	411.51	469.08	690.00	1014.0
	Standard	1	Baseline	14	624.39	75.90	340.47	415.84	500.12	820.72	1219.3
		57	Longterm	11	667.23	99.16	272.56	391.71	500.97	1011.1	1196.1

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TABLE 35/36₁₀ (Con't)

Summary of Long-Term Hemodynamic and Blood Gas Effects by Treatment Groups (Day 1 Versus Day 57)
(continued)

Fiolan (N=11)
Standard (N=14)

Hemodynamic and Blood Gases	Treatment Group	Study Day	Study Phase	N	Mean	S.E.	Summary Statistics				
							Min.	2-11e	Median	75-1h 2-11e Max.	
SV (mL/beat)	Fiolan	1	Baseline	11	39.23	4.73	16.57	30.00	32.43	51.32	70.79
	Standard	57	Longterm	10	43.70	8.10	22.50	29.07	45.00	53.05	74.14
SVR (Wood u)	Fiolan	1	Baseline	10	26.40	2.94	18.15	19.63	22.93	33.06	45.40
	Standard	57	Longterm	8	22.57	2.65	16.59	17.95	19.19	26.98	35.71
SWI (g-m/m ²)	Fiolan	1	Baseline	14	33.53	2.56	14.75	24.67	34.70	40.00	47.27
	Standard	57	Longterm	9	27.09	4.34	13.16	15.50	26.47	30.93	49.06
TPR (Wood u)	Fiolan	1	Baseline	10	24.27	4.15	12.59	13.40	19.31	42.52	63.55
	Standard	57	Longterm	5	37.57	2.07	34.41	34.41	36.00	43.31	43.31
TSR (Wood u)	Fiolan	1	Baseline	9	26.92	5.29	9.90	17.27	17.54	34.32	54.55
	Standard	57	Longterm	6	24.75	6.03	0.96	14.29	20.00	33.23	47.23
TPR (Wood u)	Fiolan	1	Baseline	11	20.62	3.39	9.79	11.07	15.55	33.49	39.05
	Standard	57	Longterm	10	15.34	2.06	7.74	9.07	12.57	16.26	33.17
TSR (Wood u)	Fiolan	1	Baseline	14	25.26	3.11	7.43	10.50	20.50	35.30	45.45
	Standard	57	Longterm	11	22.00	3.08	5.75	11.55	21.96	31.69	36.66
TPR (Wood u)	Fiolan	1	Baseline	11	29.00	3.10	10.61	20.29	26.75	30.47	50.57
	Standard	57	Longterm	10	28.33	2.64	17.27	19.51	20.02	32.93	41.43
TSR (Wood u)	Fiolan	1	Baseline	14	37.53	3.16	15.42	24.17	30.05	47.69	57.58
	Standard	57	Longterm	11	32.02	4.27	14.20	16.04	29.71	43.70	55.00

TABLE 35/36¹¹

Summary of the Changes in Long-Term Hemodynamic and Blood Gas Effects: Within-Group Comparison (Baseline to Day 57)

Flofen (N=11)
Standard (N=14)

Parameters	Treatment Group	Study day	N ¹	Mean	S.E.	Min.	X-ile	Summary Statistics			H-L ² Est.	Nonparametric 95% Confidence Interval	
								Median	75-th X-ile	Max.			
Arterial Saturation (%)	Flofen	57	10	0.50	1.20	-6.00	-3.00	2.00	3.00	7.00	0.50	(-2.50, 3.00)	
	Standard	57	21	-1.27	1.15	-10.00	-2.00	-1.00	2.00	4.00	-1.00		(-4.00, 1.50)
AVO2D (mL/dL)	Flofen	57	10	-0.06	0.37	-3.01	-1.50	-0.09	-0.03	0.71	-0.77		(-1.60, 0.04)
	Standard	57	11	-0.06	0.40	-2.71	-0.94	0.20	0.07	1.04	0.01		(-1.03, 0.07)
Cardiac Index (L/min/m ²)	Flofen	57	10	0.31	0.13	-0.00	0.00	0.19	0.45	1.17	0.23		(0.01, 0.60) *
	Standard	57	11	0.17	0.23	-0.49	-0.29	-0.10	0.45	2.26	-0.01		(-0.27, 0.00)
Cardiac Output (L/min)	Flofen	57	10	0.52	0.25	-0.16	0.00	0.27	0.60	2.20	0.30		(0.04, 1.10) *
	Standard	57	11	0.30	0.40	-1.17	-0.40	-0.10	0.00	3.00	-0.00		(-0.40, 1.32)
Heart Rate (bpm)	Flofen	57	10	5.50	4.37	-17.00	-5.00	7.00	11.00	34.00	6.00		(-4.50, 13.00)
	Standard	57	11	-1.45	4.42	-30.00	-4.00	1.00	9.00	20.00	0.50		(-12.00, 7.50)
Mixed Venous Saturation (%)	Flofen	57	10	2.90	2.70	-5.00	-1.00	1.00	4.00	26.00	1.00		(-1.50, 12.00)
	Standard	57	11	-1.64	2.30	-14.00	-0.00	-2.00	3.00	13.00	-1.20		(-7.50, 3.50)
Pco2 (mm Hg)	Flofen	57	3	2.33	1.45	0.00	0.00	2.00	5.00	5.00	2.25		M is too small
	Standard	57	3	-0.67	3.40	-7.00	-7.00	0.00	5.00	5.00	-0.50		M is too small
Pco2 (mm Hg)	Flofen	57	3	-1.33	2.33	-6.00	-6.00	1.00	1.00	1.00	-0.75		M is too small
	Standard	57	3	-21.00	13.20	-47.00	-47.00	-12.00	-4.00	-4.00	-10.75		M is too small
PAPd (mm Hg)	Flofen	57	10	-4.10	4.51	-35.00	-10.00	-5.00	7.00	13.00	-4.00		(-11.00, 6.00)
	Standard	57	21	2.00	4.30	-31.00	-3.00	1.00	12.00	25.00	2.50		(-5.00, 12.00)

* A confidence interval that does not contain 0 implies a statistically significant treatment effect. ¹Number of patients with lab values at study day 57 and also at baseline. ²McGee-Loehmann estimate for the true change from baseline.

TABLE 35/36₁₁ (Con't)

Summary of the Changes in Long-Term Hemodynamic and Blood Gas Effects: Within-Group Comparison (Baseline to Day 57) (continued)

Flofen (N=11)
Standard (N=14)

Parameters	Treatment Group	Study day	N ¹	Mean	S.E.	Min.	Max.	Summary Statistics			N-C ² Est.	Nonparametric 95% Confidence Interval
								25-th X-tile	Median	75-th X-tile		
PAPs (mm Hg)	Flofen	57	10	-7.57	4.47	-41.67	-11.33	-6.00	4.67	6.33	-5.67	(-17.03, 5.00)
	Standard	57	11	0.36	4.07	-32.07	-4.33	2.00	8.33	20.33	1.03	(-6.17, 8.33)
PAPs (mm Hg)	Flofen	57	10	-14.50	4.01	-55.00	-14.00	-12.50	-7.00	0.00	-11.00	(-29.50, -6.50) *
	Standard	57	11	-3.09	4.06	-36.00	-0.00	-5.00	9.00	12.00	-1.50	(-12.00, 6.00)
PCWP _a (mm Hg)	Flofen	57	2	-3.00	6.00	-9.00	-9.00	-3.00	3.00	3.00	2.00	N is too small
	Standard	57	4	2.00	1.96	-2.00	-1.00	1.50	5.00	7.00	2.00	N is too small
pH _a	Flofen	57	2	-0.03	0.01	-0.04	-0.04	-0.03	-0.02	-0.02	0.00	N is too small
	Standard	57	3	0.00	0.02	-0.03	-0.03	0.01	0.02	0.02	0.00	N is too small
pH _v	Flofen	57	0	-0.03	0.01	-0.07	-0.06	-0.04	0.00	0.05	-0.03	(-0.06, 0.03)
	Standard	57	0	0.01	0.01	-0.04	-0.03	0.01	0.03	0.07	0.01	(-0.03, 0.04)
PVC02 (mm Hg)	Flofen	57	0	1.30	1.52	-3.00	-2.50	0.50	4.50	9.00	1.00	(-2.50, 5.00)
	Standard	57	0	-1.00	1.37	-9.00	-3.50	-1.00	0.00	4.00	-1.50	(-5.50, 1.00)
PVO2 (mm Hg)	Flofen	57	9	9.11	0.22	-2.00	1.00	1.00	2.00	74.00	1.50	(0.00, 37.50)
	Standard	57	9	-0.22	0.03	-4.00	-2.00	0.00	1.00	4.00	0.00	(-2.00, 2.00)
PVR (Wood u)	Flofen	57	2	-6.01	2.25	-8.27	-0.27	-6.01	-3.76	-3.76	0.33	N is too small
	Standard	57	4	0.22	2.10	-5.47	-2.73	0.64	3.16	5.00	0.33	N is too small
RAP _a (mm Hg)	Flofen	57	7	-2.71	1.77	-10.00	-5.00	-4.00	5.00	5.00	-2.50	(-7.00, 2.00)
	Standard	57	9	2.22	2.05	-8.00	-2.00	3.00	7.00	12.00	2.50	(-3.00, 7.00)

* A confidence interval that does not contain 0 implies a statistically significant treatment effect. Number of patients with lab values at study day 57 and also at baseline. Hodges-Lehmann estimate for the true change from baseline.

TABLE 35/36₁₁ (Con't)

Summary of the Changes in Long-Term Hemodynamic and Blood Gas Effects: Within-Group Comparison (Baseline to Day 57) (continued)

Flolan (No11)
Standard (No14)

Parameters	Treatment Group	Study day	N ¹	Mean	S.E.	Min.	Max.	Summary Statistics			H-L ² Est.	Nonparametric 95% Confidence Interval
								25-th	Median	75-th		
SAPd (mm Hg)	Flolan	57	10	-0.98	2.39	-12.00	-7.00	-0.50	5.00	10.00	-1.00	(-6.50, 5.00)
	Standard	57	11	-7.18	2.05	-26.00	-15.00	-7.00	-1.00	5.00	-7.00	(-13.00, -1.00) *
SAPm (mm Hg)	Flolan	57	10	-2.40	1.06	-12.00	-5.00	-3.17	1.67	0.67	-2.03	(-6.03, 2.50)
	Standard	57	11	-0.55	3.25	-27.67	-13.00	-0.67	3.00	4.33	-0.50	(-16.00, -2.17) *
SAPs (mm Hg)	Flolan	57	10	-5.40	4.51	-29.00	-14.00	-2.00	7.00	10.00	-6.00	(-16.50, 6.50)
	Standard	57	11	-11.27	6.78	-69.00	-17.00	-11.00	5.00	11.00	-7.50	(-29.00, 3.50)
SOT (mL/O2/min)	Flolan	57	10	77.12	53.46	-64.01	-20.03	13.62	112.40	200.14	42.40	(-19.29, 230.30)
	Standard	57	11	13.18	70.05	-248.0	-132.6	-42.40	45.32	622.21	-39.61	(-122.60, 206.02)
SV (mL/beat)	Flolan	57	10	3.55	3.36	-16.77	-2.02	3.60	7.00	21.69	3.30	(-3.67, 11.10)
	Standard	57	11	4.57	5.93	-15.23	-7.04	-4.61	11.15	43.17	-0.52	(-7.32, 10.45)
SVR (Wood u)	Flolan	57	7	-5.69	2.20	-14.36	-12.30	-2.40	-1.43	1.53	-5.42	(-12.30, -0.43) *
	Standard	57	9	-5.66	3.48	-24.50	-9.97	-2.49	-1.50	5.90	-3.01	(-14.13, 1.65)
SVI (g-m/m ²)	Flolan	57	2	7.00	7.23	0.65	0.65	7.00	15.12	15.12	-7.02	M is too small
	Standard	57	4	-7.02	2.01	-12.20	-10.04	-6.42	-0.00	-2.97	-7.02	M is too small
TPR (Wood u)	Flolan	57	10	-5.92	2.69	-26.90	-0.01	-2.93	-0.32	1.94	-4.16	(-13.32, -0.69) *
	Standard	57	11	-0.29	3.31	-27.00	-1.60	0.90	5.96	15.11	1.07	(-9.05, 6.71)
TSR (Wood u)	Flolan	57	10	-5.42	2.31	-19.12	-11.02	-2.32	-0.61	2.71	-4.07	(-10.47, -0.61) *
	Standard	57	11	-3.22	5.40	-20.90	-0.23	-1.23	4.01	12.92	-1.46	(-11.75, 4.81)

* A confidence interval that does not contain 0 implies a statistically significant treatment effect.
 1 Number of patients with lab values at study day 57 and also at baseline.
 2 Hodges-Lehmann estimate for the true change from baseline.

TABLE 35/36₁₂

Between-Treatment Group Comparison of Changes from Baseline to Day 57 in Long-Term Hemodynamic and Blood Gas Effects

Fleiss (N=11)
Standard (N=14)

Parameters	Study Day	Fleiss		Standard		Nonsymmetric 95% Confidence Interval
		N ¹	Median Change from Baseline	N ²	Median Change from Baseline	
Arterial Saturation (%)	57	10	2.00	11	-1.00	(-2.00, 5.00)
AVO2D (mL/dL)	57	10	-0.09	11	0.20	(-2.06, 0.43)
Cardiac Index (L/min/m ²)	57	10	0.19	11	-0.10	(-0.13, 0.50)
Cardiac Output (L/min)	57	10	0.27	11	-0.10	(-0.30, 1.00)
Heart Rate (bpm)	57	10	7.00	11	1.00	(-6.00, 16.00)
Mixed Venous Saturation (%)	57	10	1.00	11	-2.00	(-3.00, 12.00)
PaCO2 (mm Hg)	57	3	2.00	3	0.00	No one too small
Pao2 (mm Hg)	57	3	1.00	3	-12.00	No one too small
PAPd (mm Hg)	57	10	-5.00	11	1.00	(-19.00, 6.00)
PAPm (mm Hg)	57	10	-0.00	11	2.00	(-10.00, 3.67)
PAPs (mm Hg)	57	10	-12.50	11	-5.00	(-20.00, -2.00) *

* A confidence interval that does not contain 0 implies a statistically significant difference between treatment groups. Number of patients with lab values at study day 57 and also at baseline. Hodges-Lehmann estimate for the true treatment difference. A positive estimate indicates a greater change from baseline with Fleiss.

TABLE 35/36₁₂ (Con't)
 Between-Treatment Group Comparison of Changes from Baseline to Day 57 in Long-Term Hemodynamic and Blood Gas Effects (continued)

Fleiss (N=11)
 Standard (N=14)

Parameters	Study Day	N ¹	Fleiss Median Change from Baseline	N ²	Standard Median Change from Baseline	M-L ³ Estimate	Nonparametric 95% Confidence Interval
PCWP _m (mm Hg)	57	2	-3.00	4	1.50	-3.50	Ms are too small
ph	57	2	-0.03	3	0.01	-0.04	Ms are too small
pH _v	57	0	-0.04	0	0.01	-0.03	(-0.00, 0.01)
PVCO ₂ (mm Hg)	57	0	0.50	0	-1.50	2.00	(-1.00, 7.00)
PV0 ₂ (mm Hg)	57	9	1.00	9	0.00	2.00	(-1.00, 5.00)
PVR (Wood U)	57	2	-6.01	4	0.64	-6.66	Ms are too small
RAP _m (mm Hg)	57	7	-4.00	9	3.00	-6.00	(-12.00, 2.00)
SAP _d (mm Hg)	57	10	-0.50	11	-7.00	6.00	(-2.00, 16.00)
SAP _m (mm Hg)	57	10	-3.17	11	-0.67	5.33	(-2.67, 16.67)
SAP _v (mm Hg)	57	10	-2.00	11	-11.00	3.00	(-12.00, 7.00)
SO ₂ (mL/102/min)	57	10	13.62	11	-42.40	74.01	(-41.09, 137.11)

* A confidence interval that does not contain 0 implies a statistically significant difference between treatment groups. Number of patients with lab values at study day 57 and size at baseline. Fleiss-Lehmann estimate for the true treatment difference. A positive estimate indicates a greater change from baseline with Fleiss.

TABLE 35/36₁₂ (Con't)

Between-Treatment Group Comparison of Changes from Baseline to Day 57 in Long-Term Hemodynamic and Blood Gas Effects (continued)

Fiolen (N=11)
Standard (N=14)

Parameters	Study Day	Fiolen		Standard		H-L ² Estimate	Nonparametric 95% Confidence Interval
		N ¹	Median Change from Baseline	N ¹	Median Change from Baseline		
SV (mL/beat)	57	10	3.60	11	-4.61	4.27	(-12.08,13.52)
SVR (Wood u)	57	7	-2.48	9	-2.49	-0.76	(-9.89,9.94)
SWI (g-m/m ²)	57	2	7.88	4	-6.42	15.51	Ns are too small
TPR (Wood u)	57	10	-2.93	11	0.90	-5.52	(-13.11,-0.19) *
TSR (Wood u)	57	10	-2.32	11	-1.23	-2.20	(-11.45,4.62)

*

A confidence interval that does not contain 0 implies a statistically significant difference between treatment groups.

¹Number of patients with lab values at study day 57 and also at baseline.

²Hodges-Lehmann estimate for the true treatment difference. A positive estimate indicates a greater change from baseline with Fiolen.

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TABLE 35/36₁₃

Adverse Experiences that Occurred in ≥3 Patients in Either Treatment Group During the Long-Term Infusion Segment

(Grouped by Maximum Seriousness of Experience)

FLOLAN® (N=11)

Standard (N=14)

Preferred Term for Adverse Experience	Maximum Seriousness	Treatment Group					
		FLOLAN				Standard	
		All AEs		AEs Associated with Drug Delivery		All AEs	
N	(% of Patients)	N	(% of Patients)	N	(% of Patients)		
Asthenia	Serious or Life-Thr.	1	(9%)	0	(0%)	4	(29%)
	Not Serious	3	(27%)	0	(0%)	1	(7%)
Diarrhea	Not Serious	3	(27%)	0	(0%)	0	(0%)
Dizziness	Serious or Life-Thr. ^a	1	(9%)	1	(9%)	2	(14%)
	Not Serious	5	(45%)	5	(45%)	2	(14%)
Dyspnea	Serious or Life-Thr.	4	(36%)	2	(18%)	5	(36%)
	Not Serious	2	(18%)	2	(18%)	2	(14%)
Edema Periph	Serious or Life-Thr.	0	(0%)	0	(0%)	3	(21%)
	Not Serious	1	(9%)	0	(0%)	1	(7%)
Headache	Serious or Life-Thr.	1	(9%)	0	(0%)	0	(0%)
	Not Serious	7	(64%)	3	(27%)	3	(21%)
Nausea	Serious or Life-Thr.	2	(18%)	1	(9%)	1	(7%)
	Not Serious	5	(45%)	3	(27%)	1	(7%)
Pain Chest	Serious or Life-Thr.	2	(18%)	1	(9%)	1	(7%)
	Not Serious	1	(9%)	0	(0%)	1	(7%)
Pain Inject Site	Not Serious	3	(27%)	3	(27%)	0	(0%)
Palpitat	Serious or Life-Thr.	0	(0%)	0	(0%)	1	(7%)
	Not Serious	0	(0%)	0	(0%)	2	(14%)
Flushing	Serious or Life-Thr.	2	(18%)	2	(18%)	0	(0%)
	Not Serious	7	(64%)	4	(36%)	1	(7%)

^a None of the AEs were life-threatening.^b The AE was life-threatening for one patient.

LIFE-THREATENING ADVERSE EVENTS:

TABLE 35/36₁₄

Adverse Event	FLOLAN®		Standard Therapy	
	Number of Patients	%	Number of Patients	%
Dyspnea	4	36%	4	29%
Chest pain	2	18%	1	7%
Nausea	2	18%	1	7%
Tachycardia	2	18%	0	0
Flushing	2	18%	0	0
Asthenia	1	9%	4	29%
Bradycardia	1	9%	0	0
Cerebrovasc. Accid.	1	9%	0	0
Convulsion	1	9%	0	0
Cough, Increase	1	9%	0	0
Cyanosis	1	9%	0	0
Dizziness	1	9%	1	7%
Extrasystole	1	9%	0	0
Fever	1	9%	0	0
Headache	1	9%	0	0
Hypotension	1	9%	0	0
Inflammation Inject. site	1	9%	0	0
Pain	1	9%	0	0
Pallor	1	9%	0	0
Supraventricular tachycardia	1	9%	0	0
Sweat	1	9%	0	0
Syncope	1	9%	2	14%
Edema, Periph	0	0	3	21%
Right Heart failure	0	0	2	14%
Vomit	0	0	2	14%

TABLE 46,

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TABLE 46₂

Table 13. Inclusion Criteria

Patient must:	
1	Be between 6 and 70 years of age
2	If female, be physiologically incapable of childbearing or practicing an acceptable method of birth control
3	Have a diagnosis of severe, symptomatic PPH and remain NYHA Class III or IV despite the attempted use of vasodilators or use of chronic vasodilators for at least one month
4	Have a chest radiograph consistent with the diagnosis of PPH performed within the previous six months. The radiograph must show clear lung fields and at least one of the following: right ventricular enlargement, prominence of the main pulmonary artery, enlarged hilar vessels, or decreased peripheral vessels
5	Have pulmonary function tests consistent with the diagnosis of PPH (predominantly normal, with only mild reductions in total lung capacity and forced vital capacity) performed within the previous year
6	Have a ventilation/perfusion scan or pulmonary angiography consistent with the diagnosis of PPH (low probability of pulmonary embolism; absence of major perfusion defects) performed within the previous year
7	Have an echocardiogram consistent with the diagnosis of PPH, specifically:
7a	evidence of right ventricular hypertrophy or dilation, and
7b	evidence of normal left ventricular function, and
7c	absence of mitral valve stenosis
8	Have a cardiac catheterization at Baseline consistent with the diagnosis of PPH, specifically:
8a	PAP _m 25 mmHg, and
8b	PCWP or a left ventricular end diastolic pressure, 15 mmHg, and
8c	PVR > 3 mmHg/L/min,
8d	absence of congenital heart disease (atrial septal defect, ventricular septal defect, partial anomalous venous drainage, however, the presence of a patent foramen ovale would not exclude patients from entry)
9	Be mentally and physically capable of learning to reconstitute FLOLAN [®] , operate the infusion pump, and maintain the central venous catheter

TABLE 46₃

Table 14. Exclusion Criteria

Patients must NOT:	
1	Be a pregnant woman (women of childbearing potential must have a negative pregnancy test)
2	Have a new type of chronic therapy (e.g., a different category of vasodilator, a diuretic, digoxin) for PPH added within the last month, excluding anticoagulants
3	Have any PPH medications, excluding anticoagulants, discontinued within the last week
4	Have any disease known to cause secondary pulmonary hypertension (e.g., obstructive lung disease, collagen vascular disease, parasitic disease affecting the pulmonary system, sickle cell anemia, mitral valve stenosis)
5	Have a contraindication to anticoagulant therapy
6	Have a musculoskeletal disorder (e.g., arthritis, artificial leg, etc.), or any other disease which is thought to limit ambulation, or be connected to a machine which is not portable
7	Be receiving an investigational drug or have participated in an investigational drug study within the past 30 days
8	Have the presence of any physiological condition which contraindicates the administration of FLOLAN®

TABLE 464

Summary of Demographic Data and PPH Information

Characteristic	Summary Statistics	Flolan	Standard
Age (years)	N Mean Std.Dev. Median Minimum Maximum	41 39.88 16.74 41.58 6.08 78.88	48 39.83 12.32 41.58 9.88 63.88
Age Category (years)	< 28 28-29 30-39 40-49 50+	5 (12.2%) 7 (17.1%) 7 (17.1%) 6 (14.6%) 14 (34.1%)	3 (7.5%) 4 (10.0%) 11 (27.5%) 12 (30.0%) 10 (25.0%)
Sex	Female Male	31 (75.6%) 10 (24.4%)	28 (70.0%) 12 (30.0%)
Race	Black Other White	4 (9.8%) 4 (9.8%) 33 (80.5%)	2 (5.0%) 4 (10.0%) 34 (85.0%)
Weight at Screen (kg)	N Mean Std.Dev. Median Minimum Maximum	41 68.16 19.69 76.58 19.08 185.88	48 72.14 22.26 68.36 37.28 198.88
Weight Category (kg)	< 58 58-59 60-69 70-79	4 (9.8%) 12 (29.3%) 2 (4.9%) 14 (34.1%)	4 (10.0%) 18 (45.0%) 7 (17.5%) 10 (25.0%)
Weight Category (kg)	80+	9 (22.0%)	9 (23.5%)
NYMA Class at Screen	III IV	31 (75.6%) 10 (24.4%)	29 (72.5%) 11 (27.5%)
No. Since PPH Diagnosis	N Mean Std.Dev. Median Minimum Maximum	41 32.13 53.92 19.57 0.28 321.78	48 25.18 58.88 11.11 0.85 195.15
Vasodilator Use	No Yes	14 (34.1%) 27 (65.9%)	16 (40.0%) 24 (60.0%)

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TABLE 46_s

BORG DYSPNEA SCORE

Following the walk, obtain the rating of dyspnea using the Borg scale as follows:

"I would like to use the following scale to indicate the maximal shortness of breath you had during the walk test (indicate the Borg Scale). If there was no shortness of breath at all you would point to 0; if the shortness of breath was not very great you would choose from 0.5 to 2; if you were somewhat more short of breath you would select 3; and if the breathing was getting very difficult, you would choose 4 to 9, depending on just how hard it was. 10 represents the greatest shortness of breath you have ever experienced in your life, and if you feel more short of breath than you have ever been in your life before, choose a number greater than 10 that represents how short of breath you feel. If one of the numbers doesn't exactly represent how short of breath you are, then you can choose a fraction between. For example, if you had shortness of breath somewhere between 4 and 5, you could choose 4.5."

- 0 = Nothing at all
- 0.5 = Very, very light (Just Noticeable)
- 1 = Very light
- 2 = Light (Weak)
- 3 = Moderate
- 4 = Somewhat heavy
- 5 = Heavy (Strong)
- 6 =
- 7 = Very heavy
- 8 =
- 9 =
- 10 = Very, very heavy (Almost Maximal)
- * = Maximal

TABLE 46.

Summary of the 6-Minute Walk Exercise Test Results

Flolan (N=41)
Standard (N=40)

Period	Treatment	N	Mean	S.E.	Min	25-th P-ile	Median	75-th P-ile	Max
Day 1	Flolan	41	306.6	10.9	2.1	244.5	307.0	365.0	559.6
	Standard	38	295.7	21.1	0.0	155.4	240.0	344.2	534.9
Day 2	Flolan	40	315.3	10.6	0.6	261.0	312.0	369.1	521.2
	Standard	39	285.5	22.0	0.0	137.2	266.7	390.1	487.4
Wk 1	Flolan	40	330.6	16.0	0.0	206.5	332.4	394.7	510.2
	Standard	39	254.9	20.2	43.9	166.4	257.3	347.0	511.2
Wk 6	Flolan	40	375.0	17.4	39.6	300.9	385.3	453.4	556.3
	Standard	37	280.0	24.6	0.0	151.0	302.1	404.2	572.1
Day 80	Flolan	41	349.9	17.0	24.4	286.2	362.4	426.7	543.2
	Standard	32	283.0	27.5	0.0	154.5	265.5	403.3	550.7

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TABLE 467

Summary of the 6-Minute Walk Exercise Test Results, Changes from Baseline

Period	Treatment	N ²	Mean	S.E.	Min	Flolan (M=41) Standard (M=99)		25-th X-ile	Median	75-th X-ile	Max	M-L ³ Est.	Nonparametric 95% Confidence Interval ⁴
						25-th X-ile	Median						
Wk 1	Flolan	40	15.0	9.2	-139	-7.2	10.9	40.0	150.0	17.4	(-0.5, 33.5)		
	Standard	37	-24.3	12.2	-309	-46.3	-10.3	15.5	149.4	-17.0	(-32.9, -1.4)		
Wk 6	Flolan	40	50.9	14.6	-81.4	-5.5	47.5	87.8	426.6	51.3	(25.0, 76.5)		
	Standard	37	-8.4	10.4	-135	-45.7	-7.0	16.2	129.2	-10.5	(-32.9, 10.6)		
Day 00	Flolan	41	34.1	10.6	-122	-0.3	31.1	71.2	212.0	39.0	(15.2, 53.2)		
	Standard	32	-7.0	10.6	-336	-44.0	-7.9	46.6	276.1	-0.2	(-36.6, 29.1)		

1 If a patient did not perform a baseline walk (study day 2) for reasons other than the patient's health, the results from study day 1 were used.
 2 Number of patients with results from both the baseline and the indicated evaluation.
 3 Hodges-Lehmann estimate for the true median change from baseline.
 4 A confidence interval that does not contain 0 implies statistical significance.

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TABLE 46_a

Summary of the Between-Treatment Comparisons of the 6-Minute Walk Exercise Test Adjusting for Baseline Walk and Vasodilator Use at Baseline (Nonparametric Analysis of Covariance - Using Analysis 2)

Week	N	Fiolan		Fiolan (N=41) Standard (N=40)		Nonparametric Analysis of Covariance (two-sided test)	
		Baseline median (meters)	Median (meters)	Baseline median (meters)	Median (meters)		
1	40	312.0	332.4	40	269.6	254.4	0.0030
6	40	312.0	305.3	40	269.6	260.1	0.0010
12	41	314.6	362.4	40	269.6	203.5	0.0020

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NOTE: Patients who did not perform the walk on Day 2 due to their health were assigned the lowest rank for the calculation of the median and test statistic. If a patient did not perform a baseline walk (study day 2) for reasons other than the patient's health, the results from study day 1 were used. For subsequent visits, patients who died or did not perform the walk due to their health were assigned the lowest rank for the calculation of the median and test statistic.

¹This method uses a Cochran-Mantel-Haenszel correlation statistic based on the residuals from an ordinary least squares regression. The regression is based on the ranks of the results from the 6-min walk.

TABLE 46₉

Listing of the Baseline Characteristics for Patients Who Died

Patient	Age	Sex	Baseline vasodilator	NYHA class	Baseline walk	Survival time (days)	Mixed venous saturation (%)	PAPs (mm Hg)	RAPs (mm Hg)	Cardiac output (L/min)	PVR (Wood u)	TPR (Wood u)	SVR (Wood u)
	44	F	No	IV	0.0	0	43	79	13	2.4		32.9	33
	16	F	No	III	427.9	69	65	72	3	4.3	15.6	16.7	17
	43	M	Yes	III	438.0	59	56	63	9	4.0	10.6	13.1	17
	43	F	Yes	IV	100.6	20	19	52	10	2.3	19.6	22.6	30
	36	F	Yes	III	336.0	57	56	69	6	6.0	7.3	0.2	12
	42	F	Yes	III	117.3	64	43	67	10	2.4		27.9	31
	30	M	Yes	IV	91.4	59	59	60	22	2.4	20.9	25.1	29
	63	M	No	IV	45.7	69	46	69	10	3.2		15.3	19

TABLE 46₁₀
Summary Comparing Baseline Characteristics of Patients Who Died to Survivors

Parameter	Treatment	Statistic or Level	Death?		Total
			No	Yes	
Age	Flo'lan	N	41		41
		Mean	39.88		39.88
		Std. Dev.	16.74		16.74
		Minimum	6.00		6.00
		Maximum	78.00		78.00
	Standard	N	32	8	40
		Mean	39.63	40.63	39.63
		Std. Dev.	12.38	12.87	12.32
		Minimum	9.00	10.00	9.00
		Maximum	41.00	62.50	61.00
Sex	Flo'lan	N	41		41
		Female	31 (75.6%)		31 (75.6%)
		Male	10 (24.4%)		10 (24.4%)
		N	32	8	40
		Female	23 (71.9%)	5 (62.5%)	28 (70.0%)
Male	9 (28.1%)	3 (37.5%)	12 (30.0%)		
Baseline vasodilator	Flo'lan	N	41		41
		No	14 (34.1%)		14 (34.1%)
		Yes	27 (65.9%)		27 (65.9%)
Standard	Standard	N	32	8	40
		No	13 (40.6%)	3 (37.5%)	16 (40.0%)
		Yes	19 (59.4%)	5 (62.5%)	24 (60.0%)
NYHA class	Flo'lan	N	41		41
		III	31 (75.6%)		31 (75.6%)
		IV	10 (24.4%)		10 (24.4%)
		N	32	8	40

TABLE 46₁₀ (Con't)

Summary Comparing Baseline Characteristics of Patients Who Died to Survivors (continued)

Parameter	Treatment	Statistic or Level	Death?		Total
			No	Yes	
NYHA class	Standard	III	25 (86%)	4 (14%)	29 (72.5%)
	Flofen	IV	7 (27%)	4 (15%)	11 (27.5%)
Baseline walk	Flofen	N	41		41
		Mean	315.74		315.74
		Std.Dev.	115.98		115.98
		Minimum	0.61		0.61
		Maximum	521.21		521.21
Mixed venous saturation (%)	Standard	N	32	0	40
		Mean	291.54	194.73	272.19
		Std.Dev.	128.19	177.04	162.22
		Minimum	60.05	0.00	0.00
		Maximum	273.86	130.97	269.60
PAPs (mm Hg)	Flofen	N	38		38
		Mean	62.48		62.48
		Std.Dev.	12.64		12.64
		Minimum	42.00		42.00
		Maximum	63.00		63.00
PAPs (mm Hg)	Standard	N	31	0	39
		Mean	60.70	51.65	50.91
		Std.Dev.	13.00	13.99	13.60
		Minimum	26.00	21.10	26.00
		Maximum	61.00	50.00	60.00
PAPs (mm Hg)	Flofen	N	41		41
		Mean	60.54		60.54
		Minimum	39.00		39.00

TABLE 46₁₀ (Con't)

Summary Comparing Baseline Characteristics of Patients Who Died to Survivors (continued)

Parameter	Flolan (Mg/dl)	Treatment	Statistic or Level	Death		Total		
				No	Yes			
PAPs (mm Hg)	Flolan	Median	Maximum	59.00	59.00	59.00		
				89.00	89.00	89.00		
PAPs (mm Hg)	Standard	N	Mean	32	0	40		
				Std.Dev.	Minimum	58.00	41.30	56.60
						14.52	11.04	13.03
						23.00	49.00	23.00
						59.00	61.50	60.00
						95.00	79.00	95.00
RAPs (mm Hg)	Flolan	N	Mean	41	0	41		
				Std.Dev.	Minimum	12.59	7.27	12.59
						1.00	1.00	1.00
						12.00	12.50	12.50
						26.00	26.00	26.00
						Standard	N	Mean
Std.Dev.	Minimum	11.76	13.25	12.06				
		7.00	6.50	7.51				
		1.00	1.00	1.00				
		10.00	15.50	12.00				
29.00	21.00	29.00						
Cardiac output (L/min)	Flolan	N	Mean	41	0	41		
				Std.Dev.	Minimum	3.52	3.52	3.52
						1.59	1.59	1.59
						1.60	1.60	1.60
						3.00	3.00	3.00
						9.34	9.34	9.34
Standard	N	Mean	32	0	40			
			Std.Dev.	Minimum	3.01	3.07	3.75	
					2.01	1.00	1.90	
					2.00	2.30	2.00	

TABLE 46₁₀ (Con't)

Summary Comparing Baseline Characteristics of Patients Who Died to Survivors (continued)

Parameter	Treatment	Statistic or Level	Death?		Total
			No	Yes	
			Flolan (N=41)		
↓ Cardiac output (L/min)	Standard	Median	3.25	2.00	3.20
		Maximum	11.90	6.00	11.90
PVR (Wood u)	Flolan	N	34		34
		Mean	15.71		15.71
		Std.Dev.	6.39		6.39
		Minimum	4.10		4.10
		Maximum	36.00		36.00
	Standard	N	24	5	29
		Mean	16.45	14.00	16.17
		Std.Dev.	7.67	5.80	7.32
		Minimum	1.70	7.30	1.70
		Maximum	30.90	20.90	30.90
TPR (Wood u)	Flolan	N	41		41
		Mean	19.09		19.09
		Std.Dev.	8.35		8.35
		Minimum	5.10		5.10
		Maximum	43.50		43.50
	Standard	N	32	8	40
		Mean	18.60	20.22	18.92
		Std.Dev.	8.04	8.29	8.65
		Minimum	4.00	8.20	4.00
		Maximum	36.00	32.90	36.00
SVR (Wood u)	Flolan	N	41		41
		Mean	25.05		25.05
		Std.Dev.	8.77		8.77
		Minimum	7.30		7.30

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TABLE 46₁₀ (Con't)

Summary Comparing Baseline Characteristics of Patients Who Died to Survivors (continued)

Parameter	Treatment	Statistic or Level	Death?		Total
			No	Yes	
SVR (Hood u)	Flolan	Median	26.30		26.30
		Maximum	47.30		47.30
	Standard	N	31	8	39
		Mean	23.67	23.52	23.64
		Std.Dev.	8.43	8.16	8.27
		Minimum	8.00	12.00	8.00
		Median	23.70	24.05	23.70
		Maximum	44.00	32.90	44.00

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TABLE 46.11
Summary of Baseline Hemodynamic and Blood Gas Measurements by Treatment Group

Normal Values	Parameter	Flolan (N=41)		Standard (N=40)		Summary statistics				
		Treatment	N	Mean	S.E.	Min.	25th %ile	Median	75th %ile	Max.
60-100	Heart Rate (bpm)	Flolan Standard	41	79.49	2.44	44.00	69.00	76.00	91.00	114.00
		Standard	40	65.93	2.34	54.00	70.00	86.00	95.00	120.00
4-8	Cardiac Output (L/min)	Flolan Standard	41	3.52	0.25	1.60	2.34	3.00	3.90	9.34
		Standard	40	3.75	0.30	1.00	2.43	3.20	4.47	11.90
2.4-2.8	Cardiac Index (L/min/m ²)	Flolan Standard	41	2.04	0.12	1.15	1.52	1.79	2.29	4.74
		Standard	40	2.13	0.16	1.19	1.46	1.65	2.08	6.47
15-30	PAPs (mm Hg)	Flolan Standard	41	90.90	2.79	62.00	80.00	97.00	110.00	131.00
		Standard	40	93.30	3.71	42.00	79.00	95.50	104.00	167.00
4-14	PAPd (mm Hg)	Flolan Standard	41	41.39	1.75	24.00	33.00	40.00	47.00	71.00
		Standard	40	41.30	1.62	13.00	36.00	42.00	47.00	59.00
9-17	PAPm (mm Hg)	Flolan Standard	41	60.54	1.07	39.00	53.00	59.00	60.00	89.00
		Standard	40	58.60	2.19	23.00	49.50	60.00	67.50	95.00
2-8	RAPm (mm Hg)	Flolan Standard	41	12.59	1.14	1.00	7.00	12.00	18.00	26.00
		Standard	39	12.06	1.20	1.00	6.00	12.00	18.00	29.00
2-12	PCNPs (mm Hg)	Flolan Standard	34	10.03	0.61	2.00	7.00	11.00	13.00	15.00
		Standard	29	10.31	0.64	5.00	8.00	10.00	13.00	16.00
	PVR (Wood u)	Flolan Standard	34	15.71	1.10	4.19	11.30	15.60	19.50	36.00
		Standard	29	16.17	1.36	1.70	10.50	16.00	20.90	30.90
	TPR (Wood u)	Flolan Standard	41	19.09	1.30	5.10	14.00	20.00	23.60	43.50
		Standard	40	18.92	1.37	4.00	11.90	19.75	25.50	36.00
100-140	SAPs (mm Hg)	Flolan Standard	41	120.90	1.03	85.00	115.00	121.00	129.00	143.00
		Standard	40	119.53	2.96	84.00	105.50	116.00	132.00	173.00

TABLE 46₁₁ (Con't)
 Summary of Baseline Hemodynamic and Blood Gas Measurements by Treatment Group (continued)

Parameter	Treatment	Standard (N=40)				Summary statistics				
		N	Mean	S.E.	Min.	25th %ile	Median	75th %ile	Max.	
SAPd (mm Hg)	Flolan	41	74.29	1.76	56.00	65.00	74.00	80.00	100.00	
	Standard	40	73.70	1.97	43.00	64.50	72.00	84.50	100.00	
SAPa (mm Hg)	Flolan	41	89.88	1.54	70.00	84.00	88.00	95.00	114.00	
	Standard	40	88.93	2.06	67.00	78.00	87.00	99.00	124.00	
SVR (Wood u)	Flolan	41	25.05	1.37	7.30	18.60	26.30	29.00	47.30	
	Standard	39	23.64	1.32	0.00	17.40	23.70	28.00	44.00	
TSR (Wood u)	Flolan	41	29.24	1.53	0.00	21.50	29.30	36.70	50.00	
	Standard	40	27.86	1.64	9.00	19.15	27.50	35.25	49.30	
SV (ml/beat)	Flolan	41	45.01	3.14	14.70	52.40	39.70	59.70	112.50	
	Standard	40	44.01	3.62	20.00	28.60	36.00	53.40	125.30	
Arterial Saturation (%)	Flolan	33	98.09	1.50	52.00	89.00	93.00	95.00	98.00	
	Standard	35	91.53	0.98	67.70	88.60	92.00	95.00	99.00	
Mixed Venous Saturation (%)	Flolan	38	62.48	2.05	42.00	52.00	63.00	71.00	92.00	
	Standard	39	58.91	2.10	26.60	46.30	60.00	71.00	88.00	
PaCO2 (mm Hg)	Flolan	34	31.33	1.31	2.70	27.00	31.50	35.00	46.00	
	Standard	35	30.73	0.96	23.00	26.00	29.00	35.00	42.00	
PaO2 (mm Hg)	Flolan	34	69.77	2.07	38.00	59.10	68.50	78.90	112.00	
	Standard	35	68.30	3.10	33.20	57.00	64.00	75.00	120.00	
pH	Flolan	34	7.44	0.01	7.34	7.41	7.45	7.48	7.49	
	Standard	35	7.46	0.01	7.30	7.42	7.46	7.48	7.57	

30-110
 30-50ml/L
 5120K work index (g·m²/min²)
 Arterio-venous O₂ diff.

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TABLE 46₁₂

Summary of the Baseline, Highest-Tolerated Dose, and Change from Baseline of Hemodynamic and Blood Gas Measurements by Treatment Group

Parameter	Fleolan (N=41)					Standard (N=40)						
	N ¹	Fleolan				N ¹	Standard					
		Baseline mean	High. tol. dose mean	Change in means	S.E. for the mean % Change difference in means		Baseline mean	High. tol. dose mean	Change in means	S.E. for the mean % Change difference in means		
Heart Rate (bpm)	41	79.49	86.24	6.76	1.16	8.5	38	86.37	92.45	6.08	1.93	7.8
Cardiac Output (L/min)	40	3.54	3.15	1.61	0.24	45.6	36	3.86	4.02	0.96	0.29	24.7
Cardiac Index (L/min/m ²)	40	2.04	2.98	0.93	0.13	45.6	36	2.19	2.72	0.53	0.16	24.3
PAPs (mm Hg)	41	98.98	98.18	-0.80	1.73	-0.8	37	91.57	91.03	-0.54	2.22	-0.6
PAPd (mm Hg)	41	41.39	38.34	-3.05	0.93	-7.4	37	40.65	38.78	-1.86	1.26	-4.6
PAPm (mm Hg)	41	68.54	58.17	-2.37	1.09	-3.9	37	57.65	56.24	-1.41	1.32	-2.4
RAPs (mm Hg)	41	12.59	12.41	-0.17	0.42	-1.4	36	11.51	10.21	-1.31	0.57	-11.3
PCMPs (mm Hg)	29	9.52	11.03	1.52	0.92	15.9	24	10.21	11.25	1.04	0.76	10.2
PVR (Wood u)	29	16.02	18.49	2.54	0.79	34.6	23	14.77	18.09	3.88	0.83	26.3
TPR (Wood u)	40	19.74	13.38	-6.47	0.88	-32.7	35	18.05	14.86	-3.98	0.82	-22.1
SAPs (mm Hg)	41	120.98	108.02	-12.95	2.18	-10.7	38	120.03	106.76	-13.26	1.77	-11.1
SAPd (mm Hg)	41	74.29	60.46	-13.83	1.36	-18.6	38	73.95	62.58	-11.37	1.21	-15.4
SAPm (mm Hg)	41	89.88	76.29	-13.59	1.48	-15.1	38	89.26	77.34	-11.92	1.20	-13.4
SVR (Wood u)	40	25.02	14.53	-10.49	0.93	-41.9	34	23.53	16.20	-7.34	0.87	-31.2
TSE (Wood u)	40	29.08	17.29	-11.78	1.09	-40.5	35	27.52	19.21	-8.31	1.14	-30.2

¹The number of patients with results from both the baseline and the Day 2 Treatment Phase evaluations.

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TABLE 46₁₂ (Con't)

Summary of the Baseline, Highest-Tolerated Dose, and Change from Baseline of Hemodynamic and Blood Gas Measurements by Treatment Group (continued)

Parameter	Flolen (N=41) ¹						Standard (N=40)					
	Flolen			Standard			Flolen			Standard		
	N ¹	Baseline mean	High. tol. dose mean	Change in means	S.E. for the mean difference	% Change in means	N ¹	Baseline mean	High. tol. dose mean	Change in means	S.E. for the mean difference	% Change in means
SV (mL/beat)	40	46.19	60.99	14.80	2.70	32.1	38	46.46	52.22	5.76	2.98	12.4
Arterial Saturation (%)	39	91.81	98.44	-0.57	0.67	-0.6	28	91.66	92.96	1.30	0.95	1.4
Mixed Venous Saturation (%)	33	63.62	69.45	5.83	1.45	9.2	30	59.36	68.25	8.89	1.32	15.0
P _a CO ₂ (mm Hg)	31	38.91	31.99	1.89	1.11	3.5	29	38.92	29.86	-1.06	0.63	-3.4
P _a O ₂ (mm Hg)	31	78.72	68.21	-2.51	3.02	-3.5	29	78.26	78.22	-0.04	3.10	-0.1
pH _a	31	7.44	7.44	0.00	0.00	0.0	29	7.45	7.46	0.01	0.00	0.2
Transcut. Blood O ₂ Sat. (%)	41	92.66	91.34	-1.32	0.54	-1.4	38	92.69	93.48	0.71	1.15	0.8

¹The number of patients with results from both the baseline and the Day 2 Treatment Phase evaluations.

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TABLE 46₁₃

Summary of the Change from Baseline to the Highest-Tolerated Dose of Hemodynamic and Blood Gas Measurements, All Patients

All patients (N¹)

Parameter	N ¹	Baseline mean	Highest tolerated dose mean	Difference in means (Max. Tol. - Baseline)	% Change in means	S.E. for the mean difference	95% Confidence Interval ² for the difference in means
Heart Rate (bpm)	79	82.88	89.23	6.43	7.8	1.18	(4.246, 8.615) *
Cardiac Output (L/min)	76	3.69	4.99	1.30	35.2	0.19	(0.925, 1.678) *
Cardiac Index (L/min/m ²)	76	2.11	2.85	0.74	35.1	0.10	(0.538, 0.946) *
PAPs (mm Hg)	78	95.42	94.74	-0.68	-0.7	1.38	(-3.431, 2.072)
PAPd (mm Hg)	78	41.84	38.55	-2.49	-6.1	0.77	(-4.022, -0.953) *
PAPm (mm Hg)	78	59.17	57.26	-1.91	-3.2	0.85	(-3.598, -0.223) *
RAPm (mm Hg)	77	12.88	11.38	-0.70	-5.8	0.35	(-1.402, -0.001) *
PCWPm (mm Hg)	53	9.83	11.13	1.30	13.2	0.61	(0.086, 2.517) *
PVR (Wood u)	52	15.47	18.66	4.81	31.1	0.58	(3.642, 6.078) *
TPR (Wood u)	75	18.96	13.65	-5.31	-28.0	0.62	(-6.544, -4.072) *
SAPs (mm Hg)	79	120.52	107.42	-13.10	-10.9	1.37	(-15.832, -10.370) *
SAPd (mm Hg)	79	74.13	61.48	-12.65	-17.1	0.92	(-14.473, -10.818) *
SAPm (mm Hg)	79	89.58	76.88	-12.78	-14.3	0.96	(-14.688, -10.881) *
SVR (Wood u)	74	24.34	15.38	-9.84	-37.1	0.67	(-10.367, -7.714) *
TSR (Wood u)	75	28.35	18.19	-10.16	-35.8	0.81	(-11.774, -8.549) *

¹The number of patients with results from both the baseline and the highest tolerated dose evaluations.

²A confidence interval that does not contain 0 implies statistical significance.

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TABLE 46₁₃ (Con't)

Summary of the Change from Baseline to the Highest-Tolerated Dose of Hemodynamic and Blood Gas Measurements, All Patients (continued)

All patients (N=81)

Parameter	N ¹	Baseline mean	Highest tolerated dose mean	Difference in means (Max. Tol. - Baseline)	% Change in means	S.E. for the mean difference	95% Confidence interval ² for the difference in means
SV (mL/beat)	75	46.32	56.98	10.58	22.9	2.06	(6.489, 14.679) =
Arterial Saturation (%)	58	91.32	91.66	0.33	0.4	0.50	(-0.836, 1.502)
Mixed Venous Saturation (%)	63	61.59	68.88	7.29	11.8	0.99	(5.302, 9.276) =
PaCO ₂ (mm Hg)	68	38.91	38.96	0.05	0.2	0.66	(-1.262, 1.366)
PaO ₂ (mm Hg)	68	78.58	69.18	-1.32	-1.9	2.35	(-5.622, 2.992)
pH	68	7.44	7.45	0.01	0.1	0.08	(0.000, 0.013) =
Transcut. Blood O ₂ Sat. (%)	76	92.67	92.29	-0.38	-0.4	0.61	(-1.602, 0.838)

¹The number of patients with results from both the baseline and the highest tolerated dose evaluations.
²A confidence interval that does not contain 0 implies statistical significance.

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TABLE 46₁₄

Summary of Baseline, Day 88, and changes from Baseline of Hemodynamic and Blood Gas Measurements, Between-Treatment Comparison

Parameter	Treatment	N ¹	Baseline		Day 88 mean	Mean change	S.E. mean change	X change in means	Difference in mean change (Flo.-Stand.) (Flo.-Stand.)	95% Confidence Interval for the diff. in mean change (Flo.-Stand.) (Flo.-Stand.)
			mean	SD						
Heart Rate (bpm)	Floien	30	79.97	11.11	79.11	-0.07	2.40	-1.1	0.96	(-2.10, 4.03)
	Standard	30	82.00	80.97		-1.03	1.50	-2.2		
Cardiac Output (L/min)	Floien	30	3.52	4.05	4.05	0.54	0.17	18.3	0.96	(0.65, 1.27) *
	Standard	30	3.98	3.47		-0.43	0.20	-10.9		
Cardiac Index (L/min/m ²)	Floien	30	2.04	2.37	2.37	0.33	0.10	16.1	0.56	(0.30, 0.74) *
	Standard	30	2.20	1.97		-0.23	0.16	-10.5		
PAPs (mm Hg)	Floien	30	97.58	90.37	90.37	-7.21	2.70	-7.4	-10.30	(-14.01, -4.75) *
	Standard	30	92.47	95.63		3.17	2.29	3.4		
PAPd (mm Hg)	Floien	30	41.16	37.80	37.80	-3.66	1.30	-0.9	-4.02	(-6.04, -2.01) *
	Standard	30	40.17	41.33		1.17	1.49	2.9		
PAPv (mm Hg)	Floien	30	59.95	55.13	55.13	-4.02	1.32	-0.0	-6.60	(-9.69, -4.67) *
	Standard	30	57.60	59.47		1.07	1.55	3.2		
RAPs (mm Hg)	Floien	36	13.11	10.94	10.94	-2.17	1.09	-16.5	-2.25	(-3.71, -0.00) *
	Standard	29	11.60	11.69		0.09	0.92	0.7		
PCMPs (mm Hg)	Floien	27	9.67	10.07	10.07	0.41	1.10	4.2	1.41	(-0.80, 3.32)
	Standard	17	10.02	9.02		-1.00	1.59	-9.2		
PVR (Wood u)	Floien	27	15.62	12.20	12.20	-3.42	0.72	-21.9	-4.95	(-6.25, -3.64) *
	Standard	17	15.53	17.05		1.52	1.23	9.0		
TPR (Wood u)	Floien	30	19.00	16.66	16.66	-4.14	0.96	-20.9	-6.10	(-7.56, -4.00) *
	Standard	30	16.16	20.20		2.04	0.99	11.2		

*The number of patients with results from both the baseline and the Day 88 evaluations. SA confidence interval that does not contain 0 implies statistical significance.

TABLE 46₁₄ (Con't)

Summary of Baseline, Day 88, and changes from Baseline of Hemodynamic and Blood Gas Measurements, Between-Treatment Comparison (continued)

Parameter	Treatment	N ¹	Baseline		Day 88 mean	Mean change	S.E. mean change	X change in mean change	Difference in mean change (Flo.-Stand.) (Flo.-Stand.)	95% Confidence Interval ² for the diff. in mean change (Flo.-Stand.) (Flo.-Stand.)
			Flofen	Standard						
SAPs (mm Hg)	Flofen	36	129.32	115.76	-4.55	3.15	-3.6	-1.29	(-5.49, 2.03)	
	Standard	39	122.83	119.57	-3.27	2.42	-2.7			
SAPd (mm Hg)	Flofen	38	74.68	69.76	-4.92	1.01	-6.6	-5.06	(-7.53, -2.60) *	
	Standard	28	74.07	74.21	0.14	1.54	0.2			
SAPm (mm Hg)	Flofen	38	89.92	85.08	-4.84	2.07	-5.4	-3.95	(-6.72, -1.18) *	
	Standard	28	90.57	89.68	-0.89	1.68	-1.0			
SVR (Wood u)	Flofen	36	24.86	28.02	-4.04	0.98	-16.3	-6.17	(-7.84, -4.51) *	
	Standard	27	23.25	25.38	2.13	1.44	9.2			
TSR (Wood u)	Flofen	38	29.37	25.79	-3.58	1.14	-19.0	-0.01	(-9.93, -6.06) *	
	Standard	28	27.86	29.58	2.43	1.68	9.0			
SV (ml/beat)	Flofen	38	45.68	52.33	6.65	2.25	14.6	10.13	(6.31, 13.94) *	
	Standard	38	47.88	44.61	-3.48	3.26	-7.3			
Arterial Saturation (%)	Flofen	29	98.29	92.29	-6.00	1.58	-2.2	2.63	(0.44, 4.62) *	
	Standard	22	91.39	90.75	-0.63	1.43	-0.7			
Mixed Venous Saturation (%)	Flofen	33	61.85	63.01	1.16	1.78	1.9	3.78	(1.00, 6.47) *	
	Standard	27	61.16	58.54	-2.62	2.05	-4.3			
Pco2 (mm Hg)	Flofen	29	33.08	33.28	0.12	0.81	0.4	1.03	(-0.14, 2.20)	
	Standard	23	31.01	30.90	-0.91	0.64	-2.9			
Po2 (mm Hg)	Flofen	29	68.49	72.13	3.64	3.74	5.3	5.66	(-0.73, 12.04)	
	Standard	23	70.15	68.13	-2.02	5.41	-2.9			

¹The number of patients with results from both the baseline and the Day 88 evaluations.
²A confidence interval that does not contain 0 implies statistical significance.

TABLE 46₁₄ (Con't)

Summary of Baseline, Day 88, and changes from Baseline of Hemodynamic and Blood Gas Measurements, Between-Treatment Comparison (continued)

Parameter	Fleian (N=41)		Standard (N=40)		Mean change	S.E. mean change	Z change in seans	Difference in mean change (Fle.- Stand.)	95% Confidence interval ² for the diff. in mean change (Fle.- Stand.)
	Treatment	N ¹	Baseline mean	Day 88 mean					
pHa	Fleian	29	7.44	7.44	-0.00	0.01	-0.0	-0.01	(-0.02, -0.00) *
	Standard	23	7.44	7.46	0.01	0.01	0.1		
Transcut. Blood O2 Sat. (%)	Fleian	37	92.49	93.22	0.73	0.53	0.6	1.76	(0.89, 2.64) *
	Standard	29	92.72	91.69	-1.03	0.74	-1.1		

¹The number of patients with results from both the baseline and the Day 88 evaluations.

²A confidence interval that does not contain 0 implies statistical significance.

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TABLE 46₁₅

Summary of the Scores of the Chronic Heart Failure Questionnaire, All Patients

Dimension	Treatment	Period	N	Mean	S.E.	Min.	Summary statistics			75th X-ile	Max.
							25th X-ile	Median	X-ile		
Dyspnea	Fiofen	Day 1	36	16.1	0.6	7.0	12.5	16.0	19.5	28.0	
		Wk 6	32	26.0	1.1	10.0	22.5	26.0	29.0	34.5	
		Day 87	35	24.4	1.1	10.0	20.0	24.0	30.0	35.0	
	Standard	Day 1	36	14.0	0.7	0.0	12.0	14.0	17.0	29.0	
		Wk 6	32	15.6	1.0	5.0	11.0	15.4	20.0	29.0	
		Day 87	26	17.3	1.4	5.0	14.0	16.5	20.0	34.0	
Fatigue	Fiofen	Day 1	40	13.3	0.8	4.0	9.5	13.0	17.0	24.0	
		Wk 6	38	17.9	1.7	7.0	15.0	18.0	21.0	28.0	
		Day 87	39	17.9	1.7	9.0	15.0	18.0	21.0	28.0	
	Standard	Day 1	40	13.0	0.9	4.0	9.0	12.0	16.0	26.0	
		Wk 6	36	13.6	0.9	4.0	10.0	12.0	16.0	27.0	
		Day 87	31	12.0	0.6	5.0	10.0	12.0	15.0	25.0	
Emotional function	Fiofen	Day 1	39	27.0	1.3	13.0	20.0	26.0	35.0	43.0	
		Wk 6	38	32.2	1.3	11.0	27.0	33.0	40.0	46.0	
		Day 87	39	33.7	1.3	12.0	29.5	34.0	40.0	49.0	
	Standard	Day 1	39	26.4	1.3	11.0	23.0	28.0	35.0	45.0	
		Wk 6	34	29.9	1.5	7.0	25.5	30.5	34.0	44.0	
		Day 87	31	30.0	1.5	14.0	23.0	30.0	36.0	48.0	
Mastery	Fiofen	Day 1	40	17.0	0.8	6.0	14.5	18.0	22.0	27.0	
		Wk 6	38	20.4	0.9	6.0	10.0	21.5	25.0	30.0	
		Day 87	39	21.0	0.7	10.0	18.0	22.0	25.0	30.0	
	Standard	Day 1	39	16.6	0.7	6.0	15.0	17.0	20.0	29.0	
		Wk 6	36	17.0	0.8	4.0	15.0	18.0	21.0	27.0	
		Day 87	31	18.7	0.8	10.0	16.0	18.0	22.0	27.0	

TABLE 46₁₆

Summary of the Chronic Heart Failure Questionnaire, Between-Treatment Comparisons of Changes from Baseline, All Patients

Dimension	Flolan (N=41)		Standard (N=90)		Nonparametric 95% Confidence Intervals
	Period	Flolan N ^a Median	Standard N ^b Median	M-L ^c Est.	
Dyspnea	Wk 6	32 0.5	32 1.0	0.0	(6.0,11.0)
	Day 87	35 0.0	26 0.0	7.0	(4.0,10.0)
Fatigue	Wk 6	30 5.0	36 0.0	5.0	(3.0,6.0)
	Day 87	39 5.0	31 0.0	5.0	(3.0,7.0)
Emotional function	Wk 6	37 5.0	35 0.0	4.0	(1.0,6.0)
	Day 87	30 6.0	30 -1.0	7.0	(3.0,10.0)
Nostalgia	Wk 6	30 3.0	35 0.0	3.0	(2.0,4.0)
	Day 87	39 3.0	30 -0.5	2.5	(1.0,4.0)

^aThe number of patients with results from both the baseline and the indicated evaluations.
^bHodges-Lehmann estimate for the true treatment effect.
^c95% confidence interval that does not contain 0 implies statistical significance.

TABLE 46.17
Summary of the Scores of the Nottingham Health Profile (Part 1), All Patients

Fiolan (N=61)
 Standard (N=99)

	Period	Treatment	N ²	Mean	S.E.	Min	25-th %ile	Median	75-th %ile	Max
Emotions/Reactions	Day 1	Fiolan Standard	39	26.8	3.7	0.0	9.0	22.8	42.9	69.0
		Standard	40	26.4	4.2	0.0	7.2	17.7	42.0	100
	Wk 6	Fiolan Standard	36	18.0	4.2	0.0	0.0	9.3	29.9	76.7
		Standard	36	20.3	4.2	0.0	0.0	11.9	20.3	100
	Day 07	Fiolan Standard	39	14.7	3.1	0.0	0.0	9.0	23.7	60.0
		Standard	31	22.4	4.1	0.0	0.0	14.0	40.3	64.7
Energy	Day 1	Fiolan Standard	41	55.7	5.7	0.0	24.0	60.0	100	100
		Standard	40	62.5	6.3	0.0	24.0	63.2	100	100
	Wk 6	Fiolan Standard	39	25.2	5.1	0.0	0.0	24.0	24.0	100
		Standard	37	53.5	6.2	0.0	24.0	60.0	100	100
	Day 07	Fiolan Standard	39	21.5	4.9	0.0	0.0	0.0	24.0	100
		Standard	31	58.3	7.1	0.0	24.0	60.0	100	100
Pain	Day 1	Fiolan Standard	39	17.3	4.4	0.0	0.0	0.0	22.9	100
		Standard	40	14.3	4.1	0.0	0.0	5.0	15.0	100
	Wk 6	Fiolan Standard	37	12.0	3.9	0.0	0.0	0.0	12.9	79.1
		Standard	37	12.0	3.9	0.0	0.0	0.0	15.0	100
	Day 07	Fiolan Standard	41	7.0	2.8	0.0	0.0	0.0	5.0	61.3
		Standard	31	6.7	3.4	0.0	0.0	0.0	10.5	100
Physical mobility	Day 1	Fiolan Standard	40	36.4	3.8	0.0	21.4	32.6	54.7	90.7
		Standard	39	44.1	3.7	0.0	22.0	43.3	56.0	100
	Wk 6	Fiolan Standard	38	21.9	2.9	0.0	9.3	21.4	32.6	66.1
		Standard	37	57.2	3.5	0.0	22.0	41.9	54.5	88.5

TABLE 46₁₇ (Con't)
 Summary of the Scores of the Nottingham Health Profile (Part 1). All Patients (continued)

Flofen (N=41)
 Standard (N=40)

	Period	Treatment	N	Mean	S.E.	Min	25-th %ile	Median	75-th %ile	Max
Physical mobility	Day 07	Flofen	40	24.0	3.0	0.0	10.0	22.0	33.0	66.1
		Standard	31	36.5	3.4	0.0	22.0	41.9	47.3	70.7
Sleep	Day 1	Flofen	41	37.3	0.6	0.0	12.6	30.9	56.6	100
		Standard	40	35.7	0.8	0.0	6.3	31.5	65.1	100
	Wk 6	Flofen	38	23.4	4.2	0.0	0.0	12.6	34.9	67.4
		Standard	37	30.5	5.9	0.0	0.0	12.6	65.1	100
Social isolation	Day 07	Flofen	41	19.0	3.9	0.0	0.0	12.6	20.7	100
		Standard	31	40.3	5.9	0.0	12.6	36.3	65.1	100
	Day 1	Flofen	41	10.9	3.7	0.0	0.0	20.1	22.5	100
		Standard	40	20.2	4.5	0.0	0.0	0.0	22.5	100
	Wk 6	Flofen	38	14.6	3.9	0.0	0.0	0.0	22.5	100
		Standard	37	18.9	4.0	0.0	0.0	0.0	22.5	100
	Day 07	Flofen	49	12.4	3.2	0.0	0.0	0.0	22.5	64.7
		Standard	31	14.8	3.8	0.0	0.0	0.0	23.5	64.7

TABLE 4618
Summary of the Responses to the Nottingham Health Profile (Part II)

Flolan (N=93)
 Standard (N=98)

Parameter	Period	Treatment	Total	Yes		No	
				N	(%)	N	(%)
Home life	Day 1	Flolan Standard	40	13	(33)	27	(68)
			40	22	(55)	18	(45)
	Wk 6	Flolan Standard	38	8	(21)	30	(79)
			37	17	(46)	20	(54)
	Day 87	Flolan Standard	39	9	(23)	30	(77)
			31	13	(42)	18	(58)
Looking after the home	Day 1	Flolan Standard	38	24	(63)	14	(37)
			40	30	(75)	10	(25)
	Wk 6	Flolan Standard	36	24	(67)	12	(33)
			36	28	(78)	8	(22)
	Day 87	Flolan Standard	38	23	(61)	15	(39)
			31	25	(81)	6	(19)
Interests & Hobbies	Day 1	Flolan Standard	40	24	(60)	16	(40)
			40	24	(60)	16	(40)
	Wk 6	Flolan Standard	37	21	(57)	16	(43)
			37	20	(54)	17	(46)
	Day 87	Flolan Standard	39	19	(49)	20	(51)
			31	19	(61)	12	(39)
Sex life	Day 1	Flolan Standard	37	21	(57)	16	(43)
			40	24	(60)	16	(40)

TABLE 46₁₈ (Con't)

Summary of the Responses to the Nottingham Health Profile (Part II) (continued)

Parameter	Period	Treatment	Total	Flolan (N=41) Standard (N=40)			
				Yes		No	
				N	(%)	N	(%)
Sex life	Wk 6	Flolan	34	13	(38)	21	(62)
		Standard	36	19	(53)	17	(47)
	Day 87	Flolan	38	16	(42)	22	(58)
		Standard	31	16	(52)	15	(48)
Social life	Day 1	Flolan	40	23	(58)	17	(43)
		Standard	40	20	(50)	12	(30)
	Wk 6	Flolan	58	16	(42)	22	(58)
		Standard	37	29	(78)	8	(22)
Day 87	Flolan	40	18	(45)	22	(55)	
	Standard	31	19	(61)	12	(39)	
Vacations	Day 1	Flolan	40	21	(53)	19	(48)
		Standard	40	27	(68)	13	(33)
	Wk 6	Flolan	37	21	(57)	16	(43)
		Standard	37	24	(65)	13	(35)
Day 87	Flolan	39	18	(46)	21	(54)	
	Standard	31	21	(68)	10	(32)	
Work	Day 1	Flolan	58	14	(37)	24	(63)
		Standard	40	24	(60)	16	(40)
	Wk 6	Flolan	36	18	(50)	26	(72)
		Standard	36	19	(53)	17	(47)

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TABLE 46₁₈ (Con't)

Summary of the Responses to the Nottingham Health Profile (Part II) (continued)

Parameter	Period	Treated	Total	Folien (N=41)		Standard (N=46)	
				Yes	No	Yes	No
				(%)	(%)	(%)	(%)
Work	Day 07	Folien	16	(39)	23	(61)	
		Standard	17	(55)	14	(45)	

TABLE 46₁₉

Dyspnea - Fatigue Rating

Parameter	Definitions of Scores
Magnitude of Tact: (at normal pace)	Extraordinary. Becomes short of breath or fatigued (hereafter called "symptomatic") only with extraordinary activity such as carrying over heavy loads on level ground, lighter loads uphill or running. No symptoms with ordinary tasks. Major. Becomes symptomatic only with such major activities as walking up a steep hill, climbing more than 3 flights of stairs or carrying a moderate load on the level. Moderate. Becomes symptomatic with moderate or average tasks such as walking up a gradual hill, climbing less than 3 flights of stairs or carrying a light load on level ground. Light. Becomes symptomatic with light activities, such as walking on the level, washing or standing. None. Symptomatic at rest, while sitting or lying down.
Magnitude of Pace:	Extraordinary. Essentially all conceivable physical tasks are performed at normal pace. Major. Major tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Light tasks can be done at normal pace. Moderate. Moderate tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Light tasks are done at a reduced pace. Light. Light tasks are done at a reduced pace. None. Symptomatic at rest.
Functional Impairment	None. Can carry out usual activities and occupation without symptoms. Slight. Distinct impairment in at least 1 activity but no activities completely abandoned. A change in activity may have occurred at work or in other activities, but the change is slight or is not clearly caused by shortness of breath or fatigue. Moderate. Patients has changed jobs or has abandoned at least 1 usual activity. Severe. Patient is unable to work or has given up most or all usual activities. Very severe. Unable to work and has given up most or all usual activities.

TABLE 46₂₀

Summary of the Dyspnea-Fatigue Rating

Flolan (N=41)
Standard (N=40)

Period	Treatment	N ²	Mean	S.E.	Min	25-th %-ile	Median	75-th %-ile	Max
Day 1	Flolan	41	4.2	0.4	0.0	2.0	4.0	6.0	9.0
	Standard	40	3.5	0.4	0.0	2.0	3.0	4.5	10.0
Wk 1	Flolan	40	4.6	0.3	0.0	3.0	4.0	6.0	9.0
	Standard	39	3.4	0.4	0.0	2.0	3.0	5.0	10.0
Wk 3	Flolan	40	5.5	0.4	0.0	3.0	5.0	7.0	10.0
	Standard	38	3.6	0.4	0.0	2.0	3.0	4.0	10.0
Wk 6	Flolan	40	5.8	0.4	0.0	3.5	5.0	8.0	12.0
	Standard	37	3.3	0.4	0.0	2.0	3.0	4.0	11.0
Wk 9	Flolan	40	5.7	0.4	2.0	3.5	6.0	7.5	10.0
	Standard	32	3.4	0.4	0.0	2.0	3.0	4.0	11.0
Day 87	Flolan	41	5.5	0.4	0.0	4.0	5.0	7.0	12.0
	Standard	31	3.5	0.5	0.0	2.0	3.0	4.0	11.0

²The aggregate score ranges from 0 to 12 (worst to best)
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TABLE 46₂₁

Summary of Dyspnea-Fatigue Rating, Between-Treatment Comparisons of Changes from Baseline

Period	Flolan (N=41)		Standard (N=40)		N-L ³ Est.	Nonparametric 95% Confidence Interval ⁴
	N ²	Median change from baseline in the aggregate score	N ²	Median change from baseline in the aggregate score		
Wk 1	40	0.0	39	0.0	0.0	(0.0,1.0)
Wk 3	40	1.0	38	0.0	1.0	(0.0,2.0)
Wk 6	40	1.5	37	0.0	2.0	(1.0,3.0) *
Wk 9	40	1.0	32	0.0	2.0	(1.0,3.0) *
Day 87	41	1.0	31	0.0	2.0	(1.0,3.0) *

¹The aggregate score ranges from 0 to 12 (worst to best) thus the change from baseline score ranges from -12 to 12 (worst to best).

²Number of patients with results from both the baseline and the indicated evaluation.

³Median-Lehmann estimate for the true treatment effect.

⁴A confidence interval that does not contain 0 implies statistical significance.

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Summary of PPH Symptoms

TABLE 4622

Flolan (Mg/1)
Standard (Mg/0)

PPH Signs	Period	Treatment	None of the Time		Some of the Time		Most of the Time		All of the Time		
			(2) N	(2) M	(2) N	(2) M	(2) N	(2) M	(2) N	(2) M	
Chest pain	Day 1	Flolan Standard	41	15	137	24	159	2	15	0	10
			40	16	140	28	150	3	10	1	13
	Wk 1	Flolan Standard	40	26	165	14	155	0	10	0	10
			39	18	146	19	149	1	13	1	13
	Wk 3	Flolan Standard	40	26	165	13	153	1	13	0	10
			38	21	155	15	139	2	15	0	10
	Wk 4	Flolan Standard	40	25	163	12	150	3	10	0	10
			37	15	141	21	157	1	13	0	10
	Wk 9	Flolan Standard	46	26	168	12	130	2	15	0	10
			32	14	144	17	153	0	10	1	13
	Day 07	Flolan Standard	41	28	149	20	149	1	12	0	10
			31	12	139	18	150	0	10	1	13
Dizziness	Day 1	Flolan Standard	41	14	154	26	163	1	12	0	10
			40	8	120	30	175	2	15	0	10
	Wk 1	Flolan Standard	40	22	153	17	143	1	13	0	10
			39	16	141	21	154	2	15	0	10
	Wk 3	Flolan Standard	40	24	160	15	138	1	13	0	10
			38	17	148	20	153	1	13	0	10
	Wk 6	Flolan Standard	40	25	163	14	155	0	10	1	13
			37	12	132	22	159	3	10	0	10

TABLE 4622 (CON'T)

Summary of PPH Symptoms (continued)

Flelan (Meal)
Standard (M=48)

PPH Signs	Period	Treatment	Total	None of the Time		Some of the Time		Most of the Time		All of the Time	
				(X)	(N)	(X)	(N)	(X)	(N)	(X)	(N)
Dizziness	Wk 9	Flelan Standard	48	26	(55)	12	(30)	2	(5)	0	(0)
			32	11	(34)	21	(66)	0	(0)	0	(0)
Dyspnea at rest	Day 07	Flelan Standard	41	26	(63)	14	(34)	1	(2)	0	(0)
			31	7	(23)	25	(74)	0	(0)	1	(3)
Dyspnea at rest	Day 1	Flelan Standard	41	22	(54)	15	(37)	3	(7)	1	(2)
			48	18	(45)	16	(40)	3	(8)	3	(8)
Dyspnea at rest	Wk 1	Flelan Standard	48	32	(67)	7	(15)	2	(4)	0	(0)
			39	22	(56)	15	(39)	4	(10)	0	(0)
Dyspnea at rest	Wk 3	Flelan Standard	40	30	(75)	0	(0)	1	(3)	0	(0)
			37	19	(51)	16	(43)	1	(3)	1	(3)
Dyspnea at rest	Wk 6	Flelan Standard	48	32	(67)	7	(15)	2	(5)	0	(0)
			37	19	(51)	15	(41)	2	(5)	1	(3)
Dyspnea at rest	Wk 9	Flelan Standard	40	29	(73)	11	(28)	0	(0)	0	(0)
			32	14	(44)	15	(47)	2	(6)	2	(6)
Dyspnea at rest	Day 07	Flelan Standard	41	33	(81)	6	(15)	0	(0)	2	(5)
			31	14	(45)	15	(48)	1	(3)	1	(3)
Dyspnea on exertion	Day 1	Flelan Standard	41	0	(0)	6	(15)	17	(41)	18	(44)
			48	0	(0)	4	(10)	14	(35)	22	(55)
Dyspnea on exertion	Wk 1	Flelan Standard	39	2	(5)	15	(38)	15	(38)	7	(18)

TABLE 4622 (CON'T)
Summary of PPH Symptoms (continued)

Fiolan (Nc41)
Standard (Nc48)

PPH Signs	Period	Treatment	Total N	None of the Time		Some of the Time		Most of the Time		All of the Time	
				(2) N	(2) M	(2) N	(2) M	(2) N	(2) M	(2) N	(2) M
Dyspnea on exertion	Wk 1	Standard	39	0	7	110	13	133	19	69	
	Wk 3	Fiolan Standard	48	5	23	158	6	181	6	151	
			38	0	8	121	16	142	14	137	
	Wk 6	Fiolan Standard	40	4	26	165	7	187	3	181	
			37	1	3	101	14	143	17	146	
Fatigue	Wk 9	Fiolan Standard	40	3	23	158	10	176	4	170	
			32	0	7	122	10	131	15	147	
	Day 07	Fiolan Standard	41	3	20	149	11	171	7	171	
			31	0	3	110	12	139	16	152	
	Day 1	Fiolan Standard	41	1	19	146	16	179	5	171	
Fatigue	Day 1	Fiolan Standard	40	0	17	143	12	158	11	159	
	Wk 1	Fiolan Standard	40	6	21	153	11	170	2	173	
			39	3	16	141	12	151	0	151	
	Wk 3	Fiolan Standard	40	0	24	140	5	143	3	146	
			38	1	20	153	11	170	6	176	
Fatigue	Wk 6	Fiolan Standard	40	7	29	173	3	183	1	187	
			37	2	17	146	13	161	5	169	
	Wk 9	Fiolan Standard	40	5	34	168	1	173	0	173	
			32	1	13	141	14	156	4	160	

TABLE 4 6₂₂ (Con't)

Summary of PPH Symptoms (continued)

Flojan (H=91)
Standard (H=91)

PPH Signs	Period	Treatment	Total	None of the Time		Some of the Time		Most of the Time		All of the Time	
				(%)	N	(%)	N	(%)	N	(%)	N
Fatigue	Day 87	Flojan Standard	41	4	(10)	29	(71)	7	(17)	1	(2)
			31	0	(0)	13	(42)	15	(48)	3	(10)
Paresthesias	Day 1	Flojan Standard	41	11	(27)	25	(61)	5	(12)	0	(0)
			40	14	(35)	22	(55)	4	(10)	0	(0)
	Wk 1	Flojan Standard	39	22	(56)	17	(44)	0	(0)	0	(0)
			39	16	(41)	21	(54)	2	(5)	0	(0)
	Wk 3	Flojan Standard	40	22	(55)	18	(45)	0	(0)	0	(0)
			38	15	(39)	22	(58)	1	(3)	0	(0)
Wk 4	Flojan Standard	40	23	(58)	15	(38)	2	(5)	0	(0)	
		37	17	(46)	18	(49)	2	(5)	0	(0)	
Wk 9	Flojan Standard	40	20	(50)	19	(48)	1	(3)	0	(0)	
		32	14	(44)	16	(50)	2	(6)	0	(0)	
Day 87	Flojan Standard	41	17	(41)	22	(54)	2	(5)	0	(0)	
		31	15	(48)	13	(42)	3	(10)	0	(0)	
Paroxysmal nocturnal dyspnea	Day 1	Flojan Standard	41	30	(73)	7	(17)	4	(10)	0	(0)
			40	20	(50)	10	(25)	1	(3)	1	(3)
Wk 3	Flojan Standard	40	30	(75)	2	(5)	0	(0)	0	(0)	
		39	32	(82)	7	(18)	0	(0)	0	(0)	
Wk 3	Flojan Standard	40	40	(100)	0	(0)	0	(0)	0	(0)	
		40	40	(100)	0	(0)	0	(0)	0	(0)	

TABLE 4622 (Con't)

Summary of PPH Symptoms (continued)

Flejan (No41)
Standard (No49)

PPH Signs	Period	Treatment	Total N	None of the Time		Some of the Time		Most of the Time		All of the Time	
				(X)	(N)	(X)	(N)	(X)	(N)	(X)	(N)
Paroxysmal nocturnal dyspnea	Wk 3	Standard	36	24	(67)	13	(36)	0	(0)	1	(3)
	Wk 6	Flejan Standard	46	38	(83)	8	(17)	0	(0)	0	(0)
	Wk 9	Flejan Standard	37	24	(65)	12	(32)	1	(3)	0	(0)
	Day 07	Flejan Standard	41	37	(90)	4	(10)	0	(0)	0	(0)
Syncope	Day 1	Flejan Standard	41	28	(68)	13	(32)	0	(0)	0	(0)
	Wk 1	Flejan Standard	46	37	(80)	9	(20)	0	(0)	0	(0)
	Wk 3	Flejan Standard	39	36	(92)	3	(8)	0	(0)	0	(0)
	Wk 6	Flejan Standard	40	37	(93)	3	(8)	0	(0)	0	(0)
	Wk 9	Flejan Standard	40	38	(95)	2	(5)	0	(0)	0	(0)
	Day 07	Flejan Standard	41	40	(98)	1	(2)	0	(0)	0	(0)

TABLE 46₂₂ (Con't)

Summary of PPH Symptoms (continued)

Flelen (No41)
Standard (No46)

PPH Signs	Period	Treatment	Total	Present		1 Pillow		2 Pillows		3 Pillows		Bed on Blocks		Sleeps In Chair	
				No. Present		No. Present		No. Present		No. Present		No. Present		No. Present	
				N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Orthopedics	Day 1	Flelen	41	15	(37)	4	(10)	14	(34)	7	(17)	1	(2)	0	(0)
		Standard	60	11	(25)	6	(10)	15	(30)	4	(10)	1	(3)	3	(10)
	Wk 1	Flelen	60	10	(45)	0	(20)	0	(20)	5	(13)	1	(3)	0	(0)
		Standard	39	12	(31)	2	(5)	20	(51)	3	(8)	0	(0)	2	(5)
	Wk 3	Flelen	40	24	(60)	3	(10)	12	(30)	1	(3)	0	(0)	0	(0)
		Standard	30	11	(29)	3	(10)	15	(39)	0	(2)	0	(0)	1	(3)
	Wk 6	Flelen	40	20	(50)	7	(10)	10	(25)	2	(5)	1	(3)	0	(0)
		Standard	37	9	(24)	3	(10)	19	(51)	4	(11)	1	(3)	1	(3)
	Wk 9	Flelen	60	24	(60)	4	(10)	11	(20)	1	(3)	0	(0)	0	(0)
		Standard	32	7	(22)	2	(6)	17	(53)	4	(13)	0	(0)	2	(6)
	Day 07	Flelen	41	22	(54)	5	(12)	12	(29)	2	(5)	0	(0)	0	(0)
		Standard	31	6	(19)	3	(10)	10	(30)	3	(10)	0	(0)	1	(3)

If present . . .

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TABLE 4623

Summary of PPH Symptoms, Between-Treatment Comparisons of Changes from Baseline

Flolan (N=41)
Standard (N=40)

PPH Symptoms	Period	Flolan		Standard Therapy		95% Confidence Intervals			
		Total ¹	N	Total ¹	N				
		P12	Less Frequent	P22	Less Frequent				
Chest pain	Wk 1	40	16	0.40	39	7	0.18	0.22	(0.00, 0.44) ²
	Wk 3	40	16	0.40	36	10	0.26	0.14	(-.09, 0.37)
	Wk 6	40	14	0.35	37	9	0.24	0.11	(-.12, 0.34)
	Wk 9	40	15	0.38	32	7	0.22	0.16	(-.08, 0.40)
	Day 87	41	9	0.22	31	5	0.16	0.06	(-.15, 0.27)
Dizziness	Wk 1	40	12	0.30	39	11	0.28	0.02	(-.21, 0.25)
	Wk 3	40	14	0.35	38	12	0.32	0.03	(-.21, 0.27)
	Wk 6	40	15	0.38	37	7	0.19	0.19	(-.03, 0.41)
	Wk 9	40	15	0.38	32	8	0.25	0.13	(-.11, 0.37)
	Day 87	41	14	0.34	31	3	0.10	0.24	(0.03, 0.45) ²
Dyspnea at rest	Wk 1	40	14	0.35	39	9	0.23	0.12	(-.10, 0.34)
	Wk 3	40	14	0.35	38	6	0.16	0.19	(-.02, 0.40)
	Wk 6	40	14	0.35	37	7	0.19	0.16	(-.06, 0.38)
	Wk 9	40	14	0.35	32	5	0.16	0.19	(-.03, 0.41)
	Day 87	41	14	0.34	31	7	0.23	0.11	(-.13, 0.35)
Dyspnea on exertion	Wk 1	40	18	0.45	39	6	0.15	0.30	(0.06, 0.52) ²
	Wk 3	40	24	0.60	38	11	0.29	0.36	(0.13, 0.59) ²
	Wk 6	40	30	0.75	37	8	0.22	0.53	(0.31, 0.75) ²
	Wk 9	40	26	0.65	32	7	0.22	0.43	(0.28, 0.66) ²
	Day 87	41	27	0.66	31	6	0.19	0.47	(0.24, 0.70) ²

¹Number of patients with results from both the baseline and the indicated evaluation.

²Proportion of patients that had symptoms less frequently.

³Large sample normal approximation. Statistical Methods for Rates and Proportions, 2nd ed., J.L. Fleiss, p29.

TABLE 46₂₃ (Con't)

Summary of PPH Symptoms, Between-Treatment Comparisons of Changes from Baseline (continued)

PPH Symptoms	Period	Fiolan (N=41) Standard (N=40)							95% Confidence Interval ³
		Total ¹	Fiolan		Total ¹	Standard Therapy		P1-P2	
			H	P1 ²		H	P2 ²		
			Less Frequent			Less Frequent			
Fatigue	Wk 1	40	13	0.33	39	9	0.23	0.10	(-.12, 0.32)
	Wk 3	40	21	0.53	38	9	0.24	0.29	(0.06, 0.52) ^a
	Wk 6	40	24	0.60	37	11	0.30	0.38	(0.06, 0.54) ^a
	Wk 9	40	23	0.58	32	8	0.25	0.33	(0.09, 0.57) ^a
	Day 87	41	19	0.46	31	8	0.26	0.28	(-.05, 0.45)
Orthopnea	Wk 1	40	8	0.20	39	7	0.18	0.02	(-.18, 0.22)
	Wk 3	40	16	0.40	38	8	0.21	0.19	(-.04, 0.42)
	Wk 6	40	12	0.30	37	8	0.22	0.08	(-.14, 0.30)
	Wk 9	40	17	0.43	32	5	0.16	0.27	(0.04, 0.50) ^a
	Day 87	41	16	0.39	31	8	0.26	0.13	(-.11, 0.37)
Palpitations	Wk 1	40	17	0.43	39	8	0.21	0.22	(-.01, 0.45)
	Wk 3	40	15	0.38	38	8	0.21	0.17	(-.05, 0.39)
	Wk 6	40	15	0.38	37	10	0.27	0.11	(-.12, 0.34)
	Wk 9	40	16	0.40	32	9	0.28	0.12	(-.13, 0.37)
	Day 87	41	14	0.34	31	7	0.23	0.11	(-.13, 0.35)
Paroxysmal noct. dyspnea	Wk 1	40	9	0.23	39	7	0.18	0.05	(-.15, 0.25)
	Wk 3	40	11	0.28	38	4	0.11	0.17	(-.03, 0.37)
	Wk 6	40	10	0.25	37	6	0.16	0.09	(-.11, 0.29)
	Wk 9	40	10	0.25	32	3	0.09	0.16	(-.05, 0.35)
	Day 87	41	11	0.27	31	3	0.10	0.17	(-.33, 0.37)

¹Number of patients with results from both the baseline and the indicated evaluation.

²Proportion of patients that had symptoms less frequently.

³Large sample normal approximation. Statistical Methods for Rates and Proportions, 2nd ed., J.L. Fleiss, p29.

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TABLE 46₂₃ (Con't)

Summary of PPH Symptoms, Between-Treatment Comparisons of Changes from Baseline (continued)

PPH Symptoms	Period	Flolan (N=41)		Standard (N=40)		P1-P2	95% Confidence Interval ³		
		Total ¹	Less Frequent		Total ¹			Less Frequent	
			N	P1 ²				N	P2 ²
Syncope	Wk 1	40	11	0.28	39	9	0.23	0.05	(-.17,0.27)
	Wk 3	40	13	0.33	38	9	0.24	0.09	(-.13,0.31)
	Wk 6	40	15	0.38	37	8	0.22	0.11	(-.11,0.33)
	Wk 9	40	12	0.30	32	7	0.22	0.08	(-.15,0.31)
	Day 87	41	15	0.37	31	7	0.23	0.09	(-.14,0.32)

¹Number of patients with results from both the baseline and the indicated evaluation.

²Proportion of patients that had symptoms less frequently.

³Large sample normal approximation. Statistical Methods for Rates and Proportions, 2nd ed., J.L. Fleiss, p29.

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TABLE 4624
 Summary of PPH Signs, Between-Treatment Comparisons of Changes from Baseline

PPH Signs	Period	Flolan (N=41)		Standard Therapy		95% Confidence Interval ¹
		Standard (N=40)		Improved		
		Total	P12	Total	M P22	
Edema	Wk 1	40	9 0.23	39	6 0.15	(-.12, 0.20)
	Wk 6	40	15 0.38	37	6 0.16	(0.00, 0.44) ²
	Day 87	40	15 0.38	31	6 0.19	(-.04, 0.42)
Hepatosomegaly	Wk 1	40	0 0.00	39	0 0.00	(-.03, 0.03)
	Wk 6	40	0 0.00	37	0 0.00	(-.03, 0.03)
	Day 87	40	0 0.00	31	0 0.00	(-.03, 0.03)
Right Vent. S3 Sound	Wk 1	40	0 0.00	39	3 0.08	(-.19, 0.03)
	Wk 6	40	2 0.05	37	2 0.05	(-.12, 0.12)
	Day 87	40	4 0.10	31	4 0.13	(-.21, 0.15)
Right Vent. S4 Sound	Wk 1	40	1 0.03	39	1 0.03	(-.10, 0.10)
	Wk 6	40	3 0.08	37	2 0.05	(-.11, 0.17)
	Day 87	40	3 0.08	31	1 0.03	(-.08, 0.10)
Jug. Ven. Dist. at 45"	Wk 1	40	0 0.00	39	3 0.08	(-.06, 0.30)
	Wk 6	40	11 0.28	37	3 0.08	(0.01, 0.39) ²
	Day 87	40	9 0.23	31	6 0.19	(-.10, 0.26)
Murmur of Pulm. Insuff.	Wk 1	40	1 0.03	39	0 0.00	(-.05, 0.11)
	Wk 6	40	0 0.00	37	0 0.00	(0.00, 0.35) ²
	Day 87	40	0 0.00	31	1 0.03	(0.00, 0.34) ²
Murmur of Trio. Insuff.	Wk 1	40	10 0.25	39	6 0.15	(-.10, 0.30)
	Wk 6	40	11 0.28	37	12 0.32	(-.27, 0.19)

¹Number of patients with results from both the baseline and the indicated evaluation.
²Proportion of the patients that reported an improvement in PPH signs.
³Large sample normal approximation. Statistical Methods for Rates and Proportions, 2nd ed., J.L. Fleiss, p29.

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TABLE 46₂₄ (Con't)

Summary of PPH Signs, Between-Treatment Comparisons of Changes from Baseline (continued)

PPH Signs	Period	Fiolan (N=41)		Standard (N=40)		P1-P2	95% Confidence Interval ⁴
		Fiolan		Standard Therapy			
		Total ¹	Improved ²	Total ¹	Improved ²		
Murmur of Tric. Inauff.	Day 87	40	13 0.33	31	8 0.26	0.07	(-.17, 0.31)
NYHA Class	Wk 1	40	2 0.05	39	1 0.03	0.02	(-.09, 0.13)
	Wk 6	40	18 0.45	37	4 0.11	0.34	(0.13, 0.55) *
	Day 87	40	16 0.40	31	1 0.03	0.37	(0.18, 0.56) *
Loud P2 Sound	Wk 1	40	0 0.00	39	0 0.00	0.00	(-.03, 0.03)
	Wk 6	40	1 0.03	37	1 0.03	0.00	(-.10, 0.10)
	Day 87	40	1 0.03	31	1 0.03	0.00	(-.11, 0.11)
Right Vent. Heave	Wk 1	40	0 0.00	39	0 0.00	0.00	(-.03, 0.03)
	Wk 6	40	0 0.00	37	2 0.05	-.05	(-.15, 0.05)
	Day 87	40	1 0.03	31	1 0.03	0.00	(-.11, 0.11)

¹Number of patients with results from both the baseline and the indicated evaluation.

²Proportion of the patients that reported an improvement in PPH signs.

³Large sample normal approximation. Statistical Methods for Rates and Proportions, 2nd ed., J.L. Fleiss, p29.

TABLE 46₂₃

Expected and Unexpected Adverse Experiences that Occurred in at Least 3 Patients in Either Treatment Group, 12-Week Treatment Segment

Adverse Experience	FLOLAN®		Standard	
	N	(%)	N	(%)
Asthenia	41	(100%)	39	(98%)
Dyspnea	41	(100%)	39	(98%)
Dizziness	37	(90%)	34	(85%)
Headache	35	(85%)	15	(38%)
Palpitations	33	(80%)	30	(75%)
Pain, chest	31	(76%)	33	(83%)
Edema	30	(73%)	30	(75%)
Nausea	28	(68%)	23	(58%)
Pain, jaw	27	(66%)	0	(0%)
Myalgia	23	(56%)	16	(40%)
Cough, increase	19	(46%)	25	(63%)
Depression	19	(46%)	23	(58%)
Vascular disorder, peripheral	19	(46%)	20	(50%)
Tachycardia	16	(39%)	13	(33%)
Diarrhea	16	(39%)	3	(8%)
Cyanosis	14	(34%)	21	(53%)
Pain, abdominal	14	(34%)	15	(38%)
Weight decrease	14	(34%)	13	(33%)
Arrhythmia	14	(34%)	11	(28%)
Hypoxia	13	(32%)	19	(48%)
Heart failure, right	13	(32%)	19	(48%)
Hypotension	13	(32%)	16	(40%)
Anorexia	13	(32%)	15	(38%)
Pain, general	13	(32%)	7	(18%)
Heart failure (Low cardiac output)	12	(29%)	21	(53%)
Flushing	11	(27%)	0	(0%)
Pallor	10	(24%)	16	(40%)
Angina pectoris	10	(24%)	11	(28%)
Fever	10	(24%)	3	(8%)
Vomit	8	(20%)	4	(10%)
Sweat	7	(17%)	9	(23%)
Bradycardia	7	(17%)	5	(13%)
Syncope	6	(15%)	11	(28%)
Ascites	6	(15%)	8	(20%)
Hemorrhage	6	(15%)	5	(13%)

TABLE 46₂₅ (Con't)

Expected and Unexpected Adverse Experiences that Occurred in at Least 3 Patients in Either Treatment Group, 12-Week Treatment Segment (continued)

Adverse Experience	FLOLAN®		Standard	
	N	(%)	N	(%)
Anxiety	5	(12%)	3	(8%)
Amblyopia	4	(10%)	2	(5%)
Nervousness	4	(10%)	1	(3%)
Confusion	3	(7%)	6	(15%)
Rash	3	(7%)	5	(13%)
Infection, general	3	(7%)	3	(8%)
Pain, back	3	(7%)	2	(5%)
Weight increase	3	(7%)	2	(5%)
Constipation	3	(7%)	1	(3%)
Hypokalemia	3	(7%)	1	(3%)
Hypesthesia	3	(7%)	1	(3%)
Arthralgia	3	(7%)	0	(0%)
Tachycardia, supraventricular	3	(7%)	0	(0%)
Rhinitis	2	(5%)	4	(10%)
Infection, urinary tract	2	(5%)	3	(8%)
Liver function abnormality	1	(2%)	4	(10%)
Ischemia, myocardial	1	(2%)	3	(8%)
Shock	0	(0%)	7	(18%)

[Table excerpted from Table 67]

TABLE 46₂₆

Randomization Results - A Chronological Listing of Patients by Enrollment Date

Date of Enrollment	Patient Number	Treatment Assignment ^a	NYHA Class	Vasodilator Use at Baseline
12-Sep-91		FL	III	yes
12-Sep-91		ST	III	no
26-Sep-91		ST	III	yes
01-Oct-91		ST	IV	no
03-Oct-91		FL	III	no
03-Oct-91		FL	III	yes
08-Oct-91		ST	III	yes
16-Oct-91		ST	III	no
24-Oct-91		FL	III	yes
29-Oct-91		FL	III	yes
31-Oct-91		ST	III	yes
07-Nov-91		FL	IV	yes
15-Nov-91		ST	IV	yes
19-Nov-91		ST	III	yes
22-Nov-91		ST	IV	no
25-Nov-91		FL	IV	no
03-Dec-91		FL	III	yes
09-Dec-91		FL	IV	yes
10-Dec-91		ST	III	yes
12-Dec-91		FL	III	yes
16-Dec-91		ST	III	yes
17-Dec-91		ST	III	yes
06-Jan-92		ST	III	no
09-Jan-92		FL	IV	no
14-Jan-92		FL	III	no
14-Jan-92		FL	III	no
16-Jan-92		ST	III	yes
16-Jan-92		FL	III	no
21-Jan-92		FL	III	yes
22-Jan-92		ST	IV	no
23-Jan-92		ST	III	yes
28-Jan-92		ST	III	no
30-Jan-92		FL	III	yes
04-Feb-92		FL	III	yes
04-Feb-92		ST	III	yes
10-Feb-92		ST	IV	yes
20-Feb-92		ST	III	yes
24-Feb-92		FL	IV	yes
25-Feb-92		FL	III	yes
25-Feb-92		ST	III	yes
26-Feb-92		FL	III	no
28-Feb-92		FL	IV	no

^a Treatment assignment: FL = FLOLAN[®] plus standard therapy
ST = standard therapy alone

TABLE 46₂₆ (Con't)

Randomization Results - A Chronological Listing of Patients by Enrollment Date (continued)

Date of Enrollment	Patient Number	Treatment Assignment ^a	NYHA Class	Vasodilator Use at Baseline
04-Mar-92		FL	III	no
09-Mar-92		ST	IV	no
09-Mar-92		ST	III	yes
10-Mar-92		FL	IV	no
16-Mar-92		FL	III	yes
18-Mar-92		FL	III	yes
19-Mar-92		FL	IV	no
23-Mar-92		ST	IV	no
23-Mar-92		FL	III	no
24-Mar-92		FL	III	yes
25-Mar-92		ST	III	yes
25-Mar-92		ST	III	no
26-Mar-92		FL	III	yes
31-Mar-92		FL	III	yes
31-Mar-92		ST	III	yes
01-Apr-92		ST	IV	yes
03-Apr-92		FL	IV	yes
06-Apr-92		ST	IV	yes
07-Apr-92		FL	III	yes
16-Apr-92		ST	III	no
21-Apr-92		FL	III	yes
21-Apr-92		ST	III	yes
21-Apr-92		ST	III	no
27-Apr-92		ST	III	no
28-Apr-92		FL	III	no
30-Apr-92		FL	III	yes
05-May-92		ST	III	yes
04-May-92		ST	III	yes
11-May-92		FL	III	no
11-May-92		FL	III	yes
11-May-92		FL	IV	yes
12-May-92		FL	III	yes
12-May-92		ST	III	yes
12-May-92		FL	III	yes
13-May-92		ST	IV	no
14-May-92		FL	III	yes
14-May-92		ST	III	no
14-May-92		ST	III	yes
15-May-92		ST	IV	no

^a Treatment assignment: FL = FLOLAN® plus standard therapy
ST = standard therapy alone

Table 46₂₇

6-Minute Walk; Baseline Values

<u>Flolan + Standard T.</u>		<u>Standard Treatment Alone</u>			<u>Additional Morbidity</u>
<u>Pt. ID #</u>	<u>Distance Walked (meters)</u>	<u>Pt. ID #</u>	<u>Distance Walked (meters)</u>	<u>Death After Randomization (Days)</u>	
	314.6		427.9		
	511.2		534.9		
	487.4		487.4		
	332.8		0.0	0	Moribund
	332.8		475.5		
	404.2		427.9	68	Hemorrhage
	352.3		427.9		
	309.4		237.4		
	279.8		422.5		
	291.7		410.6		
	394.4		374.0		
	359.4		438.0	58	Septostomy
	394.1		336.5 T		
	516.3		310.9		
	253.6		390.1		
	351.1 W		253.6		
	161.5		198.1		
	131.7		272.5 T		
	183.8		100.6	19	Digitalis Toxicity?
	68.3		266.7		
	358.4		158.5		
	270.1		336.8	56	URI
	384.0		60.0		
	306.3		117.3	43	Hyperkalemia, hypothyroidism. Digitalis Toxicity
	291.1		192.6		
	331.9		385.6		
	379.2		220.7		
	217.9		91.4		
	237.7		156.4		
	285.0		114.3		
	434.3		275.2		
	279.8 W		340.5		
	276.8		248.1		
	455.7		352.0		
	384.0		443.5		
	429.8		91.4	59	Digitalis Toxicity
	226.5 T		118.9		
	0.6		137.2		
	148.4		208.5		
	296.3		45.7	48	Hypokalemia, dig. tox.
	521.2				

T = Transplanted
W = Withdraw consent

TABLE 37₁

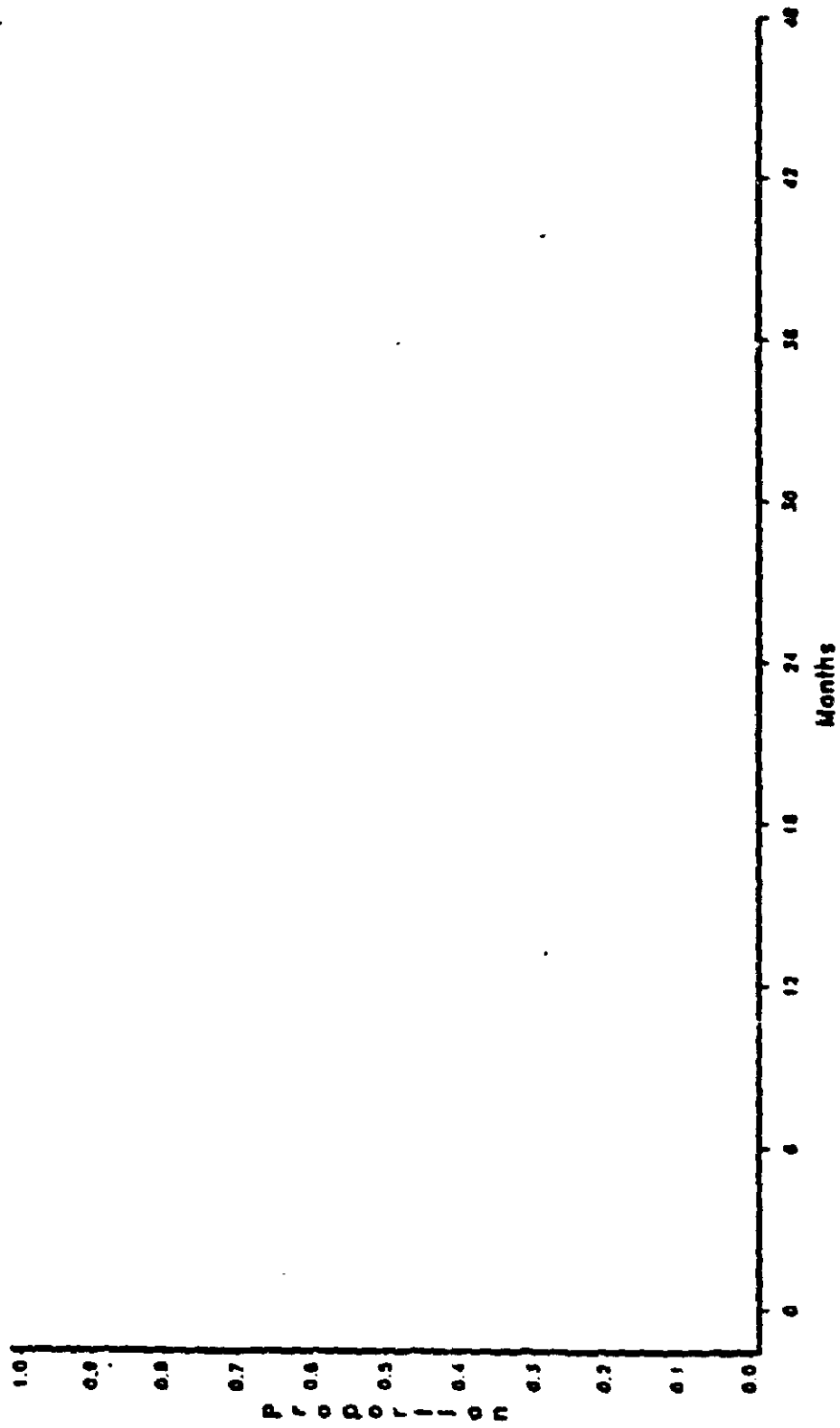
Summary of the Exercise Tolerance Test (Six-Minute Walk)

Study Day	Summary Statistics							
	N	Mean	S.E.	Min.	25-th X-1/4	Median	75-th X-3/4	Max.
Base 35/36	18	248.1	24.3	0.0	110.0	256.5	353.0	482.0
Base 37	17	369.9	27.5	106.0	300.0	306.0	420.0	540.0
6 mo.	15	376.5	31.2	174.0	277.0	413.0	487.5	575.0
12 mo.	12	347.9	41.1	161.7	221.4	374.5	428.3	604.0
18 mo.	11	415.4	42.2	153.0	310.0	416.4	526.0	588.0
24 mo.	7	499.4	68.7	210.0	413.0	539.0	562.0	732.0
30 mo.	6	393.1	73.0	188.0	300.0	423.5	480.0	632.0
36 mo.	3	486.4	110.0	250.0	250.0	489.9	629.4	629.4
42 mo.	3	238.7	111.0	60.0	60.0	214.0	442.0	442.0
48 mo.	1	341.0		341.0	341.0	341.0	341.0	341.0

NOTE: Patients 0004 and 0005 were missing baseline six minute walk tests. Their six minute walk results were used. In addition, some patients walked longer than 6 minutes. For these patients, a fraction of the total distance proportional to 6 minutes was used for the summary statistics.
 Base 37 includes nine patients who received Pilon for eight weeks in Study 35/36 and eight patients who received Standard Therapy for eight weeks in Study 35/36.

FIGURE 37₁

Proportion of Patients Surviving



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TABLE 37₂

Summary of the Nottingham Health Profile (Part I)

Fiolan (No.12)

	Study Day	N	S.E.	Summary Statistic			
				Mean	Min.	Median	Max.
Energy	Base 35/36	18	0.2	45.5	0.0	24.0	100.0
	Base 37	17	0.7	42.7	0.0	24.0	100.0
	6 mo.	16	9.6	34.0	0.0	24.0	100.0
	12 mo.	13	10.6	39.6	0.0	24.0	100.0
	18 mo.	12	11.1	27.7	0.0	12.0	100.0
	24 mo.	7	10.2	21.1	0.0	24.0	76.0
	30 mo.	6	12.2	24.3	0.0	12.0	60.0
	36 mo.	5	21.1	42.1	0.0	43.2	63.2
	42 mo.	4	17.9	31.0	0.0	30.4	57.2
	48 mo.	1		24.0	24.0	24.0	24.0
Pain	Base 35/36	18	5.3	16.9	0.0	2.9	69.1
	Base 37	17	6.9	23.0	0.0	0.0	100.0
	6 mo.	16	5.4	13.9	0.0	2.9	80.3
	12 mo.	13	6.2	10.1	0.0	0.0	79.1
	18 mo.	12	10.5	17.9	0.0	0.0	100.0
	24 mo.	7	6.9	0.6	0.0	0.0	40.0
	30 mo.	6	9.4	32.6	0.0	2.9	29.7
	36 mo.	3	0.0	0.0	0.0	0.0	n.u.
	42 mo.	3	33.3	33.3	0.0	0.0	100.0
	48 mo.	1		0.0	0.0	0.0	0.0
Emotional reaction	Base 35/36	18	5.2	24.2	0.0	22.0	70.7
	Base 37	17	5.0	16.1	0.0	0.0	76.7
	6 mo.	16	4.0	13.7	0.0	6.9	62.0
	12 mo.	13	2.2	5.7	0.0	0.0	21.2
	18 mo.	12	4.3	9.9	0.0	3.6	50.7
	24 mo.	7	5.1	13.0	0.0	9.5	34.5
	30 mo.	6	5.3	0.9	0.0	6.9	33.4
	36 mo.	3	0.0	0.0	0.0	0.0	0.0
	42 mo.	4	2.7	4.7	0.0	4.7	9.3
	48 mo.	1		0.0	0.0	0.0	0.0

TABLE 37₂ (Con't)

Flolan (No16)

Study Dy	N	S.E.	Summary Statistics				
			Mean	Min.	Median	Max.	
Sleep	Base 35/36	18	7.1	32.4	0.0	22.4	100.0
	Base 37	17	7.4	23.7	0.0	21.7	100.0
	6 mo.	16	8.2	21.5	0.0	0.0	100.0
	12 mo.	13	9.2	24.6	0.0	12.6	100.0
	18 mo.	12	10.6	26.4	0.0	12.6	100.0
	24 mo.	7	8.3	31.1	0.0	12.6	39.0
	30 mo.	6	14.9	22.3	0.0	0.0	77.4
	36 mo.	3	4.9	9.6	0.0	12.6	16.1
	42 mo.	4	18.3	26.6	0.0	14.2	77.6
	48 mo.	1		0.0	0.0	0.0	0.0
Social isolation	Base 35/36	18	8.3	17.6	0.0	11.0	79.9
	Base 37	17	6.1	13.0	0.0	0.0	64.0
	6 mo.	16	4.4	9.5	0.0	0.0	63.9
	12 mo.	13	2.7	8.2	0.0	0.0	22.5
	18 mo.	12	2.3	3.6	0.0	0.0	22.5
	24 mo.	7	3.2	3.2	0.0	0.0	22.5
	30 mo.	4	18.0	10.0	0.0	0.0	64.7
	36 mo.	3	0.0	0.0	0.0	0.0	0.0
	42 mo.	4	5.4	5.4	0.0	0.0	22.5
	48 mo.	1		0.0	0.0	0.0	0.0
Physical mobility	Base 35/36	18	5.4	32.8	0.0	31.9	70.7
	Base 37	17	5.4	24.5	0.0	11.2	66.1
	6 mo.	16	5.8	26.0	0.0	21.4	67.2
	12 mo.	13	4.8	23.3	0.0	22.0	53.4
	18 mo.	12	7.1	25.5	0.0	21.2	70.7
	24 mo.	7	5.4	23.4	0.0	22.0	64.1
	30 mo.	6	12.0	22.2	0.0	16.3	70.7
	36 mo.	3	6.2	21.9	11.2	22.0	32.4
	42 mo.	4	18.0	28.3	0.0	11.2	70.7
	48 mo.	1		0.0	0.0	0.0	0.0

TABLE 5/10₁

Table 15. Summary of Hemodynamic Parameters at Baseline

Hemodynamic Parameter (units)	Phase	N	Mean	S.E.	Min.	Max.	RS-th Z-11a	Medion Z-11a	75-th Z-11a	Max.
Heart Rate (beats/min)	Baseline	10	70.9	2.64	68.0	75.0	60.0	60.0	64.0	91.0
Cardiac Output (L/min)	Baseline	9	4.0	0.61	2.0	2.3	3.9	3.9	4.0	7.2
Cardiac Index (L/min/sq m)	Baseline	9	2.2	0.27	1.1	1.7	2.2	2.2	3.0	3.4
PAPs (mm Hg)	Baseline	10	60.2	0.47	44.0	70.0	64.5	60.0	60.0	120.0
PAPd (mm Hg)	Baseline	10	45.4	0.66	23.0	35.0	47.0	47.0	53.0	67.0
PAPm (mm Hg)	Baseline	10	59.7	0.44	30.0	47.0	61.0	61.0	70.3	87.7
PCWP (mm Hg)	Baseline	10	4.1	0.99	3.0	4.0	5.5	5.5	7.0	32.0
PVR (Wood u)	Baseline	9	15.4	2.02	4.2	8.3	16.4	16.4	19.3	32.2
TPR (Wood u)	Baseline	9	17.3	1.02	6.7	9.3	18.0	18.0	21.9	35.2
SAPs (mm Hg)	Baseline	10	114.1	3.63	97.0	100.0	111.0	111.0	110.0	135.0
SAPd (mm Hg)	Baseline	10	72.7	2.36	60.0	70.0	74.5	74.5	77.0	82.0
SAPm (mm Hg)	Baseline	10	86.5	2.10	70.0	83.3	86.0	86.0	93.0	94.0
TSR (Wood u)	Baseline	9	25.9	3.09	11.6	16.1	23.6	23.6	26.4	41.6
SV (ml/beat)	Baseline	9	61.2	7.93	24.4	25.2	52.5	52.5	72.1	85.7
SVI (g-m/m ²)	Baseline	9	30.5	3.05	14.3	21.0	31.4	31.4	41.1	43.9
O ₂ Consump (ml/min/sq m)	Baseline	9	250.0	21.7	109.0	200.0	240.0	240.0	269.0	390.0
AVO ₂ O (ml/dl)	Baseline	9	6.9	0.47	4.0	5.3	6.4	6.4	8.4	10.1
PaO ₂ (mm Hg)	Baseline	8	63.0	6.35	45.0	69.7	67.3	67.3	73.0	96.0
PaCO ₂ (mm Hg)	Baseline	7	32.1	1.46	26.0	29.2	31.2	31.2	32.5	40.0
pH _a	Baseline	7	7.5	0.01	7.4	7.4	7.4	7.4	7.5	7.5
pH _v	Baseline	6	7.4	0.01	7.4	7.4	7.4	7.4	7.4	7.5

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TABLE 20,

Demographic and Physical Exam Data

Characteristic	Summary Statistics	
Age (years)	N	39
	Mean	37.49
	Std.Dev.	11.78
	Median	39.00
	Minimum	12.00
	Maximum	65.00
Race	Black	3 (7.7%)
	White	31 (79.5%)
	Other	5 (12.8%)
Sex	Female	27 (69.2%)
	Male	12 (30.8%)
Height (cm)	N	39
	Mean	163.39
	Std.Dev.	16.79
	Median	168.00
	Minimum	95.50
	Maximum	196.00
Weight (kg)	N	39
	Mean	67.06
	Std.Dev.	15.70
	Median	63.90
	Minimum	31.00
	Maximum	107.00
Diastolic Bp (mm Hg)	N	39
	Mean	77.51
	Std.Dev.	8.04
	Median	80.00
	Minimum	60.00
	Maximum	95.00
Systolic Bp (mm Hg)	N	39
	Mean	112.97
	Std.Dev.	9.73
	Median	110.00
	Minimum	100.00
	Maximum	135.00
Pulse (beats/min)	N	39
	Mean	82.87
	Std.Dev.	12.37
	Median	84.00
	Minimum	64.00
	Maximum	110.00
Respiration (brths/min)	N	35
	Mean	18.37
	Std.Dev.	4.64
	Median	18.00
	Minimum	12.00
	Maximum	32.00

TABLE 20₂

Hemodynamic Parameters at Baseline

Hemodynamic Parameter (units)	Phase	N	Mean	S.E.	Min.	25-th %ile	Median	75-th %ile	Max.
Heart Rate (beats/min)	Baseline	39	64.0	2.20	61.0	73.0	64.0	93.0	120.0
Cardiac Output (L/min)	Baseline	37	3.1	0.21	1.0	2.3	3.0	3.7	9.1
Cardiac Index (L/min/sq m)	Baseline	37	1.0	0.10	1.1	1.4	1.7	2.0	4.0
PAPs (mm Hg)	Baseline	39	69.6	3.67	45.0	72.0	60.0	109.0	150.0
PAPd (mm Hg)	Baseline	39	41.7	1.94	20.0	35.0	40.0	46.0	82.0
PAPm (mm Hg)	Baseline	39	57.7	2.41	20.3	46.7	55.7	64.7	104.7
PCWP (mm Hg)	Baseline	37	7.2	0.52	1.0	5.0	6.0	10.0	15.0
PVR (Wood u)	Baseline	35	18.0	1.52	3.0	12.3	16.9	21.5	50.6
TPR (Wood u)	Baseline	37	20.0	1.59	5.9	14.0	19.6	25.0	54.0
RAPm (mm Hg)	Baseline	39	9.4	0.89	1.0	5.0	9.0	15.0	24.0
SAPs (mm Hg)	Baseline	39	121.3	2.60	100.0	110.0	120.0	130.0	170.0
SAPd (mm Hg)	Baseline	39	75.3	1.00	59.0	67.0	75.0	80.0	113.0
SAPm (mm Hg)	Baseline	39	90.6	2.00	73.7	80.7	90.0	95.0	132.0
SVR (Wood u)	Baseline	37	20.9	1.61	6.5	23.7	27.6	33.2	55.0
TSR (wood u)	Baseline	37	32.4	1.76	9.1	24.0	30.5	37.0	61.1
SV (ml/beat)	Baseline	37	38.0	2.71	14.0	27.7	34.9	47.3	95.1
SVI (g-m/m ²)	Baseline	35	25.5	1.76	12.2	17.3	22.0	30.6	55.9
Mixed Venous Sat. (%)	Baseline	26	223.6	11.5	116.0	107.0	209.5	250.0	370.0
AvO ₂ D (ml/dl)	Baseline	36	7.7	0.33	4.1	6.2	7.6	9.1	12.1
PaO ₂ (mm Hg)	Baseline	37	59.4	1.00	34.0	52.0	60.0	66.0	85.0
PaCO ₂ (mm Hg)	Baseline	37	20.9	0.66	22.0	26.0	29.5	31.0	39.0
pHa	Baseline	37	7.5	0.01	7.3	7.4	7.5	7.5	7.6
pHv	Baseline	37	7.4	0.01	7.3	7.4	7.4	7.5	7.5
PvO ₂ (mm Hg)	Baseline	37	29.6	0.64	19.0	27.0	29.0	31.3	39.1
PvCO ₂ (mm Hg)	Baseline	37	34.6	0.71	26.0	31.6	34.0	37.2	43.0
Resp. Rate (breaths/min)	Baseline	21	16.9	1.13	8.0	14.0	16.0	20.0	28.0

TABLE 20₃

Patients with Adverse Events Occurring At the Maximum Dose Administered During Dose Ranging

Body System:	Preferred Term for Adverse Experience	Maximum Severity: # (%)			
		Mild	Moderate	Severe	Any
	SYNCOPE	0 (0%)	1 (3%)	0 (0%)	1 (3%)
Body Abdomen	PAIN ABDO	0 (0%)	1 (3%)	1 (2.6%)	2 (5%)
Body Back	PAIN BACK	1 (3%)	0 (0%)	2 (5%)	3 (8%)
Body General	PAIN	1 (3%)	0 (0%)	1 (3%)	2 (5%)
Body-Head	HEADACHE	16 (41%)	3 (13%)	3 (3%)	24 (62%)
Body-Thorax	PAIN CHEST	3 (8%)	2 (5%)		5 (13%)
Cardiovascular Cardiac	BRADYCARDIA	0 (0%)	1 (3%)	1 (2.6%)	2 (5.1%)
Cardiovascular-Vascular	HYPERTENS	0 (0%)	1 (3%)	0 (0%)	1 (3%)
	HYPOTENS	0 (0%)	2 (5%)	0 (0%)	2 (5%)
	FLUSHING	13 (33%)	13 (33%)	2 (5%)	25 (72%)
Digestive-General	GI DISORDER	1 (3%)	0 (0%)	0 (0%)	1 (3%)
	NAUSEA	8 (20%)	3 (12.8%)	3 (8%)	16 (41%)
	VOMIT	0 (0%)	2 (5%)	0 (0%)	2 (5%)
Nervous-CNS	ANXIETY	0 (0%)	2 (5%)	1 (3%)	3 (8%)
	DIZZINESS	1 (3%)	0 (0%)	0 (0%)	1 (3%)
Respiratory General	COUGH INC	0 (0%)	0 (0%)	1 (3%)	1 (3%)
Special Senses Ear	TINNITUS	1 (3%)	0 (0%)	0 (0%)	1 (3%)

TABLE 21,

Summary of Demographic and Physical Exam Data

Characteristic	Summary Statistic	<16 Yrs	All
Age (years)	N	59	255
	Mean	6.05	33.75
	Std.Dev.	4.26	19.05
	Median	6.00	34.00
	Minimum	0.00	0.00
	Maximum	15.00	70.00
Race	Black	3 (5.1%)	20 (7.8%)
	White	45 (76.3%)	196 (76.9%)
	Other	11 (18.6%)	31 (12.2%)
Sex	Female	54 (91.5%)	160 (62.7%)
	Male	5 (8.5%)	97 (37.3%)
Height (cm)	N	58	234
	Mean	113.91	152.01
	Std.Dev.	26.65	27.73
	Median	113.50	160.50
	Minimum	56.00	56.00
	Maximum	165.00	190.50
Weight (kg)	N	59	254
	Mean	22.01	50.54
	Std.Dev.	12.60	27.33
	Median	19.50	60.20
	Minimum	2.90	2.90
	Maximum	55.50	240.50
Diastolic Bp (mm Hg)	N	56	236
	Mean	62.71	73.01
	Std.Dev.	9.79	12.67
	Median	60.00	72.00
	Minimum	40.00	40.00
	Maximum	86.00	110.00
Systolic Bp (mm Hg)	N	58	238
	Mean	99.93	114.05
	Std.Dev.	10.06	16.30
	Median	100.00	110.00
	Minimum	70.00	70.00
	Maximum	120.00	170.00

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TABLE 21, (Con't)

Summary of Demographic and Physical Exam Data

Characteristic	Summary Statistics	<16 Yrs	All
Pulse (beats/min)	N	59	246
	Mean	99.15	88.62
	Std.Dev.	21.23	14.28
	Median	100.00	86.00
	Minimum	65.00	56.00
	Maximum	150.00	150.00
Respiration (brths/min)	N	59	216
	Mean	25.03	20.76
	Std.Dev.	10.11	6.76
	Median	20.00	20.00
	Minimum	12.00	10.00
	Maximum	60.00	60.00

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TABLE 21₂

Summary of Hemodynamic Parameters at Baseline

Hemodynamic Parameter (units)	Phase	N	Mean	S.E.	Min.	25-th %ile	Median	75-th %ile	Max.
Heart Rate (beats/min)	Baseline	290	89.5	1.14	55.0	76.0	86.5	100.0	167.0
Cardiac Output (L/min)	Baseline	284	3.7	0.09	0.5	2.6	3.5	4.4	9.2
Cardiac Index (L/min/sq m)	Baseline	259	2.6	0.09	0.3	1.8	2.3	3.1	11.0
PAPs (mm Hg)	Baseline	209	89.1	1.48	32.0	74.0	87.0	104.0	179.0
PAPd (mm Hg)	Baseline	209	40.5	0.82	9.0	30.0	40.0	50.0	89.0
PAPm (mm Hg)	Baseline	209	56.7	0.98	19.0	45.7	55.3	66.7	117.0
PCWP (mm Hg)	Baseline	271	7.7	0.20	-2.0	5.0	7.0	10.0	27.0
PVR (Wood U)	Baseline	265	16.7	2.75	1.7	8.5	13.7	20.5	86.7
TPR (wood U)	Baseline	283	19.5	0.89	2.9	16.6	18.7	23.5	136.0
RAPm (mm Hg)	Baseline	265	8.0	0.39	-4.0	3.0	6.0	11.0	26.0
SAPs (mm Hg)	Baseline	289	123.4	1.23	65.0	110.0	122.0	135.0	210.0
SAPd (mm Hg)	Baseline	260	75.9	0.92	30.0	65.0	76.0	87.0	123.0
SAPm (mm Hg)	Baseline	280	91.7	0.95	51.0	80.0	91.7	102.0	142.0
SVR (Wood U)	Baseline	257	26.0	0.79	5.3	19.3	24.3	31.0	104.0
TSR (wood U)	Baseline	282	29.4	0.89	9.4	20.5	26.3	35.3	140.0
SV (ml/beat)	Baseline	284	43.0	1.20	4.7	30.2	41.0	54.0	114.5
SMI (g-m/m2)	Baseline	242	33.9	0.98	0.5	24.1	31.3	41.7	100.1
O2 Consump (ml/min/sq m)	Baseline	135	209.5	5.74	5.3	172.0	203.0	244.0	460.0
AVO2D (ml/dl)	Baseline	174	5.9	0.14	6.0	4.5	5.7	7.1	10.9
PaO2 (mm Hg)	Baseline	149	76.9	3.06	20.0	50.0	71.0	83.0	349.0
PaCO2 (mm Hg)	Baseline	144	33.0	0.51	15.0	30.0	33.0	37.0	57.0
pHa	Baseline	144	7.4	0.01	7.2	7.4	7.4	7.5	7.7

TABLE 21₂ (Con't)

Summary of Hemodynamic Parameters at Baseline

Hemodynamic Parameter (units)	Phase	N	Mean	S.E.	Min.	25-th Pctile	Median	75-th Pctile	Max.
pHv	Baseline	167	7.4	0.00	7.1	7.4	7.4	7.4	7.6
PvO ₂ (mm Hg)	Baseline	167	33.6	0.42	21.0	30.0	33.0	37.0	51.0
PvCO ₂ (mm Hg)	Baseline	167	37.6	0.43	20.0	34.0	37.0	41.0	62.0
Resp. Rate (breaths/min)	Baseline	66	22.0	1.43	10.0	16.0	20.0	22.0	30.0

(SS024(FL21LDS1112MOV93)

TABLE D
Study 50
Study 50 was initiated on July 23, 1993

Pt #	Date Entered Study	NYHA Class at Screen	Date of Death	Length of Survival	Cause of Death	Side Effects
	12/20/93	IV	12/20/93	0 days	PRHF	Hypotension, nausea, SOB
	8/31/93	IV	12/13/93	104 days	Cardiac arrest	Hypotension
	2/19/94	IV	2/21/94	2 days	Pneumonia,	Sepsis
	3/16/94	IV	3/22/94	6 days	Pulmonary hemorrhage	pulmonary edema
**	2/11/94	III	3/16/94	35 days	Hemorrhage	pneumothorax sepsis, cath. compl. thrombosis
***	2/11/94	III	3/19/94	36 days	Cardiac arrest	Battery disconnected
	2/1/94	IV	2/5/94	4 days	PRHF	Septostomy
	12/21/93	Not stated	5/13/94	4.77 mos	Cardiac arrest	
	12/23/93	" "	3/23/94	3 mos	Hemorrhage	Hemoptysis, hemothorax
	12/23/93	" "	4/23/94	4 mos	Sudden death	acute renal failure
	2/9/94	" "	8/25/94	6.53 mos	Peritoneal hemorrhage	Anorexia, splenomegaly, splenectomy
	2/9/94	" "	8/27/94	6.6 mos	PRHF	Ascites, hyponatremia
	2/9/94	" "	6/4/94	3.87 mos	Abdominal hemorrhage	Asthma, bronchitis, intra-abdominal hemorrhage
	2/9/94	" "	8/12/94	6.1 mos	PPH	Sepsis
	3/23/94	III	12/6/94	8.43 mos	PPH	Ascites, hyperkalemia, hyponatremia
	3/25/94	IV	7/11/94	3.53 mos	Pneumonia	Pneumonia
	5/4/94	IV	10/4/94	5.0 mos	PPH	Chest pain, palpitation
	6/1/94	IV	8/22/94	2.70 mos	Hypokalemia	Hypokalemia
	12/10/93	IV	11/5/94	10.87 mos	PRHF	Hyponatremia, subdural hematoma, seizures
	9/21/93	IV	12/27/93	3.2 mos	PRHF	Jaw pain
	10/17/94	IV	11/19/94	1.07	PRHF	
	1/18/94	Not stated	2/18/94	1.0 mo	PRHF	
	5/11/94	IV	8/20/94	3.33 mos	PRHF	Fluid volume overload
	12/14/94	IV	12/15/94	1 day	GI Bleeding	
	12/3/93	Not stated	8/26/94	9.8 mos	Retroperitoneal carcinoma	
	12/3/93	Not stated	4/30/94	4.9 mos	Lung transplant	
	3/9/94	IV	11/21/94	8.4 mos	Cardiopulmonary arrest	Ascites
	6/23/94	IV	7/19/94	0.87 mos	PRHF	

TABLE D (Con't.)

	11/7/94	IV	12/18/94	1.37 mos	PRHF	Ascites
	4/11/94	IV	9/2/94	4.73 mos	Respiratory failure	Jaw pain
	1/13/94	Not stated	10/26/94	9.43 mos	PRHF	Pericardial effusion
	10/12/94	III	12/13/94	1 mo	PRHF	Hemothorax pneumothorax
	10/15/94	IV	12/9/94	1.8 mos	PRHF	Syncope
	6/20/94	IV	6/22/94	2 days	Cardiogenic shock	
	12/13/94	IV	12/16/94	3 days	Not stated	In respirator
	2/11/94	Not stated	11/10/94	9 mos	PRHF	
	2/11/94	Not stated	4/21/94	2.33 mos	PRHF	Pneumonia, hyponatremia
	2/11/94	Not stated	12/27/94	10.53 mos	Streptok. anaphylaxis	
	2/11/94	Not stated	4/9/94	1.97 mos	PRHF	
	2/18/94	IV	7/23/94	5.17 mos	PRHF	
	5/23/94	III	11/5/94	5.43 mos	PRHF	
	7/18/94	III	7/23/94	0.17 mo	PRHF	
	12/27/94	III	12/28/94	1 day	PRHF	Dissection of IVC
	12/15/93	Not stated	8/10/94	7.87 mos	PRHF	
	10/2/94	IV	12/4/94	2.1 mos	PRHF	Arrhythmia
PATIENTS WITHDRAWN						
	4/11/94	III	4/22/94	11 days		Persistent nausea
	1/20/94	III	1/21/94	1 day	Lack of efficacy. He had felt better before starting flolan	Headache, chest pain, flushing
	3/20/94	III	3/24/94	4 days	Withdrew consent	Headache, nausea

PRHF=Progressive right heart failure.
 ** Originally reported in study 47.
 ***Originally reported in study 49.

The survival of patients in the NIH Registry has been reported to have been

Cl: .6 years
Cl: 6 months

CONCLUSIONS:

The side effects which were reported in this Update were similar to those, which had been reported previously i.e. the patients suffered from:

asthenia, dyspnea, tiredness, chest pain, hypoxia, death, which are symptoms/results of PPH and

also from side effects associated with the infusion of flolan: flushing, headache, jaw pain, nausea/vomiting, hypotension, hypotension/syncope, injection site reaction, anxiety/nervousness/agitation, diarrhea, sepsis, ascites, pneumothorax, hemothorax, pulmonary hemorrhage, CVA, sudden death etc.

Five patients died on the same day or 1-3 days after they were dose-ranged with flolan:

from severe hypotension
from cardiac arrest
from dissection of the IVC
from respiratory failure (prostacyclin induced?)
from bleeding.

The incidence of sepsis was 23% on the average, which is rather high. We should also remember that flolan causes tachyphylaxis, which means that the dosage must be increased continuously and considerably the longer a patient is kept on flolan.

E. Triantas
E. Triantas, MD, Ph.D.

cc:
NDA 20-444
HFD-180
HFD-180/SFredd
HFD-180/ETriantas
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
r/d 8/2/95 jgw
f/t 8/6/85 jgw
MED\N\20444508.0ET

8/7/95
Noted.
JP

Olwel

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA: 20-444
DRUG NAME: Flolan
SPONSOR: Burroughs-Wellcome

TYPE OF DOCUMENT: Approval Safety Update
DATE OF DOCUMENT: June 22, 1995
DATE RECEIVED: June 23, 1995
DATE RECEIVED BY MEDICAL OFFICER: July 3, 1995
DATE REVIEW COMPLETED: July 20, 1995

REVIEW:

Safety of the Acute Administration of Flolan:

The safety of the acute administration of flolan in patients with PPH and secondary pulmonary hypertension (SPH) continues to be evaluated in study 21 and during the dose-ranging period in the chronic study 50.

By the cut-off date of Jan 1, 1995, 719 patients received flolan during acute dose-ranging; 179 of them represent new patients since the 4-month safety update. After completion of the dose-ranging procedure patients could re-enter the same study or they could enter a long-term study. Thus 40 patients entered study 21 on multiple occasions, and another 62 of them entered one of the long-term studies after completing study 21.

The demographics of the new patients were similar to those of previous patients. The patients were generally young (mean age: 36 years) female (73%), and white (77%). The percentage of NYHA Class IV was 21% compared to 7% in the original NDA.

Safety of Chronic Treatment with Flolan:

The safety of the chronic administration of flolan was evaluated in 4 uncontrolled clinical studies, studies 37, 47, 49, and 50. At about Jan. or March 1994 all the patients remaining in studies 37, 47, and 49 were transferred to study 50, except for one patient in study 47 and 5 patients in study 49, which remain in a Canadian Center.

From Table 3 of the Update (copy on the next page) it appears that by the cut-off date of Jan. 1, 1995, 18 patients had entered study 37, 64 had entered study 47, 128 study 49, and 178 study 50. Several of these patients had entered 2 studies, one after the other as Table 4 of the Up-date (13 pages long, not attached to this review) indicates, and may have been counted twice.

Table 3 indicates that the total number of patients who entered the long-term studies by the cut-off date of Jan. 1, 1995 was 388; 55 of these patients were transplanted, 81 died, 23 have been withdrawn and 229 are still being treated with flolan.

**Table 3. Patient Accountability: Studies 37, 47, 49 and 50
Through 1 January 1995**

Protocol	Number of Patients				TOTAL
	P18:37	P18:47	P18:49	P18:50	
Entered	18 (18)	64 (64)	128 ^a (120)	178 (10)	388 (212)
Transplanted	8 (8)	16 (13)	21 (9)	10 (0)	55 (30)
Dead	6 (5)	18 (11) ^b	31 (11) ^b	26 (0)	81 (27)
Withdrew From Study	0 (0)	2 (1)	9 (6)	12 (0)	23 (7)
Alive	4 (5)	28 (39)	67 (94)	130 (10)	229 (148)

^a Excludes two patients who started on the single-vial formulation and left the study (one transplanted and one withdrew) before switching to the double-vial formulation.

^b Includes one patient death on single-vial formulation in Study 47 and Study 49 each.

() denotes corresponding number of patients reported in the Four-Month Safety Update.

So far we have received copies of the case report forms of:

the 6 patients who died in study 37,
11 of the 18 patients who died in study 47,
22 of the 31 patients who died in study 49 and
45 patients who died in study 50
i.e. we have received copies of case reports of a total of 84
patients, who died during the long-term flolan studies.

The numbers do not agree with the numbers shown in Table 3 because of the transfer of patients from studies 47, and 49 to study 50. It seems also that 3 patients who died have not been included in Table 3.

Length of Therapy: The sponsor claims that by Jan 1, 1995 chronic flolan therapy was provided for a total of 5234 patient-months. A total of 256 patients have been treated for 6 months, 176 for 12 months 77 for 24 months, 18 for 36 months and single patients have been treated for 74 and 78 months as shown below:

Follow-up time: Studies 37, 47, 49 and 50

Follow-up (months)	6	12	24	36	48	54	60	66	74	78
Number of Patients in NDA	17	14	11	7	1	1	1	0	0	0
Number of Patients in 4-Month Update	128	67	14	7	6	5	1	1	1	0
Number of Patients in Current Update	256	176	77	18	6	5	5	4	1	1

Demographics:

As in the acute studies the patients who received flolan chronically were predominantly young (mean age: 37 years), white (81%), and female (78%); 42% of them were NYHA class IV; 24% were using vasodilators.

Dosing:

The dosage of the infused flolan increased with the length of treatment as shown below:

Dosing Summary^a

Month	4-Month Update		Current	
	n	Mean dose (ng/kg/min)	n	Mean dose (ng/kg/min)
0	183	4.8	363	5.8
6	127	19.0	252	19.9
12	59	26.2	165	34.2
18	31	33.0	120	46.1
24	14	48.0	77	51
30	9	43.9	45	57
36	7	53.0	18	85.2
48	6	56.7	6	56.7
60	1	32.0	5	82.0

^a Data extracted from 4 Month Update Table 15 and current Table 7.

Compared to the dosages reported in the 4-month update the new dosages were considerably higher and confirmed the fact that flolan causes tachyphylaxis. The most common reason for dose increases was an increase in PPH symptoms. With continued dose escalations

and after years of exposure to flolan some patients reached flolan doses in excess of 200 ng/kg/min.

Effect of Age on Dosing: Patients <16 years required higher doses than older patients. In younger patients mean dosing started at 8.3 ng/kg/min and reached 178 ng/kg/min at 41 months of treatment. In older patients the mean dosage started at 5.6 ng/kg/min and reached 54.7 ng/kg/min after 41 months of treatment. After 70 months the dosage decreased in the older patients. Very few patients (4 decreasing to 1) had been treated longer than 70 months. No patients younger <16 had been treated more than 41 months.

Mean Dosage (ng/kg/min)	<16 years	>16 years
at Beginning	8.3	5.6
After 10 months	59.2	26.5
After 20 months	100.3	40.4
After 41 months	178.0	54.7
After 70 months		116.0
After 80 months		36.0
After 90 months		38.0

Race/Gender: did not seem to affect dosage.

New York Heart Association Class: Fifty-eight percent of the new patients were class III compared to 64% who were listed in the 4-month Update. There was also one patient of NYHA class II.

Adverse Events:

Events Occurring during the Dose-Ranging Period:

The number of patients who experienced side effects during the acute dose-ranging procedures are summarized in Table 12 in decreasing order of frequency. The most frequent events were as before flushing, headache, and nausea/vomiting. These were most likely due to arterial vasodilation, which is the main pharmacological effect of flolan.

Patients younger than 16 years experienced the same adverse effects as older patients, however, the frequency of some of these effects was somewhat different: flushing (14% vs 59%), and headache (9% vs 51%) were less frequent in the younger than in the older patients and jaw pain, chest pain, and dyspnea were not reported in younger patients. On the other hand, anxiety/nervousness agitation (18% vs 12%), hypertension (2.5% vs 0.3%), and (hypoxia 1.7% vs 0.3%) were more frequent in the younger patients.

**Table 12. Adverse Experiences – PPH: Frequency During Acute Dose-Ranging Procedures by Age Controlled and Uncontrolled Studies (Combined)
All Patients (N=720)
(4-Month Safety Update Table 20)**

Preferred term/combined terms	< 16 (N=116)		≥ 16 (N=604)		Total (N=720)	
	N	(%)	N	(%)	N	(%)
FLUSHING	16	(13.7)	357	(59.1)	373	(51.8)
HEADACHE	10	(8.6)	307	(50.8)	317	(44.0)
NAUSEA/VOMIT	30	(25.8)	172	(28.4)	202	(28.0)
HYPOTENS	10	(15.5)	86	(14.2)	104	(14.4)
ANXIETY/NERVOUSNESS/AGITATION	21	(18.1)	70	(11.5)	91	(12.6)
PAIN CHEST	0	(0.0)	71	(11.7)	71	(9.8)
BIZZINESS	2	(1.7)	44	(7.2)	46	(6.3)
PAIN ABDO	7	(6.0)	31	(5.1)	38	(5.2)
BRADYCARDIA	6	(5.1)	20	(3.3)	26	(3.6)
PAIN BACK	3	(2.5)	19	(3.1)	22	(3.0)
PAIN JAW	0	(0.0)	19	(3.1)	19	(2.6)
PAIN/PAIN NECK/ARTHRALGIA	0	(0.0)	13	(2.1)	13	(1.8)
TACHYCARDIA	1	(0.8)	11	(1.8)	12	(1.6)
DYSPNEA	0	(0.0)	11	(1.8)	11	(1.5)
SUFF MENODYN RESPON	0	(0.0)	0	(1.3)	0	(1.1)
HYPESTHESIA/PARESTHESIA	0	(0.0)	7	(1.1)	7	(0.9)
DIARRHEA	0	(0.0)	5	(0.8)	5	(0.6)
HYPERTENS PULM	3	(2.5)	2	(0.3)	5	(0.6)
PALPITAT	0	(0.0)	5	(0.8)	5	(0.6)
SWEAT	0	(0.0)	5	(0.8)	5	(0.6)
DYSPEPSIA	0	(0.0)	4	(0.6)	4	(0.5)
EDEMA LUNG	1	(0.8)	3	(0.4)	4	(0.5)
HYPNIA	2	(1.7)	2	(0.3)	4	(0.5)
REACT AGGRAV	0	(0.0)	4	(0.6)	4	(0.5)
VASOVAGAL EVENT	0	(0.0)	4	(0.6)	4	(0.5)
COUGH INC	0	(0.0)	3	(0.4)	3	(0.4)
CYANOSIS	1	(0.8)	2	(0.3)	3	(0.4)
PAIN EYE	0	(0.0)	3	(0.4)	3	(0.4)
TACHYCARDIA SUPVENT	0	(0.0)	3	(0.4)	3	(0.4)
TASTE PERVERS	0	(0.0)	3	(0.4)	3	(0.4)
ASTHENIA	0	(0.0)	2	(0.3)	2	(0.2)

¹This table excludes adverse experiences that occurred when the patient was on single-vial formulation.

Dose-limiting adverse events occurred in 7-20% of patients and are summarized below:

**Dose-Limiting Adverse Experiences Occurring in
≥ 5% of Patients^a**

Adverse Experience	4-Month Update N(%) (N = 541)	Current N(%) (N = 720)
headache	110 (20)	176 (24)
nausea/vomiting	109 (20)	158 (22)
flushing	76 (14)	147 (20)
hypotension	73 (14)	100 (14)
anxiety/nervousness/agitation	38 (7)	67 (9)
chest pain	36 (7)	52 (7)

^a Data extracted from 4-Month Table 21 and current Table 13

One fatal reaction occurred during Dose-Ranging during the period covered by this update. A patient became severely hypotensive approx. 8 minutes after initiation of flolan at 2 ng/kg/min. Despite maximum cardiopulmonary support she died 3 hours later. Similar single fatal events had occurred in studies 35/36, 46, and 49. The last episode was summarized in the 4-month Update.

Adverse Events Observed during Chronic Infusion of Flolan:

The most frequent of these events were asthenia (48%), dyspnea (48%), nausea and dizziness (38%) as shown in the table below:

Adverse Experiences Occurring in ≥ 25% of Patients^a

Adverse Experience	4-Month Update N(%) (N = 216)	Current N(%) (N = 392)
asthenia	130 (60)	187 (48)
dyspnea	130 (60)	187 (48)
nausea	115 (53)	149 (38)
dizziness	109 (50)	149 (38)
headache	108 (50)	148 (38)
jaw pain	108 (50)	159 (41)
chest pain	96 (44)	138 (35)
palpitations	96 (44)	143 (36)
edema	90 (42)	127 (32)
diarrhea	90 (42)	132 (34)
myalgia	90 (42)	124 (32)
injection site reaction	65 (30)	114 (29)
abdominal pain	81 (38)	109 (28)
cough increase	81 (38)	119 (30)
depression	70 (32)	97 (25)

^a Data extracted from 4-Month Update Table 23 and current Table 15.

Compared to the 4-Month Update the frequency of all listed events was lower in the current Update.

The adverse effects which occurred more frequently in patients <16 years old are shown below:

Adverse Experiences Occurring More Frequently ($\pm 10\%$) in Patients < 16 Years of Age^a

Adverse Experience	< 16 years N (%) (N = 42)	≥ 16 years N (%) (N = 350)
chills/fever/sepsis/flu	20 (48)	90 (26)
infection/rhinitis	15 (36)	66 (19)
pallor	13 (31)	64 (18)
hypoxia	12 (28)	53 (15)
myocardial ischemia	6 (14)	7 (2)

^a Data extracted from current Table 19.

The experiences which occurred less frequently in young patients are listed in the following table:

Adverse Experiences Occurring Less Frequently ($\geq 10\%$) in Patients <16 Years of Age^a

Adverse Experience	< 16 years N (%) (N = 42)	≥ 16 years N (%) (N = 350)
palpitations	12 (28)	131 (37)
edema	11 (26)	125 (36)
depression/depression psychotic	6 (14)	91 (26)
ascites	1 (2)	56 (16)
hyperesthesia/ hypesthesia/paresthesia	1 (2)	42 (12)

^a Data extracted from current Table 19.

The frequency of events associated with bleeding was the same as before:

Adverse Experiences Associated with Bleeding^a

Adverse Experience	4-Month Update N(%) (N = 216)	Current N(%) (N = 392)
hemoptysis	11 (5)	20 (5)
thrombocytopenia	4 (2)	12 (3)
hemorrhage at injection site	11 (5)	10 (3)
hemorrhage	7 (3)	9 (2)
GI hemorrhage	4 (2)	6 (2)
anemia	3 (1)	5 (1)
ecchymosis	3 (1)	5 (1)
petechia	4 (2)	4 (1)
melena	2 (1)	3 (1)
vaginal hemorrhage	2 (1)	2 (1)
coagulation disorder	1 (<1)	1 (<1)
hematuria	1 (<1)	1 (<1)

^a Data extracted from 4-Month Update Table 23 and current Table 15.

Serious and/or Life Threatening Adverse Reactions Associated with the drug Delivery System:

These are shown in Table 13. The most frequent complaints were reactions at the injection site (14%), and sepsis (10%). The incidence of pneumothorax was 2%.

The incidence of sepsis generally in the long-term studies is shown below. The highest incidence occurred in study 46: 49%, which was about double of what it was observed in the other studies.

Incidence of Sepsis

Study	FLOLAN Pts with Sepsis/Total	Number of Episodes	Patient- Months of Exposure	Infections/ patient/year
35/36	0/11	0	22	0.00
37	5/18	12	610	0.24
46	5/42	5	123	0.49
47	11/64	33	1424	0.28
49	17/128	35	1920	0.22
50	11/178	15	1135	0.16
Total		100	5234	0.23

**Serious and/or Life-Threatening Adverse Experiences
Associated with the Drug Delivery System**

Adverse Experience	4-Month Update N (%) N = 197	Current N (%) (N = 372)
inject site reaction	19 (10)	53 (14)
sepsis	16 (8)	37 (10)
pneumothorax	1 (1)	7 (2)
dyspnea	4 (2)	6 (2)
procedural complication	1 (1)	5 (1)
hypoxia	2 (1)	4 (1)
cellulitis	1 (1)	3 (1)
chest pain	3 (2)	3 (1)
hemothorax	1 (1)	3 (1)
infection	2 (1)	3 (1)
pallor	1 (1)	3 (1)
cyanosis	0	2 (1)
hypotension	2 (1)	2 (1)
syncope	0	2 (1)
abcess inject site	0	1 (<1)
asthenia	1 (1)	1 (<1)
cerebral infarct	0	1 (<1)
cerebral vascular accident	1 (1)	1 (<1)
chills	0	1 (<1)
dizziness	1 (1)	1 (<1)
hemorrhage, inject site	1 (1)	1 (<1)
hyperventilation	1 (1)	1 (<1)
hypesthesia	0	1 (<1)
fever	0	1 (<1)
ixufam inject site	1 (1)	1 (<1)
laryngismus	0	1 (<1)
nausea	1 (1)	1 (<1)
pain, inject site	1 (1)	1 (<1)
shock	1 (1)	1 (<1)
pneumonia	0	1 (<1)
thrombosis	0	1 (<1)
vomiting	1 (1)	1 (<1)

Thromboembolic Events: A total of 7 cases of CVA were reported during the long term studies.

Fatal Events:

The Approval Safety Update included copies of the case report forms of 54 patients who had died more recently during the long-term studies with flolan. Eight of these reports (3700014 from study 37) and (4902115, 4902116, 4908108, 4909105, 4913106, 4913107, 4913110 from study 49) had been submitted before. I have summarized the relevant information from the case reports in Tables A, B, C and D along with information about the patients who had died previously in the same studies. Most patients (42) died from progressive right heart failure, 6 from hemorrhage, 10 from sudden death/cardiac arrest/shock, a few from arrhythmia, pneumonia and/or electrolyte abnormalities. Two fatalities one due to hypotension and another due to pulmonary hemorrhage were attributed to flolan by the investigators.

Study 49: At screen (before they were infused with flolan) the patients who died in study 49 were classified as follows:

Class III	5
Class IV	17

These patients survived for:

Class III:	4.6 ± 4.3 months; range 1 to 10 months
Class IV:	3.4 ± 3.9 months; range 0 days to 13 months.

Study 50: At screen the 45 patients who died in study 50 had been classified as follows:

Class III	7
Class IV	22
Class not marked:	16

These patients survived for:

Class III	2.5 ± 3.2 months, range 1 day to 8.4 months
Class IV	2.7 ± 2.9 months; range 0 days to 10.9 months
Unclassified	5.7 ± 3 months; 1 to 10.5 months.

Combination of the data of both studies gave the following results:

Survival of patients of Class III:	3.4 ± 3.6 months
Survival of patients of Class IV:	3.0 ± 3.3 months

We do not have the data of the patients who were transplanted or the data of all the patients who were withdrawn. We cannot therefore calculate the survival rates. A gross comparison with the NIH Registry data does not indicate any advantage for flolan.

TABLE A

Patients Who Died in Study #37
Study 37 was the continuation of Study 35/36, which was initiated on April 10, 1987. Study 37 itself was initiated on August 25, 1987

Pt # and NYHA Class	Date Entered	Date of Death	Period in Study	Cause of Death	Side Effects
C* IV	1/23/89	3/29/93	4 years, 2 months	Not stated	Diarrhea, pneumonia, fluid retention
F* III	9/15/87	2/16/90	2 years, 5 months	Cardiopulmonary Decompensation	Pump stoppage, sepsis, hyponatremia, catheter clotted
F* III	12/16/87	10/23/88	10 months	Progression of PPH	Interruption of flofan flow associated with heparin flushing, Death
C* III	10/10/88	5/21/90	1 year 8 months	Sudden death	Thromboembolism, arrhythmia
F* IV	2/13/89	11/7/93	4 years, 9 months	PRHF	Catheter infection, persistent PGI ₂ syndrome**, sepsis, hepatorenal failure, numbness, pump malfunction, abnormal ECG, abdominal edema, sweating, lethargy, fever, nausea/vomiting, septal infarct., M.I., confusion, ascites, ileus
F* III	5/3/89	7/9/92	3 years, 2 months	Progression of PPH	Cardiovascular collapse

* C=the pt. was a control pt. in Study 35/36; F=the pt. was a flofan pt. in Study 35/36.
** = Jaw/taste bud pain, muscle aches, diarrhea.

TABLE B

Patients Who Died in Study #47
Study #47 was the continuation of Study 46. Study 46 was initiated on September 12, 1991
and Study 47 on December 1991

Pt. #	Date Entered Study	Onset of Event which Lead to Death	Date of Death	Cause of Death	Period in Study	NYHA Class	Side Effects
C*	12/5/91	11/21/92	12/24/92	Hepatic Encephalopathy	1 year, 19 days Autop.	III	Cirrhosis, G.I. bleeding IHSS*, CAD
F*	4/9/92	6/31/92	10/9/92	Massive GI bleeding	6 months Autop.	II then III and IV	Thrombocytopenia, Hx of Episaxis Cath. Infection Sepsis
C*	12/18/91	9/11/92	10/8/92	Compl of PPH	8 months 21 days	III	Ascites, ↓ urine output
F*	1/24/92	12/10/92	12/11/92	PRHF	10 months 18 days Autop.	III	Diarrhea Photosensitivity, vomiting, pleural effusion
C*	4/6/92	8/8/93	8/8/93	PRHF	1 year 4 months	III, IV	Palpitations, cyanosis, dyspnea
F*	5/11/92	5/19/93	5/19/93	Sudden death	1 year 8 days	III	Diarrhea, rash, vomiting, ascites, CVA
C*	6/3/92	11/13/92	11/14/92	septicemia	5 months 11 days	IV	Diarrhea, Elevated Liver Enzymes
F*	4/30/92	11/20/92	11/22/92	PRHF	6 months 22 days Autop.	III	Nausea ↓ digoxin level
F*	3/5/92	5/13/92	5/31/92	PRHF	2 months 26 days Autop.	IV	Pleural effusion Thrombocytopenia, severe ascites, dig. tox.
C*	3/10/92	7/16/92	7/16/92	PRHF	4 months 6 days	III	Allergy, Thrombocytopenia ascites, hypoNa, hyperK., renal insufficiency
F*	7/2/92	10/10/92	10/10/92	Staph Aureus Septicemia	3 months 8 days Autop.	IV	UTI, diarrhea, cath. dislodged

C*=patient had received standard treatment in Study 46; F*=patient had received flolan in Study 46
*IHSS=Idiopathic Hypertrophic Subaortic Stenosis.
PRHF=progressive right heart failure

TABLE C

Data from the Patients Who Died in STUDY #49.

Pt #	Date Entered Study	NYHA Class	Date of Death	Cause of Death or Discontinuation	Side Effects	Length of Survival in Study
	11/10/92	IV	11/21/92	sudden death	persist. nausea, vom., recurr. SVT	11 days
	2/3/93	III	4/10/93	arrhythmia	Ventricular tachycardia	2 months 6 days (66 days)
	6/16/93	III	7/25/93	PRHF		39 days
	12/14/92	IV	1/5/93	unknown		22 days
	8/24/92	IV	9/1/92	PRHF		8 days
	2/12/93	IV	2/17/93	CNS INJURY		5 days
	3/13/93	IV	6/29/93	SUDDEN DEATH	hypotension	3 1/2 mos (108 days)
	8/9/93	IV	8/12/93	RESP. FAILURE		3 days
	10/22/92	IV	12/17/92	FAILED TRANSPLANT	DVT, depression	36 days
	1/20/93	IV	1/20/93	CARDIAC ARREST,	Renal failure, hepatomegaly	0 days
	4/12/93	III	5/14/93	PRHF		32 days
	4/5/93	IV	8/11/93	PRHF	Hypotension, severe SOB	4 months 6 days (128 days)
	6/16/93	IV	7/1/93	PRHF	Pulmonary edema	15 days
	8/12/93	IV	10/29/93	PRHF	Hickman dislodged from venous access	78 days
	9/8/93	IV	1/25/94	PRHF	diarrhea, flushing	139 days
	6/9/93	IV	2/18/94	PRHF	ascites, sepsis, bilateral knee infection	8 mos
	7/30/93	IV	9/13/93	Cardiogenic shock	red macular rash	45 days
	12/17/92	IV	9/11/93	Resp. Failure		7 1/2 mos
	5/10/93	III	3/18/94	massive hemoptysis	pneumonia	10 mos
	5/12/93	IV	2/16/94	arrhythmia	cath. infection nausea, vomiting	9 mos
	6/28/93	III	3/7/94	Multi-organ Failure	sepsis, resp. failure, catheter infection	8 mos + 1/3 mo.
	5/25/93	IV	7/3/94	PRHF	thrombocytopenia, dyspnea, chest pain, UR infection, delirium, CHF, nausea, cough, sepsis, jaw pain, muscle pain	1 yr. 1 mo.

PRHF=Progressive right heart failure.

TABLE D
Study 50
Study 50 was initiated on July 23, 1993

Pt #	Date Entered Study	NYHA Class at Screen	Date of Death	Length of Survival	Cause of Death	Side Effects
	12/20/93	IV	12/20/93	0 days	PRHF	Hypotension, nausea, SOB
	8/31/93	IV	12/13/93	104 days	Cardiac arrest	Hypotension
	2/19/94	IV	2/21/94	2 days	Pneumonia,	Sepsis
	3/16/94	IV	3/22/94	6 days	Pulmonary hemorrhage	pulmonary edema
**	2/11/94	III	3/16/94	35 days	Hemorrhage	pneumothorax sepsis, cath.compl. thrombosis
***	2/11/94	III	3/19/94	36 days	Cardiac arrest	Battery disconnected
	2/1/94	IV	2/5/94	4 days	PRHF	Septostomy
	12/21/93	Not stated	5/13/94	4.77 mos	Cardiac arrest	
	12/23/93	" "	3/23/94	3 mos	Hemorrhage	Hemoptysis, hemothorax
	12/23/93	" "	4/23/94	4 mos	Sudden death	acute renal failure
	2/9/94	" "	8/25/94	6.53 mos	Peritoneal hemorrhage	Anorexia, splenomegaly, splenectomy
	2/9/94	" "	8/27/94	6.6 mos	PRHF	Ascites, hyponatremia
	2/9/94	" "	6/4/94	3.87 mos	Abdominal hemorrhage	Asthma, bronchitis, intra-abdominal hemorrhage
	2/9/94	" "	8/12/94	6.1 mos	PPH	Sepsis
	3/23/94	III	12/6/94	8.43 mos	PPH	Ascites, hyperkalemia, hyponatremia
	3/25/94	IV	7/11/94	3.53 mos	Pneumonia	Pneumonia
	5/4/94	IV	10/4/94	5.0 mos	PPH	Chest pain, palpitations
	6/1/94	IV	8/22/94	2.70 mos	Hypokalemia	Hypokalemia
	12/10/93	IV	11/5/94	10.87 mos	PRHF	Hyponatremia, subdural hematoma, seizures
	9/21/93	IV	12/27/93	3.2 mos	PRHF	Jaw pain
	10/17/94	IV	11/19/94	1.07	PRHF	
	1/18/94	Not stated	2/18/94	1.0 mo	PRHF	
	5/11/94	IV	8/20/94	3.33 mos	PRHF	Fluid volume overload
	12/14/94	IV	12/15/94	1 day	GI Bleeding	
	12/3/93	Not stated	8/26/94	9.8 mos	Retroperitoneal carcinoma	
	12/3/93	Not stated	4/30/94	4.9 mos	Lung transplant	
	3/9/94	IV	11/21/94	8.4 mos	Cardiopulmonary arrest	Ascites
	6/23/94	IV	7/19/94	0.87 mos	PRHF	

TABLE D (Con't.)

11/7/94	IV	12/18/94	1.37 mos	PRHF	Ascites	
4/11/94	IV	9/2/94	4.73 mos	Respiratory failure	Jaw pain	
1/13/94	Not stated	10/26/94	9.43 mos	PRHF	Pericardial effusion	
10/12/94	III	12/13/94	1 mo	PRHF	Hemothorax pneumothorax	
10/15/94	IV	12/9/94	1.8 mos	PRHF	Syncope	
6/20/94	IV	6/22/94	2 days	Cardiogenic shock		
12/13/94	IV	12/16/94	3 days	Not stated	In respirator	
2/11/94	Not stated	11/10/94	9 mos	PRHF		
2/11/94	Not stated	4/21/94	2.33 mos	PRHF	Pneumonia, hyponatremia	
2/11/94	Not stated	12/27/94	10.53 mos	Streptok. anaphylaxis		
2/11/94	Not stated	4/9/94	1.97 mos	PRHF		
2/18/94	IV	7/23/94	5.17 mos	PRHF		
5/23/94	III	11/5/94	5.43 mos	PRHF		
7/18/94	III	7/23/94	0.17 mo	PRHF		
12/27/94	III	12/28/94	1 day	PRHF	Dissection of IVC	
12/15/93	Not stated	8/10/94	7.87 mos	PRHF		
10/2/94	IV	12/4/94	2.1 mos	PRHF	Arrhythmia	
PATIENTS WITHDRAWN						
4/11/94	III	4/22/94	11 days		Persistent nausea	
1/20/94	III	1/21/94	1 day	Lack of efficacy. He had felt better before starting floan	Headache, chest pain, flushing	
3/20/94	III	3/24/94	4 days	Withdrew consent	Headache, nausea	

PRHF=Progressive right heart failure.
 ** Originally reported in study 47.
 ***Originally reported in study 49.

The survival of patients in the NIH Registry has been reported to have been:

Class III: 2.6 years

Class IV: 6 months

CONCLUSIONS:

The side effects which were reported in this Update were similar to those, which had been reported previously i.e. the patients suffered from:

asthenia, dyspnea, tiredness, chest pain, hypoxia, death, which are symptoms/results of PPH and

also from side effects associated with the infusion of flolan: flushing, headache, jaw pain, nausea/vomiting, hypotension, hypotension/syncope, injection site reaction, anxiety/nervousness/agitation, diarrhea, sepsis, ascites, pneumothorax, hemothorax, pulmonary hemorrhage, CVA, sudden death etc.

Five patients died on the same day or 1-3 days after they were dose-ranged with flolan:

from severe hypotension
from cardiac arrest
from dissection of the IVC
from respiratory failure (prostacyclin induced?)
from bleeding.

The incidence of sepsis was 23% on the average, which is rather high. We should also remember that flolan causes tachyphylaxis, which means that the dosage must be increased continuously and considerably the longer a patient is kept on flolan.

E. Triantas
E. Triantas, MD, Ph.D.

CC:
NDA 20-444
HFD-180
HFD-180/SFredd
HFD-180/ETriantas
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
r/d 8/2/95 jgw
f/t 8/6/85 jgw
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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA-20444

OCT 14 1994

DRUG: Flolan, PGI₂
CLASS: Vasodilator, platelet aggregation inhibitor
PROPOSED INDICATION: Treatment of primary pulmonary hypertension (PPH). Flolan is available in Canada for compassionate use to evaluate pulmonary vasoreactivity in patients with PPH and SPH.
SPONSOR: Burroughs-Wellcome

DATE OF Submission: July 27, 1994
DATE RECEIVED: July 27, 1994
DATE RECEIVED BY M.O.: July 29, 1994
DATE REVIEW COMPLETED: Oct. 5, 1994

REVIEWER: E. Triantas, M.D., Ph.D.

TYPE OF SUBMISSION: 4-Month Safety Update. This includes adverse reaction events which occurred in the flolan studies till August 31, 1993 and survival data till March 22, 1994. There are 7 volumes of material and include CRFs of patients who died in studies #47, 49, and of one patient who died in study #37.

INTRODUCTION:

Burroughs-Wellcome have supported 9 studies to provide evidence that flolan is effective for the treatment of PPH. Two of the studies (35/36 and 46) were controlled. The others (37, 47, 49, 50 and 5/10, 20, and 21) were uncontrolled.

Studies 35/36, 46, and 37, have been described in detail in the MO Review of the original NDA. Studies 35/36 and 46 are summarized in Table 1. These studies have been completed. Study 37 is the uncontrolled continuation of study 35/36 and is summarized in Table 2 along with study 47, which is the uncontrolled continuation of study 46. Studies 37 and 47 are still ongoing.

Studies 49 and 50 were initiated after the cut-off date of the NDA to provide uncontrolled chronic flolan therapy to patients with NYHA functional Class III and IV patients, who had not received previously chronic flolan therapy in controlled trials. These studies have not been described in detail by the sponsor. They are briefly summarized in Table 3. Study 49 was initiated on August 24, 1992, and study 50 on July 23, 1993. Both studies are ongoing.

TABLE 1
CLINICAL STUDIES ON PPH
Supported by Burroughs-Wellcome

Controlled Studies

Study #	Investigator	Stratification Criteria	Design	Stages	Duration	NYHA Class	#Pts		Flolan Dose (ng/kg/min)
							F	C	
35	Rubin	Use of oral Vasodilator	Controlled open Parallel random.	1. Dose-Rang.	1-2 h	II	1	1	2-12
				2. Long-Term	8 wk				4, 6
36	Rubin Barst McGoon	Use of oral Vasodilator	as above	as above	1-2 h	III	8	7	2-22
					8 wk				IV
46	17 centers incl. those of investig. listed above	Use of oral vasodilator, NYHA class, Study center	as above	as above	1-2 h 12 wk	III	31	29	22-20

TABLE 1, (continued)

Study #	Distance Walked, Difference from Baseline (meters)		Hemodynamic Effects of Flolan		Hemod. Effects Sign. Diff. Between Groups	Nottingham Profile Sign. Diff. Bet. Groups	Deaths	
	F	C					F	C
35/36	73	-5	TPR TSR SVR PAPs	CI CO	PAPs TPR favoring flolan	Physical Mobility	2*	3
46	30	-50	TPR TSR SVR PVR SAPd PAP RAP	CI CO S V AS MVS Tc ₂	CI, CO, SV, PAP, PVR, TPR SAP, SVR, TSR, Arter. satur. in favor of flolan.	emotions energy, sleep home care, vacations	0	8

Deficiencies

35	Open, bias in rand. & discontin. of pts. favoring flolan, ineligible patients, deaths due to cardiac catheterization. Investigator interference with walk test.	F=flolan C=control
46	Open, bias in random. & discontin favoring flolan. Deaths due to electrolyte imbalance, dig. toxicity. Investigator interfer. with questionnaires. Lack of clin. chem. hematology and ECG data.	

TABLE 2 Summary of Clinical Trials in PPH

Uncontrolled, Chronic Studies: Sponsored by Burroughs Wellcome Co.: Ongoing from original NDA

Study Number or Primary Author	Principal Investigator (Number of Sites)	Study Status/ Report Status (Starting Date)	Design	Number Entered Each Treatment/Sex	Age Range (years)	Treatment Doses (mg/kg/m ²)	Duration of Drug Treatment
BW37	Multiple (4)	Ongoing/ Interim report (25Aug87)	Uncontrolled, chronic, open, multicenter, continuation	M = 6 F = 12	12 - 66	FLOLAN® (eprosuccinate sodium): 2 to 125	Chronic: up to 6.5 years

Uncontrolled, Chronic Studies: Sponsored by Burroughs Wellcome Co.: Initiated since original NDA

BW47	Multiple (17)	Ongoing/ Not available (18Dec91)	Uncontrolled, chronic, open, multicenter, continuation	M = 16 F = 48	6 - 70	FLOLAN: 1-174	Chronic: up to 30 months
BW49	Multiple (19)	Ongoing/ Not available (24Aug92)	Uncontrolled, chronic, open, multicenter	M = 24 F = 96	0 - 72	FLOLAN: 1.5-495	Chronic: up to 22 months
BW50	Multiple (20)	Ongoing/ Not available (23Jul93)	Uncontrolled, chronic, open, multicenter	M = 3 F = 7	0 - 58	FLOLAN: 2-14	Chronic: up to 1 month

TABLE 3

Key characteristics of Studies 47, 49 and 50 are summarized below:

Key Characteristics of Uncontrolled Chronic Studies

Study 47	Study 49	Study 50
Objective Provide chronic infusion of FLOLAN® (epoprostenol sodium) to patients with severe PPH who completed Study 46, and provide additional safety and health economic information	Objective Provide chronic infusions of FLOLAN to patients with severe PPH who were not enrolled in Study 46 for whom no satisfactory alternative therapy is available and provide additional safety and health economic resource consumption information	Objective Provide compassionate-use chronic infusions of FLOLAN to patients with severe PPH and provide additional safety and survival information
Design Multicenter, open-label, uncontrolled trial	Design Multicenter, open-label, uncontrolled trial	Design Multicenter, open-label, uncontrolled trial
Dosage Patients were to receive an initial intravenous infusion of FLOLAN at 4 ng/kg/min less than maximum tolerated dose determined during dose ranging; doses during chronic therapy phase were adjusted based on the occurrence of adverse events and emergence of PPH symptoms	Dosage Patients were to receive an initial intravenous infusion of FLOLAN at 4 ng/kg/min less than maximum tolerated dose determined during dose ranging; doses during the chronic therapy phase were adjusted based on the occurrence of adverse events and emergence of PPH symptoms	Dosage Patients were to receive an initial intravenous infusion of FLOLAN at the optimal dose determined during dose ranging (cardiac catheterization not required); doses were adjusted during the chronic therapy phase based on the occurrence of adverse events and emergence of PPH symptoms
Assessments Dyspnea fatigue rating by investigator PPH signs and symptoms Survival Adverse experiences Health economics	Assessments PPH signs and symptoms Survival Adverse experiences Health economics	Assessments Serious adverse experiences Survival
Entry Criteria Patients completing Study 46	Entry Criteria NYHA Class III or IV PPH and no satisfactory treatment alternatives Men or non-pregnant women using birth control No contraindication to anticoagulant therapy 6 years of age or older	Entry Criteria NYHA Class III or IV PPH and no satisfactory treatment alternatives Men or non-pregnant women using birth control No contraindication to anticoagulant therapy

UPDATE DATA:

Survival

The sponsor summarized the survival data of the patients from all the ongoing long-term studies (37, 47, 49, and 50) in the following table:

**Patient Accountability: Studies 37, 47, 49 and 50
Through 22 March 1994: Survival Analyses**

Protocol	Number of Patients				TOTAL
	P18:37	P18:47	P18:49	P18:50	
Entered	18 (18)	64 (64)	128 ^a (0)	66 (0)	276 (82)
Transplanted	8 (8)	15 (5)	11 (0)	0 (0)	34 (13)
Dead	6 (6)	12 (7)	20 (0)	4 (0)	42 (13)
Withdrew From Study	0 (0)	2 (0)	7 (0)	4 (0)	13 (0)
Alive ^a	4 (4)	35 (52)	90 (0)	58 (0)	187 (56)

^a Excludes two patients who started on the single-vial formulation and left the study (one transplanted and one withdrew) before switching to the double-vial formulation

() denotes corresponding data reported in the NDA

The table shows that by March 22, 1994, a total of 276 patients had entered these studies. Thirty-four of the patients received transplants, 42 died, 13 withdrew and 187 were still alive at the time of the report.

The sponsor then analyzed the combined survival data from all long-term studies, (i.e. studies #35/36, 37, 46, 47, 49, and 50) and compared them with the NIH National registry data (Table 4). They claim that flolan provided a consistent benefit in survival across all studies compared to both the patients who did not receive flolan in the Burroughs-Wellcome studies (they had received only standard treatment i.e oral vasodilators, diuretics, digitalis, anticoagulants, antihypertensives, etc.) and to those who had participated in the NIH Registry and had also received standard treatment. They found that the probability of survival at all times was better for the flolan patients than it was for the control patients or for the NIH patients. According to their claims the median survival of the flolan patients was 49.4 months compared to 8.8 months for the patients who had received the standard therapy. (The median survival for the NIH Registry was 31.2 months (2.6 yrs) for class III patients and 6 months for Class IV.)

TABLE 4

**Survival: Descriptive Statistics
Burroughs Wellcome Co. Studies 35/36, 37, 46, 47, 49 and 50 and NIH Registry
NYHA Classes III/IV Only**

Follow-up Time in months	Flelen		Standard		NIH Registry	
	Survival Proportion	Number Of Patients Followed	Survival Proportion	Number Of Patients Followed	Survival Proportion	Number Of Patients Followed
0	1.00	245	1.00	53	1.00	138
2	0.94	199	0.81	46	0.84	114
3	0.93	180	0.71	18	0.81	118
4	0.91	147	0.71	3	0.72	97
12	0.84	83	0.71	3	0.64	85
18	0.80	29	0.71	3	0.56	73
24	0.80	19	0.47	1	0.52	68
30	0.80	7		0	0.47	56
36	0.60	3		0	0.43	47
42	0.40	2		0	0.41	39

Patients are Censored at Cross-over or Transplant.

Length of Follow-up: The number of patients who were followed-up for 6 months and over is shown below:

Number of Patients Receiving Chronic FLOLAN Therapy in Studies 37, 47 and 49

Follow-up (months)	6	12	18	24	30	36	42	48	56	57	58	59
Number of Patients in NDA	17	14	12	11	9	7	5	1	1	1	1	1
Number of Patients in Safety Update	127	59	31	14	9	7	6	6	4	3	2	1

The number of patients decreased precipitously after 6 months from 127 at 6 months to 9 at 30 months, to 6 at 48 months and to 1 at 59 months.

Flolan Dosage: As stated in the review of the original NDA the dosage of flolan had to be increased as the treatment continued in order to obtain satisfactory results (Tachyphylaxis). Tachyphylaxis was also observed in the new studies. The table below shows that during the first month the mean dosage of flolan was 5 ng/kg/min. The dosage increased gradually and by the end of 36 months it reached 53 ng/kg/min. At 56 months it was 62 ng/kg/min.

Comparison of Dosing^a

Month	Mean Dose (ng/kg/min)		Mean Number of Dose Adjustments Per Patient Per Month		Percentage of Patients Receiving Dose Adjustment	
	NDA	Update	NDA	Update	NDA	Update
0	6.9	4.8				
6	11.5	19.0	0.6	1.2	35	55
12	17.6	26.2	1.0	1.1	28	49
18	25.9	33.0	0.3	1.1	25	58
24	36.7	48.0	0.7	1.4	45	64
30	38.5	43.9	1.0	0.1	44	11
36	52.9	53.0	0.4	0.1	28	14
42	42.0	51.5	0.2	0.2	20	16
48	28.0	56.7	0.0	0.7	0	50
56	30.0	62.0	0.0	0.0	0	0
57	32.0	60.0	1.0	0.3	100	33
58	32.0	45.5	0.0	0.5	0	50
59	32.0	32.0	0.0	0.0	0	0

^a Data extracted from NDA Table 16 and Update Table 15.

After this period the dosage appears to have decreased. This is most likely due to the fact that very few patients (3 down to 1) were followed after 56 months. There is a great variability among patients regarding optimum floian dosage. In the new studies it varied from 1 to 495 ng/kg/min. Patients younger than 16 years required higher dosages and twice as many dose adjustments each month than the older age group (2.3 vs 1.2 adjustments). On the average the dose increased by 2 ng/kg/min every month. The most common reason for dose increase was an increase in PPH symptoms.

With continued dose escalations and after years of exposure some patients had reached doses in excess of 100 ng/kg/min. One infant received 495 ng/kg/min.

SAFETY DATA:

Safety data have been summarized till August 31, 1993.

Overall Summary Adverse Experiences During Acute Dose-Ranging Procedures:

Adverse Experiences Occurring in ≥5% of Patients*

Adverse Experience	NDA N(%) (N = 391)	Update N(%) (N = 541)
flushing	225 (58)	292 (54)
headache	192 (49)	253 (47)
nausea/vomiting	124 (32)	169 (31)
hypotension	61 (16)	79 (15)
anxiety/nervousness/agitation	44 (11)	62 (12)
chest pain	43 (11)	57 (11)
dizziness	31 (8)	39 (7)
abdominal pain	20 (5)	33 (6)

* Data extracted from NDA Table 58 and Update Table 19.

This table includes experiences from 541 patients who had received floian in the form of Dose-Ranging. Dose-ranging lasted usually for 1-2 hours. The table shows that side effects were frequent. The most frequent events during this period were flushing, headache, and nausea/vomiting. More than one half of the patients

felt flushing, almost one half felt headaches and about one third suffered nausea/vomiting. Hypotension, nervousness, and chest pain were less frequent.

Adverse Experiences Observed during the Chronic Therapy Studies:

Up to August 31, 1993, 216 patients had received flolan as chronic therapy. Side effects during this period were more frequent than they were during dose-ranging (Table 5). At least 60% of the patients included in the Update had some adverse reaction and many patients had more than one. The most frequent of the reactions were asthenia (60%), dyspnea (60%), nausea (53%), dizziness (50%), headache (50%), jaw pain (50%), chest pain (44%), diarrhea (42%), and palpitations (44%).

Study 37 is the longest running PPH study with a follow-up up to 6 years. The incidence of adverse events in this study was considerably higher than in the Update, which includes many patients with short follow-ups (1 month to 20 months). The results suggest that the longer a patient receives folan the higher are the chances that he/she will experience more side effects, mainly weakness, dyspnea, nausea, diarrhea, and reactions at the injection site.

TABLE 5
Adverse Experiences Occurring in ≥25% of Patients*

Adverse Experience	NDA (Study 37) N (%) (N=18)	Update N (%) (N=216)
asthenia	16 (89)	130 (60)
dyspnea	16 (89)	130 (60)
nausea	14 (78)	115 (53)
dizziness	12 (67)	109 (50)
headache	11 (61)	108 (50)
jaw pain	11 (61)	108 (50)
chest pain	11 (61)	96 (44)
palpitations	8 (44)	96 (44)
edema	5 (28)	90 (42)
diarrhea	16 (89)	90 (42)
myalgia	7 (39)	90 (42)
abdominal pain	8 (44)	81 (38)
cough increase	5 (28)	81 (38)
depression	6 (33)	70 (32)
injection site reaction	14 (78)	65 (30)
pain	12 (67)	60 (28)
hypotension	7 (39)	60 (28)
tachycardia	7 (39)	60 (28)
right heart failure	6 (33)	56 (26)
anorexia	4 (22)	55 (25)
pallor	11 (61)	55 (25)
rash	9 (50)	53 (25)

* Data extracted from NDA Table 76 and Update Table 23.

Adverse Experiences Associated with Bleeding:

Adverse Experiences Associated with Bleeding^a

Adverse Experiences	N (%) (N=216)
hemorrhage at injection site	11 (5)
hemoptysis	11 (5)
hemorrhage	7 (3)
GI hemorrhage	4 (2)
petechia	4 (2)
anemia	3 (1)
ecchymosis	3 (1)
melena	2 (1)
vaginal hemorrhage	2 (1)
coagulation disorder	1 (<1)
hematuria	1 (<1)

^a Data extracted from Update Table 23.

Although PGI₂ is an inhibitor of platelet aggregation, relatively few hemorrhages have been reported (23%). The most frequent site of hemorrhage was the injection site (5%) and the lungs (hemoptysis, 5%). General hemorrhage or GI hemorrhage were less frequent.

Adverse Experiences Occurring more Frequently in Patients $\leq$ 16 years Old:

**Adverse Experiences Occurring More Frequently ($\geq$ 10%)
in Patients $<$ 16 Years of Age**

Adverse Experience	$<$ 16 years N (%) (N = 24)	$\geq$ 16 years N (%) (N = 192)
cough increased	12 (50)	69 (36)
chills/fever/sepsis/flu	13 (54)	57 (30)
tachycardia	10 (42)	50 (26)
pallor	10 (42)	45 (23)
hypoxia	9 (38)	38 (20)
bradycardia	6 (25)	14 (7)
back pain	4 (17)	11 (6)
myocardial ischemia	6 (25)	5 (3)

Compared to older patients, young patients seemed to suffer more frequently from cough (50% vs 36%), infections (54% vs 30%), tachycardia (42% vs 26%), hypoxia (38% vs 20%), bradycardia (25% vs 7%), myocardial ischemia (25% vs 3%) and backpain (17% vs 6%) during long-term therapy with flolan.

Serious and Life Threatening Adverse Experiences:

These reactions are summarized in Table 6. They are listed separately for the controlled studies (35/36, and 46), study 37, and for all studies together i.e. including also studies 47, 49, and 50. They include reactions from 216 patients.

Considering that the controlled studies lasted for only 2 or 3 months and that the majority of the data in the Update came from studies 47, 49, and 50 which are relatively new studies with a short follow-up (20 months, 1 year, and one month respectively) the most representative results for the long-term treatment with flolan, are those of study 37 (with a follow-up of up to 6 years).

The data from this study indicate that the most frequent serious and life threatening events during the long-term treatment with flolan were: dyspnea (78%), asthenia (67%), dizziness (50%), syncope (39%), chest pain (39%), and inflammation at the injection site (also 39%; Table 6).

Drug Delivery System Malfunctions:

Drug Delivery System Malfunctions

System	Malfunction	Study 46 Number of Patients (% of Patients) (N = 41)	Update Number of Patients (% of Patients) (N = 187)
Catheter	occluded	1 (2)	15 (8)
	perforation in catheter	5 (12)	19 (10)
	catheter dislodgment	4 (10)	16 (8)
	nonfunctional, reason unk	0 (0)	3 (2)
	other	9 (22)	49 (25)
Pump - human	reconstitution error	0 (0)	6 (3)
	programming error	2 (5)	10 (5)
	other	7 (17)	24 (12)
Pump - mechanical	pump stopped	5 (12)	16 (8)
	accelerated infusion	0 (0)	1 (1)
	other	2 (5)	17 (9)

TABLE 6
Serious and/or Life-threatening Adverse Experiences
Occurring in ≥ 5 Patients^a

Adverse Experience	Studies 35/36, 46 (N=52) N (%)	Study 37 (N=18) N (%)	Update (N=216) N (%)
sepsis	5 (10)	5 (28)	26 (12)
injection site inflammation/ reaction	1 (2)	7 (39)	25 (12)
dyspnea	4 (8)	14 (78)	22 (10)
chest pain	2 (4)	7 (39)	19 (9)
asthenia	1 (2)	12 (67)	15 (7)
dizziness	1 (2)	9 (50)	11 (5)
infection	0 (0)	5 (28)	10 (5)
syncope	1 (2)	7 (39)	10 (5)
hypotension	1 (2)	5 (28)	9 (4)
nausea	2 (4)	5 (28)	9 (4)
pallor	1 (2)	7 (39)	9 (4)
ascites	0 (0)	2 (11)	8 (4)
cyanosis	1 (2)	5 (28)	7 (3)
diarrhea	1 (2)	6 (33)	7 (3)
flushing	2 (4)	4 (22)	7 (3)
hypoxia	1 (2)	4 (22)	7 (3)
procedural complications	2 (4)	5 (28)	7 (3)
pneumonia	1 (2)	0 (0)	7 (3)
tachycardia	2 (4)	4 (22)	7 (3)
depression	0 (0)	5 (28)	6 (3)
peripheral edema	0 (0)	5 (28)	6 (3)
vomiting	0 (0)	4 (22)	6 (3)
cough increase	1 (2)	3 (17)	5 (2)
headache	1 (2)	3 (17)	5 (2)
heart failure, right	0 (0)	4 (22)	5 (2)
hypesthesia	0 (0)	2 (11)	5 (2)
pain	1 (2)	3 (17)	5 (2)

^a Data extracted from Update Table 23 and NDA Tables 64 and 76.

In this Update only 187 of the 216 patients have been included. It appears that the flolan delivery system malfunctioned in 176 of these patients i.e. in 94% of them, which is a very high incidence except if two or more of these malfunctions occurred in the same patient, in which case fewer patients must have experienced malfunctions of their delivery system but several of them must have experienced more than one malfunction. The Delivery System malfunctions involved mainly the catheter and less so the pump. Pump malfunctions were due either to human error (20%) or to a mechanical fault of the pump itself (18%).

The majority of the malfunctions in all categories have been classified as "other" which does not explain what these really were. Of the remaining malfunctions 10% involved catheter perforation, 8% catheter dislodgment, 8% occlusion, 5% programming error and 8% pump stoppage.

Serious Life-Threatening Adverse Experiences Associated with the Drug Delivery System:

**Serious and/or Life-Threatening Adverse Experiences
Associated with the Drug Delivery System**

Adverse Experience	Update N (%) N = 197	Adverse Experience	Update N (%) N = 197
inject site reaction	19 (10)	hemorrhage, inject site	1 (1)
sepsis	16 (8)	pain, inject site	1 (1)
dyspnea	4 (2)	procedural complication	1 (1)
chest pain	3 (2)	shock	1 (1)
infection	2 (1)	cerebral vascular accident	1 (1)
hypotension	2 (1)	pallor	1 (1)
hypoxia	2 (1)	dizziness	1 (1)
nausea	1 (1)	hyperventilation	1 (1)
vomiting	1 (1)	pneumothorax	1 (1)
asthenia	1 (1)	hemothorax	1 (1)
cellulitis	1 (1)	inflamm inject site	1 (1)

This Update includes only 197 of the 216 patients. There were 22 cases of serious reactions at the injection site including inflammation, hemorrhage, and pain and 19 cases of sepsis or infection, two cases of hypotension, one of shock, and one each of CVA, pneumothorax, and hemothorax.

Four additional cases of CVA, not associated with the drug delivery system, were observed during the flolan studies raising the total number of strokes to 5 (2%).

Incidence of Sepsis:

A more detailed report regarding the incidence of sepsis during the flolan studies among 264 patients is shown below:

Incidence of Sepsis

Study	FLOLAN® Pts with Sepsis/Total	Number of Episodes	Patient- Months of Exposure	Infections/ patient/year
35/36	0/11	0	22	0.00
37	5/18	12	574	0.25
46	5/41	5	123	0.49
47	9/64	18	853	0.25
49	9/120	10	548	0.22
50	0/10	0	5	0.00
Total		45	2125	0.25

Sepsis occurred in 28/264 patients (11%). The total number of episodes was 45 i.e. some patients must have had more than one episode. The incidence of sepsis/patient/year was 0.25.

Two patients died from septicemia attributed to the drug delivery system.

Side Effects Reported in the Literature and in Studies for Other Indications:

Safety data from all the studies supported by Burroughs-Wellcome (and this includes also studies for other indications besides PPH), from the literature and from emergency use of flolan and from the Clinical Safety Surveillance Service of the Wellcome Research Laboratories of UK are discussed briefly in the Safety Update. The sponsor asserts that all the reported side effects had been observed previously and have been reported in the NDA. They claim that there were no deaths reported during this period in studies using flolan for other indications.

REVIEW of the CRFs of the Patients who died in Studies 37, 47, and 49. All patients in these studies were receiving flolan.

The sponsor has not provided narrative descriptions of death as required by the Regulations. I have briefly summarized each case from the patients' CRFs in the following Tables.

Study #37:

Study 37 had recruited 18 patients. By March 22, 1994, 10 of these patients had died and 8 had been transplanted. We have received only the CRFs of 5 of the patients who died (see Table below), 4 with the NDA and one with the Update.

Patients Who Died in Study #37
Study 37 is the continuation of study 35/36, which was initiated on April 10, 1987. Study 37 itself was initiated on August 25, 1987.
The total number of patients in study 37 was 18.

Pt # and NYHA Class	Date Entered	Date of Death	Period in Study	Cause of Death	Side Effects
C* IV	1/23/89	3/29/93	4 years, 3 months	Not stated	Diarrhea, pneumonia, fluid retention
F* III	9/15/87	2/16/90	2 years, 5 months	Cardiopulmonary Decompensation	Pump stoppage, sepsis, hyponatremia, catheter clotted
F* III	12/16/87	10/23/88	10 months	PPH	Interruption of flolan flow associated with heparin flushing
C* III	10/10/88	5/21/90	1 year 6 1/2 months	Sudden Death	Thromboembolism, arrhythmia
F* III	5/3/89	7/9/92	3 years 2 months	Progression of PPH	Cardiovascular collapse

* C=the pt. was a control pt. in Study 35/36; F=the pt. was a flolan pt. in Study 35/36.

Four of the 5 patients who died, were Class III when they entered Study 37, and one was Class IV. [The initial distribution of patients in Study 37 by NYHA class was: Class II: 1 patient, Class III: 14 patients and Class IV: 3 patients.] These patients died within 10 months to 4 years and 3 months from the time of recruitment. The cause of death was most likely progression of PPH in all of them.

During the study these patients had suffered diarrhea, pneumonia, sepsis, hyponatremia, arrhythmia, and thromboembolism. In two of these patients the flolan delivery system malfunctioned (thrombosis, and pump stoppage, interruption of flolan flow after heparin flushing).

Study #47:

Study 47 had 64 patients. By March 22, 1994, 12 of these patients had died, 15 had been transplanted and 2 had been withdrawn. We have received the CRFs of only 11 of the patients who died (Table 7) and none of those who withdrew. Of the 11 patients who died, 7 were Class III when they entered the study, 3 were Class IV, and

TABLE 7

Patients who Died In STUDY # 47
Study 47 was the continuation of study 46. Study 46 was initiated on September 12, 1991 and study 47 on December 1991.
The total number of patients in study 47 was 64.

Pt#	Date Entered Study	Onset of Event which Lead to Death	Date of Death	Cause of Death	Period in Study	NYHA Class	Side Effects
	12/5/91	11/21/92	12/24/92	Hepatic En. sphenopathy	1 year, 19 days Autop.	III	Cirrhosis, G.I. bleeding IHSS*, CAD
	4/9/92	8/31/92	10/9/92	Massive GI Bleeding	6 mos 22 days Autop.	II then III and IV	Thrombocytopen. Hx of Epistaxis Cath infect., Sepsis
	12/18/91	9/11/92	10/8/92	Compl of PPM	9 mos 21 days	III	Ascites, urine output
	1/24/92	12/10/92	12/11/92	PRNF	10 mos 18 days Autop.	III	diarrhea photosensitivity, vomiting, pleural effusion
	4/6/92	8/8/93	8/8/93	PRNF	1 year, 4 mos	III, IV	palpitations, cyanosis, dyspnea
	5/11/92	5/19/93	5/19/93	sudden death	1 year, 8 days	III	diarrhea, rash, vomiting, ascites, CVA
	6/3/92	11/13/92	11/14/92	septicemia	5 mos, 11 days	IV	diarrhea, Elevated liver enzymes
	4/30/92	11/20/92	11/22/92	PRNF	6 mos, 23 days Autop	III	nausea, digoxin level
	3/5/92	5/13/92	5/31/92	PRNF,	2 mos, 26 days Autop.	IV	pleural effusion Throbocytopenia, severe ascites dig tox
	7/2/92	10/10/92	10/10/92	Staph Aureus Septicemia	3 mos, 8 days Autop	IV	UTI, diarrhea, cath. dislodged
	3/10/92	7/16/92	7/16/92	PRNF	4 mos 6 days	III	Allergy, Thrombocytopenia ascites, hypoNa, hyperK., renal insufficiency

* IHSS=Idiopathic Hypertrophic Subaortic Stenosis.
PRNF=progressive right heart failure

one was Class II. These patients died between 3 months and 1 year plus 4 months after they entered Study 47. The cause of death was progressive right heart failure (5), septicemia (2), hepatic encephalopathy, massive GI bleeding, sudden death, and "complication of PPH". Six of these patients seemed to have developed liver damage (cirrhosis, G.I. bleeding, ascites, elevated enzymes), 3 thrombocytopenia, 1 CVA and another hyponatremia and hyperkalemia.

Study #49

By March 22, 1994, 128 patients had entered Study 49. Twenty of these patients died, 11 were transplanted, and 7 were withdrawn. We have received the CRFs of only 13 of the patients who died and 3 of those who withdrew (Table 8). Ten of the patients who died belonged to NYHA Class IV and 3 to class III. The 13 patients died between 0 days and 4 months from the day they had been recruited. The cause of death was listed as progressive right heart failure (5), sudden death/cardiac arrest (3), arrhythmia, respiratory failure, failure of transplant, CNS injury, and unknown.

Of the 3 patients who withdrew, whose CRFs we received, one withdrew because of lack of efficacy of flolan, another withdrew because of adverse reactions (ascites, SOB, weakness), and the third because he developed pulmonary congestion during dose-ranging. The clinical condition of patient improved considerably after he discontinued flolan. "The ascites disappeared, SOB decreased, weakness resolved and clinically he felt better." One month later he reported that he was feeling great.

EVALUATION OF THE UPDATE DATA BY THE REVIEWER

Survival:

The table representing the survival data submitted by the sponsor (Table 4 on p. 6 of this review) is useless. They have not explained to us how they got these results i.e. they have not summarized for us when each of the studies started, when each of the patients entered the respective study, and when each of them died, withdrew, was switched over to flolan, or was transplanted.

Most importantly, the data which were collected from the controlled studies are unreliable. Studies 35/36, and 46 were open. There is evidence that bias was introduced in the randomization of the patients of these studies, especially in study 46. This study did not have a predetermined randomization code but used a computer generated adaptive randomization procedure, which did not work when Dr. Ross Pierce from DSI visited the sponsor's premises. The

TABLE 8

Data from 13/20 Patients Who Died and 3/7 Patients Who Withdrew from STUDY #49 Study 49 Was Initiated on August 24, 1992.
The Total Number of Patients in Study 49 was 128.

Pt #	Date Entered Study	NYHA Class	Date of Death	Cause of Death or Discontin.	Side Effects	Length of Survival in Study
	11/10/92	IV	11/21/92	sudden death	persist. nausea, vom., recurr. SVT	11 days
	2/3/93	III	4/10/93	arrhythmia	Ventricular tachycardia	2 months 5 days (66 days)
	6/16/93	III	7/25/93	PRHF		39 days
	12/14/92	IV	1/5/93	unknown		22 days
	8/24/92	IV	9/1/92	PRHF		8 days
	2/12/93	IV	2/17/93	CNS INJURY		5 days
	3/13/93	IV	6/29/93	SUDDEN DEATH	hypotension	3 1/2 mos (108 days)
	8/9/93	IV	8/12/93	RESP. FAILURE		3 days
	10/22/92	IV	12/17/92	FAILED TRANSPLANT	DVT, depression	1 mo, 26 days (108 days)
	1/20/93	IV	1/20/93	CARDIAC ARREST,	Renal failure, hepatomegaly	0 days
	4/12/93	III	5/14/93	PRHF		32 days
	4/5/93	IV	8/11/93	PRHF	Hypotension, severe SOB	4 months 6 days (128 days)
	6/16/93	IV	7/1/93	PRHF	Pulmonary edema	15 days
	1/20/93	III	3/9/93 Withdrew	Lack of Efficacy		1 mo 17 days (48 days)
	3/8/93	III	5/18/93 Withdrew	Adv React. @		2 mo 10 days (71 days)
	6/22/93	III	6/23/93 Withdrew	Acute Pulmonary Congestion during Dose-Ranging		1 day

PRHF = Progressive right heart failure.

@ After the discontinuation of flolan the nurse noted on the patient's CRF that "Ascites disappeared, SOB decreased, weakness resolved, clinically felt better. 6/19/93 Patient reports feeling great".

patients were "randomized" after they had been thoroughly screened and evaluated and their condition was very well known to the randomizers. All the severely ill patients were "randomized" to the control group.

In addition, flolan patients, who suffered complications during cardiac catheterization or dose-ranging were withdrawn from the studies (they were allegedly "not randomized"), while control patients who suffered similar complications were kept in the studies.

The survival data reported by the sponsor are unreliable.

The results of study 49 support the conclusion that flolan is not such an effective drug as the sponsor wants us to believe. As explained earlier, this study was uncontrolled and was initiated to provide treatment to patients with severe PPH similar to the patients who had been used in Study 46. By March 22 of 1994, this study had accumulated 128 patients. All of them were receiving flolan. Twenty of these patients died within 0 and 128 days, most of them within 71 days (Table 8) i.e. in less than 3 months, which was the length of study 46. If flolan were as "effective" as Study 46 purports to have shown, none of these patients would have died.

Flolan Dosage:

The data indicate that flolan causes tachyphylaxis or tolerance. The longer a patient receives flolan the more his dosage must be increased in order to control the symptoms of PPH. However, increasing the dosage, increased the incidence of side effects.

It can be argued that the dosage of flolan must be increased because of the progression of a patient's disease. This argument leads to the conclusion that flolan cannot delay the progression of PPH. No matter how we try to explain the increasing requirements for flolan, the net result is that as treatment continues flolan becomes less and less effective (if it ever was).

Side Effects:

The Update shows that the incidence of side effects increased as treatment with flolan continued. The longer the patients were on flolan, the more side effects they suffered. Tables 5 and 6 show that the incidence of side effects was highest in study 37 where some patients were followed up to 6 years. The incidence was lower in the Update, which includes data from many new patients with short follow-ups, while the lowest incidence was observed in the controlled studies, which lasted for only 2 (study 35/36) and 3

months (study 46).

The most frequent and life-threatening adverse reactions, which were reported were dyspnea (78%), asthenia (fatigue) (67%), dizziness (50%), chest pain (39%), and syncope (39%) (Table 6, study 37). These reactions are identical to the very symptoms of PPH. Among the adverse reactions reported after long-term treatment with flolan were also cyanosis (28%), hypoxia (22%), tachycardia (22%), depression (28%), peripheral edema (28%), and right heart failure (22%), which are also symptoms of PPH. It appears therefore that during long-term therapy flolan becomes unable to control the symptoms of PPH. In addition, flolan causes adverse effects of its own: infection at the infusion site, general infection (sepsis), diarrhea, hypotension, nausea, flushing, headache, paresthesias and pulmonary congestion. The drug delivery system has also its share of side effects: thrombosis, embolism (CVA), perforation of catheter or vein, reconstitution error, programming error, accelerated infusion, pump stoppage (causing rebound hypertension and death), pneumothorax, hemothorax, etc.

Re-review of the incidence of side effects, which were reported for the controlled Studies (study 46 and study 35/36) shows that the incidence of side effects in these studies was much higher than it is shown in the Update for them. In Study 46 (Table 68 of the sponsor, attached to this review) the incidence of asthenia was 100%, dyspnea also 100%, dizziness 90%, headache 85%, palpitations 80%, etc. The incidence of side effects in study 35/36 was lower than it was in study 46, but still it was considerably higher than what is shown in the Table on page 21, vol. 5.1 of the Update (copied for this review as Table 6, page 13. Compare with Table 56 from study 35/36, also attached to this review). It appears that contrary to the claims of the sponsor, flolan does not seem to improve the symptoms of PPH.

CONCLUSIONS:

1. The Safety Update is deficient:
 - a) Narrative summaries of the patients who died or withdrew are not included.
 - b) CRFs of 13 patients who died (1 from Study 37, 1 from Study 47, 7 from Study 49 and 4 from Study 50) and 10 from those who withdrew have not been submitted.
2. Reliable evidence that flolan prolongs survival has not been presented.
3. Flolan causes tachyphylaxis (tolerance) or it is unable to

affect the progression of PPH.

4. Flolan does not seem to control the symptoms of PPH.
5. Flolan administration can cause serious and life-threatening adverse events (sepsis, thromboembolism, pulmonary edema, pneumothorax, hemothorax, systemic hypotension, rebound pulmonary hypertension and death).

RECOMMENDATIONS

We need the advice of the Advisory Committee. It seems to me than the long-term studies with flolan should be terminated.

E. Triantas, M.D. Ph.D.
E. Triantas, M.D., Ph.D.

cc:
NDA 20-444
HFD-180
HFD-180/SFredd
HFD-180/ETriantas
HFD-181/CSO
HFD-180/JChoudary
HFD-180/JGibbs
r/d 9/29/94 jgw
MED\N\20444409.2ET

10/14/94

Obtain request!
will schedule Advis. Com. review.
will await their further review before
considering appropriate action on
application.

[Signature]

STUDY 46

Table 68. Expected and Unexpected Adverse Experiences that Occurred in at Least 3 Patients in Either Treatment Group, 12-Week Treatment Segment

Adverse Experience	FLOLAN®		Standard	
	N	(%)	N	(%)
Asthenia	41	(100%)	39	(98%)
Dyspnea	41	(100%)	39	(98%)
Dizziness	37	(90%)	34	(85%)
Headache	35	(85%)	15	(38%)
Palpitations	33	(80%)	30	(75%)
Pain, chest	31	(76%)	33	(83%)
Edema	30	(73%)	30	(75%)
Nausea	28	(68%)	23	(58%)
Pain, jaw	27	(66%)	0	(0%)
Myalgia	23	(56%)	16	(40%)
Cough, increase	19	(46%)	25	(63%)
Depression	19	(46%)	23	(58%)
Vascular disorder, peripheral	19	(46%)	20	(50%)
Tachycardia	16	(39%)	13	(33%)
Diarrhea	16	(39%)	3	(8%)
Cyanosis	14	(34%)	21	(53%)
Pain, abdominal	14	(34%)	15	(38%)
Weight decrease	14	(34%)	13	(33%)
Arrhythmia	14	(34%)	11	(28%)
Hypoxia	13	(32%)	19	(48%)
Heart failure, right	13	(32%)	19	(48%)
Hypotension	13	(32%)	16	(40%)
Anorexia	13	(32%)	15	(38%)
Pain, general	13	(32%)	7	(18%)
Heart failure (Low cardiac output)	12	(29%)	21	(53%)
Flushing	11	(27%)	0	(0%)
Pallor	10	(24%)	16	(40%)
Angina pectoris	10	(24%)	11	(28%)
Fever	10	(24%)	3	(8%)
Vomit	8	(20%)	4	(10%)
Sweat	7	(17%)	9	(23%)
Bradycardia	7	(17%)	5	(13%)
Syncope	6	(15%)	11	(28%)
Ascites	6	(15%)	8	(20%)
Hemorrhage	6	(15%)	5	(13%)

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From STUDY 46

(Continuation)

Table 68. Expected and Unexpected Adverse Experiences that Occurred in at Least 3 Patients in Either Treatment Group, 12-Week Treatment Segment (continued)

Adverse Experience	FLOLAN®		Standard	
	N	(%)	N	(%)
Anxiety	5	(12%)	3	(8%)
Amblyopia	4	(10%)	2	(5%)
Nervousness	4	(10%)	1	(3%)
Confusion	3	(7%)	6	(15%)
Rash	3	(7%)	5	(13%)
Infection, general	3	(7%)	3	(8%)
Pain, back	3	(7%)	2	(5%)
Weight increase	3	(7%)	2	(5%)
Constipation	3	(7%)	1	(3%)
Hypokalemia	3	(7%)	1	(3%)
Hypesthesia	3	(7%)	1	(3%)
Arthralgia	3	(7%)	0	(0%)
Tachycardia, supraventricular	3	(7%)	0	(0%)
Rhinitis	2	(5%)	4	(10%)
Infection, urinary tract	2	(5%)	3	(8%)
Liver function abnormality	1	(2%)	4	(10%)
Ischemia, myocardial	1	(2%)	3	(8%)
Shock	0	(0%)	7	(18%)

[Table excerpted from Table 67]

STUDY 35/36

**Table 56. Adverse Experiences that Occurred in ≥3 Patients in Either Treatment Group During the Long-Term Infusion Segment
(Grouped by Maximum Seriousness of Experience)**

FLOLAN® (N=11)
Standard (N=14)

Preferred Term for Adverse Experience	Maximum Seriousness	Treatment Group					
		FLOLAN		Standard			
		All AEs N	(% of Patients)	AEs Associated with Drug Delivery N	(% of Patients)	All AEs N	(% of Patients)
Asthenia	Serious or Life-Thr.	1	(9%)	0	(0%)	4	(29%)
	Not Serious	3	(27%)	0	(0%)	1	(7%)
Diarrhea	Not Serious	3	(27%)	0	(0%)	0	(0%)
Dizziness	Serious or Life-Thr. ^a	1	(9%)	1	(9%)	2	(14%)
	Not Serious	3	(45%)	3	(45%)	2	(14%)
Dyspnea	Serious or Life-Thr.	4	(36%)	2	(18%)	5	(36%)
	Not Serious	2	(18%)	2	(18%)	2	(14%)
Edema Periph	Serious or Life-Thr.	0	(0%)	0	(0%)	3	(21%)
	Not Serious	1	(9%)	0	(0%)	1	(7%)
Headache	Serious or Life-Thr.	1	(9%)	0	(0%)	0	(0%)
	Not Serious	7	(64%)	3	(27%)	3	(21%)
Nausea	Serious or Life-Thr.	2	(18%)	1	(9%)	1	(7%)
	Not Serious	5	(45%)	3	(27%)	1	(7%)
Pain Chest	Serious or Life-Thr.	2	(18%)	1	(9%)	1	(7%)
	Not Serious	1	(9%)	0	(0%)	1	(7%)
Pain Inject Site	Not Serious	3	(27%)	3	(27%)	0	(0%)
Palpitat	Serious or Life-Thr.	0	(0%)	0	(0%)	1	(7%)
	Not Serious	0	(0%)	0	(0%)	2	(14%)
Flushing	Serious or Life-Thr.	2	(18%)	2	(18%)	0	(0%)
	Not Serious	7	(64%)	4	(36%)	1	(7%)

^a None of the AEs were life-threatening.

^b The AE was life-threatening for one patient.

The multidisciplinary reviews are the summary basis of approval.

CRO
oliver

EXCLUSIVITY SUMMARY FOR NDA # 20-444 SUPPL # _____

Trade Name Flolan for Injection Generic Name Epoprostenol Sodium Injection

Applicant Name Burroughs Wellcome Company HFD # 180

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES / / NO / /

b) Is it an effectiveness supplement? YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / x / NO / ___ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5-year period of marketing exclusivity

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength and route of administration, previously been approved by FDA for the same use?

YES / ___ / NO / x /

If yes, NDA # _____ Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / ___ / NO / ___ /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes,, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2' YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!	
IND #	YES /___/	!	NO /___/ Explain: _____
		!	_____
Investigation #2		!	
IND #	YES /___/	!	NO /___/ Explain: _____
		!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1		!	
YES /___/ Explain	_____	!	NO /___/ Explain _____
	_____	!	_____
	_____	!	_____
Investigation #2		!	
YES /___/ Explain	_____	!	NO /___/ Explain _____
	_____	!	_____
	_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / /

If yes, explain: _____

Karen Oliver
Signature
Title: CSO

March 31, 1995
Date

Stephen R. [Signature]
Signature of Office
Division Director

9/5/95
Date

cc: Original NDA

Division File

HFD-84

09 N 11-1-79
20-444



Burroughs Wellcome Co.
February 28, 1994

3030 Cornwallis Road
P.O. Box 12700
Research Triangle Park, N.C. 27709-2700

cables & telegrams
Telcord Raleigh, N.C.
TWX 5109270915
tel. 919-248-3000

Donald A. Knight
Vice President
Drug Regulatory Affairs and
Scientific Administration

Original New Drug Application

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20852



Re: NDA 20-444
FLOLAN® (epoprostenol sodium)
for Injection

Dear Sir/Madam:

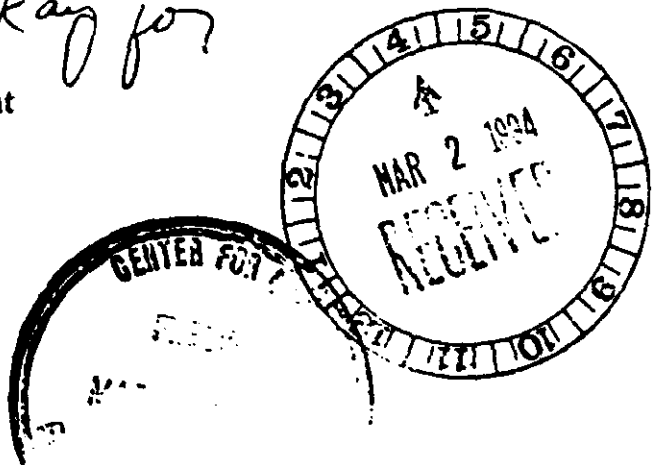
We are submitting herewith, in accordance with 21 CFR 314, an Original New Drug Application to provide for the use of FLOLAN (epoprostenol sodium) for Injection in the treatment of primary pulmonary hypertension (PPH). This application is submitted for review by the Division of Gastrointestinal and Coagulation Drug Products.

By this letter, Burroughs Wellcome Co. certifies that we have not or will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)] of the Food, Drug, and Cosmetic Act in connection with the above referenced NDA.

We further certify that a field copy of the Chemistry, Manufacturing and Control Section (Item 3) of this application has been provided to our local FDA district office.

Sincerely,

Anne McKay for
Donald A. Knight



Attachment 2 to Form FDA 356h

ITEM 13

**PATENT AND EXCLUSIVITY INFORMATION ON PRODUCT OF
BURROUGHS WELLCOME CO., RESEARCH TRIANGLE PARK, NC 27709**

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

1. **Active Ingredient(s):** Epoprostenol Sodium
2. **Strength(s):** 0.5 mg and 1.5 mg vials
3. **Trade Name:** FLOLAN
4. **Dosage Form, Route of Administration:** Freeze-dried powder for injection
5. **NDA Number:** 20-444
6. **Applicable patent numbers assigned to Burroughs Wellcome Co.:**

Patent No. 4,335,139	Patent No. 4,539,333	Patent No. 4,883,812
Expiration: June 15, 1999	Expiration: September 3, 2002	Expiration: September 3, 2002

Applicable patent licensed by Burroughs Wellcome Co. from Upjohn

Patent No. 4,338,325
Expiration July 6, 1999

Pursuant to Section 505(j)(4)(D)(ii) and Section 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, we are requesting a five-year period of marketing exclusivity from the date of approval of this NDA for FLOLAN (epoprostenol sodium) for Injection.

This request for exclusivity is based upon the fact that FLOLAN is a new chemical entity, no salt or ester of which has been previously approved for marketing in the United States.


Michael J. Dalton, Pharm.D.
Head, Department of Pharmaceutical Products
Drug Regulatory Affairs

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 7, 1995

FROM: Director, Division of Gastrointestinal and Coagulation
Drug Products, HFD-180

SUBJECT: Flolan for Injection for PPH in Children.

TO: NDA 20-444

In the approvable letter for Flolan for Injection we had limited the claim to adults since what pediatric data were available had not been separately analyzed or reviewed. On April 13, 20 and 28, 1995 the sponsor provided in a reviewable format the data available, and on May 22, 1995 they proposed the following text for the Precautions section:

Pediatric Use: No adequate and well-controlled studies have been performed in pediatric patients. However, sixty-three pediatric patients less than 16 years of age with pulmonary hypertension have received FLOLAN during acute dose ranging (59). The mean maximum dose in patients less than 16 years of age was significantly greater than the mean maximum dose in adults during acute dose ranging (25 ng/kg/min and 8.6 ng/kg/min, respectively) (60). A limited number of pediatric patients less than 16 years of age (n=5) with PPH in NYHA functional Class III or Class IV have received FLOLAN chronically in controlled clinical trials (61). In contrast to acute dose ranging, mean chronic infusion rates were only slightly higher to pediatric patients than for adults; this difference did not reach statistical significance (62). There were no important differences in the adverse event profiles between adult and pediatric patients (63).

This memorandum considers the adequacy of the available data to support inclusion of a pediatric statement in the labeling.

In the submissions they provided a table of results in 63 children (infants to 16 years of age males and females) who had acute dose ranging. 43 of these children had primary pulmonary hypertension (PPH). 20 had secondary.

A comparison of mean change from baseline for patients with pulmonary hypertension less than 16 years of age (n=60) and those 16 years of age or older (n=314) are provided as follows:

Parameter	Category ¹	At Maximum Tolerated Dose or Maximum Dose ²								95% Confidence ³ Interval for the mean change
		N	Mean	S.E.	Min.	25th I-ile	Median	75th I-ile	Max.	
Heart Rate (bpm)	< 16 Years	60	7.87	2.27	-32.00	-2.50	6.50	20.00	40.00	(3.32, 12.41) *
	≥ 16 Years	314	6.64	0.62	-19.00	2.00	0.00	10.00	30.00	(7.42, 9.85) *
	Combined	374	6.51	0.63	-19.00	2.00	0.00	10.00	40.00	(7.27, 9.76) *
Cardiac Output (L/min)	< 16 Years	54	0.77	0.14	-1.10	0.22	0.42	1.05	4.10	(0.44, 1.05) *
	≥ 16 Years	301	1.42	0.07	-2.97	0.64	1.20	2.02	9.10	(1.27, 1.57) *
	Combined	355	1.32	0.07	-2.97	0.60	1.05	1.94	9.10	(1.19, 1.46) *
Cardiac Index (L/min/m ²)	< 16 Years	53	1.02	0.29	-1.30	0.21	0.70	1.30	10.60	(0.44, 1.59) *
	≥ 16 Years	283	0.79	0.09	-1.63	0.19	0.67	1.16	4.72	(0.71, 0.87) *
	Combined	336	0.83	0.06	-1.63	0.37	0.67	1.19	10.60	(0.71, 0.94) *
PAPs (mm Hg)	< 16 Years	59	-0.07	2.13	-50.00	-20.00	-5.00	3.00	30.00	(-12.32, -3.81) *
	≥ 16 Years	311	-2.30	0.74	-49.00	-10.00	-2.00	0.00	50.00	(-3.84, -0.92) *
	Combined	370	-3.29	0.72	-50.00	-13.00	-2.50	3.00	50.00	(-4.49, -1.80) *
PAPd (mm Hg)	< 16 Years	59	-0.01	1.55	-46.00	-10.00	-6.00	0.00	20.00	(-9.92, -3.70) *
	≥ 16 Years	311	-2.00	0.60	-43.00	-6.00	-2.00	1.00	15.00	(-3.67, -2.97) *
	Combined	370	-3.51	0.62	-46.00	-8.00	-3.00	1.00	20.00	(-4.36, -2.60) *
RAPs (mm Hg)	< 16 Years	59	-7.23	1.67	-49.33	-10.33	-5.67	0.00	23.33	(-10.58, -3.89) *
	≥ 16 Years	311	-2.72	0.47	-45.00	-7.00	-2.67	3.00	10.67	(-3.64, -1.80) *
	Combined	370	-3.64	0.68	-49.33	-8.00	-3.00	2.67	23.33	(-4.39, -2.50) *
RAPd (mm Hg)	< 16 Years	54	-0.57	0.29	-6.00	-2.00	0.00	1.00	0.00	(-1.15, -0.00) *
	≥ 16 Years	237	-0.17	0.19	-13.00	-2.00	0.00	2.00	0.00	(-0.54, 0.21) *
	Combined	291	-0.24	0.16	-13.00	-2.00	0.00	2.00	0.00	(-0.57, 0.00) *
PCWPs (mm Hg)	< 16 Years	47	-0.60	0.60	-21.00	0.00	0.00	0.00	2.00	(-1.45, 0.29) *
	≥ 16 Years	181	0.09	0.28	-13.00	-1.00	0.00	2.00	20.00	(-0.47, 0.63) *
	Combined	228	-0.07	0.25	-21.00	-1.00	0.00	1.00	20.00	(-0.58, 0.43) *
PVR (Wood u)	< 16 Years	42	-6.90	1.22	-30.97	-0.35	-5.70	-3.37	7.63	(-9.46, -4.51) *
	≥ 16 Years	179	-4.12	0.30	-17.61	-6.03	-3.50	-1.71	9.40	(-4.71, -3.53) *
	Combined	221	-4.66	0.34	-30.97	-6.04	-3.70	-1.76	9.40	(-5.34, -3.99) *
TPR (Wood u)	< 16 Years	52	-9.14	1.40	-46.45	-11.70	-6.55	-3.07	6.70	(-11.95, -6.33) *
	≥ 16 Years	290	-5.15	0.27	-27.00	-7.15	-4.61	-2.10	0.40	(-5.68, -4.63) *
	Combined	350	-5.75	0.31	-46.45	-7.56	-4.70	-2.33	0.40	(-6.37, -5.13) *
SAPs (mm Hg)	< 16 Years	60	-12.45	2.26	-49.00	-26.30	-11.00	1.00	21.00	(-16.96, -7.94) *
	≥ 16 Years	313	-15.42	0.95	-46.00	-25.00	-14.00	-0.00	33.00	(-17.20, -13.56) *
	Combined	373	-16.94	0.87	-46.00	-25.00	-13.00	-3.00	33.00	(-16.66, -13.72) *
SAPd (mm Hg)	< 16 Years	60	-11.05	1.40	-36.00	-19.50	-10.50	-3.00	15.00	(-14.82, -8.00) *
	≥ 16 Years	311	-14.39	0.67	-47.00	-20.00	-13.00	-7.00	10.00	(-15.71, -13.00) *
	Combined	371	-13.90	0.61	-47.00	-20.00	-13.00	-7.00	10.00	(-15.18, -12.77) *
SAPm (mm Hg)	< 16 Years	60	-12.05	1.64	-39.00	-22.33	-11.33	-2.03	13.67	(-15.34, -8.74) *
	≥ 16 Years	311	-14.71	0.72	-49.33	-21.00	-13.00	-7.00	13.67	(-16.12, -13.29) *
	Combined	371	-14.28	0.66	-49.33	-21.67	-12.67	-6.67	13.67	(-15.58, -12.90) *
SVI (Wood u)	< 16 Years	48	-11.30	1.51	-48.65	-10.79	-9.01	-3.99	3.90	(-14.34, -8.20) *
	≥ 16 Years	234	-10.67	0.43	-35.00	-10.10	-9.01	-5.05	7.50	(-11.31, -9.64) *
	Combined	282	-10.61	0.40	-48.65	-10.10	-9.01	-5.00	7.50	(-11.67, -9.76) *
TSI (Wood u)	< 16 Years	53	-11.68	1.40	-49.10	-13.62	-9.70	-5.60	3.13	(-14.66, -8.71) *
	≥ 16 Years	297	-10.97	0.43	-40.20	-14.50	-9.09	-4.03	0.49	(-11.81, -10.13) *
	Combined	350	-11.00	0.43	-49.10	-14.50	-9.04	-4.00	0.49	(-11.92, -10.25) *
SV (mL/beat)	< 16 Years	53	5.20	1.11	-10.47	1.23	3.50	0.52	30.74	(2.98, 7.41) *
	≥ 16 Years	298	11.06	0.70	-20.49	2.73	9.15	16.00	00.37	(9.51, 12.60) *
	Combined	351	10.17	0.70	-20.49	2.52	8.23	15.92	00.37	(8.80, 11.54) *
PaCO2 (mm Hg)	< 16 Years	53	-0.74	0.55	-9.00	-2.00	-1.00	1.00	6.00	(-3.06, 0.37) *
	≥ 16 Years	162	-1.41	0.34	-12.00	-3.00	-1.00	0.00	20.30	(-2.87, -0.74) *
	Combined	195	-1.29	0.30	-12.00	-3.00	-1.00	1.00	20.37	(-1.88, -0.71) *
PaO2 (mm Hg)	< 16 Years	66	6.97	4.34	-25.00	-7.00	0.00	0.00	165.00	(-1.76, 15.71) *
	≥ 16 Years	170	1.30	1.76	-55.00	-7.00	0.00	7.60	190.00	(-2.09, 0.86) *
	Combined	216	2.57	1.67	-55.00	-7.00	0.00	0.00	190.00	(-0.71, 5.86) *
pH	< 16 Years	52	0.00	0.01	-0.10	-0.01	0.01	0.02	0.07	(-0.01, 0.01) *
	≥ 16 Years	160	0.02	0.00	-0.07	-0.00	0.01	0.03	0.11	(0.01, 0.02) *
	Combined	192	0.01	0.00	-0.10	-0.01	0.01	0.03	0.11	(0.01, 0.02) *
Arterial Saturation (%)	< 16 Years	2	-1.50	3.50	-5.00	-5.00	-1.50	2.00	2.00	(-48.97, 42.97) *
	≥ 16 Years	67	0.45	0.51	-0.50	-1.00	0.00	2.00	17.00	(-0.57, 1.47) *
	Combined	69	0.40	0.50	-0.50	-1.00	0.00	2.00	17.00	(-0.61, 1.40) *

¹Each row of the table represents unique patients. Since patients could enter the acute dose-ranging studies (05/10, 20, and 21) multiple times, only the first dose-ranging segment per patient is summarized. Similarly, since a few patients from the chronic infusion studies (35/36, 37 and 46) may have been in previous studies, only the first dose-ranging segment per patient across all studies is summarized.

²This table summarizes the acute hemodynamics and blood gases at the maximum tolerated dose for Protocol 35/36 and 46 and the acute hemodynamics and blood gases at the maximum dose for Protocols 05/10, 20 and 21.

³A confidence interval (paired t-test) that does not contain 0 implies statistical significance.

We do not have the breakdown for only the primary pulmonary hypertension patients. However, the acute Flolan results, comparing adults and children, are similar for some parameters, but different in others. There appears to be more reduction from baseline for pulmonary artery pressure, right atrial pressure, total peripheral resistance. These differences could well be due to differences in demographic factors, maximum dose achieved or other factors between the groups. Indeed the sponsor found that significantly more children achieved a maximum dose than the adults, but again stage of disease and other factors may be related to these differences. In any case the sponsor has stated, in reply to our inquiry, that acute response does not predict chronic response or benefit.

In the chronic controlled studies 35/36 and 46, 9 children were enrolled. 5 were randomized to Flolan, 4 to standard therapy.

It appears that the 5 patients randomized to Flolan were in study 46, while 2 standard therapy patients were enrolled in study 35/36 and 2 in study 46. The demographics of these patients is as follows:

Parameter	Statistic or Level	Treatment		Total
		Flolan	Standard	
Age (years)	N	5	4	9
	Mean	11	12	11
	Std.Dev.	3	3	3
	Median	11	11	11
	Minimum	6	9	6
	Maximum	15	15	15
Age Category (years)	N	5	4	9
	<10	1 (20.0%)	1 (25.0%)	2 (22.2%)
	10-12	3 (60.0%)	2 (50.0%)	5 (55.6%)
	15+	1 (20.0%)	1 (25.0%)	2 (22.2%)
Sex	N	5	4	9
	Female	4 (80.0%)	3 (75.0%)	7 (77.8%)
	Male	1 (20.0%)	1 (25.0%)	2 (22.2%)
Race	N	5	4	9
	White	5 (100.0%)	4 (100.0%)	9 (100.0%)
Weight at Screen (kg)	N	5	4	9
	Mean	41.3	44.0	42.5
	Std.Dev.	23.2	5.4	16.0
	Median	30.0	40.0	40.0
	Minimum	19.0	37.2	19.0
	Maximum	80.0	50.0	80.0
Weight Category (kg)	N	5	4	9
	<20	1 (20.0%)	0 (0.0%)	1 (11.1%)
	20-29	1 (20.0%)	0 (0.0%)	1 (11.1%)
	30-39	1 (20.0%)	1 (25.0%)	2 (22.2%)
	40-49	1 (20.0%)	2 (50.0%)	3 (33.3%)
	50+	1 (20.0%)	1 (25.0%)	2 (22.2%)
NYHA Class at Screen	N	5	4	9
	III	4 (80.0%)	4 (100.0%)	8 (88.9%)
	IV	1 (20.0%)	0 (0.0%)	1 (11.1%)
Vasodilator Use	N	5	4	9
	No	1 (20.0%)	1 (25.0%)	2 (22.2%)
	Yes	4 (80.0%)	3 (75.0%)	7 (77.8%)

With the small cohorts involved, no statistical tests were applied to the results which although variable show no numerical differences between treatments.

For study 46 exercise capacity at 12 weeks there was a deterioration of 83.2 meters in the Flolan group (n=5) compared to the standard therapy group (n=2) of 23.8 meters where 404 and 505 meters were the baselines for each group respectively. In study 35/36 only standard treatment patients (n=2) were available for analysis and in these from a baseline of 326 meters there was a decrease of 123 meters at eight week numerically. Combining studies 35/36 and study 46 with baselines of 404 and 442 for Flolan and standard therapy a change (deterioration) of 83 and 36 meters were noted respectively at last visit. Numerically the results favor standard therapy. These analyses assigned the lowest rank to patients who died, but analysis using LOCF or excluding patients who died gives similar results.

For death, one standard treatment patients died during the controlled trial. No Flolan patient died. Over a 15 month follow-up period one Flolan patient died. Much cannot be made of this.

The statement proposed by the sponsor is noted on the first page of this review. While I wish we had sufficient data to know whether Flolan were safe and effective in children, I do not believe we can make a recommendation in the labeling at this time. The statement as presented could be construed as a recommendation in children even with the disclaimer. While we should ask for the sponsor's commitment to do controlled studies in this population, I do not think we have sufficient data to include a pediatric recommendation in the labeling at this time.


Stephen Fredd, M.D.

CC:
NDA 20-444
HFD-180
HFD-180/ETriantas
HFD-181/CSC/KOliver
HFD-180/SFredd:6/7/95
f/t deg: 6/7/95/6/8/95
MEMO\FLOLAN.OSF

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 18, 1995
FROM: Director, Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
SUBJECT: Data Quality Questions
TO: NDA 20-444

Dr. Temple in his review of this NDA mentioned some data quality points raised by the medical officer. Specifically several patients were noted to have walking distances reported after withdrawal or transplantation. I believe the explanation for most of this (as discussed at the advisory committee) was that the last observation was carried forward for patients who died or were transplanted, while those too ill to walk were assigned 0 meters.



Stephen Fredd, M.D.

CC:
NDA 20-444
HFD-180
HFD-180/SFredd:5/18/95
f/t deg: 5/18/95
MEMO\NDA20444.6SF

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 11, 1995
FROM: Director, Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
SUBJECT: Biopharm. Review February 9, 1995
TO: NDA 20-444

In Dr. Choi's biopharm. review of 2/9/95, she requests that the firm continue to try to develop an appropriate assay for epoprostenol. We contacted the firm to see if they would commit to this in Phase IV. They did not feel this would be productive. I do not believe we can delay approval for this reason, and an approvable action has been issued.



Stephen Fredd, M.D.

CC:
NDA 20-444
HFD-180
HFD-427/Dr. Choi
HFD-427/Dr. Chen
HFD-181/CSO/KOliver
HFD-180/SFredd:5/11/95
f/t deg: 5/11/95
MEMO\NDA20444.4SF

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 25, 1995

FROM: Director, Division of Gastrointestinal and Coagulation
Drug Products, HFD-180

SUBJECT: Approvable Recommendation for Flolan for Patients with
Primary Pulmonary Hypertension, NDA 20-444.

TO: Director, Office of Drug Evaluation I, HFD-100

*Noted: Agree with approval
recommendation*

Burroughs Wellcome requests approval of Flolan (epoprostenol sodium) for injection to treat adults and children with primary pulmonary hypertension, NYHA Class III and Class IV, to improve survival, exercise capacity and quality of life. The primary effectiveness data comes from 2 studies (35/36 and 46) which were randomized, open comparisons of Flolan versus standard therapy on exercise capacity (the primary endpoint), quality of life, hemodynamics and survival (a secondary endpoint in study 46). Information as presented by the sponsor to the Cardiorenal Drugs Advisory Committee on February 23, 1995 is summarized below. *2/5/8/95*

For study 46 the entrance criteria were:

- Age: 6-70 years
- Diagnosis of PPH without history of SPH or Congenital Heart Disease
 - PAPm $\geq$ 25 mmHg
 - PCWp (or LVEDP) $\leq$ 15 mm Hg
 - PVR $>$ 3 mm Hg/L/min
- NYHA Class III/IV despite use of vasodilators
- No new PPH therapy added within last month
- No PPH therapy discontinued within last week (other than anticoagulants)
- No contraindication to anticoagulants
- If female, not pregnant and practicing birth control
- Judged capable of operating infusion system
- Not have any other condition that limits exercise
- Not receiving other investigational agents

The patients were randomized by an urn type of adaptive method which we have found acceptable with the study proceeding as follows:

		Day 2	Weeks				
			1	3	6	9	12
Epoprostenol	Central Line Initiate epoprostenol	• Exercise	X		X		X
		• O ₂ L			X		X
Standard		• Signs	X		X		X
		• Symptoms	X	X	X	X	X
		• Dyspnea Fatigue Rating	X	X	X	X	X
		• Hemodynamic Profile					X

41 patients were randomized to Flolan, 40 to standard therapy. 41 Flolan patients completed 12 week assessments compared to 32 standard therapy patients (8 had died).

Demographic means re age, sex, race etc. were well balanced. The baseline six minute walk in meters was:

	<u>Flolan</u>	<u>Standard</u>
Mean ± SD	316 ± 116	272 ± 142
Median	315	270

While not significantly different, there is a suggestion that Flolan patients were advantaged re the six minute walk parameter in terms of mortality prognosis. However, the correlation of mortality and the results of a six minute walk was not known prior to this study (although it is a reasonable presumption), and patients were not stratified prospectively on this parameter. As the medical officer notes more of the standard therapy patients did very poorly on this test (< 120 meters walked in six minutes) than Flolan patients. The 120 meter cut off here is arbitrary and based on seeing these results.

Our statistician provides the following analysis of those with poor six minute walk results:

Baseline Imbalance(Walking Distance)

Baseline walk distance	Treatment	
	Flolan	Standard
< 120	2/41 (4.9%)	9/40 (22.5%)
> 120	39/41 (95.1)	31/40 (77.5)

Two-sided p-value Fisher's exact test= .0255

Of the 11 patients with baseline six minute walks of < 120 meters, 5 died, and all of those who died were assigned to standard therapy. Whether this imbalance should or can be considered in an adjusted re-analysis of the endpoints is controversial. It is argued that this imbalance vitiates the mortality result which was 0 in the Flolan group, 8 in the standard group ($p \approx 0.0027$).

Additionally the medical officer reasons patients were entered in the study who should not have been such as a patient with a history of bleeding, assigned to standard therapy and died of bleeding. We have obtained a more complete report on that patient, and it is clear that the history of bleeding was not a contraindication for anticoagulants or entrance into the study, and the death was due to primary pulmonary hypertension. I think since the randomization plan and execution were acceptable, the uncorrected result should also be accepted.

As to the primary endpoint, change in walking distance, the results (with or without statistical adjustment) are less controversial.

	Epoprostenol			Standard			p-value
	n	Baseline (meters)	Week 12 (meters)	n	Baseline (meters)	Week 12 (meters)	
LOCF (mean ± se)	41	316 ± 18.1	348 ± 17.4	40	272 ± 22.5	257 ± 24.0	0.003
Non-parametric: Method 1 (median)	41	315	362	40	270	204	0.002
Non-Parametric: Method 2 (median)	41	315	362	40	270	204	<0.0001

There is some gain in the Flolan treated group while those on standard therapy deteriorate.

Two quality of life instruments were used in this study: the Nottingham Park questionnaire and the Congestive heart failure questionnaire. The results were as follows:

Dimensions	Change from Baseline				Between Treatment Comparison
	n	Epoprostenol Median	n	Standard Median	
NHP^a (median)					
Emotional Reaction	37	-10.5	31	0.0	*
Energy	39	-38.8	31	0.0	
Pain	39	0.0	31	0.0	
Physical Mobility	39	-11.2	30	-6.4	
Sleep	41	-15.1	31	0.0	*
Social Isolation	40	0.0	31	0.0	
CHQ^b (median)					
Dyspnea	35	8.0	26	0.0	*
Fatigue	39	5.0	31	0.0	*
Emotional Function	38	6.0	30	-1.0	*
Mastery	39	3.0	30	-0.5	*
Dyspnea- Fatigue	41	1.0	31	0.0	*

^a Negative change = improvement from baseline
^b Positive change = improvement
* indicates significant difference

Improvements in dyspnea and fatigue seem reasonable as to what the drug can do with improvements in other parameters (emotional function, sleep, mastery-whatever that is) perhaps secondary to cardiovascular improvement.

Study 35/36 was a randomized, open study of 26 patients meeting the following entrance criteria:

- Age: 6 months - 70 Years
- Diagnosis of PPH
 - PAPm $\geq$ 25 mmHg
 - TPR $\geq$ 5 mmHg/L/min
or
PVR > 3 mmHg/L/min
 - $\geq$ 10 mmHg gradient between PAPm and PCWpm
- If female, not pregnant and practicing birth control
- No change in PPH therapy within 14 days prior to study
- No clinically significant arrhythmias or laboratory assessments inconsistent with PPH
- Not receiving other investigational agents

Randomization of the patients was 1:1 and not by an adaptive method.

The schedule for the conduct of the study was as follows:

		Weeks			
		Day 2	1	4	8
Epoprostenol	• Central Catheter (Epoprostenol only)	X			
	• Initiate Epoprostenol	X			
	• Exercise	X		X	X
	• QoL		X	X	X
Standard	• Hemodyn/Blood Gas Profile				X

The primary endpoint was change in exercise capacity from baseline for the six minute walk.

11 patients were randomized to Flolan, 14 to Standard, there is some dispute about 1 patient where, though the envelope was opened and there is some indication on a form that randomization

occurred, the investigator claims the patient was never randomized to Flolan (as per the envelope) and no drug was given. The 25 randomized patients were well-balanced as to age, sex, weight. Most were NYHA Class III.

The baseline 6 minute walk did not favor Flolan.

	<u>Flolan</u>	<u>Standard</u>
Mean $\pm$ SE	225 $\pm$ 46	213 $\pm$ 40
Median	213	254

Of the 25 randomized, 1 patient died on Flolan, 3 on standard therapy.

For analysis of the change in six minutes walking distance the following plan was implemented:

- Parametric Analysis of Variance (protocol specified)
 - Last observation carried forward (LOCF); patients too ill to walk assigned 0 meters
- Non-parametric Analysis of Covariance
 - Patients unable to walk at baseline or Week 8 or who died: assigned 0 meters
 - OLS^a Regression of Week 8 ranks on covariates (baseline walk, baseline vasodilator use)
 - CMH^b Analysis of residuals

The results as per this plan are:

	<u>Epoprostenol</u>			<u>Standard</u>			p-value
	n	Baseline (meters)	Week 8 (meters)	n	Baseline (meters)	Week 8 (meters)	
Parametric (LOCF) (mean $\pm$ se)	11	225 $\pm$ 45.7	364 $\pm$ 23.0	14	213 $\pm$ 39.7	242 $\pm$ 42.9	0.043
Non-Parametric (median)	11	213	386	14	254	248	0.045

It should be noted that in this open study coaching was permitted, and that might have introduced some bias in the result. However, I think as for replication of the walking distance finding (uncoached) in study 46, it is acceptable.

The secondary endpoint was a quality of life evaluation done with the Nottingham Park instrument only. The only finding here is on physical mobility, and this does not replicate the findings in study 46.

Hemodynamic evaluations, while not an efficacy endpoint, were done in both studies and in a recent (April 20, 1995) revision of that data previously provided significant differences in cardiac output, cardiac index, pulmonary artery pressure, and pulmonary vascular resistance were found. I have attached a copy of this new data-analysis to this memorandum.

While there are longer term Flolan administration cohorts (extending studies 46 and 35/36), these do not have concomitant control, and I am not certain what to make out of comparisons of outcome (death) to historical databases. I think from an efficacy point of view we need to make our decision based on studies 46 and 35/36, and I think efficacy on reduction of the risk of death, walking distance and hemodynamics has been demonstrated.

For safety, this is not an innocuous or easy to administer drug. A central venous line must be placed and constant intravenous dosing with the adjustments over time is needed. In acute dose ranging of 541 patients, 4 patients (0.76%) had pulmonary edema which rapidly reversed after discontinuation of the infusion. Nausea, vomiting, anxiety, flushing, hypertension, headache were frequently (greater than 10% of cases) reported.

In chronic use, n = 216, with over half being exposed for 6 months, headache, jaw pain, flushing, diarrhea, chills/fever/sepsis. Flu syndrome, anxiety, inflammation and pain at the injection site were seen numerically more frequently on Flolan than standard therapy. There were malfunctions of the catheter as well as the pump by both human and mechanical error. The incidence of sepsis is displayed in the following chart:

Study	Epoprostenol Pts with Sepsis/ Total	Number of Episodes	Patient- Months of Exposure	Infections/ Patient/Year
35/36	0/11	0	22	0.00
37	5/18	12	574	0.25
46	5/41	5	123	0.49
47	9/64	18	953	0.25
49	9/120	10	548	0.22
50	0/10	0	5	0.00
Total		45	2125	0.25

While this is not benign therapy, I think the consequences of the disease are worse, and since I believe the drug improves hemodynamics, exercise capacity and the chance for survival in severely affected individuals, I think the drug should be proved. The medical officer has a strong belief that the drug should not be approved, and this perspective must be considered.

Our proposed draft labeling does not include pediatric patients at this time since the company has yet to provide an analysis of what cases they have. There is also a warning not to use the drug for patients with left heart failure, since in a study of such cases mortality was worse on Flolan.

Please consider the information available, and decide how you wish to go on this somewhat difficult call. We have provided an approvable letter for your consideration, and will be glad to meet with you to discuss.



Stephen Fredd, M.D.

CC:-
NDA 20-444
HFD-180
HFD-180/ETriantas
HFD-713/MA1-Osh
HFD-713-MHuque
HFD-181/CSO/KOliver
HFD-180/SFredd:4/26/95
f/t deg: 4/26/95/4/27/95
MED\MEMO\NDA20444.OSF

Burroughs Wellcome Co.
 P18:46
 Flolan®(epoprostanol sodium)

Table 43
 Summary of Baseline, Day 88, and Changes from Baseline of Hemodynamic and Blood Gased Measurements
 Between Treatment Comparisons

Corrected³ NDA Table

Parameter	Treatment	N ¹	Baseline		Day 88 mean	Mean change	S.E. mean change	% change in means	Difference in mean change (Flo.- Stand.)	95% Confidence interval ² for the diff. in mean change (Flo.- Stand.)
			mean	Day 88 mean						
Heart Rate (b/m)	Flolan	38	79.97	79.11	-0.87	2.48	-1.1	0.96	(-5.22, 7.15)	
	Standard	38	82.88	80.97	-1.83	1.58	-2.2			
Cardiac Output (L/min)	Flolan	38	3.52	4.05	0.54	0.17	15.3	0.96	(0.34, 1.58) *	
	Standard	38	3.90	3.47	-0.43	0.28	-10.9			
Cardiac Index (L/min/m ²)	Flolan	38	2.04	2.37	0.33	0.10	16.1	0.56	(0.20, 0.92) *	
	Standard	38	2.20	1.97	-0.23	0.16	-10.5			
PAPs (mm Hg)	Flolan	38	97.58	90.37	-7.21	2.70	-7.4	-10.38	(-17.69, -3.07) *	
	Standard	38	92.47	95.63	3.17	2.29	3.4			
PAPd (mm Hg)	Flolan	38	41.16	37.58	-3.66	1.38	-8.9	-4.82	(-8.89, -0.76) *	
	Standard	38	40.17	41.33	1.17	1.49	2.9			
PAPm (mm Hg)	Flolan	38	59.95	55.13	-4.82	1.32	-8.0	-6.68	(-10.73, -2.63) *	
	Standard	38	57.68	59.47	1.87	1.55	3.2			
RAPm (mm Hg)	Flolan	36	13.11	10.94	-2.17	1.09	-16.5	-2.25	(-5.18, 0.68)	
	Standard	29	11.68	11.69	0.09	6.92	0.7			
PCWPm (mm Hg)	Flolan	27	9.67	10.07	0.41	1.18	4.2	1.41	(-2.52, 5.33)	
	Standard	17	10.82	9.82	-1.00	1.59	-9.2			
PVR (Wood u)	Flolan	27	15.62	12.20	-3.42	0.72	-21.9	-4.95	(-7.62, -2.27) *	
	Standard	17	15.53	17.05	1.52	1.23	9.8			
TPR (Wood u)	Flolan	38	19.88	15.66	-4.14	0.96	-20.9	-6.18	(-8.97, -3.40) *	
	Standard									

¹The number of patients with results from both the baseline and the Day 88 evaluations.

²A confidence interval that does not contain 0 implies statistical significance.

³A programming error was found in the computation of the confidence intervals was found and corrected.

Burroughs Wellcome Co.
 P18:46
 Flolan®(epoprostenol sodium)

Table 43
 Summary of Baseline, Day 88, and Changes from Baseline of Hemodynamic and Blood Gased Measurements
 Between Treatment Comparisons

Corrected³ NDA Table

Parameter	Treatment	N ¹	Baseline		Day 88 mean	Mean change	S.E. mean change	X change in means	Difference in mean change (Flo.- Stand.)	95% Confidence interval ² for the diff. in mean change (Flo.- Stand.)
			mean	Day 88 mean						
TPR (Wood u)	Standard	38	18.16	20.20	2.04	0.99	11.2			
SAPs (mm Hg)	Flolan	38	120.32	115.76	-4.55	3.15	-3.8	-1.29	(-9.58, 7.01)	
	Standard	38	122.83	119.57	-3.27	2.42	-2.7			
SAPd (mm Hg)	Flolan	38	74.68	69.76	-4.92	1.81	-6.6	-5.86	(-10.85, -0.88) *	
	Standard	28	74.07	74.21	0.14	1.54	0.2			
SAPw (mm Hg)	Flolan	38	89.92	85.88	-4.04	2.07	-5.4	-3.95	(-9.56, 1.66)	
	Standard	28	98.57	89.68	-8.89	1.68	-1.0			
SVR (Wood u)	Flolan	36	24.86	28.82	4.04	0.98	16.3	-6.17	(-9.53, -2.81) *	
	Standard	27	23.25	25.38	2.13	1.44	9.2			
TSR (Wood u)	Flolan	38	29.37	23.79	-5.58	1.14	-19.8	-8.01	(-11.92, -4.10) *	
	Standard	28	27.86	29.50	2.43	1.68	9.0			
SV (ml/beat)	Flolan	38	45.68	52.33	6.65	2.25	14.6	10.13	(2.45, 17.81) *	
	Standard	38	47.88	44.41	-3.48	3.26	-7.3			
Arterial Saturation (%)	Flolan	29	98.29	92.29	-6.00	1.58	-2.2	2.63	(-1.79, 7.05)	
	Standard	22	91.39	90.75	-0.63	1.43	-0.7			
Mixed Venous Saturation (%)	Flolan	35	61.85	63.81	1.96	1.78	1.9	3.78	(-1.64, 9.19)	
	Standard	27	61.16	58.54	-2.62	2.05	-4.3			
PaCO2 (mm Hg)	Flolan	29	33.88	33.20	-0.68	0.81	0.4	1.83	(-1.33, 3.38)	
	Standard	23	31.81	30.90	-0.91	0.84	-2.9			

¹The number of patients with results from both the baseline and the Day 88 evaluations.

²A confidence interval that does not contain 0 implies statistical significance.

³A programming error was found in the computation of the confidence intervals was found and corrected.

Burroughs Wellcome Co.
 P18:46
 Flolan®(epoprostenol sodium)

Table 43
 Summary of Baseline, Day 88, and Changes from Baseline of Hemodynamic and Blood Gased Measurements
 Between Treatment Comparisons

Corrected³ NDA Table

Parameter	Treatment	N ¹	Baseline	Day 88	Mean	S.E.	%	Difference	95% Confidence
			mean	mean	change	mean	change	in	in mean change
							means	(Flo.- Stand.)	(Flo.- Stand.)
PaO2 (mm Hg)	Flolan	29	68.49	72.13	3.64	3.76	5.3	5.66	(-7.21, 18.52)
	Standard	23	70.15	68.13	-2.02	5.41	-2.9		
pHa	Flolan	29	7.44	7.44	-0.00	0.01	-0.0	-0.01	(-0.04, 0.01)
	Standard	23	7.44	7.46	0.01	0.01	0.1		
Transcut. Blood O2 Sat. (%)	Flolan	57	92.49	93.22	0.73	0.53	0.8	1.76	(0.00, 3.52) *
	Standard	29	92.72	91.69	-1.03	0.74	-1.1		

¹The number of patients with results from both the baseline and the Day 88 evaluations.

²A confidence interval that does not contain 0 implies statistical significance.

³A programming error was found in the computation of the confidence intervals was found and corrected.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-444

Trade (generic) names Flolan (epoprostenol sodium) Injection

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim, *but have not as yet been separately analyzed and provided.*
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

[Lined area for explanation]

Laura M. ...
Signature of Preparer

April 27 1995
Date

cc: Orig NDA
HFD-180Div File
NDA Action Package

Pharm

DEC 21 1994

NDA 20,444

Review #1

Sponsor & Address: Burroughs Wellcome Co.
Research Triangle Park, NC

Reviewer: Ke Zhang, Ph.D.
Pharmacologist

Date of Submission: February 28, 1994

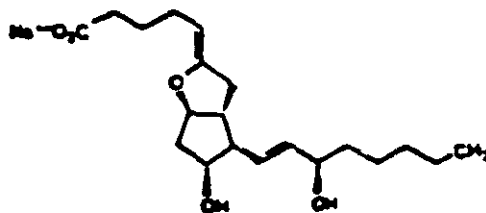
Date of HFD-180 Receipt: March 1, 1994

Date of Review: December 21, 1994

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

DRUG: FLOLAN/Epoprostenol sodium/Prostacyclin sodium/ PGI_2 /PGX/4AU76 sodium
/U-53,217A
0.5 mg or 1.5 mg FLOLAN sterile freeze-dried powder for intravenous injection in
sterile diluent (glycine buffer)

(5Z,9 α ,11 α ,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid
monosodium salt



Molecular formula: $\text{C}_{20}\text{H}_{31}\text{NaO}_5$,

MW: 374.45

CATEGORY: Vasodilator/inhibitor of platelet aggregation

Related IND/NDA: IND
NDA

Marketing Indications and Dose: FLOLAN is indicated in adults and children for long-term continuous treatment of primary pulmonary hypertension. The intravenous infusions of FLOLAN should be first initiated at 2 ng/kg/min and increased by increments of 2 ng/kg/min every 15 minutes until dose-limiting pharmacological effects are elicited (acute dose ranging). The maximum tolerated dose (MTD) which does not elicit dose-limiting pharmacological effects is then determined. The chronic continuous intravenous infusions of FLOLAN should be started at 4 ng/kg/min less than the MTD or at one-half the MTD if the MTD is less than 5 ng/kg/min.

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of Study	Study #	Lot #	Testing Lab
Pharmacology			
<u>Absorption, Distribution, Metabolism and Excretion (ADME)</u>			
Absorption: rats, cats, rabbits and dogs	published reports & 7200-80-7222-041		BW
Distribution: rats and rabbits	published reports & BDPG-78-1 7200-80-7222-006 7200-80-7256-005 7200-78-7222-048 7200-79-7222-024		
Metabolism: <i>In vivo</i> : rats, dogs and monkeys	published reports & 7200-81-7222-005		
<i>In vitro</i> : lung, liver and kidney	published reports		
Excretion: rats, dogs and monkeys	published reports & BDPG-80-2		BW

BW = Burroughs Wellcome

NDA 20444

5 OF 8

Type of Study	Study #	Lot #	Testing Lab
<u>Acute Toxicity</u>			
<u>i.v. :</u>			
Mice	BPAT 78/32 BPAT 78/34 BPAT 81/54 BPAT 81/13	13501-FHL-9 13501-FHL-9 14285-FHL-18A 14285-FHL-12	BW BW BW BW
Rats	BPAT 80/22	FHL-11	BW
<u>Subacute Toxicity</u>			
Rats:			
1. 2-week s.c.	BPAT 78/10	13501-FHL-9	BW
2. 14-day i.v. infusion	BPAT 80/14C	14285-FHL-11	UJ
Dogs:			
3. 30-day i.v. infusion	7205/82/7263/005	14813-BDT-118A	UJ
4. 30-day i.v. infusion: a study of reversibility of hematological changes	7205/82/7263/006	14813-BDT-118A	UJ
Monkeys:			
5. 2-week i.v. infusion	BPAT 78/16	13501-FHL-9	BW
<u>Special Study</u>			
1. A 2-week toxicity study of 6-keto-PGF _{1α} by i.v. infusion in monkeys	BPAT 79/4	13501-FHL-9	BW
2. Study on the proliferative responses of abraded mouse skin	BPAT 78/4	13197-FKL-56	BW

BW = Burroughs Wellcome

UJ = Upjohn

Type of Study	Study #	Lot #	Testing Lab
<u>Mutagenicity Study</u>			
1. Ames assay	7200/81/7263/001	AZ 14285 FHL-21B	UJ
2. Rat micronucleus test	0013/81/763/002	A4-15569-BDT-7A	UJ
3. DNA damage/alkaline elution assay in CHLV-79 cells	7263/80/7263/023	A3,14285FHL-21B	UJ
<u>Reproductive Toxicity Study</u>			
1. Subcutaneous Segment I. fertility and general reproductive study in rats	7205/81/7263/006	A2,14466-FHL-114	UJ
2. Subcutaneous Segment II. teratology study in rats	BPAT 78/27	13501-FHL-9	BW
3. Subcutaneous Segment II. teratology study in rabbits	BPAT 78/31	13501-FHL-9	BW
4. Supplementary subcutaneous Segment II. teratology study in rabbits	BPAT 79/21	13501-FHL-9	BW
5. Subcutaneous segment III. perinatal/postnatal study in rats	7205/81/7263/004	A2,14466-FHL-114	UJ

BW = Burroughs Wellcome

UJ = Upjohn

The following studies were previously submitted to NDA 19,607 resubmission dated March 23, 1988: (1). pharmacology, (2) ADME, (3). acute toxicity studies in mice and rats, (4). 14-day toxicity studies in rats and monkeys, (5). 30-day toxicity studies in dogs, (6). a special toxicity study in mouse skin abrasion test, (7). a two week intravenous infusion toxicity study of 6-oxo-PGF_{1α} in monkeys; (8). reproductive toxicity studies: a Segment I fertility and general reproductive study in rats, a Segment II teratological study in rats, two Segment II teratological studies in rabbits and a Segment III perinatal and postnatal study in rats. These studies were previously reviewed on August 15, 1988. In IND amendment dated June 11, 1992, the following genetic toxicity studies were included: Ames test, rat micronucleus test and DNA damage/alkaline elution assay in CHLV-79 cells. These studies were previously

reviewed on November 20, 1992. Appropriate portions of the above reviews are either integrated or reproduced in entirety in the present review. In addition, new studies submitted in the present NDA have also been reviewed.

PHARMACOLOGY:

Epoprostenol is a synthetic prostacyclin (PGI_2). FLOLAN is the sodium salt of epoprostenol. Naturally occurring prostacyclin, a metabolite of arachidonic acid, is produced in vascular endothelium with potent vasodilatory and platelet aggregation inhibitory activities. The pharmacological activities of FLOLAN have been extensively characterized in both *in vitro* and *in vivo* preparations and some of these studies were previously reviewed under NDA. Appropriate portions of that review are integrated in the following. The citations and references to page and volume numbers from the previous review are shown in bold face since they are not included in the present NDA.

Primary activity

1. Vasodilation: Prostacyclin is synthesized and released from vascular endothelium. FLOLAN has been demonstrated to be a potent vasodilator in both *in vitro* and *in vivo* preparations. It can produce both pulmonary and systemic vasodilations.

A. Pulmonary Vasodilation:

FLOLAN is proposed to be used in patients with primary pulmonary hypertension. Thus, it is important to characterize the pharmacological profiles directly related to pulmonary vasodilation. PGI_2 is produced in the lungs of the guinea pig (Dawson, et.al., 1976, summary), rat (Al-Ubaidi & Bakhle, 1-80, summary), cat (Gryglawski, et al., 1978b), rabbit (Moncada, et.al., 1978), dog (Hyman, et al., 1978a), and man (Al-Ubaidi & Bakhle, 1980). FLOLAN passes through pulmonary circulation unchanged (Dusting, et.al., 1978c) in contrast to PGF_1 and PGE_2 . It is the only metabolite of arachidonic acid that dilates the mature pulmonary vascular bed (Hyman & Kadowitz, 1979, Kadowitz, et.al., 1978).

FLOLAN has been demonstrated to dilate the pulmonary vessels in both *in vitro* and *in vivo* preparations. In isolated lung preparations from newborn lambs, continuous infusion of epoprostenol sodium ($0.4 \mu\text{g}/\text{kg}/\text{min}$) into the pulmonary artery significantly decreased the pressor response (the pulmonary arterial pressure) induced by thromboxane A_2 analogue by ~50% (Yoshimura et al., 1989a). In this study, epoprostenol sodium also aggravated the edema induced by thromboxane A_2 analogue and in a separate study (Yoshimura et al, 1989b), it was demonstrated that epoprostenol sodium increased the pulmonary vascular permeability to protein. At 0.1-28 ng/kg and 10-1,000 ng/ml, it dilates the pulmonary vascular bed of the fetal lambs where its potency is greater than PGE_1 , but less than PGE_2 . At 150 ng/min, FLOLAN also

decreased arterial pressure in the perfused lobar vascular bed of cat lung and reversed the hypertension and platelet aggregation induced by locally applied ADP or the endoperoxide analogue, U-46,619 (Hyman, et.al., 1978a). In anesthetized dogs, continuous infusion of epoprostenol reduced pulmonary vascular resistance in a dose dependent manner (Steffen and dela Mata, 1990). At 0.3 $\mu\text{g}/\text{kg}/\text{min}$, epoprostenol reduced the resistance $\sim 44\%$ and pulmonary arterial pressure $\sim 30\%$. In the dog, iv infusion of arachidonic acid at 50-800 $\mu\text{g}/\text{kg}/\text{min}$ decreased pulmonary arterial pressure, an effect mimicked by iv infusion of FLOLAN at 0.2-0.8 $\mu\text{g}/\text{kg}/\text{min}$ (Mullane, et.al., 1979). The pulmonary hypotensive effects of FLOLAN were also found in conscious animals. In conscious calves, epoprostenol, infused intravenously at 100 $\text{ng}/\text{kg}/\text{min}$, reduced pulmonary (from 120 to 96 mmHg) and systemic (88 to 74 mmHg) arterial blood pressures (Orton et al., 1988). It also increased the pulmonary blood flow from 4 to 5 l/min.

FLOLAN has also been demonstrated to effectively reduce the pulmonary hypertension induced by experimental interventions. For example, intravenous infusion of epoprostenol at 10 $\text{ng}/\text{kg}/\text{min}$ reduced the hypoxia-induced increase in pulmonary vascular resistance by $\sim 50\%$ in anesthetized dogs (Gerber et al., 1980) and at 5 $\mu\text{g}/\text{kg}/\text{min}$ totally abolished the hypoxia-induced increase in mean pulmonary arterial pressure in anesthetized dogs with pretreatment of indomethacin (Rubin & Lazar, 1981). In contrast, intravenous infusion of PGE_2 at doses up to 100 $\text{ng}/\text{kg}/\text{min}$ had no effects on the hypoxia-induced increase in pulmonary vascular resistance in anesthetized dogs (Gerber et al., 1980). Intravenous infusion of epoprostenol at 50 $\text{ng}/\text{kg}/\text{min}$ effectively prevented the pulmonary hypertension induced by the monocrotaline infusion (Czer et al., 1986). In this study, intravenous injection of monocrotaline at 30 mg/kg increased the mean pulmonary arterial blood pressure $\sim 146 \pm 22\%$ of the baseline and the pulmonary vascular resistance $297 \pm 100\%$ in the absence of epoprostenol. These monocrotaline-induced pressor responses were totally prevented by pretreatment with epoprostenol (50 $\text{ng}/\text{kg}/\text{min}$). In anesthetized cats, continuously intravenous infusion of epoprostenol at 300 $\text{ng}/\text{kg}/\text{min}$ for 20 min reduced the hypoxia-induced increase in pulmonary arterial blood pressure by $\sim 70\%$ and abolished the hypoxia-induced increase in pulmonary vascular resistance (Tadepalli, 1992). In anesthetized pig with glass bead embolization-induced pulmonary hypertension, continuously intravenous infusion of epoprostenol at 242 ± 69 $\text{ng}/\text{kg}/\text{min}$ reduced the pulmonary arterial blood pressure by $\sim 21\%$ and the pulmonary vascular resistance by $\sim 40\%$ (Prielipp et al., 1991). In anesthetized sheep with thromboxane A_2 -induced pulmonary hypertension, continuously intravenous infusion of epoprostenol at 0.8 ± 0.3 $\mu\text{g}/\text{kg}/\text{min}$ reduced pulmonary arterial blood pressure by $\sim 16\%$, pulmonary vascular resistance by $\sim 45\%$ and systemic vascular resistance by $\sim 57\%$ (Prielipp et al., 1988). It also increased cardiac output by $\sim 85\%$. In conscious sheep, continuously intravenous infusion of epoprostenol at 500 $\text{ng}/\text{kg}/\text{min}$ totally prevented the thrombin-induced increases in the pulmonary arterial blood pressure, pulmonary capillary pressure and pulmonary vascular resistance.

In general, FLOLAN is a potent pulmonary vasodilator and therefore is expected to be therapeutically useful in the patients with primary pulmonary hypertension.

B. Systemic vasodilation:**In Vitro Studies:**

Pharmacological profile of FLOLAN as a vasodilator were characterized in isolated vascular smooth muscles. FLOLAN has been demonstrated to relax isolated vascular strips. In isolated rabbit mesenteric arteries, epoprostenol sodium (5×10^{-7} M) reduced the contractile responses induced by either nerve stimulation or exogenous administration of noradrenaline or angiotensin II ~40% compared to the control (sponsor's report MANB/78/0205). An enzyme in microsomal fractions of blood vessels, e.g. aorta, can convert prostaglandin endoperoxides, such as PGG₂ or PGH₂, into prostacyclin. Therefore, prostacyclin can be produced by incubating PGG₂ or PGH₂ in vascular microsomes containing the microsomal enzyme. Prostacyclin (produced by incubating PGG₂ or PGH₂ in the pig aortic microsomes) was demonstrated to relax the rabbit mesenteric and coeliac arterial strips (Bunting, et al., 1976) and the bovine coronary arterial strips (prostacyclin = 1 µg/4 ml, sponsor's report MANB/78/0054). The relaxations were profound but transient. In these studies, it was also found that PGG₂, PGH₂ and sodium arachidonate relaxed the coronary arterial strips with less potency than prostacyclin. The relaxation induced by PGG₂, PGH₂ and sodium arachidonate were abolished by 15-hydroperoxy arachidonic acid (1-2 µg/ml, 15-HPAA), a specific inhibitor of prostacyclin synthetase. However, 15-HPAA did not greatly affect the relaxation induced by exogenous prostacyclin. These results suggest that the relaxation induced by PGH₂ and sodium arachidonate is mediated by prostacyclin. In contrast, PGE₂ (100 ng/ml) and TXA₂ (50 ng/ml) produced contractions in the coronary arterial strip (sponsor's report MANB/78/0054). The rat, rabbit and the bovine cerebral arteries synthesize 6-keto PGF_{1α}, the breakdown product of FLOLAN (Abdel-Hamlin, et.al., 1980; Hagen, et.al., 1979, summary). The synthesis is localized in the cerebral vessels and capillaries. Prostacyclin was generated by exogenous arachidonic acid in the human and baboon cerebral arteries (Boullin, et.al., 1979) and which also relaxed human and baboon cerebral arteries *in-vitro*. FLOLAN is a potent vasodilator of bovine coronaries *in-vitro* at 0.02-1 µg/ml; and the isolated hearts of the rat, guinea pig, and rabbit at 0.3-100 nM and at 50-100 ng/kg (Link et.al., 1978, and Schror et.al., 1978, summary).

In Vivo Studies:

The vasodilatory effects of prostacyclin were further characterized in *in vivo* preparations. Prostacyclin has been demonstrated to exert a direct vasodilation in vascular beds. For example, in agreement with the results obtained in the *in vitro* studies, epoprostenol reduced the increases in the perfusion pressure in the superior mesenteric artery induced by sympathetic nerve stimulation or exogenous administration of norepinephrine in anesthetized rats (Li et al., 1985). In this study, epoprostenol was infused into the superior mesenteric artery and at 10 nmol/L, epoprostenol sodium significantly inhibited the increase in the perfusion pressure induced by sympathetic nerve stimulation or exogenous administration of norepinephrine ~50%. In a separate study in anesthetized rats (Kaminski & Proctor, 1989), small mesenteric arteries

were occluded for 5 minutes and then released. During the reperfusion period, vehicle alone or vehicle containing either PGI₂ (3×10^7 M), adenosine (ADO, 10^{-4} M) or acetylcholine (ACH, 10^{-5} M) was applied for 30 minutes. During the first minute of reperfusion, the arteries were significantly dilated in all groups including vehicle alone as indicated by the increases in the arterial diameters and blood flow. The arterial diameters were $\sim 140\%$ and blood flow $>300\%$ of the baseline levels (preocclusion) in all groups. However, at 30 minutes of reperfusion, blood flow fell to $\sim 51\%$ of baseline level (preocclusion) in vehicle control group. In contrast, with either PGI₂, ADO or ACH, the vasodilation was persistent. For example, at 30 minutes of reperfusion, the arterial blood flow in all treatment groups remained $\sim 230\%$ of the baseline levels (preocclusion). In anesthetized rabbits, infusion of prostacyclin (~ 2.5 ng/ml) into the microvasculature of the epigastric island flap increased the microvascular blood flow $\sim 130\%$ compared to the control (Knight et al., 1986). In this study, the blood flow was determined using a Laser Doppler flowmeter. In anesthetized dogs, intra-arterial injection of prostacyclin ($\sim 0.1-1$ μ g for 10-32 kg body weight) or PGE₂ ($0.1-1$ μ g) reduced the perfusion pressure in the mesenteric and femoral vascular beds ~ 30 mmHg (Dusting & Vane, 1980). Both prostacyclin at 1 μ g and PGE₂ at 0.5 μ g increased the coronary blood flow. The amplitude of the increase in the blood flow was about the same. Local injections of FLOLAN into the coronaries of the dog at 50-500 ng/kg increased the coronary blood flow without systemic effects and is more potent coronary dilator than PGE, (Dusting, et.al., 1978a). Local application of FLOLAN onto the left ventricle at 50-500 μ g produced profound and prolonged coronary vasodilation suggesting rapid absorption of the drug through myocardium into the coronary vasculature. Thus, on the heart, it has beneficial actions in the myocardial ischemia, reduces the oxygen demand of the heart by decreasing the work load, and decreases the peripheral resistance. Coronary blood flow was increased following intravenous administration of epoprostenol in anesthetized dogs. For example, epoprostenol increased the left anterior descending coronary (LAD) blood flow $\sim 200\%$ following injection of epoprostenol at 3 μ g into LAD coronary artery (Hintze and Kaley, 1984). Intrarenal infusion of FLOLAN (10-30 ng/kg/min) in the rat and dog reduces renal vascular resistance and causes a redistribution of renal blood flow towards the inner cortex (Gerber, et.al., 1978). Thus, it induces diuresis and natriuresis in dogs, cats and rats; increases the plasma renin activity via direct action on the kidney and also via reflex mechanisms. The intracarotid injection of FLOLAN at 100 ng/kg/min or 500 ng/kg/min increased cerebral flow by 71% and 22% accompanied by hypotension and tachycardia (Pickard, et.al., 1980). Topical application of FLOLAN onto the dog cerebral cortex also causes local vasodilation, and injection in the carotid artery in the baboon increased cerebral blood flow dose-dependently (Pickard, et.al., 1980).

Systemic hypotensive effects of prostacyclin were demonstrated in both anesthetized and conscious animals. In *in-vivo* experiments, FLOLAN is a potent vasodilator resulting in the lowering of systolic and diastolic blood pressure in all experimental animals. For example, in rats, at doses of $1-4$ μ g/kg, hypotension is accompanied by reflex tachycardia. At doses of $10-100$ ng/kg/min, FLOLAN prevents the onset of hypertension in the Goldblatt renal hypertension rat model (Sutler & Weeks, 1980, summary). BP returns to normal upon

discontinuing the infusion. The pronounced hypotension is associated with short-lived hypothermia, behavioral depression, and swelling of the paws (Weeks & Compton, 1979, summary). In a separate study in anesthetized rats, intravenous injection of epoprostenol sodium resulted in decrease in blood pressure in a dose dependent manner (Armstrong et al., 1978 and sponsor's report 7200/78/7222/036). The threshold dose of epoprostenol for lowering the blood pressure was 0.125 $\mu\text{g}/\text{kg}$. Epoprostenol at 8 $\mu\text{g}/\text{kg}$ reduced diastolic blood pressure up to 100 mmHg and its metabolite, 6-oxo-PGF_{1 α} , at this concentration did not produce any effects (Armstrong et al., 1978). The hypotension caused tachycardia (3-66 beats/min) as reflex in origin. In the other study in rats (sponsor's report 7200/78/7222/036), the threshold dose of epoprostenol for lowering the blood pressure was between 1.0 and 3.2 ng/kg/min and epoprostenol at 1-10 ng/kg/min reduced arterial blood pressures up to $\sim$ 17 mmHg ($\sim$ 15%). At 100 ng/kg/min, epoprostenol reduced the pressure $\sim$ 53 mmHg ($\sim$ 50%). In anesthetized rabbits, the threshold dose of epoprostenol for lowering the blood pressure was $\sim$ 0.125 $\mu\text{g}/\text{kg}$ and epoprostenol at 1-16 $\mu\text{g}/\text{kg}$ reduced diastolic blood pressure $\sim$ 35-55 mmHg (Armstrong et al., 1978). In contrast, 6-oxo-PGF_{1 α} at 16 $\mu\text{g}/\text{kg}$ was inactive. In this study hypotension also caused tachycardia. The hypotensive effects of prostacyclin were also compared with those of PGE₂ in both rats and rabbits (Armstrong et al., 1978). In both species, PGE₂ mimicked the hypotensive effects of prostacyclin but was less potent than prostacyclin. For example, prostacyclin was $\sim$ two times in rabbits or $\sim$ 4-8 times in rats more potent than PGE₂. In addition, prostacyclin does not lose its activity when passing through the pulmonary circulation in contrast to PGE₂. These results suggest that prostacyclin is more beneficial over PGE₂ in lowering pulmonary blood pressures and it is therapeutically useful in clinical situations such as primary pulmonary hypertension. The hypotension was also found following intravenous infusion of epoprostenol sodium in rabbits (Cairns et al., 1991). In this study, epoprostenol at 15-150 ng/kg/min reduced the mean blood pressure $\sim$ 5-19%. Intravenous administration of epoprostenol sodium (3 $\mu\text{g}/\text{kg}$) reduced the left ventricular systolic pressure $\sim$ 30 mmHg in anesthetized rabbits (Lidbury et al., 1990). This action was transient. The hypotensive effects of epoprostenol were also found in anesthetized dogs. For example, intravenous infusion of epoprostenol sodium at 0.3 $\mu\text{g}/\text{kg}/\text{min}$ reduced the total peripheral resistance and mean arterial pressure $\sim$ 60%, increased the cardiac output and stroke volume $\sim$ 40% (sponsor's report TPZZ/90/0081). Heart rate was slightly increased ($\sim$ 10%) in this study. Similar results were found in separate studies in dogs (Chapple et al., 1980, Czer & Moser, 1983, Chiavarelli et al., 1982, Hintze et al., 1979, Aiken & Shebuski, 1979 and sponsor's report 7243/78/7243/038). The hypotensive responses following intravenous infusion of epoprostenol were also found in anesthetized cats, pigs and monkeys (Hintz et al., 1984, Prielip et al., 1991, sponsor's reports BPHP/82/0053 and 7200/79/7231/048).

In conscious animals (rats and dogs), epoprostenol reduced blood pressure in a dose dependent manner. In dogs, epoprostenol sodium (1-3 $\mu\text{g}/\text{kg}$) decreased the mean arterial pressures $\sim$ 30-50% (sponsor's reports 7243/78/7243/038 and 7243/79/7243/021). These results were consistent with the results obtained in the studies with the anesthetized dogs. In unanesthetized rats, intravenous infusion of epoprostenol at 1.0 $\mu\text{g}/\text{kg}/\text{min}$ reduced the mean arterial pressure $\sim$ 40 mmHg accompanied by tachycardia (sponsor's report 7200/78/7222/036).

In conscious Goldblatt rats, intravenous infusion of epoprostenol at 100 ng/kg/min for 6 day completely inhibited the onset of hypertension (sponsor's report 7200/79/7222/045). In the same model with 4-week established renal hypertension, epoprostenol, intravenously infused at 100 ng/kg/min for 7 days, reduced mean aortic blood pressure (~ 8 mmHg) within 4 hours after the dosing and this reduction lasted for 2 days. After discontinuing the infusion of epoprostenol, the blood pressure was elevated above the pretreatment values and remained for ~ 5 days (~ 18 mmHg above the pretreatment control). Bolus intravenous injection of epoprostenol (120-150 ng) reduced mean arterial blood pressure (~ 6.5 mmHg) and the blood pressure (~ 9 mmHg) elevated by angiotensin II in conscious rats (Spitz et al., 1985).

2. Cardiac Effects:

A. ECG, cardiac output and heart rate

The effects of epoprostenol on cardiodynamics and ECGs were studied in anesthetized and conscious dogs. Epoprostenol, intravenously infused at 0.01-1.0 $\mu\text{g}/\text{kg}/\text{min}$ (sponsor's reports BPHP/82/0053 and TPZZ/90/0081) or injected at 3 μg into the left circumflex coronary artery (Hintz and Kaley, 1984), did not significantly alter the ECGs in the anesthetized dogs. In conscious dogs, the left ventricular end diastolic diameter was decreased by intravenous injection of epoprostenol ~ 3.0 at 0.5-2.0 $\mu\text{g}/\text{kg}$ (Nganele & Hintze, 1987 and 1990).

Decreases in diastolic and systolic pressures (~ 60-100 mmHg) accompanied with increases in cardiac output (~ 378 ml/min) and stroke volume (~ 2.0 ml) were also found following intravenous infusion of epoprostenol sodium (1.0 $\mu\text{g}/\text{kg}/\text{min}$) in anesthetized dogs (sponsor's report BPHP/82/0053). The effects of FLOLAN on heart rate were variable. Heart rate was decreased ~ 10% following infusion of epoprostenol sodium (0.25 to 0.5 $\mu\text{g}/\text{kg}/\text{min}$) into the left atrium (Chapple et al., 1980). The decrease in heart rate was also seen in separate studies in dogs following intravenous injection of FLOLAN (Kaley et al., 1980, Hintze and Kaley, 1984 and Panzenbeck et al., 1988). In 6 dogs, iv infusions at 100 and 250 ng/kg/min decreased mean aortic pressure by 18% and 37%, respectively, with no changes in the heart rate. At 250 ng/kg/min, heart rate was decreased by 10 and 17% in 2 dogs. In another 6 dogs, 250 and 500 ng/kg/min FLOLAN decreased the blood pressure by more than 40% without changing heart rate. Bolus injections of 500 to 1,000 ng/kg FLOLAN into the atrium of the same dogs reduced blood pressure to the same degree and slowed heart rate by 10%.

B. Effects in Myocardial Infarction

FLOLAN reduced the infarct size in the dog and cat. At 0.32 $\mu\text{g}/\text{kg}/\text{min}$, it decreases oxygen demand of ischemic dog heart by lowering the mean arterial pressure from 121 ± 8 to 90 ± 3 mmHg without increasing heart rate. Mortality is reduced from 6 of 17 in the control group to none of the 9 dogs in the FLOLAN group. FLOLAN at 0.5 nmol/kg/min decreased

the release of cathepsin D and creatine phosphokinase from the infarcted areas of the cat heart and again reduced mean arterial pressure without increasing heart rate. Thus, FLOLAN seems to show beneficial effects in the animal models of myocardial infarction.

C. Arrhythmogenic and Anti-arrhythmic Activities

The effects on the cardiac rhythm vary with dose of FLOLAN and the experimental procedure. FLOLAN produced arrhythmias in the rat and cat after acute coronary artery occlusion; in the rat it increases arrhythmias and ventricular fibrillation following coronary occlusion but decreases infarct size in the survivors. High doses of FLOLAN (400 ng/kg/min, iv) were arrhythmogenic. In the dog, following coronary occlusion, it decreased the incidence of ventricular fibrillation and this was independent of any effect of FLOLAN on antecedent ectopic rhythms.

3. Anti-platelet Aggregation: The naturally occurring prostacyclin is the most potent endogenous inhibitor of platelet aggregation known. FLOLAN was also demonstrated to be a potent platelet aggregation inhibitor in *in vitro*, *ex vivo* and *in vivo* preparations.

In-Vitro Tests

In *in-vitro* test, FLOLAN reduces ADP-induced platelet aggregation using platelet rich plasma. ED₅₀ in the human, dog, rat, rabbit, horse, and sheep platelet rich plasma within one minute of the ADP addition ranges between 0.5 and 3.7 ng/ml (Whittle, et.al., Prostaglandins 16:373-388, 1978). FLOLAN remains bound to platelets and therefore affords longer action. FLOLAN inhibits platelet shape change with an ID₅₀ of 2.3 nM (Ehrman and Jaffe, 1980, sponsor's summary). It inhibits the expression of platelets procoagulant action (Ehrman and Jaffe, 1980, Harsfelv, et.al., 1980, sponsor's summary) and the expression of fibrinogen receptors on the platelet surface (Hawinger, et.al., 1980, sponsor's summary).

Ex Vivo Studies:

Epoprostenol inhibited platelet aggregation induced by ADP in platelet-rich plasma in rabbits, dogs and monkeys. In rabbits, intravenous infusion of epoprostenol sodium inhibited the platelet aggregation in platelet-rich plasma induced by ADP with IC₅₀ of 0.24 µg/kg/min (sponsor's report BPPS/85/0006). In a separate study, intravenous injection of epoprostenol at 3 µg/kg inhibited ~93% the platelet aggregation in arterial blood from anesthetized rabbits (Lidbury et al., 1990). In dogs with fresh venous thrombosis, intravenous infusion of epoprostenol at 50 ng/kg/min inhibited platelet accretion *in vivo*, decreased the platelet aggregation induced by ADP by ~95% and the mean arterial pressure by ~86% compared to pre-infusion values (Czer et al., 1983). These effects were dose dependent and correlated each other closely, implying that the anti-platelet aggregate effect of prostacyclin may be therapeutically beneficial in the pathological conditions, such as thromboembolisms in the patients with hypertension. In a separate study in the anesthetized dogs subjected to the regional

myocardial ischemia followed by 20 min reperfusion, intravenous infusion of epoprostenol at 100 ng/kg/min reduced ~33% the platelet aggregation induced by ADP (Jouve et al., 1985a). In this study, epoprostenol also reduced the mean blood pressure, systemic vascular resistance and incidence of postischemic ventricular fibrillation, suggesting that FLOLAN may be also useful in the patients with acute myocardial ischemia. Intravenous infusion of epoprostenol at 0.64 $\mu\text{g}/\text{kg}/\text{min}$ completely inhibited the platelet aggregation induced by ADP in arterial blood from monkeys (sponsor's report BPHP/82/0053). In anesthetized baboon, bolus intravenous injection of epoprostenol inhibited the platelet aggregation induced by ADP in a dose dependent manner with IC_{50} of 0.34 ng (sponsor's report 7200/79/7231/048).

In Vivo Studies:

In anesthetized rats, intravenous infusion of epoprostenol at 0.5 $\mu\text{g}/\text{kg}/\text{min}$ totally prevented the fall in platelet count induced by ADP and at 2 $\mu\text{g}/\text{kg}/\text{min}$ increased the bleeding time from ~120 sec to ~900 sec (sponsor's report BPPS/85/0006). Intravenous infusion of epoprostenol at 500 ng/kg/min decreased the incidence of near-total occlusion (0/6 in treated and 5/6 in control groups) in anesthetized rats with a non-occlusive thrombus formed in the femoral artery and (1/5 in treated and 4/5 in control groups) in anesthetized rabbits (Bailes et al., 1988). The platelets in thrombi were less in treated group with epoprostenol of 500 ng/kg/min (25-50%) than in control group (50-75%) in rats and (25% in treated and 25-75 in control groups) in rabbits (Bailes et al., 1988). Intravenous infusion of epoprostenol at 400 ng/kg/min increased the mean bleeding time by ~95% in anesthetized rabbits (Klokkevold et al., 1992). The accumulation of platelets on the subendothelial surface of aorta was reduced by intravenous infusion of epoprostenol at 850 ng/kg/min by ~72% in rabbits (Groves et al., 1986). Intravenous infusion of epoprostenol at 50 ng/kg/min almost totally abolished the uptake of ^{125}I -labelled platelets onto the venous thrombi in 7/8 dogs (Czer et al., 1983). Intravenous infusion of epoprostenol at 50 ng/kg/min effectively abolished the decline in platelet number (thrombocytopenia) in anesthetized dog subjected to monocrotaline-induced lung injury (Czer et al., 1986). Intravenous infusion of epoprostenol at 150 ng/kg/min completely inhibited platelet aggregation induced by ADP in platelet-rich plasma and abolished the reduction of blood flow induced by platelet thrombi in dogs (sponsor's report 7200/78/7222/044). A similar result was also found in a separate study in anesthetized dogs (sponsor's report 7200/79/7222/043).

In the rabbit, at 50 ng/kg/min *iv* FLOLAN prevented electrically induced thrombus formation in the carotid artery and increased the bleeding time by 100%, the effects that can be doubled by 200 $\mu\text{g}/\text{kg}/\text{min}$ of theophylline (Ubatuba. et.al. 1979, sponsor's summary). At 100-500 ng/ml FLOLAN causes a dose-dependent increase in the time to thrombus formation induced in venules and arterioles by iontophoretic application of ADP to the vessels of the exerted golden hamster cheek pouch (Higgs, et al., 1978a). At 500 ng/ml, thrombus formation is completely prevented. FLOLAN (0.5-2.0 $\mu\text{g}/\text{kg}/\text{min}$) decreased dose-dependently the mortality of rabbits from sudden death as a result of platelets aggregation caused by *iv* arachidonic acid.

Other antiaggregatory prostaglandins such as PGE₁, and PGD₂ are ineffective in this model. FLOLAN prevents the occlusion of the coronary arteries due to thrombi at doses of 15-150 ng/kg/min in the dog, and improves the blood flow.

FLOLAN also desegregates platelet clumps after they have been formed (Gryglawski, et.al., 1978a, 1978b, sponsor's summary) in the cat at concentrations of 0.2-5.0 ng/ml. This action is potentiated by theophylline. At 1-16 nM, FLOLAN also inhibits mobilization of fibrinogen-binding sites on human platelets *in-vitro*, which may limit the extent of fibrinogen-platelet interactions (Gerber and Hawinger, 1982, sponsor's summary). It also induces fibrinolytic activity both in the canine lung (Utsunomiya, et.al., 1980, summary) and human skin via induction of a protease plasminogen activator at concentrations of 0.1-10 µg/ml.

4. Mechanisms of Action: FLOLAN is a potent systemic and pulmonary vasodilator and a platelet aggregation inhibitor. Both the vasodilation and anti-platelet aggregation induced by FLOLAN have been demonstrated to be mediated by activation of adenylate cyclase via PGI₂ receptors. The kinetic analysis of binding of PGI₂ to its receptors was performed in both pulmonary (lung homogenates) and platelet membranes.

A. Receptor Binding:

Lung

The ligand binding study revealed that there were two receptor sites for prostacyclin in the membranes isolated from guinea pig lungs (lung homogenates). The dissociation constants (K_d) of [³H] prostacyclin were 16 nM and 258 nM for high and low affinity sites, respectively (Macdermot et. al., 1981). The binding capacities (B_{max}) were 105 and 1257 fmoles [³H]prostacyclin per mg of membrane protein for the high and low affinity sites, respectively. The pulmonary effects, including relaxation of the pulmonary vascular smooth muscle and reduction of the pulmonary blood pressures, may be mediated by the high affinity (K_d = 16 nM) PGI₂ receptor population. It appears that pulmonary effects of PGI₂ are largely confined to the arteriolar beds. PGI₂ had the highest potency for the high affinity site among the prostaglandins and the rank order of potency was PGI₂ > PGE₁ > 6β-PGI₁ > PGE₂.

Platelets

The three naturally occurring prostaglandins, PGD₂, PGE₁, and PGI₂ (FLOLAN) prevent platelet aggregation via stimulation of platelet adenyl cyclase. A number of techniques such as radioligand binding, species sensitivity, pharmacological receptor antagonists and biochemical studies on adenyl cyclase stimulation and desensitization have shown that platelets appear to have at least two receptor sites, one for FLOLAN and PGE₁, and the second for PGD₂. By using particulate fractions of bovine platelets, it has been shown that FLOLAN binds specifically to two sites with dissociation constants (K_d) of 35 ± 7 nmol/L and 320 nmol/L (Schillinger and Prior, 1980, cited in sponsor's summaries). The binding capacities (B_{max}) are 0.36 and

2.82 pmol/mg/protein for the high and low affinity sites, respectively. The radioligand binding studies with intact human platelets showed dissociation constants of 12.1 ± 2.7 and 909 ± 236 nmol/L, and binding capacities for the two sites were 93 ± 21 and $2,700 \pm 700$ pmol/mg/protein, respectively. Receptor activation of either site causes an elevation of cellular adenosine 3' 5'-monophosphate (cAMP) via stimulation of the platelets microsomal adenylyl cyclase (Gorman et al., 1977; Tateson, et al., 1977, sponsor's summary). However, PGI₂ is ~10 times more potent than PGD₂, 30 times more potent than PGE₁, and more than 1000 times more potent than 6-oxo-PGF_{1 α} , a metabolite of PGI₂ (Tateson et al., 1977). Dissociation constants for the high affinity, low capacity site of human, canine, and rats are 63, 42, and 55 nmol/L, respectively (Schillinger and Prior, 1980).

B. Activation of Adenylate Cyclase:

Vascular Smooth Muscle

FLOLAN relaxes the vascular smooth muscle via the stimulation of adenylate cyclase, and elevation of cAMP which subsequently leads to the relaxation of light chain linkages leading to the relaxation of smooth muscle (Miller et al., 1979a, and Kukovetz and Holsman, 1984).

Platelets

The inhibition of platelet aggregation by FLOLAN is correlated with activation of adenylyl cyclase which leads to a substantial increase in the platelet intracellular cAMP (Gorman et al., 1977, Tateson et al., 1977). It is 10x more potent than PGD₂, 30x more potent than PGE₁, (Moncada, and Vane, 1977, summary) and 1000x more potent than adenosine (Born, 1962) or 6-keto-PGF_{1 α} , (the breakdown product of PGI₂) in stimulating adenylyl cyclase. FLOLAN's platelet anti-aggregatory action is mediated via stimulation of platelet adenylyl cyclase. This action of FLOLAN is potentiated by methylxanthine (theophylline) and dipyridamole, both of which are phosphodiesterase inhibitors and which raise platelet cAMP. On the other hand, FLOLAN's action is antagonized by epinephrine, ADP, and collagen (which deplete platelet cAMP), and also by thromboxane A₂ precursor, PGH₂, a potent platelet aggregating agent. FLOLAN's platelet anti-aggregation action may also be mediated via cytoplasmic calcium levels (regulated by cAMP) upon which the platelet shape changes, aggregation and the release depend.

Other Tissues

On other tissues, FLOLAN's action may depend on the initial level of adenylate cyclase activation before the treatment: FLOLAN at 0.1-100 μ M reduced histamine-stimulated elevation of cAMP (Soll, 1980), but in the absence of histamine, at 10-100 μ M, it increased cAMP in the gastric mucosa of the dog (Soll, J. Clin Invest. 65:1222-1229, 1980, Simon, et.al., Prostaglandins 21:353-365, 1980).

Epoprostenol sodium was also found to activate adenylate cyclase in human foreskin fibroblasts (sponsor's report 7200/79/7222/004).

Secondary Activity

1. Neuropharmacology: Intravenous or subcutaneous administration of epoprostenol at concentrations of 1 mg/kg or above induced hypoactivity, deep slow breathing and hypothermia in mice and rats (sponsor's reports BPAT/78/32, BPAT/78/34, BPHP/78/1 and BPAT/80/22).

2. Respiratory Pharmacology: Effects of FLOLAN on bronchial smooth muscle and pulmonary functions were characterized in both *in vitro* and *in vivo* preparations. In isolated guinea pig tracheal strips, epoprostenol induced either contraction or relaxation depending upon the concentration administered. For example, epoprostenol at low concentration (10^{-9} to 10^{-7} M) produced relaxation and at high concentration (10^{-4} M) produced contraction (sponsor's report BCPU-78-12). Epoprostenol inhibited the contractile response induced by carbachol (~60% inhibition at 3×10^{-4} M), histamine (~75% inhibition at 10^{-5} M) and 4β -phorbol dibutyrate (~55% inhibition at 10^{-4} M) in isolated guinea pig tracheal strips (Wasserman et al., 1980 and Obianime et al., 1989). Epoprostenol, given intra-peritoneally, increased the survival rate (7/8 at concentration of 10 mg/kg) in the histamine-induced bronchocontraction (90% died) in guinea pigs (sponsor's report BPHP/78/0032). Epoprostenol, given intra-peritoneally, delayed the onset of histamine-induced asphyxial collapse in a dose dependent manner in conscious guinea pigs (Wasserman et al., 1980). In this study, at concentration of 10 mg/kg, epoprostenol completely prevented the bronchocontraction. In anesthetized dogs, the increase in pulmonary resistance and the decrease in dynamic compliance induced by $\text{PGF}_{2\alpha}$ were inhibited by aerosolized epoprostenol in a dose dependent manner (Wasserman et al., 1980). At 0.2%, the inhibition was about 84% and 60% for pulmonary resistance and the dynamic compliance, respectively. The inhibition was also seen when epoprostenol was given intravenously in the same study. For example, epoprostenol, given intravenously at concentration of 30 $\mu\text{g}/\text{kg}$, inhibited the increase in pulmonary resistance by ~86% and the decrease in dynamic compliance by ~67%. In a separate study in anesthetized dogs, epoprostenol at 1.0 $\mu\text{g}/\text{kg}$, given intravenously, inhibited the increase in pulmonary resistance and the decrease in dynamic compliance induced by histamine and acetylcholine ~15% (sponsor's report BPHP/78/0032). Epoprostenol, infused intravenously at 50 ng/kg/min, totally abolished the increase in extravascular lung water induced by monocrotaline in anesthetized dogs (Czer et al., 1986) and reduced the increase in pulmonary lymph flow induced by thrombin from ~37 to 16 ml/hour at 500 ng/kg/min in conscious sheep (Periman et al., 1986). In isolated newborn lamb lungs, epoprostenol infused via a pulmonary arterial cannula at 0.4 $\mu\text{g}/\text{kg}/\text{min}$, attenuated the increase in pulmonary pressure induced by a thromboxane A_2 (TXA_2) analogous (9,11-epithio-11,12-methano- TXA_2) but increases the edema induced by TXA_2 analogous as evidenced by increased transvascular fluid filtration (by ~121%) (Yoshimura et al., 1989a).

At 80-160 ng/ml, it relaxed isolated strips of human tracheal, bronchial and bronchiolar smooth muscle. At 200 ng/kg/min *iv* infusion, it reversed oleic-acid-induced respiratory distress in the dog by protecting against the impairment of gas exchange following increased pulmonary vascular permeability and edema. The pulmonary embolism induced by autologous blood clots, hypoxia, and increased physiological dead space in the dog were reversed by FLOLAN at 100 ng/kg/min while maintaining cardiac output. At 30-1,000 ng, it dilates the constricted pulmonary vascular bed, prevents intrapulmonary platelet aggregation induced by ADP and dilates constricted airways. It does not affect pulmonary function and thus may have beneficial effects in the presence of pulmonary disease (sponsor's summary).

3. Gastrointestinal Pharmacology:

A. Secretion

FLOLAN inhibits gastric acid secretion *in-vivo* in the rat and dog, and *in-vitro* in the rat stomach (Whittle, 1981b). FLOLAN by *iv* infusion is more antisecretory agent than PGE₂: the ID₅₀ dose for FLOLAN was 0.2 µg/kg/min and 0.8 µg/kg/min for PGE₂ in the rat (Whittle, 1981, Clinical Pharmacology of Prostacyclin, eds. Lewis and O'Grady). It acts as an antisecretory agent by acting on the parietal cells as shown by studies with isolated cells from the dog and rabbit stomachs (Soll, 1980) by exerting an inhibitory action on adenylate cyclase. Epoprostenol, infused intravenously 0.1 and 0.2 µg/kg/min, inhibited the histamine-induced acid secretion in conscious dogs (Kauffman et al., 1979). At 0.2 µg/kg/min, the inhibition was ~47%. The inhibition of histamine-induced acid secretion was also found in a separate study in conscious dogs (sponsor's report 7200/78/7222/043). The IC₅₀ was ~6 µg/kg/min.

B. Motility

It has little or no significant action on the GI motility but has some antidiarrheal action via an unclear mechanism. Gastric emptying was decreased in fasted rat following subcutaneous administration of epoprostenol (sponsor's report BCPU-78-12). The gastric emptying (the % recovery of the total dose of ⁵¹Cr at 45 minutes in small intestine after dosing) was ~49% in control, 8%, 4% and 2% at the doses of epoprostenol of 0.02, 0.2 and 2.0 mg/kg, respectively.

C. Cytoprotection

FLOLAN and other prostanoids inhibit gastric damage and erosions induced by a variety of agents: non-steroidal antiinflammatory drugs, topical irritants such as salts, ethanol, castor oil, acids, and alkalis. This cytoprotective action of FLOLAN may be mediated via one of the several following mechanisms: increase in the gastric microcirculation, H⁺ ion flux, Na⁺ or Cl⁻ transport or mucous alkaline secretion or enhancing the cellular integrity of gastric mucosa.

Epoprostenol inhibited the ethanol-induced gastric lesions in conscious rats with IC_{50} of 2 mg/kg orally and 1 mg/kg subcutaneously (sponsor's report 7200/77/7222/028). Epoprostenol, given subcutaneously, inhibited the gastric mucosal erosion induced by indomethacin with IC_{50} of 35 μ g/kg/hour in anesthetized rats (Whittle et al., 1978).

4. Reproductive Pharmacology:

A. Uterine Motility

In the non-pregnant human myometrium *in-vitro*, FLOLAN at a concentration of μ g/ml induces a biphasic response: short lasting contraction followed by a lasting relaxation and disappearance of spontaneous tone. On the pregnant human uterus *in-vivo*, FLOLAN has no significant effect (Omini et. al., 1978). It also inhibits the contractions induced by $PGF_{2\alpha}$ but not those by acetylcholine, barium chloride, or vasopressin. 6-oxo- $PGF_{1\alpha}$ weakly contracts uterine muscle. Further, it relaxes the human fallopian tube (at 200 ng/ml) and partially reverses $PGF_{2\alpha}$ contractions, but 6-oxo- $PGF_{1\alpha}$ is a weak contractor (Omini et.al., 1978).

B. Serum Hormone Levels in Rats

In oestradiol-treated, ovariectomized female rats, epoprostenol, given intravenously at 600 μ g, increased serum luteinizing hormone (LH) by ~196% and prolactin by ~1400% with 15 minute of administration and had no effect on follicle stimulating hormone (FSH) (sponsor's report 7253/78/7253/023).

C. Pregnancy

In the pregnant dog, the uterine venous and arterial plasma concentrations are significantly increased (ng/ml, respectively) as compared to the arterial plasma concentrations in the non-pregnant dogs (less than 0.2 ng/ml). The pregnant uterus does not inactivate FLOLAN, and furthermore, intrauterine FLOLAN at doses of up to 100 ng/kg/min has no consistent effect on uterine hemodynamics although it does increase intraamniotic fluid pressure significantly (Gerber et.al., 1981, J. Clin Invest. 67: 632-636).

D. Vas Deferens

FLOLAN inhibits the adrenergic contractile phase more potently than non-adrenergic phase.

E. Deciduogenic Action

In immature rat uterus sensitized with progesterone, FLOLAN elicits the formation of deciduomata in response to trauma, similar to other prostanoids- PGE_1 , PGE_2 , and $PGF_{2\alpha}$.

5. Renal Pharmacology:

A. Excretory Function

Intrarenal infusion of FLOLAN markedly increases the renal blood flow without changing glomerular filtration rate. In the dog it promotes diuresis and natriuresis and excretion of Na^+ , K^+ , Cl^- ions: at 1 ng/kg/min, it produces a significant increase in urine flow and excretion of Na^+ , K^+ without affecting the renal blood flow, renal vein, renin, heart rate, and blood pressure. At 3 ng/kg/min, blood pressure drops with increase in renal vein renin. While 6-oxo-PGF_{1 α} at 100 ng/kg/min produces significant diuresis and increase in sodium excretion without affecting potassium loss or free water clearance, FLOLAN increases dose-dependently (0.3-30 ng/kg/min) the renal volume in the dog and these effects are considered to be direct action on the kidneys by increasing the renal blood flow.

In rats with acute ischemic renal failure induced by clamping left renal artery for 40 minutes, epoprostenol, infused intravenously at 8 ng/kg/min, increased glomerular filtration estimated by the inulin clearance (Lifschitz & Barnes, 1984). The inulin clearance was 0.05 and 0.22 ml/min in control and epoprostenol treated (8 ng/kg/min) groups, respectively. A similar result was also found in another group of rats subjected to fluid-expansion and acute ischemic renal failure. In this study, the inulin clearance was 0.04 ml/min in the control group and 0.9 ml/min epoprostenol treated (8 ng/kg/min) group. In the ischemic kidney, less cellular necrosis and cast formation were found in the epoprostenol-treated animals compared to the control. In a separate study in uninephrectomized rats subjected to 40 min renal artery occlusion followed by reperfusion, epoprostenol, infused intravenously at 160 ng/kg/min, improved renal function. In the epoprostenol treated group (160 ng/kg/min), the urine volume, urine osmolality, urine creatinine and creatinine clearance were significantly increased 45%, 41%, 35% and 156%, respectively, compared to the control (Finn et al., 1987). The renal necrosis was also less in the epoprostenol treated group in this study. Intravenous infusion of epoprostenol at 0.4 nmol/kg/min decreased glomerular filtration rate by ~38% in anesthetized rabbits (Cairns et al., 1991). Intravenous infusion of epoprostenol at 0.1 $\mu\text{g}/\text{kg}/\text{min}$ significantly reduced urine volume by ~31% and sodium excretion by ~39% in unanesthetized, saline-loaded rats (sponsor's report 7200/78/7222/036). Intra-arterial infusion of epoprostenol at 1.2 $\mu\text{g}/\text{kg}/\text{min}$ increased Na^+ , K^+ , Cl^- and HCO_3^- excretion by ~13, 14, 25 and 65%, respectively in conscious dogs (sponsor's report 7243/79/7243/021). The urine flow was also increased following administration of epoprostenol at 0.34 $\mu\text{g}/\text{kg}/\text{min}$.

B. Renin

FLOLAN releases renin from the renal cortex via multiple mechanisms which have not been clearly understood. In the rabbit, at 0.1-10 μM , it stimulates renin release from the renal cortex, and in the dog it does so at 1-100 ng/kg/min. Epoprostenol, infused intravenously at

100 ng/kg/min, increased plasma renin activity in conscious rats (sponsor's report 7200/78/7222/036). A similar effect was also observed in conscious dogs (sponsor's report 7243/79/7243/021). In this study, intra-arterial infusion of epoprostenol sodium at 1.0 $\mu\text{g}/\text{kg}/\text{min}$ increased plasma renin activity by $\sim 92\%$.

6. Inflammatory Pharmacology: Local injection of epoprostenol at 1.0 μg into the subplantar surface of the rat hind limb induced edema at 20 min (sponsor's report TPHS/77/0002). In this study, epoprostenol also produced significant hyperalgesia. Local extracellular administration of epoprostenol at 3×10^{-10} M per site potentiated the edema formation induced by C5a des Arg, an inducer of edema, in the skin in anesthetized rabbits (Rampart and Williams, 1986). In this study, intravenous administration of epoprostenol at 50 ng/kg/min attenuated the increases in skin plasma volume induced by intra-dermal injections of epoprostenol sodium and the polymorphonuclear leukocyte (PMN)-dependent edema induced by C5a des Arg and Leukotriene B₄. It potentiates bradykinin-induced plasma exudation. Administration of epoprostenol intrapleurally at 1 μg reduced edema as evidenced by inhibition of the 3 hour exudate volume by $\sim 22\%$ induced by carrageenan (sponsor's report TPHS/77/0002). Intra-peritoneal administration of epoprostenol inhibited the release of slow-reacting substance of anaphylaxis from rat peritoneal cells with IC₅₀ of 0.5 $\mu\text{g}/\text{kg}$ (Burks and Garland, 1976). Local application of epoprostenol at 5 $\mu\text{g}/\text{ml}$ partially reversed the leukocyte adhesion in the mesenteric microcirculation induced by local application of zymosan-activated complement in anesthetized rats (Jones and Hurley, 1984). 6-oxo-PGF_{1 α} has been detected in the inflammatory exudates of animals and in patients with inflammatory conditions such as rheumatoid arthritis and other chronic conditions. FLOLAN causes erythema in humans and thus the generation of PGE₂ and prostacyclin in damaged tissues can explain the characteristic erythema of acute inflammation. While it does not affect the interaction between immune complexes and PMN, it prevents the ensuing PMN migration and secretion of platelet activating factor at concentrations as low as 10^{-9}M . In rabbits, infusion of FLOLAN (10-50 ng/kg/min) prevents immune complex-induced neutropenia and thrombocytopenia as well as embolization of PMNs into the pulmonary capillary network.

7. Other Effects:

A. Cytoprotective effects: Besides its cytoprotective action on the gastric mucosa (mentioned above), FLOLAN also decreases oxygen demand and the release of lysosomal hydrolase, cathepsin D and creatine phosphokinase from the infarcted areas during myocardial infarction in the cat at doses of 0.5 nmol/kg/min infused intravenously (Ogletree et.al., 1979, *Europena J. Pharmacol.* 56: 95-103). In the cat, it decreases the hypoxia-induced damage by inhibiting the release of beta-glucuronidase and cathepsin D from the liver, and finally FLOLAN at 0.25 $\mu\text{g}/\text{kg}/\text{min}$, reduces the degree of ischemic renal damage during renal transplants in the dog (Mundy et.al. 1980, *Transplantation* 30: 251-255). In contrast to TXA₂ (which has cytolytic activity on the gastric mucosa, myocardium, and the liver), FLOLAN can exert protective action against experimental damage in these tissues by reversing the vasoconstriction and platelet plugging actions of TXA₂. It preserves the integrity of platelets, reduces the breakdown of

plasma phosphatides during storage and preserves the internal structures of platelets without affecting the platelet cAMP. In isolated rat liver cells, epoprostenol at 30 ng/ml, given 30 min after exposure of the cells to carbon tetrachloride, decreased the cytotoxic index by 66% at 4 hours after exposure to carbon tetrachloride (Guarner et al., 1985). In isolated rat liver subjected to 30 min total hepatic ischemia prior to the removal of the liver, epoprostenol at 0.1 $\mu\text{g/ml}$ significantly increased the ADP/O ratio (1.71) compared to the control (1.57) (Okabe et al., 1986). ADP/O ratio represents the efficiency of oxidative phosphorylation in mitochondria and the reduction of the ratio indicates the "uncoupling" of phosphorylation from oxidation in the respiratory chain. In rat cerebellar cultures subjected to 30 min anoxia, the severe swelling and degenerative changes of neurons and glia induced by anoxia were found much less pronounced in the culture pretreated with epoprostenol at 0.5 $\mu\text{g/ml}$ (Renkawek et al., 1986).

B. Effects on bile flow: Epoprostenol, infused at 250 ng/kg/min into portal vein did not significantly change the bile flow, the output of bile acid, Na^+ , K^+ and HCO_3^- and pancreatic secretory flow (Fukumoto et al., 1986).

C. Effects on lipid peroxidation: Intravenous infusion of epoprostenol at 2 ng/kg/min reduced the adrenalin-stimulated myocardial lipid peroxidation as evidenced by decreasing the concentration of the metabolites of peroxidation, such as malondialdehyde by 40% and the lipid soluble fluorescent materials in myocardium by 55% compared to the adrenaline only in anesthetized rabbits (Herbaczynska-Cedro & Gordon-Majszak 1986).

D. Effects during viral infection: Intravenous infusion of epoprostenol at 20 ng/kg/min did not significantly change the clinical course of the infection in a rhesus monkey infected with Ebola virus (Fisher-Hoch et al., 1985).

E. Effects on epithelial electrophysiology: In isolated rat and rabbit colons with intact epithelium, epoprostenol at 10^{-6} and 10^{-7} M increased the difference in transepithelial potential by -2 mV and the short circuit current by $20 \mu\text{A/cm}^2$ in rats and $40 \mu\text{A/cm}^2$ in rabbits (Phillips & Hoult, 1988). In a cell line (MDCK1 cells) derived from canine kidney, epoprostenol added directly to the culture dish via an osmotic minipump at 3.6 ng per hour was able to maintain the chloride gradient across the cells treated with indomethacin (to block endogenous PG synthesis), suggesting that the chloride gradient may be, partially, mediated by prostacyclin (Lifschitz, 1986).

F. Effects on tumors: In anesthetized, tumor-bearing rats, intravenous infusion of epoprostenol at 160 ng/kg/min increased the tumor inorganic phosphorous peak area by -40% measured by magnetic resonance spectroscopy and decreased pH in tumor by -0.05 to 0.2 units (Tozer et al., 1990). The increase in the tumor inorganic phosphate and decrease in tumor pH may be due to reduction of the tumor blood flow which appears to be cytotoxic to the tumor cells. The metastatic spread of certain tumors may depend on platelet emboli and local clotting. FLOLAN at $100 \mu\text{g/kg}$ *iv* has shown anti-metastatic activity in the mouse melanoma model (Honn, et.al., 1981, Science, 212: 1270-1272).

G. Effects in endotoxic shock: The exact role of FLOLAN in the endotoxic shock is not known. However, increased levels of 6-oxo-PGF_{1 α} (1.63 ± 0.27 ng/ml) have been measured in the arterial blood of rabbits (Bult, et.al., 1980) and about 3 ng/ml in the baboons after the administration of endotoxin (Harris, et.al., 1980). In sheep, FLOLAN (0.1-0.2 μ g/kg/min) protects the lungs against injury induced by endotoxin, while in the dog and cat (Demling, et.al., 1981, Surgery, 89: 257-263), it improves splanchnic blood flow and decreases the formation and release of lysosomal hydrolase (cathepsin D). Intravenous injection of epoprostenol at 0.2 μ g/kg increased the survival rate (3 survivals out of 5 animals, 60%) compared to control (4 survivals out of 24, 17%) in conscious rats following endotoxin shock (sponsor's report 7263/86/020). However, no survival was found in the treatment group with epoprostenol at higher concentration (6 μ g/kg).

H. Glucose Metabolism: In the isolated perfused rat pancreas, FLOLAN, unlike PGE₁, PGE₂, and PGF_{2 α} , is a weak stimulus for either glucagon or insulin secretion. At high doses (0.1-1 μ g/kg/min), FLOLAN produces significant hyperglycemia in the rabbit at 1, 2, 3 hr post-infusion. However, no insulin or catecholamine levels were detected in the rabbit plasma.

In the monkey (*E. patas*), FLOLAN at 1 μ g/kg/d infused iv did not affect the levels of T₃, T₄, free fatty acids, insulin and glucagon at 60 min post infusion. Plasma glucose levels were raised at 60 minutes but not at earlier times. However, due to small number of animals used in the study (3), there was a large variability in the plasma glucose levels, thus, no definitive conclusions could be drawn from the study (# BPAT 79/06, p 4.03644, volume 1.13). In a repeated study (# BPAT 79/08: p 4.03662, volume 1.13), the hyperglycemia was not observed when the monkeys were pre-treated with a sympathetic ganglion blocking agent suggesting that the hyperglycemia observed earlier could have been due to stress (FLOLAN-induced hypotension and hypothermia) acting via an autonomic reflex, and not related to FLOLAN treatment.

I. Other Hormonal Effects: In the monkey (*E. patas*), FLOLAN at a single sc dose of 30 mg/kg produced significant rise in the serum cortisol levels as compared with controls (cortisol values at 2 min were: 45 and 60 μ g/100 ml in the control and treatment group, respectively; and at 24 hr: the values were: 28, 60 μ g/100 ml, (above the range of the assay), respectively. T₃, and T₄ were unaffected by the FLOLAN treatment (study # BPAT 79/07, p 4.03677, volume 1.13).

In summary, both *in vitro* and *in vivo* studies have demonstrated that FLOLAN is a potent vasodilator. It relaxes systemic, pulmonary and coronary arterial vessels and thus decreases the systemic and pulmonary arterial blood pressures. It also increases cardiac output. FLOLAN has also been demonstrated to be a potent platelet aggregatory inhibitor. Combination of the effects of decreases in the systemic and pulmonary arterial blood pressures and increase in the cardiac output would reduce the afterload on the right ventricle and improve pulmonary blood flow. This would provide symptomatic relief in the patients with primary pulmonary

hypertension. Both systemic and pulmonary thromboembolisms are known risk factors in the patients with the primary pulmonary hypertension. Therefore, the anti-platelet aggregation activity of FLOLAN would be useful in reduction of the chance of the life-threatening complication (thrombotic occlusion) in these patients.

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION (ADME):

Epoprostenol is stable at pH 10 or greater and rapidly hydrolyzed to 6-keto PGF_{1 α} at physiological pH and temperature. 6-keto PGF_{1 α} is ~ 1000 times less potent than epoprostenol. Epoprostenol is also rapidly and extensively metabolized to a number of other metabolites (see below). Due to its chemical instability and rapid metabolism, many investigators have measured total radioactivity and the metabolites of epoprostenol, such as 6-keto PGF_{1 α} , as indices of the concentration of epoprostenol. Pharmacokinetic property of FLOLAN have been characterized in the rat, cat, rabbit, dog and monkey. The radioactivity was assayed using liquid scintillation spectrometer. The metabolites were measured using gas chromatograph and mass spectrometer, HPLC, TLC and radioimmunoassay techniques.

Rat:

Comparison between the *in vivo* rate of metabolism of prostaglandin I₂ and its blood-pressure-lowering response after intravenous administration in the rat (Biochimica Biophysica Acta, 574:182-186, 1979)

Methods: The hypotensive effect of epoprostenol was compared with its rate of metabolism in male Wistar rats. Following intravenous administration of PGI₂ and 9 β -[³H]-PGI₂ (40-50 ng), the arterial blood pressure was monitored and the blood samples were collected. The radioactivities were analyzed using liquid scintillation spectrometer.

Results: The maximum hypotensive response was detected at ~ 15 seconds after intravenous administration of 40 ng (body weight: 200-300 g) PGI₂. The hypotensive response was quickly returned to the baseline within ~ 15 seconds from the maximum response. More than 95% of the tritium co-chromatographed with 6-keto-PGF_{1 α} by 30 seconds after intravenous administration of ~ 50 ng tritium labeled PGI₂. The rate of disappearance of PGF_{1 α} was relatively slow (40% by 2 minutes). The results suggest that PGI₂ is rapidly metabolized.

Distribution and excretion of radioactivity in plasma and tissues after the subcutaneous administration of prostacyclin-9-³H to male and female rats (BDPG 78-1 and BDPG 80-2)

Methods: The distribution of radioactivity in plasma and tissues was measured in rats at 0.5, 1, 2, 4, 24 and 72 hours after subcutaneous administration of 100 μ g/kg 9-³H-epoprostenol sodium with specific radioactivity of 1.0 Ci/mmol. The radioactivity in the following tissues

was measured: brain, fat, heart, kidney, liver, lung, muscle, pancreas, skin, spleen, testis, stomach, small intestine, large intestine and injection site. Urine and feces were collected at daily intervals for total three days. The radioactivity was measured by liquid scintillation spectrometer.

Results: The highest levels of radioactivity were observed in the tissues associated with route of excretion including kidney (505-662 ng equiv./g), liver (413-453 ng equiv/g) and small intestine (225-252 ng equiv./g) at 30 minutes after dosing. The lowest levels were detected in brain and fat tissues (< 10 ng equiv./g). The levels of radioactivity were rapidly fallen. - At 24 hours after dosing, the radioactivity was less than 10 ng equiv./g in all tissues except in kidney (~26-32 ng equiv./g). About 40% and 58% of the administrated dose were recovered within 72 hours in urine and feces, respectively.

Tissue distribution of tritium labelled prostacyclin in the rat (7200/78/7222/048)

The tissue distribution of radioactivity was measured in rats following intravenous administration of tritium labelled prostacyclin or 6-keto PGF_{1 α} . The specific radioactivity was 79 Ci/mole. Rats were injected with 1 ml of a solution containing 10.12 μ Ci 11-[³H]-prostacyclin. The result revealed a pattern of tissue distribution similar to the studies reviewed above (BDPG 78-1 and BDPG 80-2). The highest levels of radioactivity were observed in the kidney, liver and small intestine.

Tissue distribution and biliary excretion of prostacyclin metabolites in the rat (J. Pharmacol. Exp. Ther. 214:24-30, 1980)

Methods: The tissue distribution of radioactivity was measured following intravenous administration of tritium labelled prostacyclin or 6-keto PGF_{1 α} in the bile in bile duct cannulated rats. The specific radioactivity was 79 Ci/mole. Rats were injected with 1 ml of a solution containing 10.1 μ Ci (48 μ g) 11-[³H]-prostacyclin. Radioactivity was measured using liquid scintillation spectrometer.

Results: The result showed that ~37% of the administrated radioactivity was detected in the bile within three hours after a single bolus intravenous administration. The two major metabolites identified in the bile were 6-keto-2,3-dinor-PGF_{1 α} and 13,14-dihydro-6,15-diketo-2,3-dinor-PGF_{1 α} -glucuronide. Each of these metabolites accounted for ~33% of the radioactivity in the bile. Following metabolites were also detected in the bile: 6-keto-PGF_{1 α} , 13,14-dihydro-6,15-diketo-PGF_{1 α} , 13,14-dihydro-6,15-diketo-2,3-dinor-PGF_{1 α} , 13,14-dihydro-6,15-diketo-20-carboxy-2,3-dinor PGF_{1 α} and 2,3,4,5,6-pentanor-PGF_{1 α} - γ -lactone. The proposed pathways for the formation of these metabolites and their estimated percentage of radioactivity in the rat bile are depicted in the following figure.

Figure 2. Proposed pathways for the formation of eprostenol (PGI₂) metabolites present in rat bile.

The identities of the numbered compounds are:

Estimate of
Percentage of
Bile
Radioactivity

Metabolism of prostacyclin in rat (Biochemistry 17(19): 4096-4101, 1978)

Methods: The metabolism and excretion were studied in rats following a single intravenous administration (0.14 mg per rat, 4.4 μ Ci) and a continuous intravenous infusion (0.56-3.2 mg/kg/day) of 11-³H prostacyclin. The specific radioactivity was 79 Ci/mole. The radioactivity was measured by liquid scintillography. The metabolites were identified by gas chromatography and mass spectrometry.

Results: The results revealed that the major routes of excretion were by urine (33% of the administrated dose detected within 3 days) and by feces (44 %) following a single intravenous administration. Seven PGI₂ metabolites were identified in the urine following the continuous intravenous infusion of 11-³H prostacyclin. The proposed pathways for the formation of these metabolites and their estimated percentage of radioactivity in the rat urine are depicted in the following figure.

Figure 1. Proposed pathways for the formation of epoprostanol (PGI₂) metabolites present in rat urine.

The identities of the numbered compounds are:

Estimate of
Percentage of
Urinary
Radioactivity

The following two studies (#7200/80/7222/006 and #7200/80/7256/005) in rats were previously reviewed under NDA and the review is reproduced below.

Study # 7200/80/7222/006 [p 4.04018]

Title: Studies on the Metabolism of FLOLAN. Metabolic Disposition of 11-³H-FLOLAN After a Single Intravenous Dose in the Rat.

Date: Study conduct dates not reported, Report date: 3/10/80

Conducting Lab:

MATERIALS AND METHODS

Animals: 8 female UTC/SD rats, 180-200 g.

Dose: A single iv dose of 83 ug (11.7 uCi)/rat.

Methods: Each rat was administered the labelled FLOLAN iv and complete urine and fecal collections were made for 10 days. At the end, all the rats were killed and tissues were collected for radioactivity measurements.

Results: The urinary and fecal excretion of the labelled FLOLAN on day 10 was 49.41±3.85 and 35.03±9.15% (total of 84.44±10.12%), respectively. The remaining 15% radioactivity could not be accounted for, possibly from the radioactivity sticking to the collecting vessels and that could not be washed to measure. About 95% of the radioactivity was recovered in the first 72 hours (in comparison to 25 hours in another study, see below). There was no loss of ³H label through expiration. The excretion of radioactivity occurred in two phases: in the first early rapid phase, $t_{1/2}$ was 22.69±5.73 hour, and in the later slow phase, $t_{1/2}$ was 100.75±28.02 [less than 3% of the total dose]. Based on tissue distribution studies, and data from 3 rats [due to very high variability] only about 0.21±0.05% radioactivity remained in the body with no substantial amounts concentrated in any one particular organ, except in one of 8 rats, where FLOLAN had accumulated in the spleen up to 51% of the total radioactivity. Fecal excretion of 35% in the rat was in agreement with the biliary excretion of about 40% within the first 3 hours of dosing suggesting that FLOLAN may be directly excreted into the bile.

In summary, most of FLOLAN is excreted within the first 3 days after administration, the C-11 position, which contains the ³H, appears to be metabolically stable since only trace amounts of tritiated water could be detected in the urine, and FLOLAN does not accumulate in any one organ in the rat.

7200/80/7255/005

Title: Metabolism of 11b-³H-U-53,217A in Rats. Radioactivity Balance Study Following Intravenous Administration and Estimation of Radiation Exposure to Humans.

Conducting Lab:

Dates: September 18, 1980

MATERIALS AND METHODS

Chemical: 11b-³H-U-53,217A

Animals: 5 rats

Doses: A single iv dose at 105 ug/kg (about 25 ug/rat, 13 uCi/rat).

Methods: Each rat, housed individually in the standard metabolic cage, was injected with the radiolabelled test substance and complete urinary and fecal collections were made for 7 days in the standard metabolic studies. At the end, the rats were autopsied and tissues were collected for measuring radioactivity by liquid scintillation/HPLC techniques.

Results: The urinary and fecal excretion of ³H-FLOLAN was 36.63±2.45 (std.dev) and 61.43±2.39%, respectively (a total of 98.0±0.97%). About 95% of the urinary excretion was complete within the first 25 hours, and 98% of the fecal excretion was complete in 42 hours. The tissue levels of the labeled FLOLAN were 47-151, 13-43, less than 74, and less than 17 pg/g tissue in the bladder, spleen, eye, and the cellular material (blood cells), respectively. The rate of disappearance of FLOLAN from these organs was not estimated.

Dog:

Elimination of prostacyclin (PGL₂) and 6-oxo-PGF_{1α} in anesthetized dogs (J. Pharm. Pharmacol. 31:529-532, 1979)

Methods: The elimination of prostacyclin and 6-oxo-PGF_{1α} was studied following a continuous intravenous infusion (1 μg/kg/min for 10 minutes) of prostacyclin or 6-oxo-PGF_{1α} in three dogs. The plasma concentration of 6-oxo-PGF_{1α} was measured by radioimmunoassay.

Results: The results showed that the steady state concentrations of 6-oxo-PGF_{1α} were rapidly achieved (within 10 minutes) after administration of both prostacyclin and 6-oxo-PGF_{1α}. The plasma concentrations of 6-oxo-PGF_{1α} were ~30-64 ng/ml following administration of prostacyclin and ~40-80 ng/ml following administration of 6-oxo-PGF_{1α}. After termination of the infusion, the plasma concentration of 6-oxo-PGF_{1α} declined bi-exponentially. The initial, rapid component (α phase) and the late, slow component (β phase) reflected the rate of elimination and release from sites of distribution, respectively. The half lives were ~0.5 to 1.6 minutes for α phase and ~10 to 20 minutes β phase, respectively.

Circulating prostacyclin metabolites in the dog (J. Pharmacol. Exp. Ther. 224 (3): 692-698, 1983)

Methods: The plasma concentrations of prostacyclin metabolites were determined following a single intravenous administration of 11β-³H-PGI₂ (5 μg/kg) with specific activity of 416 μCi/mg in five dogs. The blood samples were withdrawn at 0.33, 0.67, 1, 3, 5, 20, 30, 60 and 120 minutes after dosing. The metabolites were identified using TLC and liquid chromatography.

Results: PGI₂ was rapidly metabolized. The identified metabolites were 6-keto-PGF_{1α}; 6-keto-PGE₁; 2,3-dinor-6-keto-PGF_{1α}; 2,3-dinor-13,14-dihydro-6,15-diketo-20-carboxyl-PGF_{1α} and 2,3,18,19-tetranor-13,14-dihydro-6,15-diketo-20-carboxyl-PGF_{1α}. The plasma disappearance curve for PGI₂ metabolites was biphasic with a rapid half life of 22.2 seconds and a slow half life of 86.1 minutes. A major metabolite, 6-keto-PGF_{1α}, was identified in plasma 20 seconds after the injection of the drug. By 30 minutes, the major metabolites were 16- and 18- carbon dicarboxylic acids. By 60 minutes, the predominant metabolites were two unidentified polar compounds. The percentage of the major metabolites detected in the plasma was summarized in the following table.

Metabolite	Time after dosing, minutes	% in plasma
6-keto-PGF _{1α}	0.33	65
16,18-carbon dicarboxyl acids	20-30	25-35
unknown polar compound	60	85

Vascular sensitivity to prostaglandin I₂ and urinary excretion of 6-oxo-prostaglandin E₁ in conscious dogs (Clinical science 71:527-532, 1986)

Methods: PGI₂ was infused intravenously into dogs at rate of 7.5, 15 or 30 ng/kg/min for four hours. The metabolites of PGI₂ were measured by gas chromatography and mass spectrometry.

Results: The results indicated that the urinary excretion of 6-oxo-PGF_{1α} increased as the infusion rate of PGI₂ increased. The linear relationship between urinary excretion of 6-oxo-PGF_{1α} and the rate of infusion of PGI₂ was described by the equation of $Y = 0.4212X + 2.702$ ($r = 0.99$), where $Y =$ urinary 6-oxo-PGF_{1α} (ng/min) and $X =$ the infusion rate (ng/kg/min). For example, at the infusion rate of 30 ng/kg/min, the urinary excretion of 6-oxo-PGF_{1α} was ~15 ng/min. The calculated basal rate of entry of prostacyclin into the systemic circulation in conscious dogs was 4 ng/kg/min.

The following two studies (#7200/80/7222/041 and #7200/81/7222/005) in dogs were previously reviewed under NDA 19,607 on August 15, 1988 and the review is reproduced below.

Study #7200/80/7222/041

Title: Metabolism of FLOLAN. V. Absorption, Excretion, and Plasma Levels of U-53,217A-H in the Female Dog.

Date: Study conduct dates not reported, Report date: 11/12/80

Laboratory:

MATERIALS AND METHODS

Chemical: 11b-³H-FLOLAN, specific activity 502 uCi/mg.

Animals: 3 Female beagle dogs, each weighing about 11 kg.

Dose: 100 ng/kg/min FLOLAN by continuous iv infusion for 5.5 hr.

Methods: The labelled agent was infused iv continuously for 5.5 hr via an indwelling catheter and the urine samples were collected from the urinary bladder catheter at 2, 4, 5 hr during infusion, 8 hr post infusion, and then at 24-hr intervals for 7 days. Blood samples were collected at 2, 4, 5 hr during infusion, 15, 30, 45, 60, 120, & 180 min after stopping the infusion.

Results: During the infusion, all three dogs became depressed, listless, and vomited frequently with some bile in one of them. The plasma levels of FLOLAN at 3 hr into infusion were 27.82±21.19 ng/ml and there was a consistent decrease upon termination of infusion with a mean disappearance of $t_{1/2}$ of 44.96±5.40 minutes. About 98% of the radioactivity was recovered (88% in the urine and about 10% in the feces), and greater than 95% of the dose was excreted within first 48 hours. Negligible amounts of ³H was excreted via expiration.

Further, about 60% of the radioactivity was excreted in the urine during the infusion period of 5 hr, and the rate of excretion was estimated at 90% in an average of 7.1±0.2 hours, while in the feces, the rate of excretion was 21.3±9.1 hours. On a comparative note, in the rat (see below), about 35-60% of FLOLAN was excreted via feces, while in the dog, it was 10%.

Summary: In the dog, although greater than 95% of radioactivity was excreted in 48 hours, same as in the rat, excretion route was different in the dog with 90% in the urine and 10% in the feces, while in the rat fecal route accounted for about 35-40% of the administered FLOLAN at a dose of 100 ng/kg.

Study # 7200/81/7222/005

Title: Metabolism of FLOLAN. VI Isolation and Characterization of the Major Urinary Metabolites of PGI₂ in the Dog.

Date: 2/11/81

MATERIALS AND METHODS

Chemical: 11b-³H-U-53,217A; specific activity 502 uCi/mg.

Animals: 3 Female beagle dogs

Dose: 100 ng/kg/min infused iv.

Methods: ³H-FLOLAN was infused iv for 5.25 hr at a rate of 12.5 ul/min and the urine samples were collected as before (earlier study # 7200/80/7256/005), i.e. at 24-hr intervals for 7 days, and the radioactivity was determined by standard HPLC and liquid scintillation techniques. Urinary metabolites were isolated and identified.

Results: At this dose of 100 ng/kg/min, which was 10x higher than the dose intended for humans, and 5x higher than the dose tested in the monkeys, the dogs were depressed and experienced vomiting (GI distress) similar to that seen in the rats and monkeys. One dog was unable to tolerate this dose and thus on day 4 the dose of FLOLAN was reduced to 50 ng/kg/min for the remainder of the study.

About 80% of radioactivity was excreted in the urine within 7 hours of infusion. The metabolites that were identified and their estimated abundance are shown in Figure 2 (see page 25 of this review, attached is sponsor's figure 2, page 4.04090) and Table 7 below.

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The major metabolites were: 9,11,19-tri-OH-6,15-diketo-2,3-dinor-prostan-1-oic acid (22.8%), and 9-11,di-OH-6,15-keto-2,3-dinor-prostan-1-oic acid (11.4%). The metabolite, 6-keto-PGF_{1α}, and other monoketo metabolites of FLOLAN were not detected in the urine of dogs. The hydroxy metabolites that have been identified in the rat and the monkey were not identified in the dog, but according to the sponsor, efforts are underway to identify these in the dog. The other glucuronide conjugates, not yet identified, may be present in the feces or in the bile.

Monkey:

Metabolism of prostacyclin in cynomolgus monkey (Prostaglandins 21(2): 307-314, 1981)

Methods: The metabolism of prostacyclin was studied in three monkeys following an intravenous infusion of 11-³H-PGI₂. The initial rate of infusion was ~4 mg/monkey/day for three days and then the rate was increased to 8 mg/monkey/day on day 4. The infusion was continued for total 7 days. The metabolites of PGI₂ were measured by reverse phase column chromatography and gas chromatography-mass spectrometry.

Results: The results indicated that 12 metabolites were identified in urine and accounted for ~50% of the urinary radioactivity. The proposed pathways for the formation of these metabolites and their estimated percentage of radioactivity in the monkey urine are depicted in the following figure.

Figure 4. Proposed pathways for the formation of epoprostenol (PGI₂) metabolites present in monkey urine.
The identities of the numbered compounds are:

**Estimate of
Percentage of
Urinary
Radioactivity**

The major metabolite in urine was unchanged 6-keto-PGF_{1α} (16% of the urinary radioactivity), suggesting that monkey is not able to metabolize 6-keto-PGF_{1α} as extensively as the rat. In the rat, little 6-keto-PGF_{1α} was detected in the urine (Biochemistry 17(19): 4096-4101, 1978).

Cat:

Formation and elimination of prostacyclin metabolites in the cat *in vivo* as determined by radioimmunoassay of unextracted plasmas (European J. Pharmacology 74:19-26, 1981)

Methods: The metabolism of prostacyclin was studied following an intravenous bolus injection of prostacyclin sodium at 500 ng/kg. The metabolites of PGI₂ were separated by TLC and then measured by radioimmunoassay.

Results: The results indicated that 6-keto-PGF_{1α} was detected right after dosing and declined rapidly with a mean half life of 1.38 minutes (ranging minutes). 13,14-dihydro-6,15-diketo-PGF_{1α} appeared ~ 1 minutes after dosing and declined slower with a mean half life of 8.4 minutes (ranging minutes). After ~ three minutes, 13,14-dihydro-6,15-diketo-PGF_{1α} was predominant due to its relative longer half life.

Elimination from the circulation of cats of 6-keto-prostaglandin E₁ compared with prostaglandins E₂ and I₂ (J. Pharm. Pharmacol. 35:724-728, 1983)

Methods: The plasma concentrations of 6-keto-PGF_{1α}, 6-keto-PGE₁ and PGE₂ were measured using radioimmunoassay following intravenous bolus injection of epoprostenol sodium, 6-keto-PGE₁ and PGE₂ at 5 μg/kg in cats. Blood samples were collected before and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 15 minutes after dosing.

Results: The results indicated that the peak concentrations of 6-keto-PGF_{1α}, 6-keto-PGE₁ and PGE₂ were reached at ~ 1 minutes and elimination half lives were 1.16-2.01, 1.04-2.19 and 0.29-1.08 minutes for 6-keto-PGF_{1α}, 6-keto-PGE₁ and PGE₂, respectively.

Rabbit:

Intravenous administration of prostacyclin in rabbits: elimination kinetics and blood pressure response (J. Lab. Clin. Med. 107(3):187-193, 1986)

Methods: The elimination of prostacyclin was studied following either an intravenous bolus injection of ³H-PGI₂ at 107 ng/kg or an intravenous infusion of ³H-PGI₂ at 4.2, 27, 85, 241 and 604 ng/kg/min for one hour. The blood samples were withdrawn at 1, 1.5, 2, 4, 6, 9, 12, 16

and 20 minutes after the intravenous bolus injection. After the intravenous infusion, the blood samples were withdrawn at 1, 4, 8, 15, 30, 45 and 60 minutes. The amount of $^3\text{H-PGI}_2$ was determined using a beta counter. The blood pressure response was also determined following intravenous administration of prostacycline.

Results: Following intravenous bolus injection, the terminal elimination half life for $^3\text{H-epoprostenol}$ was 2.7 minutes, calculated systemic clearance and the whole body volume of distribution were 93 ml/kg/min and 357 ml/kg, respectively. Following continuous intravenous infusion, the steady state concentrations were reached within 15 minutes after the infusion and increased linearly with increase in the infusion rate. The steady state concentrations of $^3\text{H-PGI}_2$ were _____ ng/ml at the infusion rate of _____ ng/kg/min, respectively. Prostacyclin decreased the mean arterial blood pressure in a concentration-dependent manner when the steady state plasma concentrations were greater than _____ ng/ml. It decreased _____ mm Hg at the steady state plasma concentration of _____ ng/ml.

Pharmacokinetics of prostacyclin (Circulation 68 (Supp III): 414, 1983 and Thromb and Haemost 50:341, 1983)

These two similar studies were submitted in abstract formats. The *in vitro* stability of $^3\text{H-PGI}_2$ was determined in rabbit whole blood and plasma. The *in vivo* pharmacokinetics were studied in conscious and anesthetized rabbits following a bolus intravenous injection of $^3\text{H-PGI}_2$ at 85 ng/kg and a continuous infusion of $^3\text{H-PGI}_2$ at 4, 85 and 640 ng/kg/min. $^3\text{H-PGI}_2$ and $^3\text{H-6-keto-PGF}_{1\alpha}$ were measured using HPLC. The results indicated that the *in vitro* half lives of $^3\text{H-PGI}_2$ were 11.7 ± 3.1 for blood and 11.5 ± 1.7 minutes for plasma, respectively. The results obtained from the *in vivo* study indicated that the data for $^3\text{H-PGI}_2$ were fit to a 3 exponential equation and the *in vivo* elimination half life of $^3\text{H-PGI}_2$ following intravenous bolus injection of $^3\text{H-PGI}_2$ at 85 ng/kg was 2.9 minutes. The calculated whole body of distribution was 1015 ml/kg and the calculated whole body clearance rate was 4.27 ml/kg/sec or 256 ml/kg/min. The steady state plasma levels of $^3\text{H-PGI}_2$ were reached within 15 minutes and they were 0.061, 1.37 and 7.99 ng/ml following continuous infusions of $^3\text{H-PGI}_2$ at 4, 85 and 640 ng/kg/min, respectively.

In Vitro Studies:

Rabbit:

Pulmonary metabolism of prostacyclin (PGI_2) in the rabbit (Biochem. Biophys. Res Commun. 83(2):731-738, 1978)

Methods: Metabolism of $9\text{-}^3\text{H-PGI}_2$ was studied in the isolated perfused rabbit lung preparation and in the post-microsomal supernate of rabbit lung homogenate. The specific radioactivity was $36.8 \mu\text{Ci}/\mu\text{mole}$. $9\text{-}^3\text{H-PGI}_2$ at $15.5 \text{ Ci}/\text{mmole}$ was injected into the arterial inflow over a period of 5 minutes. The venous effluents were collected for total 30 minutes. The metabolites in the effluents were separated by TLC and identified by gas chromatography and mass spectrometry.

Results: Two major metabolites were identified as 6-keto-PGF_{1 α} (represented 65% of the total radioactivity) and 6,15 diketo-13,14 dihydro PGF_{1 α} (14%) in the perfusate from the isolated lung. In the incubations of 9-³H-prostacyclin with the lung homogenate, 6,15 diketo-13,14 dihydro PGF_{1 α} was identified as the major metabolite and represented ~ 25-36% of the total radioactivity.

Hepatic metabolism of prostacyclin (PGI₂) in the rabbit: formation of a potent novel inhibitor of platelet aggregation (Biochem. Biophys. Res. Commun. 93(2):486-494, 1978)

Methods: Metabolism of prostacyclin was studied in the isolated perfused rabbit liver. 9-³H-PGI₂ at 1.8 μ Ci/mM was infused into the liver through the cannula inflow for 5 minutes. The effluents were collected for total 30 minutes. The metabolites in the effluents were separated by TLC and identified by gas chromatography and mass spectrometry.

Results: Five metabolites were identified in the perfusate. They were 19-hydroxy-6-keto-PGF_{1 α} , 6-keto-PGF_{1 α} , dinor-6-keto-PGF_{1 α} , pentanor-PGF_{1 α} and a 6-keto-PGE₁-like substance. Among them, 19-hydroxy-6-keto-PGF_{1 α} and 6-keto-PGF_{1 α} represented 5% and 45%, respectively, of the total radioactivity. Pentanor-PGF_{1 α} and a 6-keto-PGE₁-like substance accounted for 39%. Presence of dinor and pentanor derivatives of 6-keto-PGF_{1 α} suggests that β -oxidation and oxidative-decarboxylation occur in the liver as the major metabolic pathway of PGI₂.

Metabolism of prostacyclin in the rabbit kidney (J. Biol. Chem. 254(1):12-14, 1979)

Methods: Metabolism of prostacyclin was studied in the isolated perfused rabbit kidney. 9-³H-PGI₂ at 15.5 μ Ci/ μ mol was infused into the kidney through the arterial cannula inflow for 5 minutes. The venous and ureteral effluents were collected for total 30 minutes. The metabolites in the effluents were separated by TLC and identified by gas chromatography and mass spectrometry.

Results: The results indicated that the major metabolites were 7,9-dihydroxy-4,13-diketo-dinoprostanic acid and dinor-6-keto-PGF_{1 α} , the products of β -oxidation. They represented 25% and 10% of the total radioactivity.

Urinary and systemic metabolites of prostacyclin in the perfused rabbit kidney (Renal Physiol. Basel, 5:186-191, 1982)

Methods: Metabolism of prostacyclin was studied in the isolated perfused rabbit kidney. Prostacyclin was labeled with tritium at C16 to C19 positions and infused into kidney at 0.23 μ g/min for 60 minutes. The metabolites in the effluents were separated by TLC and identified by gas chromatography and mass spectrometry.

Results: Dinor-keto-PGF_{1 α} and 6-keto-PGF_{1 α} were detected from ureteral and venous effluents. Dinor-keto-PGF_{1 α} , the product of β -oxidation, represented 9.6% of the total radioactivity in ureteral venous effluent and 9.1% in renal venous effluent. 6-keto-PGF_{1 α} accounted for 39.2% in ureteral and 58.2% in renal venous effluents, respectively.

Transformation of prostacyclin (PGI₂) to a biologically active metabolite: 5(6)-oxido-PGI₂ by cytochrome P450-dependent epoxygenase (Adv. Exp. Med. Biol. 281:245-250, 1990)

Methods: Metabolism of prostacyclin was studied in the isolated perfused rabbit kidney. 9-³H-PGI₂ at 12.76 μ Ci/mole was infused into the kidney through the renal artery. The venous and ureteral effluents were collected for total 30 minutes. The metabolites in the effluents were separated by TLC and identified by gas chromatography and mass spectrometry.

Results: 5-hydroxy-6-keto-PGF_{1 α} , pentanor PGF_{1 α} and 6,15-diketo-13,14-dihydro PGF_{1 α} were identified in the renal perfusate. 5-hydroxy-6-keto-PGF_{1 α} represented 34% of the total radioactivity. The other two metabolites accounted for 44%. Formation of 5-hydroxy-6-keto PGF_{1 α} in the kidney suggests that epoxidation of prostacyclin is an alternative pathway of PGI₂ metabolism.

Monkey:

Metabolism of prostacyclin: Oxidation by rhesus monkey lung 15-hydroxyl prostaglandin dehydrogenase (Arch. Biochem. Biophys. 189(1):92-96, 1978)

Methods: 15-hydroxyl prostaglandin dehydrogenase (15-OH-PGDH) was prepared from rhesus monkey lung. PGI₂ or 6-keto-PGF_{1 α} (270 nmol) was incubated in 1 ml of 50 mM tris (pH=8.5) containing 1 mg of 15-OH PGDH from the rhesus monkey lung. The reaction products (metabolites) were identified by gas chromatography and mass spectrometry.

Results: Both epoprostenol and 6-keto-PGF_{1 α} were metabolized to 6,15-diketo-PGF_{1 α} by 15-PGDH. However, the oxidation of epoprostenol was 4-6 times faster than that of 6-keto-PGF_{1 α} .

The *in vivo* pharmacokinetics of prostacyclin in human were not studied due to the inherent nature of the drug molecule, continuous biosynthesis and rapid metabolism, low concentrations in plasma and lack of a sensitive, specific and precise assay. Intravenous infusion is the proposed route of administration and thus the bioavailability is not a concern. The available clinical experience indicated that the continuous infusion is required to maintain effective concentrations in patients, suggesting that epoprostenol is rapidly metabolized and not accumulated in the human body. The *in vitro* studies revealed that the half lives of prostacyclin were ~6 and 11 minutes in the human blood and plasma, respectively. 6-keto-PGF_{1 α} was also the major plasma metabolite in human. It represented ~42% of the total radioactivity. The recoveries of radioactivity within 7 days after 24 hour infusion of prostacyclin were 82% in

urine and 4% in feces. The major metabolite identified in urine was 2,3-dinor-6-keto-PGF_{1α}. To compare the similarities and differences among the species including the rat, dog, monkey, cat, rabbit and man, the pharmacokinetic studies were summarized and presented in the following tables.

Comparison of pharmacokinetics between the rabbit, cat and dog

Species	Dose	T _{ss} (min)	C _{ss} (ng/ml)	T _{1/2α} (min)	T _{1/2β} (min)	Analyte
Rabbit	4 * 85 * 640 * 107 **					³ H-PGI ₂ . . .
Cat	100 * 500 **					. 6-keto-PGF _{1α}
Dog	1000 *					.

* = continuous i.v. infusion (ng/kg/min), ** = i.v. bolus (ng/kg), T_{ss} = time to steady state concentration, C_{ss} = steady state concentration.

Comparison of major route of excretion between the rat, dog, monkey and man

	Rat	Dog	Monkey	Man
Urine (% of given dose)	33-49	80-88	45	82
Feces (% of given dose)	35-61	10	----	4

In brief, following intravenous continuous infusion of FLOLAN, its steady state plasma levels measured by either ³H-epoprostenol or ³H-metabolites were reached within 10-15 minutes in rabbits and dogs and within ~ 45-60 minutes in cats. The steady state plasma levels increased linearly with increase in the infusion rate. Following intravenous bolus injection, FLOLAN was quickly eliminated in the dog, rabbit and cat with t_{1/2α} = 0.5-1.5 minutes and t_{1/2β} = 1.29-14 minutes. FLOLAN was quickly metabolized to a number of metabolites. Seven urinary metabolites in rats, 6 in dogs and 12 in monkeys have been identified. The major metabolites include 6-keto-PGF_{1α} detected in the bile (9.2% of radioactivity) in rats and in the urine (16%) in monkeys. Other major metabolites detected in urine are 9,11-dihydroxy-2,3,19,20-tetranor-6,15-diketo-prostan-3,18-dioic acid (19%), 9,11,15,19-tetrahydroxy-2,3-dinor-6-keto prostan-13-en-3-oic acid (17.1%) in rats, 9,11,19-trihydroxy-6,15-diketo-2,3-dinor prostan-1-oic acid or 9,11,20-trihydroxy-6,15-diketo-2,3-dinor prostan-1-oic acid (22.8%) and 9,11-dihydroxy-6,15-diketo-2,3-dinor prostan-3,20-dioic acid (11.4%) in dogs. The calculated systemic clearance and the whole body volume of distribution were 93 ml/kg/min and 357 ml/kg, respectively in rabbits. The *in vitro* studies indicated that the lung, kidney, liver and blood vessels had the capability to metabolize FLOLAN. Tissue distribution studies indicated that the highest levels of radioactivity were detected in the tissues associated with route of excretion including the kidney, liver and small intestine in rats. The major routes of excretion are by urine (33-49% of the given dose in rats, 80-88% in dogs, 45% in monkeys and 82% in men) and feces (35-61% in rats, 10% in dogs and 4% in men).

TOXICOLOGY:

ACUTE TOXICITY:

The following two acute toxicity studies were not previously submitted: an acute single-dose intravenous toxicity study in mice (BPAT 81/54) and a comparative acute single dose intravenous toxicity study (BPAT 81/13).

An acute single-dose intravenous toxicity study in mice of U-51787, U-53772A, U-54779, U-55175 and U-58018A compared with epoprostenol (Study # BPAT 81/54)

Testing Laboratory: Sponsor's laboratory

Study start and completion dates: February 2, 1981 and February 17, 1981

GLP and OAU compliance statement: Sponsor included a quality assurance statement. No statement of compliance with GLP regulation was included.

Animals: Males (33.1 ± 0.27 g, 42 days old) and females (23.4 ± 0.17 g, 42 days old) CD1 mice from Charles River, UK. Ltd.

Methods: Total 86 male and 86 female mice were employed in this study. Single intravenous doses of epoprostenol (50 and 100 mg/kg), U-51787 (6-oxo-PGF_{1 α} , 50 mg/kg), U-53772A (5(E) PGI₂, 10 mg/kg), U-54779 (6R- Δ^4 -PGI₁, 50 mg/kg), U-55175 (6S- Δ^4 -PGI₁, 50 mg/kg) and U-58018A (Diepoxy PGI₁, 100 mg/kg) were given to groups of 8-10 male and female mice. Control groups received control vehicle only (10 ml/kg glycine buffer). The animals were observed for signs of toxicity right after dosing and at 5, 20 and 80 minutes, 4, 12 and 24 hours on day 1, day 2 and thereafter at 2-4 day intervals until 14 days after dosing. Body weights were recorded immediately before dosing, on days 1, 2, 4, 7, 11 and 14 or 1, 2, 6, 10 and 14 after dosing. Autopsy examination was performed on all animals at termination.

Results: Clinical signs were similar in all test groups and included hypoactivity, ataxia, loss of righting reflex, slowed and/or deepened respiration, piloerection and reddening of pinnae, muzzle and paws. The body weight gains were not obviously different between control and test groups at the end of the study. The autopsy examination at termination revealed that there were no treatment-related abnormalities. One mortality was a male mouse in the group of U-55175. The autopsy examination showed that this male mouse had frothing from nose and congested/hemorrhagic lungs.

A comparative acute single dose intravenous toxicity study of $\Delta 6$ -prostaglandin I₂ ($\Delta 6$ -PGI₂) and prostacyclin (PGI₁) in male mice (Study # BPAT 81/13)

Testing Laboratory: Sponsor's laboratory

Study start and completion dates: April 16, 1980 and April 30, 1980

GLP and OAU compliance statement: Sponsor included a quality assurance statement. No statement of compliance with GLP regulation was included.

Animals: Males (23.8 - 24.2 $\pm$ 0.49 g, age was not specified) CD1 mice from Charles River, UK. Ltd.

Methods: Total 55 male mice (CD1, supplied by Charles River) were employed in this study. Single intravenous doses of PGI₂ (0.01, 0.1, 1.0 and 100 mg/kg) and $\Delta 6$ -PGI₁ (0.01, 0.1, 1.0, 10, 100 mg/kg) were given to groups of 5 male mice. Control group received control vehicle only (10 ml/kg glycine buffer). The animals were observed for signs of toxicity right after dosing and at 5, 20 and 80 minutes, 4, 12 and 24 hours on day 1 and days 2, 4, 6, 8, 10, 12 and 14 days after dosing. Rectal temperature was measured when the animals were observed for signs of toxicity. Body weights were recorded immediately before dosing and then every 2 days for 14 days. Autopsy examination was performed on all animals at terminations.

Results: Clinical signs were similar in all test groups and included hypoactivity, ataxia, loss of traction reflex, bradypnea, ptosis, piloerection and reddening of pinnae, muzzle and paws. The mean body weights were not significantly different between the control and test groups. Body weight gains were not obviously different between control and test groups except that at dose of 1 mg/kg or greater the body weights were slightly (2.5-5%) depressed 1-2 days after dosing. Rectal temperature was depressed in a dose-dependent manner following administration of either PGI₂ or $\Delta 6$ -PGI₁. The maximum fall of the mean temperature in 100 mg/kg groups were ~ 3 - 4° C compared to the control. The autopsy examination at termination revealed that there were no treatment-related abnormalities. One mortality was in the group of 100 mg/kg PGI₂.

The following toxicity studies were previously submitted to NDA _____ and reviewed on August 15, 1988 and this review is reproduced on the following pages.

General Comments

Chemical

The lot/batch numbers used in individual studies are shown in Table 1. In all the studies, except where indicated, FLOLAN was the sodium salt of prostacyclin, and was dissolved in 0.05M Tris-HCl, pH 8.4, or Glycine buffer, pH 10.5. Sponsor did not provide any explanation for using two different buffers in different studies. However, neither buffer had any significant, at least pharmacologic effects of FLOLAN tested at 0.125, 0.5, or 2 ug/kg, in either buffer (0.05M Tris buffer, pH 10.5, or 0.05M Glycine buffer, pH 10.5).

FLOLAN solutions were generally prepared immediately before injecting due to the unstable nature of the drug, and it was tested periodically to ensure that its stability and potency (platelet antiaggregatory activity) remained constant throughout testing.

GLP Compliance

Most studies sponsored or conducted by the sponsor were performed prior to the GLP regulations becoming effective on June 20, 1979. At the time, Burrows Wellcome Labs did not have Quality Assurance units in operation, and thus many details that are currently required by FDA's GLP regulations were not adhered to by the study labs. These deviations were in the areas of monitoring the personnel records, protocols, standard operating procedures, the records of maintenance of chemical storage, testing, and study records not signed by study directors. However, in the presence of such minor departures from GLP regulations, in this reviewer's opinion, the studies should not be considered invalid unless severe deficiencies (such as missing animals, missing histology data etc.) are encountered which was not the case in this NDA.

Acute Studies

Two acute toxicity studies were conducted with mice and one with rats. These are summarized in Table 8 (page 28 of this review). Briefly, an iv LD₅₀ in the mice was greater than 10 mg/kg. The major toxic effects were: flushing, hypoactivity, hunching, slow breathing, and dose-related hypothermia (with a maximum temperature drop of 3.2°C).

In the rat, an iv LD₅₀ for both male and female rats was estimated at 66.3 mg/kg. The major toxic effects were: flaccid paralysis, hypoactivity, ataxia, lost or weak righting reflex, slow or deep labored breathing, ptosis, and piloerection, dose-dependent hypothermia.

Table 2
Summary of Acute Toxicity Studies with FLOLAN (NDA)

Report #	Animal, #/sex/gr	Doses, # of days observed	Significant Effects/Comments
BPAT 78/32* Aug/79	Mice, 10/sex/gr	0, 0.1, 0.3, 1, 10 mg/kg observed for 10 d, <u>iv</u>	LD ₅₀ - greater than 10mg/kg; hypoactivity, deep slow breathing, hunching, flushing, hypothermia.
BPAT 78/34* Aug/78	Mice, 10/sex/gr	0, 0.003, 0.03, 0.1, 0.3 and 1 mg/kg, <u>iv</u> ; observed for 3 days.	Hypoactivity, hunching, slow breathing, flushing, dose- dose-related hypothermia.
BPAT 80/22 Dec/79	Rats, 10/sex/gr	0, 0.0001, 0.01, 1.0, 100 mg/kg, <u>iv</u> ; observed for 2 weeks; doses 25, 35, 50, 70, 84 mg/kg were also tested.	LD ₅₀ - 66.3 mg/kg (51.3-77.5); hypoactivity, ataxia, labored breathing, flaccid paralysis, hemorrhagic patches in a few rats.

Addendum: In study BPAT 78/32, one male mouse died in the 10 mg/kg group. There were no mortality in study BPAT 78/34. In study BPAT 80/22, there was no mortality in the 35 mg/kg group and 2 female rats died in the 50 mg/kg group. Therefore, the minimal lethal doses were identified at 10 mg/kg in mice and 50 mg/kg in rats.

Subacute Toxicity Studies

Study # BPAT 78/10

Title A Two-week Subacute Toxicity Study of FLOLAN by Subcutaneous Injection in the Rat.

Dates: 10/79-11/77

MATERIALS AND METHODS

Animals: Histar rats, 15/sex/treatment group.

Doses: 0 (control, 0.05M Tris buffer, pH 9.0-9.5 [p 4.02473]; [Protocol mentions pH 8.4 [p 2.02482]; 1, 10, 100 ug/kg, sc, once daily, 7d/wk, for 2 wks.

The doses for this study were selected on the basis of a previous dose-range finding study with rats (BPAT 77/12, dated 2/77). In this study, FLOLAN was injected sc at single doses of 1, 10, 30 or 60 mg/kg and the rats were observed for 7 days. There were no deaths. The major toxic effects seen were depression, labored breathing, and dose-dependent hypothermia (with a maximum drop of rectal temperature by 5-6 °F), cardiotoxicity (evidenced by depressed S-T segment, ischemia, and necrosis of the cardiac muscle). The lower dose, 1 mg/kg (10³x the anticipated human dose of 10 ng/kg/min) was without any significant toxic effects.

Methods: Animals were injected FLOLAN sc at doses indicated above once daily, 7d/week, for 2 weeks. During the experiment, the changes in the following parameters were made: general behavior, body weight, vaginal smears, food and water intake, daily; and urinalyses were performed on day 12. ECG was recorded on days 0, 7, 13; BP was recorded on pre- and post-dosing on days 1 and 11; rectal temperature on days 1, 8, 12 (pre- and 30 and 120 minutes post-injection); heart rate and pulse were recorded on days 0, 7, 13; and hematology on days 0, 13 or 14 of dosing. Ophthalmoscopy was recorded on days 0, 13 or 14 of dosing. Blood was collected from orbital sinus during pre-dosing and later from cardiac puncture and analysed for all standard hematological parameters and blood chemistry. At termination all animals were autopsied and processed for standard histological examination of tissues and organs.

Results: Stability tests showed significant amount of variability in terms of its human platelet antiaggregatory action, specially when the sample contained high concentrations of FLOLAN. ED₅₀ of samples were measured for thawed and frozen samples. For thawed sample containing 0.2 ug/ml, the ED₅₀ ranged between _____ ug on days 0, 7, 14, and 21; while at higher concentration of 20 ug/ml the ED₅₀ ranged between _____ ug/ml, respectively.

For the frozen samples of 0.2 ug/ml concentration, ED₅₀'s ranged between _____ ug/ml, and for 20 ug/ml concentration, values were _____. These data suggest that frozen samples were generally more potent (retained potency) than thawed samples, and that higher concentrations remained more stable than diluted samples.

General appearance: Generally normal appearance was observed in most animals. Due to peripheral vasodilatory effect of the drug, reddening of the ears and feet and some prostration was noticed in 100 ug/kg rats. Blood vessels of the iris were markedly dilated in this group of male and female rats, and slightly dilated in 10 ug/kg rats. Breathing was labored in 100 ug/kg group male and female rats.

Body Weight: There was significant variation in the body weight gain of animals during the study. FLOLAN at 1 and 10 ug/kg had no significant changes in the the body weight gain, while at 100 ug/kg, FLOLAN slightly reduced body weight gain of rats: controls gained 22 grams while 100 ug/kg animals gained only 14 grams.

Food Intake: FLOLAN at 100 ug/kg decreased food intake slightly in the animals, while the lower doses did not. On day 13, the control animals consumed 90.7 ± 10.25 g of food while the 100 ug/kg group rats consumed 72.5 ± 12.7 g (not significantly different).

Ophthalmoscopy: The ophthalmoscopic examinations did not reveal any significant abnormalities which could be considered drug related.

Rectal temperature: At 100 ug/kg dose, there was a significant fall in the body temperature, by 2 °C in the male rats and 3°C in females, while the lower doses did not affect body temperature significantly at 30 min post-injection.

ECG: The ECG recordings on days 0, 7, 13, prior to injection, and 15 min post-injection were performed. The heart rates were calculated from these tracings. The changes in these measurements compared to pre-dose measurements were analyzed by ANOVA with repeated measurements. No significant changes in the heart rate were seen as a result of FLOLAN treatment; possibly due to large variations in the heart rate in individual animals. For example, at 10 ug/kg/min and on day 7, the mean changes in the heart rate [bpm] 15 minutes after dosing as compared to the pre-dosing heart rates in the male and female rats were 52.5 ± 34.21 , and 25.8 ± 33.16 , respectively; and at 100 ug/kg, the changes were 95.8 ± 44.44 and 100.6 ± 54.18 , respectively; while in the control male and female rats were: 9.5 ± 22.13 and -6.0 ± 21.78 , respectively. Similar variable rates were recorded on day 13.

Similarly ECG parameters, PR (msec), QRS (msec), R (mv), S (mv), & S-T (mv) waves were compared with pre-dose values (in mill seconds) and no treatment related effects were observed at lower doses. At 100 ug/kg the polarity and size of the ST segment was depressed significantly from pre-dose values of + 0.06 to -0.17 mv 15 minute post-injection. The amplitude of the S wave was increased at 100 ug dose from 0.26 to 0.49, 15 minute post-injection.

Pulse Rate In the male rats the pulse rate increased dose-dependently to 19/min (5%), 62/min (15%) and 132/min (32%) at 1, 10, and 100 ug, respectively. In the female rats, a similar trend was seen, i.e. the pulse increased by 7, 10, and 24% at 1, 10, 100 ug doses, respectively.

Blood Pressure: Although there was a large variability, treatment related decrease in BP was evident. In male rats the mean fall in BP on day 13 was 47 mmHg (30%) and 19 mmHg (9%) at 100 and 10 ug/kg doses, in females the changes were 36 mmHg (25%) and 14 mmHg (7%) at these doses, respectively. Changes at 1 ug were not significant due to large variability.

Hematology: The only significant ($p < 0.01$) treatment related change observed in both male and female animals was a decrease in prothrombin time. Pro-times in the control, 1, 10, 100 ug/kg/min dose groups were 10.88, 10.50, 10.49, and 10.14 in the females, and in the males, 11.67, 10.53, 10.47, and 10.20 sec, respectively. Although these decreases (maximum of 7-12%) were statistically significant ($p < 0.001$), biologically they were not since the changes were not pronounced.

Blood Chemistry: No significant dose related changes were seen.

Urinalysis: No dose related changes were seen.

Autopsy: Occasional changes in absolute organ weights were seen but not relative to body weight.

Histology:

(1) Heart: Occasional needle tracks, foci of chronic inflammatory cell infiltrates and areas of hyperchromasia were seen in the myocardium in both control and treated rats from all groups. This effect did not seem to be drug related.

(2) Lungs: Peribronchiolar lymphoid hyperplasia and perivascular infiltrates of lymphocytes were seen in the lungs of 5 control rats (2M and 3F) and one female rat in 100 ug/kg dose groups; this effect did not seem to be drug related. Moreover, these changes were commonly seen in the rats.

(3) Liver: No significant drug related changes were seen except glycogen deposits in the livers of 2 control male rats and 4 female rats in the 100 ug/kg dose group. Majority of female rats from both groups had some glycogen deposits. These effects were not clinically and statistically seem to be significant.

(4) Kidneys: No significant changes were observed in the kidneys of any treated or control animals.

Injection sites: Varying degrees of hemorrhages, thrombi and minimal necrosis were seen in both groups of animals.

Summary: Daily sc injection of 1, 10, 100 ug/kg FLOLAN for 2 weeks did not produce any significant toxicity in the rats. The pharmacological effects seen were drop in BP, reflex increase in HR, peripheral vasodilation, depression of ST wave, although dose-dependent were transient. Behavioral depression was dose dependent, more in the male rats than in the females. Body weight and food intake were all decreased at 100 ug/kg in the male but not in the female rats. However, these effects were observed at extremely high doses, upto 100 ug/kg, about 10,000x the anticipated human dose of 10 ng/kg/min. The effects on the heart rate and ECG were inconsistent and non-significant due to large variations, and thus could not be attributed to FLOLAN.

Addendum: At 100 $\mu\text{g}/\text{kg}/\text{day}$, FLOLAN significantly decreased the body weight gain (22 grams gained in control and 14 grams gained in treated animals). The signs of toxicity observed at 100 $\mu\text{g}/\text{kg}/\text{day}$ were reddening of the ears and feet, hypothermia and labored breathing. Therefore, the toxic doses were 100 $\mu\text{g}/\text{kg}/\text{day}$ or greater. The no effect dose was estimated 10 $\mu\text{g}/\text{kg}/\text{day}$.

Study # 7200/80/7263/001

Title: U-53,217A: 14-Day Continuous Intravenous Infusion of FLOLAN, sodium salt in Rats.

Dates: 9/10/79-10/10/79

Chemical: FLOLAN, Lot #14285-FHL-11, in glycine buffer, 0.05M, pH 10.5, stored frozen at -20°C or less. Stability and purity were checked periodically.

Animals: Rats, (COBS.CD [SDRR] rats from Charles River), 70 d old, females 200 g, males, 300 g; 5/sex/group.

Doses: 0 (Control vehicle), 56, 180, 560 ng/kg/min.

Doses were selected from an earlier study (not provided by sponsor) where 56 ng/kg/min was the no-effect dose on blood pressure and 560 was MTD that was anticipated to produce behavioral toxicity (depression) and swelling of the paws.

Methods: Animals were infused FLOLAN at a constant rate of 0, 56, 180, and 560 ng/kg/min daily (equivalent to daily doses of 80.6, 259, and 806 ug/kg) for 14 days via iv infusion indwelling catheters. The iv infusion catheters were implanted according to the method of J.R Weeks (Prostaglandins, 17(4):495-499, 1979). The infusion pump delivered the FLOLAN or the control buffer at a rate of 1.3 ul/min. Standard observations were made pre-dosing, during dosing, and before and at termination. Animals were autopsied and appropriate organs/tissues were examined macro- and microscopically.

Results: There were no deaths. Reddening of the ears, paws, etc. (due to peripheral vasodilation) was evident in almost all high dose animals. Excessive tearing from both eyes was observed in two high dose female rats 2 to 48 minutes post-infusion. This was observed in a few animals in the mid dose group; no such effects were seen in the low dose group animals.

Body weights: There were decreases in body weight of all treated male rats 48 hour post-infusion; body weights were 97.9, 94.5, 90.7% of the initial weights in the low, mid, and high dose groups, respectively. The weight loss, however, was transient. The 14-day body weight was significantly less in the high dose group. In females, body weight decrease was less severe and of shorter duration than in the males. But the animals had recovered by the end of the experiment.

Food/Water intake: In the male rats, the group mean food consumption decreased dose-dependently ($p < 0.05$). Food consumed in the controls, 56, 180, 560 ng/kg/min dose groups was 414±61, 430±69, 365±22, and 324±31 g, respectively. Females in the respective groups consumed 395±67, 380±24, 366±8, and 368±36 g. Water intake increased significantly both in the high dose male and female rats.

Body Temperature: Significant dose-related drop in body temperature was found at 24-72 hours for male rats, and at 24 hours for female rats, and the values returned to control values within 4 days post-infusion for males and 2 days for females. The temperature fell by about 2°F in the male rats and 3°F in the female rats, and the animals recovered within 2 hours after dosing. The lower doses 56 and 180 ng/kg/min were without any significant effect.

Ophthalmoscopy: No significant effects were noted except that three rats (one in the 56 and 2 in the 560 ng/kg/min group) developed keratitis.

Hematology: Both thrombocytopenia and leukopenia were dose-dependent effects (Table 9 below), with a maximum of 50% drop in platelets in the 560 ng/kg/min dose group, and about 42% drop in leukocytes. There were no other significant changes in any other hematologic parameters.

Table 9
Platelets (x1,000/cumm) in Rats with FLOLAN

Treatment	Males	Females
Control	834±187	942±374
Low dose	718±107	858±271
Mid Dose	717±108	660±93
High Dose	434±126	464±157

Clinical Chemistry: There was a dose-dependent (but not statistically significant) drop in creatinine phosphokinase (CPK) levels in the male rats probably due to decreased platelets, since platelets are one source of CPK.

Organ Weights: No significant changes were found in any organ examined.

Histopathology: The lesions that were rare such as endocardial and valvular lesions in the right heart, and thrombosis in branches of the pulmonary artery did not seem to be drug related, but probably due to indwelling catheter.

Bone Marrow: The M:E ratios (myelocytes to erythrocytes) in the combined male and female rats in the control, 56, 180 and 560 ng/kg/min groups were 0.571±0.2, 0.656±0.24, 0.912±0.37 and 0.831±0.24 (std.dev), respectively, significantly higher at $p < 0.05$ in the mid and high dose groups, thereby suggesting an increase in the leukocytes or a decrease in the number of erythropoietic cells. No absolute bone marrow count was taken. No abnormalities in the megakaryocytes were seen.

Summary: The high dose of FLOLAN, 560 ng/kg/min caused lethargy, peripheral vasodilation, significant drop in body temperature, decreased food intake, increased water intake, thrombocytopenia and leukopenia in the rats. The mid dose (180 ng/kg/min) was the no-toxic dose. Since the changes in body weight gain were transient and not high enough, an MTD could not be estimated.

Study # 7205/82/7263/005

Title: U-53,217A: 30-Day Continuous Intravenous Infusion study on Unanesthetized Beagle Dogs

Dates: 8/6/81-10/29/81

MATERIALS AND METHODS

Chemical: U-57,217, lot # (A4) 14813-BDT-118A in 0.025 M glycine buffer, pH 10.5, stored at - 20°C.

Animals: Beagle dogs, 2/sex/group, average 9-18 months old, 7-13kg. Animals were catheterized for continuous iv infusion and were allowed 10 days to recover from surgery.

Doses: 0 (Control), 12.5, 40, 125 ng/kg/min. Doses were selected on the basis of a previous study (not provided by sponsor) where 100 ng/kg/min was infused into 2 dogs for 14 days and which resulted in GI toxicity and thrombocytopenia.

Methods: Animals were infused with the appropriate doses at a constant infusion volume of 8.99ml/day continuously for 30 days and were observed at least once daily for changes in general behavior and body weights prior to dosing, and at 4 day intervals during dosing and prior to necropsy. They were also observed for morbidity, signs of toxicity, and clinical chemistry changes, hematology, urinalysis on days: 2x pre-test, on days 15 and 29 of the study. Bone marrow was also examined at termination. At the end, the dogs were autopsied. Organs/tissues were weighed, and examined macro-and microscopically. In addition to the determination of standard hematology parameters, studies with platelets were conducted such as: platelet cAMP, platelet morphology [by scanning and transmission electron microscopy (SEM, TEM)], and platelet size distribution.

Results: Minor incidences of infusion technique-related problems such as infections at the site of injection etc. were observed; these are not discussed further in this review. In the mid dose, 1 of 4 dogs had soft feces on day 2, vomiting on day 6; in high dose group (125 ng/kg/min) all dogs had varying degree of GI distress-3 of 4 had vomitted, had diarrhea (severe in some cases) with blood in stools; and refused food during the initial infusion period.

Body weights of male dogs decreased minimally: 103, 99.3, 97.3% of the initial values in group 1, 2, and 3, respectively. The female dogs lost body weight from 8-14% initially but over the next few days gained about 3-5%. However due to small number of animals in each test group the changes seen in the test group animals were not significantly different from controls.

Food intake was variable, and generally significantly lower than controls; particularly male dogs refused to eat during the first week of study. But later both male and female dogs resumed normal eating. Correspondingly, water intake increased but was variable throughout and was parallel to food consumption.

Body temperature: Generally, hypothermia was noticed in most animals; limbs and skin surface felt cooler, distal skin temperature was 4.3 °C below the control body temperature of the dog; the mean skin temperature in high dose dogs was 5.2 °C below the control values; rectal temperature, however, of all treated animals was comparable to the controls.

Ophthalmic examination: No significant abnormal findings were recorded.

Hematology: Significant changes seen were as follows:

- (i) Decreased peripheral platelets in male and female dogs in mid and high dose groups during the first eight days of treatment. Platelet counts ($\times 1,000/\text{cumm}$) in the males were: 385 ± 5 , 304 ± 14 , 181 ± 27 , 86 ± 14 ; in the females were: 362 ± 72 , 291 ± 11 , 223 ± 40 , 80 ± 6 in controls, 12.5, 40, and 125 ng/kg/min groups, respectively. A similar trend was observed till termination of the study. There was no significant change in the prothrombin times at any time during the study. Further, platelet half-life for dose levels was somewhere between 3-9 days assuming that there was continuing release of platelets from the bone marrow since there was an increase in the platelet diameter.
- (ii) White blood cells (lymphocyte and segmented neutrophils) were also decreased at 40 and 125 ng/kg/min doses but not at 12.5 ng/kg/min. On day 2 and 10, leukocytes decreased significantly (see Table 10 below) but not on day 29 (Table 11 below). A maximum decrease was about 45% at the highest dose. Changes in erythrocytes were not significant.

Table 10
Leukocytes (x1,000/cumm), in Dogs (n=2) treated with FLOLAN

Treatment	Males/Females, Combined	
	Day 2	Day 10
Control	16.65	15.78
Low dose	14.90**	13.32**
Mid Dose	10.70**	11.42**
High Dose	9.65**	10.30**

*=p / 0.05, **= p / 0.001, the values are group means.

Table 11
Leukocytes * in the Beagle Dogs Treated with iv FLOLAN

Hematologic Parameter	MALES Treatment groups				FEMALES Treatment Groups			
	1	2	3	4	1	2	3	4
<u>Leukocytes</u> x1,000/cumm Day -1	13.4 ± 1.0	14.0 ±0.9	10.2 ±0.6	11.6 ±2.2	11.3 ±0.0	13.2 ±0.2	13.0 ±1.7	11.30 ±0.9
Day 29	15.4 ±0.5	13.0 ±2.1	9.45 ±0.0	9.40 ±2.0	11.1 ±0.3	11.8 ±1.2	12.2 ±0.9	10.9 ±2.6
<u>Lymphocytes</u> /cumm Day -1	5.90 ±0.8	5.29 ±0.9	3.79 ±0.3	5.13 ±0.5	6.01 ±0.9	4.82 ±0.5	5.20 ±0.1	3.94 ±0.1
Day 29	5.90 ±0.5	4.51 ±0.8	3.44 ±0.1	3.75 ±0.3	4.82 ±0.03	4.58 ±0.8	5.71 ±0.06	3.02 ±0.3
<u>Neutrophils</u> Day -1	5.93 ±0.1	7.18 ±0.1	5.08 ±0.2	4.89 ±1.0	4.64 ±0.8	7.44 ±0.4	6.33 ±1.8	6.39 ±0.6
Day 29	7.94 ±0.6	7.12 ±1.2	5.05 ±0.4	4.67 ±1.3	5.17 ±0.6	6.13 ±0.2	5.69 ±1.5	6.56 ±2.0

*-These values have been extracted from the sponsor's tables for days -1 and 29, although the determinations were made on days -1, 2, 4, 6, 8, 10, 12, 15, 20, 24, and 29 of the study. Dose groups: control, 12.5, 40, 125 ng/kg/min.

Serum Chemistry: Aspartic transaminase (AST) decreased dose-dependently in high and mid dose dogs at mid-term and termination (Table 12 below). Alanine transaminase (ALT) levels were depressed in high dose dogs at termination, and ALP (alkaline phosphatase) was slightly decreased also in high dose dogs at pre-test and at mid-term. Although there were no clear dose-dependent changes in ALT levels (Table 12 below), there was a trend toward decrease in the ALT levels in a dose-dependent manner. Serum calcium levels decreased and increased in some dogs and at different times during the study and thus significance of these changes is unclear. Serum potassium levels were significantly lower ($p < 0.05$) in all treated dogs on day 15, particularly in high dose male dogs, 4.22 mEq/L compared to 4.78 mEq/L in controls, which could have resulted from severe diarrhea and or vomiting.

Table 12
Serum AST (MU/ml) and ALT (IU/L) levels on day 29
in Dogs treated with FLOLAN

Treatment	Males/Females, Combined	
	AST	ALT
Control	53.5	21.2
Low dose	37.2	20.8
Mid Dose	34.7*	17.0
High Dose	27.5**	14.0**

*= $p < 0.05$. **= $p < 0.01$

Platelet Studies: Platelet cAMP levels that are normally increased with exogenous FLOLAN did not change with infusion in control dogs. However, the animals had lost this responsiveness by 25, 55, and 75%, at 12.5, 40, and 125 ng/kg/min doses, respectively. This desensitization was maximum on day 3 and continued throughout the test period of 30 days. Platelet aggregability was markedly increased dose-dependently when determined in 2 control, one dog each in low and mid dose group dogs. Platelet aggregability could not be determined in the high dose dogs due to lack of sufficient platelets (possibly from thrombocytopenia).

Platelet size distribution was such that high dose group dogs had larger platelets (presumably immature cells) after 2 days of infusion and persisted throughout the study. This shift toward larger size platelets was dose-dependent (2.4 ± 0.59 , 2.64 ± 0.57 , 3.18 ± 0.86 , and 3.33 ± 1.10 microns, with control, 12.5, 40, and 125 ng/kg/min doses, respectively). Platelet morphology showed more extensive vesicular or canalicular system in platelets in the treated dogs, possibly related to 'age' of platelets, assuming that increased average size was indicative of increased turnover.

Bone marrow: The M:E ratios were comparable in the treated and control dogs ($1.41 \pm 0.37:1$ and $1.53 \pm 0.32:1$).

Urinalyses: No significant changes were seen.

Pathology: Serosal hemorrhagic lesions were found in the GI tract of two high dose dogs (1M, 1F). Megakaryocytes were found trapped in the pulmonary capillary bed of one control male dog, and 2M and 2F each in the mid and high dose groups, and this effect was considered treatment-related (page 4.02760).

Summary: The most significant changes seen in this study were the development of thrombocytopenia, and leukopenia at 40 and 125 ng/kg/min doses. Lethargy, hypothermia, peripheral vasodilation and other effects that were dose-dependent in most cases, were the same effects that were seen in other studies with other laboratory animal species. The lowest dose of 12.5 ng/kg/min was the no-toxic dose. An MTD could not be estimated because the loss of body weight gain, eventhough 8-14%, was not statistically significant and was observed in the female dogs, and was regained quickly.

Study # 7205-82-7263-006.

Title: U-53217A (FLOLAN): Formation and Reversibility of Hematological Changes in Beagle Dogs, Report E-269.

Dates: 9/29/81-1/27/82

MATERIALS AND METHODS

Chemical: U-53,217 (FLOLAN), Lot # (A4) 14813-BDT-118A in glycine buffer, pH 10.5.

Animals: 4 Beagle dogs, 2/sex, 6.9-7.2 mo. old, 7.92-11.2 Kg.

Doses: Single dose, 125 ng/kg/min, infused continuously for 30 days, in 0.05M glycine buffer, pH 10.5

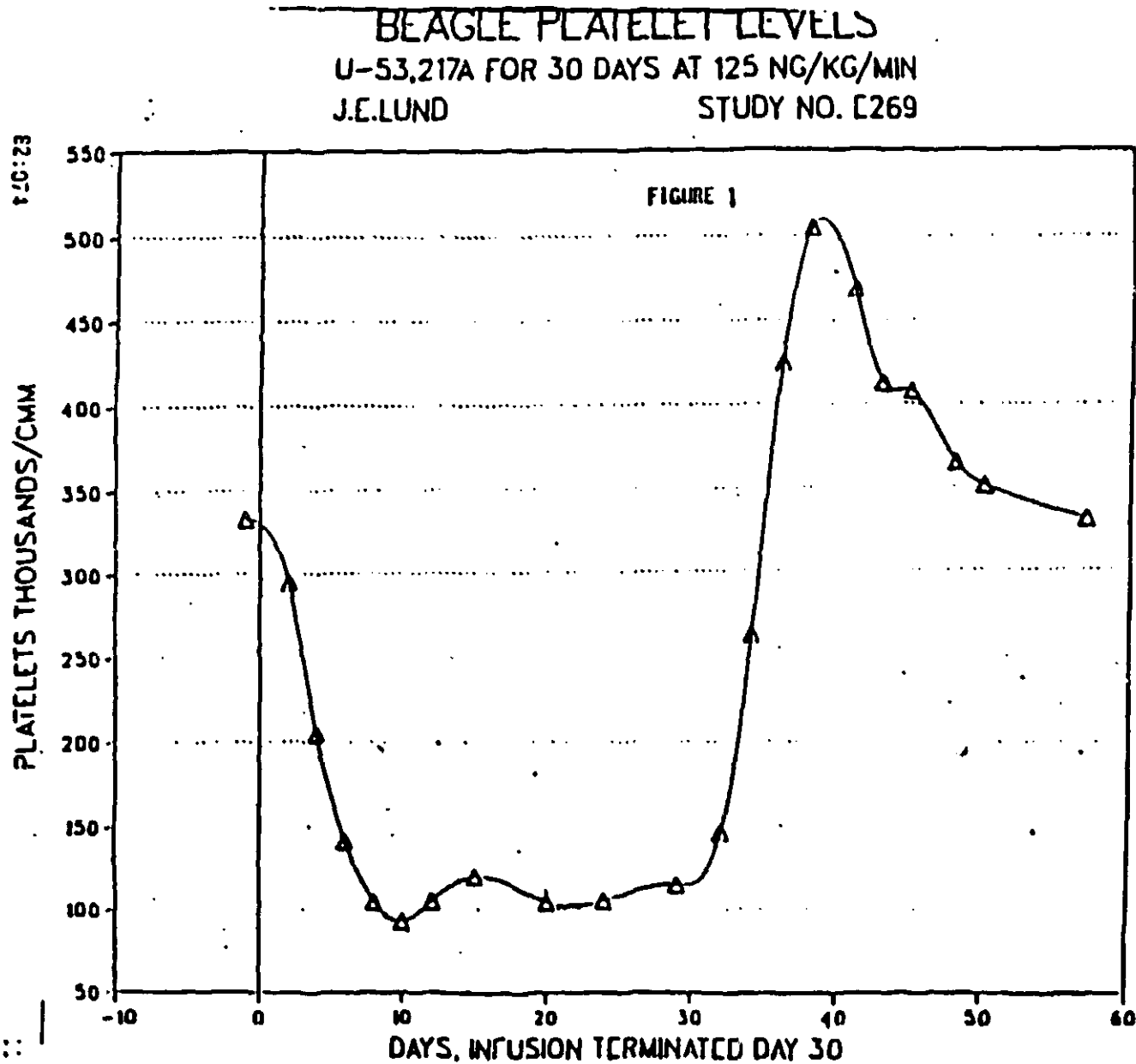
Methods: FLOLAN was infused, via a jugular catheter, continuously at a rate of 8.9 ml/day, at a dose of 125 ng/kg/min for 30 days. Clinical observations were made once daily, except on weekends. Body weights were recorded on day 4; and clinical data recorded weekly, and during reversal period and just prior to necropsy on day 120 (day 90 after the last injection). Blood samples were collected pretest, on day -21, -1, 15, 29 and 120 for hematology and serum chemistry. Animals were sacrificed on day 120 for histopathology.

Results: All animals vomited daily frequently for about 7 days, developed diarrhea for days 2-6, were inactive and refused to eat. However, GI symptoms abated by day 10-13.

Body Weights: Dogs lost body weight by about 13% during the first few days, decreased from average rate of 9.35 Kg on day -1 to 8.17 Kg on day 4, but later recovered and remained normal during the recovery period.

Hematology: Lymphocytes decreased below the pre-test levels on days 2-4 in all animals, but returned to normal by day 8. The numbers remained within the normal range of 2,800 to 4,000; segmented neutrophils initially increased but later returned to levels below the pre-test levels and remained low throughout and so did the white blood cells. Platelets decreased initially but later increased by 66% above the pre-test levels for 8 days, and decreased and later stabilized within about 20 days post-infusion. (Figure 3 on page 40 of this review, attached is sponsor's Figure 1 on page 4.02984)

Figure 3 (cont) -



Studies with Platelets: The responsiveness of the adenylate cyclase/cAMP system to FLOLAN was examined. Normally, platelet cAMP levels markedly increase in response to exogenous FLOLAN. However, during infusion, the dogs had an approximate 75% loss in sensitivity to FLOLAN. This desensitization was maximum on days 3 to 30 but had returned to normal by day 5 after infusion was discontinued. Due to these changes in the platelets, additional studies with platelets were conducted. The observed thrombocytopenia was thought to be most likely the result of increased peripheral utilization of platelets rather than decreased bone marrow production. Thrombocytopenia was reversible 5 days after discontinuing therapy.

Serum Chemistry: No significant change of any importance except slight decreases and increases in the BUN levels.

Urinalysis: No significant changes were seen.

Summary: Following a continuous iv infusion with FLOLAN for 30 days, there were GI changes and body weight changes in the dogs, but later the animals recovered. Thrombocytopenia appeared to be due to increased peripheral utilization rather than decreased bone marrow production and that thrombocytopenia was rapidly reversed after discontinuing drug therapy. The response of platelet cAMP to FLOLAN was decreased by 75% during infusion and which recovered by day 5 post-infusion.

Study # BPAT 78-16

Title: A Subacute Toxicity Study of FLOLAN by iv Infusion in Anesthetized Monkeys.

Dates: 11/77-12/77

MATERIALS AND METHODS:

Chemical: 4UA 76, Lot # AI 13501-FHL-9, in 0.05M Tris buffer, pH 9.5

Animals: 16 monkeys (E. patas), about 4kg bw, 2/sex/group.

Doses: 0 (control), 10, 100, 1,000 ng/kg/min via discontinuous iv infusion.

The above doses for this study were selected from a previous dose-range finding study conducted with one male monkey (E. patas) where FLOLAN (in 0.05M Tris buffer) was injected sc at single doses increasing from 1 to 10, 30, and 60 mg/kg, once on days 1, 2, 3, and 4, respectively. The toxic signs were depression, flushing, salivation, hypothermia, hypotension, tachycardia, and papillary necrosis of the heart muscle. However, these were extremely high doses. Buffer used was 0.05M Tris buffer, pH 9.5 (but protocol mentions pH 8.4).

Methods: Groups of anesthetized (by chloralose) monkeys were infused FLOLAN at doses of 10, 100, or 1,000 ng/kg/min for 60 minutes, 3 times per week, for 2 weeks. Control monkeys were infused buffer for the same period. Various observations (see below) were made before, during, and after the infusion of FLOLAN: appearance-daily; body weight, weekly; BP and HR on days pre-infusion, during infusion every 15 minutes for 60 minutes on days 0, 7, 14; capillary fragility on days 0, 7, 14, before and at the end of infusion; platelet aggregation on days 0, 14, before and at end and one hour post-infusion. ECG was recorded pre-infusion, days 2, 11/12 of dosing, at 30 minutes, and at the end of infusion. The rectal temperature, hematology, blood chemistry, ophthalmoscopy, urinalysis and bleeding time were all recorded generally pre-drug, at least two times during infusion, and at the end of infusion. At the end, animals were sacrificed and autopsied; all the organs were collected, examined macro- and microscopically.

Results: There were no deaths. One of the 4 high dose (1,000 ng/kg/min) monkeys developed frequent vomiting and diarrhea; and one control monkey developed violent trembling. No FLOLAN-related changes in body weight occurred. The systolic BP dropped dose-dependently, maximum drop by 37 mmHg (32%) 30 min post-infusion at 1,000 ng/kg/min. The diastolic BP dropped by an average of 62 mmHg (78%) after 1,000 ng/kg/min and 17 mmHg (21%) with 100 ng/kg/min dose. Similar changes were seen on days 7-14.

Rectal Temperature: Hypothermia (drop by a less than 1°F) was observed in animals but without any consistent trend.

ECG: The heart rate increased significantly ($p < 0.05$) on day 2 (34% at 1,000 ng/kg/min, none at 100, or 10 ng/kg/min 60 minute post-infusion), but there were large variations, possibly from anesthesia. There were no changes in any of the ECG parameters.

Bleeding time: Bleeding time on day 2 and 11/12, before and after infusion were increased (2x) at 1,000 ng/kg/min ($p < 0.05$) and some increase, but not significant at 100 ng/kg/min.

Platelet aggregation: Sponsor stated (with some data) that a number of difficulties were encountered in determining the platelet aggregation potential of FLOLAN, and these were due to inconsistency in obtaining platelet count of the platelet rich plasma, and unstable nature of FLOLAN. Nevertheless, the data showed that FLOLAN did not have inhibitory effect on platelet aggregation at concentrations of 10 and 100 ng/kg/min. However, at 1,000 ng/kg/min, there was a marked inhibition of platelet aggregation 1 hr after infusion.

Hematology: There was a significant variation in prothrombin time (PT) and activated partial thromboplastin time, but in neither case there was a dose-related effect in any direction.

Blood chemistry: No treatment-related or dose-related changes were seen in any parameter except glucose levels, which were increased at 1,000 ng/kg/min (in 3 of 4 monkeys; the values were: 16.6 in the treated group and 6.0 mM/L in the controls). The lower doses had no such effects.

Urinalysis: Occasionally glucose was found in the urine of a few animals but this might be related to high blood glucose levels.

Ophthalmoscopy: No significant drug related effects were seen.

Autopsy: Patchy discoloration of the lungs was seen in 1M and 1F monkeys in the 1,000 and 100 ng/kg/min dose groups, respectively.

Histology

Heart: Minimal focal chronic inflammatory cell infiltration in the myocardium was seen in controls and treated monkeys. In the monkey treated with 1,000 ng/kg/min, there was a degenerative lesion in the papillary muscle of the heart. The lesion consisted of necrotic and degenerative muscle fibers with a chronic inflammatory cell infiltrate. There was no evidence of such lesions in the other 3 monkeys in this group.

Lungs: In the lungs of two monkeys (1F, 100 ng, 1M in 1,000 ng dose), there were patchy discolorations.

Injection site: In the saphenous veins there were partially organized occlusive thrombi; all had thickened walls with varying degree of chronic inflammatory cellular infiltrates. In the monkeys treated with 1,000 ng/kg/min, there were more cellular inflammatory reactions in the veins than those in the other groups. Less severe effects were seen in the lower dose group monkeys.

Summary: In the monkey, BP decreased at 1,000 ng, with diastolic pressure falling by 78%, and systolic pressure by 32% during infusion; the infusion of 100 ng resulted in a drop of diastolic pressure by 21% and none in the systolic pressure. But these effects were not observed with repeated dosing. Heart rate increased reflexly by 34% at 1,000 ng; bleeding times increased (2x) at 1,000 ng, and some increase at 100 ng/kg/min; plasma glucose increased somewhat, patchy discoloration of lungs developed in two monkeys, thrombi formed at injection sites and chronic inflammatory infiltrates were found in the heart of few animals. Inhibition of platelet aggregation was observed at 1 hour post-infusion with 1,000 ng/kg. The lower doses of 10 or 100 ng/kg/min were without any significant toxic effect and thus 100 ng/kg/min was the no-toxic dose, which was still 10x higher than the anticipated human dose.

SPECIAL TOXICITY STUDIES

Study # 78/04

Title: Effects of Prostacyclin and Several Related Compounds on the Proliferative Response of Abraded Mouse Skin.

Since adenylyl cyclase, via cAMP, regulates epidermal proliferation in conditions such as psoriasis, and since FLOLAN increases cellular cAMP, FLOLAN and related compounds were tested in this test to see if repeated application of these compounds would alter the proliferative response induced in the mouse epidermis.

Dates: Study conduct dates were not reported; Date of issue of report: July 1977.

MATERIALS AND METHODS

Chemicals: (i) solvent-Ethanol/propylene glycol (70:30), (ii) FLOLAN, sodium salt, 4UA76 AD, Lot # 13197-FKL-5E, (iii) FLOLAN, phenyl phancyl ester, 5UA77 AD, lot # 13501-FHL-13; (iv) Compound 454c77, ref # A1054/119F.

Animals: Male C57BL mice, 25 g; 12 untreated controls, and 10/test agent or control solvent group.

Doses: 0.1 ml of 1% solution of the test agent or control vehicle applied dermally three times/daily on the abraded skin.

Methods: 0.1 ml of 1% solution of the test agent or the control vehicle were applied to each mouse (10/group, except the controls) on the abraded skin (prepared by anesthetizing mice prior to application) 3 times daily during the 24 hour period of the study. There was no positive control group. Two mice from each group were killed at 0, 24, 48, 72, 96, and 144 hours post-application. Prior to sacrifice, each mouse was given colchicine (BDH, 0.1mg, ip) to arrest the mitotic activity. Histology of the abraded skin was carried out and mitotic counts determined.

Results: There were no abnormal changes in behavior and appearance in any animal following skin application of FLOLAN. Multiple applications of either solvent, sodium salt of FLOLAN, phenyl phancyl ester of FLOLAN, or compound 454c77, did not alter the proliferative response of the abraded mouse skin. Neither test agent altered the mitotic activity of cells, nor produced any gross or histological appearance of the abraded mouse skin. It is not clear from the data whether this was due to the failure of absorption of the test agent, alteration in the cAMP levels, or difficulties encountered in counting the mitotic cells due to the presence of hair follicles. This was further confounded by lack of positive control in the study.

Summary: FLOLAN and related compounds did not affect the proliferation of the abraded skin of the mouse.

Study # BPAT 79/04

Title: Two week Subacute Toxicity Study of 6-Oxo-PGF_{1α} by Intravenous Infusion in the Anesthetized Monkey

Dates: 8/21/78-9/8/78

MATERIALS AND METHODS

Chemical: 6-Oxo-PGF_{1α}, prepared from FLOLAN sodium (4UA76, batch AI, lot # 13501-FHL-9 by Upjohn, dissolved in saline and stored at -20 °C. Stability was confirmed periodically by HPLC.

Animals: Monkeys (Erythrocebus patas), 6-8kg, Charles River, 3/sex/group.

Doses: 0 (control, saline, 8 ml/hr), test agent 1 ug/kg/min infused intravenously for 60 minutes.

6-Oxo-PGF_{1α} is a primary metabolite of FLOLAN (FLOLAN) and also becomes one of the six identified impurities in the prostacyclin, upto a maximum concentration of 5.8%. The manufacturer's stability data place a maximum limit of not greater than 10%. The other metabolites and their limits are: (ii) 6-R- PGI₂, [not greater than 1.25%], (iii) 5E-PGI₂, [not greater than 2.5%], (iv) 6S- PGI₂, [not greater than 0.5%], (v) diepoxy-PGI₂, [not greater than 0.5%], and (vi) -6-PGI₂, [not greater than 3%]. The total amount of impurities should not be greater than 15% (p 1, vol 1, amendment of 3/23/88).

Methods: The monkeys were infused the appropriate agent (control) or the test agent intravenously for 60 minutes, 3 days/week for 2 weeks. Standard observations of daily behavior, general appearance, body weight changes, BP/HR (day 0 and 14 at 30 and 60 min post-infusion), ECG (day 0 and 14 at prior and at termination of infusion), hematology/clinical chemistry (day 0, 14, 15), urinalyses, and ophthalmoscopy were made on all animals. At termination, animals were autopsied and their organs/tissues weighed, examined macro- & microscopically.

Results: There were no significant changes in any of the parameters measured in any animal treated with 6-Oxo-PGF_{1α} at a dose of 1 ug/kg/min when compared to the controls. However, histological examination showed that three treated monkeys had developed small lesions in the heart: one male monkey (#2848) had one small lesion in the papillary muscle, another male monkey (#2804) had two small lesions in the atrial wall, and a 3rd monkey (#2821), also in the treatment group had one small mixed infiltrate perivascular focus in the ventricle wall. In comparison, one control monkey (#2816) had two mononuclear foci, an interstitial and the other perivascular in the ventricle. However, the tested dose of the metabolite was about 1000x the levels that would be expected from 10 ng/kg/min dose of FLOLAN in man.

GENETIC TOXICOLOGY:

The following genetic toxicity studies were previously submitted to IND (Amendment #116) on June 11, 1992 and reviewed on November 20, 1992. The reviews are reproduced below.

Evaluation of U-53,217A in the Salmonella/microsome Test (AMES assay) in CHLV-79 Cells

Testing Laboratories:

Study Dates: June 30-December 9, 1980

Date of Report: January 27, 1981

GLP Requirements: A Statement of compliance with the GLP regulations and quality assurance unit was included, but with the following caveats.

- 1) No analytical data are available to confirm the identity, purity or composition of the test article.
- 2) No stability data are reported for the specific test article formulation used in this study.
- 3) Concentration assays were not performed on the formulated test article used to dose the test system.
- 4) Dates of actual data collection (i.e., colony counts) are not in the raw data due to the design of the data collection forms (dates will be recorded in future studies).

Drug Batch No.: Az 14285-FH1-21B

Methods: U-53,217A (FLOLAN), at doses of 250, 500, 1000, 2000 ug/plate, was tested for its mutagenic potential in the AMES assay using strains TA98, TA100, TA1535, TA1537 and TA1538, in the presence or absence of S-9 liver microsomal fraction, containing hepatic metabolizing enzymes. Three positive controls (cyclophosphamide, 9-aminoacridine and 2-acetylaminofluorene) were also tested.

Results: All three positive controls (cyclophosphamide, 9-aminoacridine and 2-acetylaminofluorene) produced the expected mutagenic responses. FLOLAN produced no evidence of bacterial mutagenicity at any dose tested with or without an in vitro metabolic activation system. However, due to the inherent instability of the FLOLAN and lack of analytical data concerning its identity, composition and purity as well as that of the test article formulation, these results are at present non interpretable.

The Micronucleus Test with Prostacyclin (U-53,217A)
(Study No. E-014)

Testing Laboratories:

Study Dates : May 20-May 22, 1981

Date of Report: October 1, 1981

GLP Requirements: The Sponsor stated that the study was conducted in compliance with the GLP regulations with the exception that the concentration of the test article was not determined during the study.

Animals: Male Sprague Dawley Rats; (144-179 g; age 5-8 wks)

Drug Batch No.: A4-15569-BDT-7A

Methods: Ten rats per group received 2 equal doses of prostacyclin (i.p., 2.0 ml vol.) 24 hr apart to give a total dose of 10, 20 and 40 mg/kg. Another group received vehicle and a fifth group received cyclophosphamide (1 ml/kg of a 20 mg/ml solution in 2 doses). Six and 24 hours following the second dose Animals were sacrificed, followed by microscopic examination of bone marrow polychromatic erythrocytes (PCEs) for the presence of micronuclei.

Results: Cyclophosphamide, a mutagen requiring metabolic activation, significantly increased the incidence of micronucleated PCEs over controls. None of the prostacyclin groups exhibited a statistically significant increase in the rate of PCEs over controls, nor was the test for a positive dose response relationship statistically significant. These results suggest that prostacyclin did not produce chromosomal damage or lagging chromosomes in the bone marrow PCEs from rats.

Evaluation of U-53,217A (PGI₂) in the DNA Damage/Alkaline Elution Assay (Study No. D-184)

Testing Laboratories:

Study Dates: June 20-July 19, 1980

Date of Report: October 15, 1980

GLP Requirements: The Sponsor stated that the study was conducted in compliance with GLP regulations except for the

following: 1) no stability data were generated for the formulated test article; 2) no uniformity or concentration data were generated for the formulated test article.

Drug Batch No.: A-3 12285-FHL-21B

Methods: Cultured Chinese hamster lung V-79 cells were exposed to prostacyclin (0.03, 0.3 and 3 mM = 0.012, 0.12 and 1.2 mg/ml) for two hours or four hours in the presence or absence of a hepatic metabolizing system (S-9 hepatic microsomal fraction). Following exposure, ¹⁴C-DNA was isolated and examined for single strand breaks. Positive controls (methyl-N'-nitro-nitrosoguanidine 0.015 mM; Benzo(A)Pyrene, 0.1 mM; 4-nitroquinoline-1-oxide, 0.1 mM and β-naphthylamine, 0.1 mM) were also tested.

Results: Exposure of the cells to U-53,217A (prostacyclin) for either 2 or four hours in the presence and absence of a hepatic metabolizing system did not result in the detectable increases in the elution of single stranded ¹⁴C-DNA from the filters. In contrast, 2-hr exposure to methyl-N'-nitro-nitrosoguanidine produced significant DNA damage. Significant DNA damage was also produced by reactive metabolites of Benzo(A)Pyrene, 4-nitroquinoline-1-oxide, and β-naphthylamine, in the presence of the S-9 hepatic metabolizing system. Cell viability was not determined. These data suggest that U-53,217A (PGI₂) does not interact directly and is not metabolized to products which interact with cellular DNA, to induce single strand breakage.

REPRODUCTIVE TOXICOLOGY:

The following reproductive toxicity studies were previously submitted to NDA on March 23, 1988 and reviewed on August 15, 1988. The reviews are reproduced on the following pages.

REPRODUCTIVE TOXICOLOGY:

Study # 7205/81/7263/006

Title: U-53,217A (FLOLAN): A Segment I. Fertility and General Reproductive Performance in the Rat.

Dates: August 29, 1980-March 23, 1981

Conducting Lab:

MATERIALS & METHODS

Animals: Rats 48 males (weighing 116-133 g, 39 d old, 12/group) and 95 virgin female rats (10-12 wks old, 216-278 g, 24/group).

Chemical: U-53,217A (FLOLAN), lot # A-2, 14466-FHL-114, in 0.05M Glycine buffer, pH 10.5

Doses: 0 (control, buffer), 10, 30, or 100 ug/kg, sc on specified days (see below).

Methods: Male rats were administered FLOLAN once daily for 60 days prior to mating, and during 14-day breeding period, and female rats were dosed 14 days before mating, during breeding, throughout gestation and lactation until weaning (day 21 postpartum). Standard breeding procedures were followed. The sires that did not inseminate were sacrificed and their reproductive organs were preserved for later histological examination. Half the number of dams (12 of 24) were sacrificed on day 13 of gestation and the uterus of each was examined for the number of implantations and live/dead embryos and the number of corpora lutea. The remaining dams were allowed to deliver their litters. The following observations were recorded: number of live and dead pups, sex and weight of each pup, and any skeletal abnormalities in the dead pups. On day 21 postpartum, pups (see below) were selected for various tests and the remaining pups and dams were sacrificed and necropsied for histological examinations. One male and one female pup from 10 litters of each group were selected for M-maze testing, 2M, 2F pups from each group for each of the tests: pivoting, surface righting, auditory startle response, and developmental changes. For reproductive performance, 1M and 1F pups were allowed to grow till 70 days of age, when they were mated. Then the males were sacrificed and dams were allowed to deliver. The number of live/dead pups (F₂ generation), their weight, sex, litter size were recorded, then sacrificed and examined for any internal visceral or external and skeletal abnormalities.

Results: There were signs of depression in both male and female rats at 10 ug/kg dose, but the animals recovered within 5-10 minutes of dosing. The animals in the 30 and 100 ug/kg group were depressed severely accompanied by ataxia and these effects persisted for 2 hr following dosing. With regard to reproduction parameters, the number of dams delivering, lengths of gestation, number of live pups born, litter size, pups surviving to days 4 and 21 postpartum, pup weights at birth etc were all unaffected by FLOLAN treatment. The behavioral responses in the M-maze, pivoting, and righting reflex were also not affected by any dose of FLOLAN. In the case of auditory startle response, the 10 ug/kg pups responded positive to the stimulus as compared to the controls. Although sponsor stated that these differences were significant and were shown in Appendix III, but these data could not be located in the said appendix. Furthermore, the treatment with FLOLAN at doses up to 100 ug/kg did not produce any changes in the reproductive performance of the F₀ rats in the standard Segment I study.

In summary, administration of FLOLAN to rats at doses of 10, 30 or 100 ug/kg prior to mating, during mating, during gestation and lactation did not produce any reproductive toxicity.

Study # BPAT 78/27

Title: Segment II. Fetal Toxicity and Teratogenicity of Subcutaneous FLOLAN in the Rat.

Dates: 3/7/78-4/13/78

MATERIALS AND METHODS

Animals: Pregnant female Wistar rats, 20/group.

Chemical: 4UA-76 AI, Lot # 13501-FHL-9, in diluent 0.05M Tris buffer, pH 10.5 (protocol mentions on p 4.03323, pH 9.5).

Doses: Control (vehicle), 1, 10, 100 ug/kg/d.

Methods: Pregnant rats were dosed with FLOLAN sc, once daily, on days 6-16 of pregnancy. Animals were observed for changes in body weight, general behavior, fertility, and on day 20 of pregnancy, all dams were killed and examined internally. Each fetus was weighed, sexed and examined externally for signs of abnormalities. Each dam was examined for the number of corpora lutea, implantations, live fetuses (weights), early/late dead embryos, fetal sex, and fetal abnormalities. Following external examination, all fetuses were further examined by one of three investigative procedures for any abnormalities of the internal organs (by open dissection), detailed examination of fetuses by serial slices, and skeletal examinations. [The number of litters for these examinations were 19, 20, 19 and 19 in the control, 1, 30 and 100 ug/kg groups, respectively]. The sponsor also tested FLOLAN for its potency and

stability as platelet antiaggregatory agent. For analysis of the data, the biological unit was the dosed female and comparisons were made on the 'per dam' basis, and fetal abnormalities were compared on the 'per litter' basis, instead of usual 'per fetus' basis.

Results

Potency of the sample: The ability to inhibit ADP induced platelet aggregation by FLOLAN was determined in various samples and compared with a reference material, 13501.FHL-9. FLOLAN was found to be stable and potent throughout the 14-day period of testing.

The general behavior of dams during dosing was normal; the number of live fetuses, sex ratio, fetal weights, etc in treated animals was not significantly different from the controls. The data shown below have been extracted from the sponsor's Table 1 page 4.03333 and these suggest that FLOLAN at doses of up to 100 ug/kg/d did not produce any fetal toxicity or teratogenicity in the rat.

Table 13
Teratogenicity Study in the Rat administered FLOLAN

Observation	Control	1 ug/kg/d	10 ug/kg/d	100 ug/kg/d
# of dams pregnant	20	20	19	20
# dams examined on day 20	20	20	19	20
Total # of implants	262	253	240	237
Mean # of implants	13.1	12.7	12.6	11.9
# litters examined	19	20	19	19
Total # of fetal deaths	49 (18.7%)	23 (9.1%)	8 (3.3%)	24 (10.1%)
Total # of live normal fetuses	213	230	232	213
Mean # live fetuses/dam	10.6	11.5	12.2	10.6
Total # malformed fetuses*	0	0	0	0
Mean body wt. of fetuses	3.53g	3.66g	3.74g	3.79g

*Malformations: There were no major malformations observed in any litter. However, minor anomalies such as distended kidneys, dilated kidney pelvis or enlarged ureter were seen. The total number of litters with these anomalies were 0, 10, 5, and 6 of the examined 19, 20, 19, and 19 litters, in the control, 1, 10, and 100 ug/kg/d groups, respectively. Other minor anomalies reported were those that affected kidneys (like enlarged kidneys, enlarged ureter etc.) and these were spread across the treatments groups with no significant FLOLAN-related effect. Skeletal examination of all fetuses did not reveal any abnormal ossification anomalies that were significantly different from controls. Further, the doses were extremely high.

In summary: FLOLAN up to 100 ug/kg/d (10,000x the human dose) did not produce any significant fetal toxicity, maternal toxicity or teratogenicity in the rat.

Study # BPAT 78/31

Title: Segment II. Fetal Toxicity and Teratogenicity of Subcutaneous FLOLAN in the Rabbit

Dates: 2/27/78-4/28/78

Conducting Lab: BW

MATERIALS AND METHODS

Chemical: 4UA 76 AI, Lot # 13501-FHL-9, in 0.05M Tris buffer, pH 9.5.

Animals: Uniparous female Dutch rabbits, 8 months old, 12/group.

Doses: Control (Glycine buffer, pH 9.5), 1, 10, 100 ug/kg/d, sc. once daily, on days 6-18 of pregnancy, in a constant volume of 0.5 ml/kg.

Methods: Artificially inseminated rabbits were administered FLOLAN at indicated dosages once daily on days 6-18 of pregnancy. Animals were observed daily for changes in body weight, general behavior and well-being, morbidity and mortality. The dams that showed severe debility were killed and examined internally. All the dams were sacrificed on day 28, and a record of the following was made: number of corpora lutea, implantations, live fetuses, early/late dead embryos, fetal sex and weights, and fetal abnormalities (external, visceral, and skeletal via open dissection, serial slices and skeletal examinations).

Results: Sponsor submitted an amended report dated 10/78 in which they corrected various discrepancies reported earlier, including the number of animals per group. In the amended report the number is 15/group while in the previous report it was 12/group; and FLOLAN was diluted by Tris buffer, pH 10.5.

Lethargy/prostration was noticed in almost all treated animals, probably from vasodilatory effects of the drug and or poor conditions of health. The pregnancy success rate was somewhat poor in controls and 1 ug/group, probably from poor health, drug-induced lethargy/prostration, or from high rate of infestation (8/48 animals). The number of dams pregnant, number of corpora lutea and other parameters are summarized in Table 14 on page 48 of this review. There was no significant difference in any of these parameters in the FLOLAN treatment groups when compared to controls. The data on malformations are presented below.

It should be noted that the sponsor presented the data on the basis of 'litter' (highly unusual) and not on the basis of 'fetuses with anomalies'. Therefore, in order to obtain an accurate picture of teratogenic potential of FLOLAN, the 'litter' data were recalculated by determining the litter size (# live fetuses/dam), the number of litters

examined, fetuses examined and those found abnormal. This procedure could not be applied to historical control data, because the litter size and specific fetuses with anomaly were not provided for the historical controls.

Malformations: Both major and minor malformations were observed in FLOLAN treatment and control groups (Table 14). The major malformations were: domed head (1.3% and 1.6% in 1 and 100 ug/kg dose group, respectively, none in the control and 10 ug/kg groups); cleft palate (1.3% only in 100 ug/kg; and none in the control, 1 and 10 ug/kg groups); one hind foot abnormally curved (2.7%, and 1.6% in 1 and 10 ug/kg groups, respectively; none in the control and 100 ug/kg groups). The incidence of other minor anomalies such as dropped wrist was 3.2% in the 10 ug/kg group. In all, the number of fetuses with malformations were 0/48, 2/36, 3/61 and 2/73 in the control, 1, 10, 100 ug/kg groups, respectively. The corresponding number of litters examined were 8, 6, 9, and 12, respectively. When compared to historical controls (see Table 15, prepared from sponsor's table on page 4.03403), the incidence of malformations in the FLOLAN treated groups appears to be higher, however, because of many problems with the historical data presentation (see footnote under Table 15), comparisons between the results from this study and the historical data could not be made.

The incidence of other anomalies are also shown in Table 14. There was no clear trend in terms of a specific abnormality seen in any one treatment group. The type of anomaly and the number of pups that had developed any of these anomalies was not significantly higher than historical controls. Eventhough the historical control data (Table 15 below, extracted from sponsor's Table on page 4.03403) were presented for the period of 1973-1978, the conditions under which the studies were conducted, compounds tested, and the number of fetuses affected were not provided making comparisons with the current study difficult.

Skeletal examinations did not reveal any abnormal ossification anomalies that were significantly different in the FLOLAN treatment groups from the controls.

Table 14
- Teratogenicity Study in the Rabbit administered FLOLAN

Observation	Control	1 ug/kg/d	10 ug/kg/d	100 ug/kg/d
# of pregnant dams examined	8	6	9	12
Total # of Corpora lutea	72	61	86	114
Total # of implants	53 (73%)	46 (75%)	69 (80%)	87 (76%)
Mean # of implants	6.6	7.7	7.7	7.3
Total # of fetal deaths	5 (9.4%)	10 (21.7%)	8 (11.6%)	14 (16.1%)
Total # of live fetuses	48	36	61	73
Total # of normal fetuses	48	34	58	71
Total # of malformed fetuses*	0	2 (5.6%)	3 (4.9%)	2 (2.7%)
Mean # of live fetuses	6	6	6.8	6.1
Mean # of normal fetuses	6	5.7	6.4	6.1
Mean body wt. of fetuses	31.4	26.9	32.6	32.5

Observations at external examination

# litters examined	8	6	9	12
Total # fetuses, recalculated	48	36	61	73
Domed head	0/48	1/36	0/61	1/73
Cleft palate	0/48	0/36	0/61	1/73
One foot abnormally curved	0/48	1/36	1/61	0/73
dropped wrist	0/48	0/36	2/61	0/73

Observations at Open dissection

# litters examined	7	6	9	11
# litters with anomalies	0	2	1	3
# fetuses examined	42	34	58	67
Heart*	0/42	0/34	0/58	3/67
Liver, pale lobe	0/42	2/34	0/58	0/67
Spleen, absent	0/42	1/34	0/58	0/67
Small pancreas	0/42	1/34	0/58	0/67
Kidney and ureter absent	0/42	1/34	0/58	0/67
Stomach distended, and small intestine adhering to rectum	0/42	0/34	1/58	0/67

Observations at Wilson's serial examination

# litters examined	8	6	8	11
# fetuses examined	48	36	54	67
Palate, irregularly ridged	3/48	0/36	2/54	2/67
dilated lateral ventricles in the brain,	0/48	1/36	0/54	0/67
amorphous material across pleural surface of diaphragm,	0/48	0/36	1/54	3/67
mottled liver, dilated	2/48	1/36	0/54	2/67
kidney, enlarged urinary bladder, and small testis				

* - Divided ventricles at the apex of the heart with or without hemorrhage.

Table 15
Historical Record for Selected Abnormalities among Dutch Rabbits

Abnormality	Historical Record, 1973-78		Prostacyclin	
	# control rabbits	# occasions	Total # rabbits	# occasions
Hydrocephalus	109	2 (1.8%)	27	3 (11%)
Cleft palate	109	1 (0.9%)	27	1 (3.7%)
Heart defects*	109	0	27	3 (11%)
Irregularly ridged palate	109	10 (9.1%)	27	4 (14.8%)
Dropped wrist or ankle	109	3 (2.7%)	27	5 (18.5%)

*The heart defects were not further specified. Whether the incidences reported were based on the number of fetuses with abnormality or the number of dams (litters), was also not clear from this table. Number of 'occasions' was not further defined? Data under prostacyclin seem to be pooled from several experiments. Further, the doses of FLOLAN tested were also not clear.

Summary: The dosing of rabbits at doses of 1, 10, and 100 ug/kg/day did not produce any significant maternal or fetal toxicity or any teratogenic effects which could be attributed to such high doses of FLOLAN.

Study # BPAT 79/21

Title: A Supplementary Fetal Toxicity and Teratogenicity Study of Subcutaneous FLOLAN in the Rabbit

The rationale for conducting a second supplementary study in the rabbit was to clarify the original findings (study #78/31) and to assist the assessment of FLOLAN. Sponsor stated that because there was low pregnancy rate, either from poor health of rabbits or infestations, the teratogenic potential of FLOLAN in the rabbit could not be assessed).

Dates: 8/7/78-9/12/78

MATERIALS AND METHODS

Animals: Pregnant uniparous Dutch female rabbits, 8 months old, 18/group inseminated.

Doses: 0 (control glycine buffer, pH 10.5), 1, 10, 100.ug/kg/day

According to the protocol for conducting this supplementary study to assess fetal toxicity and teratogenicity of FLOLAN, page 4.03407, 4 groups of rabbits, 18/each were to be used, and doses to be employed were control, 1, 10, 100 ug/kg. in 0.05M Tris buffer at pH 10.5, but in the study reviewed below used only two groups of animals (Control, and 100 ug/kg/day, in 0.05 glycine buffer, pH 10.5) each consisting of 26 and 44 animals per group, respectively.

Methods: Drug was administered subcutaneously once daily on days 6-18 of pregnancy. Dams were observed daily for changes in body weight, general behavior and well-being morbidity and mortality. Dams that were morbid were killed and examined to determine the cause of death. Dams were sacrificed on day 28 of pregnancy with following observations recorded: number of corpora lutea, implantations, live fetuses, early/late dead embryos, and fetal abnormalities. All fetuses were examined for internal visceral and skeletal abnormalities by open dissection, and serial slice techniques.

CV monitoring: Eight of 18 dams in each treatment group were chosen for monitoring BP, HR, and ECG on days 6, 13, and 18 after insemination. In view of the likely trauma involved, these dams were excluded from subsequent detailed examination of fetuses collected on day 28. The results for these are reviewed below separately.

Results: Two control dams died without any apparent cause. Body weight was not significantly affected by treatment and neither was general behavior or appearance that could be attributed to the administration of FLOLAN. Vasodilation as evident by reddening of the ears, nose and the periphery was observed in all the treated animals within 2-5 minutes of drug administration. The other effects which were observed generally were difficulty in breathing and prostration lasting for about 25 minutes after injection but the animals recovered within about 30 minutes.

Implantations: Three (3) of 16 (18 %) controls and 9 of 36 (25 %) treated animals failed to conceive (4 of 9 treated animals were found to have developed interstitial nephritis of the kidneys and 1 of 9 had developed an epitheloid granuloma of the mesenteric nodule. However, these effects did not appear to be FLOLAN-related. Among the dams that were pregnant, there was no difference in the number of implantations, survival, live fetuses, sex ratio, and gross fetal abnormalities in the treated rabbits as compared to the controls. These data are summarized in Table 16, the data are recalculated on the basis of 'fetuses' and were extracted from various tables in the submission.

There were occasional abnormalities such as domed head fetus in 100 ug/kg dose but were not significantly different from the controls and thus did not seem to be drug related.

Table 16
Teratogenicity study (#79/21) in the Rabbits treated with FLOLAN

	Control	100 ug/kg/d
# of dams inseminated	18	36
# litters obtained	13	26
Mean # of corpora lutea	7.8	8.4
Mean # of implants	6.7 (86%)	7.1 (84%)
Mean # live litters	5.1	6.6
<u>Observations at external examination</u>		
# of litters examined	13	25
# fetuses examined	79	169
Domed head	0/78	1/169
Palate, irregular & ridging	0/78	1/169
dropped wrist	0/78	1/169
abnormal skull closure	1/78	0/169
<u>Observations at open dissection</u>		
# of litters examined	13	25
# fetuses with examined	78	162
Heart, enlarged and enlarged ventricles	2/78	1/162
Pale liver	0/78	1/162
Large gall bladder	0/78	1/162
Right kidney and ureter missing	1/78	1/162
<u>Observations at Wilson's serial Examination</u>		
# litters examined	12	25
# fetuses examined	72	169
# fetuses with various anomalies*	14/72 (19.4%)	30/169 (17.7%)

* = anomalies involved the heart, kidneys, liver, gall bladder, urinary bladder, and others, the type seen in the earlier study (#BPAT 7, '31). There were no significant difference in the type or number of these anomalies in the treated group from those in the controls. Skeletal examinations also did not reveal any significant ossification anomalies related to FLOLAN treatment.

The results from this study suggest that the number of fetuses with malformations or any skeletal anomalies in the FLOLAN 100 ug/kg group, individually or combined (not often done), were not significantly higher than those in the controls.

Cardiovascular System: There was no significant effect on BP in the treated dams. Heart rate was significantly increased in the controls more than in the treated animals on days 6 and 13, with recovery in about 10 minutes. The changes were somewhat higher in controls than in the treated animals. Maximum hypotension and reflex tachycardia were seen on day 6-18.

ECG: One dam in the 100 ug group showed evidence of regular atrial parasystole and intermittent ventricular ectopic beats after dosing on day 6 and before and after dosing on days 13 and 18.

In summary, FLOLAN at 100 ug/kg (10,000x the anticipated human dose) administered on days 6-18 of pregnancy to rabbits produced no adverse effects on the embryonic survival, fetal development or growth. It did not produce teratogenic effects that were significantly different from controls. These were also not significantly different from historical controls, even though, the latter were reported on the basis of 'litter'.

Study # 7205/81/263/004

Title: A Segment III Peri- and Postnatal Study in Rats.

Dates: October 21, 1980-November 5, 1980

Conducting Lab: BW

MATERIALS AND METHODS

Chemical: U-53,217A, Lot # A2-14466-FHL-114, in 0.05M glycine buffer, pH 10.5, stored at -20°C until use.

Animals: Pregnant female rats, Upj: TUC (SD) spf strain, 24/group, 12-16 week old, 220-260g.

Doses: 0 (control), 10, 30, 100 ug/kg.

Methods: This study was conducted to assess the effects of FLOLAN on the late stages of gestation, parturition, lactation, and the rearing of young until weaning in the rat (day 21 postpartum). Female pregnant rats were administered FLOLAN sc once daily on gestation day 15 through day 21 post-partum in a constant volume of 1 ml/kg. Following observations were made: general behavior of dams was recorded daily, body weights on days 0, 7 of gestation and daily during dosing, and length of gestation. Dams were allowed to deliver and number of live/dead pups born, their weight, sex, were all recorded on post partum day 0, 4, 21. At necropsy, dams/pups were observed for any unusual gross findings followed by histopathologic examinations.

Results: There were no deaths in the treated dams, and FLOLAN did not affect the maternal weight either. Animals were depressed proportional to the dose, with ataxia lasting for 3 hours, and which developed in 30 and 100 ug/kg dose group rats. The length of gestation was 21.9, 22.0, 22.2, and 22.4 days in the control, 10, 30, and 100 ug/kg/d groups, respectively, which shows that there was an increase of gestation by about 12 hours (2.2%) in the 100 ug/kg/day dose group as compared to the controls. This increased gestation was probably caused by general toxicity toward the dam and not a direct effect on fetal development.

The percentage of pups born alive, size of the litter, and the proportion of pups surviving to day 4 did not differ significantly in the test groups. However the litter proportion of pups surviving to day 21 decreased significantly with increasing dose of FLOLAN, as compared to those on days 0 and 4. For example, the number of pups that survived to day 21 were 258, 250, 226, and 185 in the control, 10, 30, and 100 ug/kg dose groups, respectively, with significant difference ($p \leq 0.05$) between the high dose and the controls. While the number of pups surviving to day 4 were not significantly decreased in the high dose group as compared to those in the control group. (See Table 17 on page 54 of this review, attached is sponsor's Table 4, p 4.03499).

Summary: FLOLAN at doses of upto 100 ug/kg did not adversely effect parturition, lactation, or pup survival in the rat. No significant reproductive toxicity was observed in this study probably because the doses were not high enough to produce such toxicity in the rat. On the other hand, the maximum dose tested was about 10,000x the anticipated human dose, and further, higher doses might have caused severe depression/ataxia that would have prevented normal reproductive functions.

Table 4

PST 0-297
U-53,217A

Summary of Statistical Analysis for Segment III Study of U-53,217A

	U-53,217A ug/kg			
	0.0	10.0	30.0	100.0
No. dams inseminated	24	22	24	24
No. dams pregnant	22	22	23	19
No. dams died during study	0	0	0	0
No. dams delivered litters	22	22	21	15
Mean dam body weight gain (g) ^{NS}	106.4	109.9	106.8	107.0
Mean gestation length (days) ^a	21.9	22.0	22.2	22.4
Total pups delivered	253(11.8)	256(11.6)	240(11.4)	202(11.2)
No. live pups born	253(11.8)	252(11.5)	236(11.2)	199(10.8)
Percent live pups/total pups ^{NS}	98.5	98.4	98.3	93.5
No. live pups at 4 days	258	250	231	196
Percent live at 4 d./live at birth ^{NS}	99.5	99.2	97.9	98.4
No. live pups at 21 days	258	250	225	185
Percent live at 21 d./live at birth ^b	99.6	99.2	95.8	97.9
Lactation index ^b	1.00	1.00	97.8	99.5
(No. live at 21 d./no. live at 4 d.)				
Mean weight live pups at birth (g) ^{NS}	7.0	7.1	7.0	7.1
Mean weight live pups at 4 days (g) ^{NS}	12.3	12.6	12.1	12.5
Mean weight live pups at 21 days (g) ^{NS}	56.2	58.4	55.5	59.1

^{NS}Treatment group means not significantly different.

^{NS}Proportions per litter did not increase or decrease significantly with increased dose of U-53,217A.

^aTreatment group differences in mean length of gestation were statistically significant, p<.05

^bLitter proportions decreased significantly with increased dose of U-53,217A, p<.05.

LABELLING:

The labelling is according to 21 CFR, Subpart B. The following revisions in the labelling are recommended:

1. Sponsor's Version:

OVERDOSAGE: Signs and symptoms of excessive doses of FLOLAN reported in clinical trials are consistent with the dose-limiting pharmacologic effects of FLOLAN and include flushing, headache, hypotension, tachycardia, nausea, vomiting, and diarrhea (82). Treatment should be supportive and may require appropriate dose reduction of FLOLAN.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unspecified concentration of FLOLAN. The patient vomited and became unconscious with an initially unrecordable blood pressure. FLOLAN was discontinued and the patient regained consciousness within seconds. No fatal events have been reported following overdose of FLOLAN (83).

Acute intravenous limit tests have been performed in mice and rats. In mice, the median lethal dose was not determined since animals recovered from bolus injections of up to 60 mg/kg (84). Inactivity, bradypnea, hypothermia, ataxia, and skin flush (increased redness) were observed in mice administered doses of 1 to 10 mg/kg (85). In rats, the median lethal dose was estimated at 66.3 mg/kg (86). Death was preceded by collapse and respiratory failure within 1 to 10 minutes of injection.

Evaluation:

The information on minimal lethal i.v. doses was not included in the third paragraph.

Suggested Version:

OVERDOSAGE: Signs and symptoms of excessive doses of FLOLAN reported in clinical trials are consistent with the dose-limiting pharmacologic effects of FLOLAN and include flushing, headache, hypotension, tachycardia, nausea, vomiting, and diarrhea (82). Treatment should be supportive and may require appropriate dose reduction of FLOLAN.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unspecified concentration of FLOLAN. The patient vomited and became unconscious with an initially unrecordable blood pressure. FLOLAN was discontinued and the patient regained consciousness within seconds. No fatal events have been reported following overdose of FLOLAN (83).

Single intravenous doses of FLOLAN at 10 and 50 mg/kg were lethal to mice and rats, respectively. Symptoms of acute toxicity were hypoactivity, ataxia, loss of righting reflex, deep slow breathing and hypothermia.

2. Sponsor's Version:

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis bioassays and genetic toxicology studies have not been performed with epoprostenol. Fertility was not impaired in rats given epoprostenol by subcutaneous injection at doses of 10, 30, and 100 $\mu\text{g}/\text{kg}/\text{day}$.

Evaluation: In sponsor's version, sponsor stated that genetic toxicity studies have not been performed with epoprostenol. However, the mutagenic potential of FLOLAN was assayed in Ames test, micronucleus test in rats and DNA damage/alkaline elution test in cultured Chinese hamster lung V-79 cells. Although the results in all three tests were negative, the Ames test and DNA damage/alkaline elution assay were not interpretable because of lack of data concerning the stability and concentration of epoprostenol, its inherent nature and instability, rapid metabolism and extremely short *in vitro* half life (~1-3 minutes). We recommend sponsor to include the result of the micronucleus test in the labelling.

Suggested Version:

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential. Micronucleus test in rats revealed no evidence of mutagenicity. Fertility was not impaired in rats given FLOLAN by subcutaneous injection at doses up to 100 $\mu\text{g}/\text{kg}/\text{day}$, [600 $\mu\text{g}/\text{m}^2/\text{day}$, 2.5 times the recommended human dose (4.6 ng/kg/min or 245.1 $\mu\text{g}/\text{m}^2/\text{day}$, i.v.) based on body surface area].

3. Sponsor's Version:

Pregnancy: Teratogenic Effects: Pregnancy Category C. Epoprostenol was not teratogenic in the rat or rabbit at 1, 10, and 100 $\mu\text{g}/\text{kg}/\text{day}$ given subcutaneously during critical periods of organogenesis. However, the mean length of gestation was significantly ($P < 0.05$) increased in pregnant rats given 30 or 100 $\mu\text{g}/\text{kg}/\text{day}$. Parturition and the rearing of young were not affected. There are no adequate and well-controlled studies in pregnant women. FLOLAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Evaluation:

The length of gestation was slightly but statistically significantly increased in the treated groups compared to the control. The length of gestation was 21.9, 22.0, 22.2 and 22.4 days in the control, 10, 30, and 100 $\mu\text{g}/\text{kg}/\text{day}$ groups, respectively. The maximum prolongation was 12 hours at 100 $\mu\text{g}/\text{kg}/\text{day}$ (600 $\mu\text{g}/\text{m}^2/\text{day}$, 2.5 times the recommended human dose based on body

surface area). The 95% confidence intervals of the length of gestation were 21.72-22.1, 21.74-22.18, 21.99-22.49 and 22.00-22.78 days for the control, 10, 30 and 100 $\mu\text{g}/\text{kg}/\text{day}$, respectively (pair comparison) and they overlap. Therefore, this slight prolongation may not be biologically significant and the labelling should be revised as follows.

Suggested Version:

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in pregnant rats and rabbits at doses up to 100 $\mu\text{g}/\text{kg}/\text{day}$ (600 $\mu\text{g}/\text{m}^2/\text{day}$ in rats, 2.5 times the recommended human dose, and 1180 $\mu\text{g}/\text{m}^2/\text{day}$ in rabbits, 4.8 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to FLOLAN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

SUMMARY AND EVALUATION:

Epoprostenol is synthesized prostacyclin (PGI_2). FLOLAN is the sodium salt of epoprostenol. Naturally occurring prostacyclin, a metabolite of arachidonic acid, is produced in vascular endothelium with potent vasodilatory and anti-platelet aggregation activities. It has been demonstrated that FLOLAN is a potent vasodilator and inhibitor of platelet aggregation in both *in vitro* and *in vivo* studies. It relaxes systemic and pulmonary arterial vessels and thus decreases the systemic and pulmonary arterial blood pressures. It also increases cardiac output. The decreases in the systemic and pulmonary arterial blood pressures and the increase in the cardiac output would reduce the afterload on the right ventricle and improve pulmonary blood flow. This would provide symptomatic relief in the patients with primary pulmonary hypertension. Both systemic and pulmonary thromboembolisms are known risk factors in these patients. Therefore, the anti-platelet aggregation activity of FLOLAN would be useful in reduction of the chance of the life-threatening complication (thrombotic occlusion) in these patients. The mechanisms responsible for the vasodilation and anti-platelet aggregation are not fully understood. However, it has been shown that FLOLAN activates the adenylate cyclase via PGI_2 receptors and thus elevates intracellular cAMP levels in both vascular smooth muscles and platelets. The elevated cAMP then produces both vasodilation and inhibition of platelet aggregation.

In the present NDA, sponsor is requiring to market FLOLAN for treatment of primary pulmonary hypertension in adults and children. The treatment will be indefinite. In support of this NDA, the following studies were submitted: pharmacological studies, absorption, distribution, metabolism and excretion (ADME): *in vivo* studies in rats, dogs, monkeys, cats and rabbits and *in vitro* studies in rabbits and monkeys, toxicity studies: (1). acute i.v. toxicity studies in mice and rats, (2). a 2-week s.c. toxicity study in rats and 2-week i.v. toxicity studies in rats and monkeys, (3). 30-day i.v. toxicity studies in dogs, (4). a special toxicity study of mouse skin abrasion test, (5). a 2-week i.v. toxicity study of 6-oxo- $\text{PGF}_{1\alpha}$ (a major metabolite

of PGI₂) in monkeys; (6). s.c. reproductive toxicity studies: a Segment I fertility and general reproductive study in rats, a Segment II teratological studies in rats, two Segment II teratological studies in rabbits and a Segment III perinatal and postnatal study in rats; and (7). mutagenicity studies: Ames test, rat micronucleus test and DNA damage/alkaline elution assay.

FLOLAN is stable at pH 10 or greater and rapidly hydrolyzed at physiological pH and temperature to 6-keto PGF_{1α}, a 1000-fold less potent metabolite. Following intravenous continuous infusion of FLOLAN, its steady state plasma levels measured by either ³H-epoprostenol or ³H-metabolites of epoprostenol were reached within 10-15 minutes in rabbits and dogs and within ~45-60 minutes in cats. The steady state plasma levels increased linearly with increase in the infusion rate. Following intravenous administration, FLOLAN was quickly eliminated in all species tested including the rat, cat, rabbit, dog, and monkey. The elimination half lives were ~1-3 minutes in cats and rabbits and ~12-14 minutes in dogs. FLOLAN was quickly metabolized to a number of metabolites. Seven urinary metabolites in rats, 6 in dogs and 12 in monkeys have been identified. 6-keto-PGF_{1α} is a major metabolite in the bile and urine (rat bile, 9.2% of radioactivity, monkey urine, 16% and uncertain in dogs). The other major urinary metabolites are 9,11-dihydroxy-2,3,19,20-tetranor-6,15-diketo-prostan-3,18-dioic acid (rat, 19%), 9,11,15,19-tetrahydroxy-2,3-dinor-6-ketoprostan-13-en-3-oic acid (rat, 17.1%), 9,11,19-trihydroxy-6,15-diketo-2,3-dinor prostan-1-oic acid or 9,11,20-trihydroxy-6,15-diketo-2,3-dinor prostan-1-oic acid (dog, 22.8%) and 9,11-dihydroxy-6,15-diketo-2,3-dinor prostan-3,20-dioic acid (dog, 11.4%). The calculated systemic clearance and the whole body volume of distribution were 93 ml/kg/min and 357 ml/kg, respectively in rabbits. The *in vitro* studies indicated that the lung, kidney, liver and blood vessels had the capability to metabolize FLOLAN. Tissue distribution studies revealed that the highest levels of radioactivity were detected in the tissues associated with route of excretion including the kidney, liver and small intestine. The major route of excretion was by urine (80-88% of the given dose) in dogs and men. In rats, 33-49% of the administered dose was recovered in urine and 35-61% in feces.

In the acute i.v. toxicity studies, the major signs of toxicity, including hypoactivity, ataxia, loss of righting reflex, deep slow breathing and hypothermia, were observed in both mice and rats. These signs of toxicity were observed in a few incidence at concentrations as low as 0.003 mg/kg in mice and 0.01 mg/kg in rats. The minimal lethal doses were 10 mg/kg in mice and 50 mg/kg in rats.

In the 2-week toxicity study in rats (BPAT 78/10), FLOLAN was given subcutaneously to rats at doses of 1, 10 and 100 μg/kg/day for 2 weeks. At 100 μg/kg/day, FLOLAN significantly decreased the body weight gain in male animals. The signs of toxicity observed at 100 μg/kg/day were reddening of the ears and feet, hypothermia and labored breathing. The no effect dose was identified at 10 μg/kg/day.

In the other 2-week toxicity study in rats (BPAT 80/14C), continuous intravenous infusion of FLOLAN was given to rats at 56, 180 and 560 ng/kg/min for two weeks. The signs of toxicity, including lethargy, decrease in food intake, increase in water intake, hypothermia,

thrombocytopenia and leukopenia were observed mainly at dose of 560 ng/kg/min. The pathological examination revealed that there were endocardial granulation tissues in the right heart at 56 and 560 ng/kg/min groups (female) and thickened atrioventricular valves at 560 ng/kg/min group (male). Sponsor claimed that these changes were related to the indwelling intravenous catheter. However, no indication can be found that the cannula was in the heart in these rats with the lesions. The no effect dose cannot be established.

In the 30-day toxicity study in dogs (7205/82/7263/005), FLOLAN was intravenously infused at 12.5, 40 and 125 ng/kg/min for 30 days. The major signs of toxicity were vomiting, diarrhea and bloody stools observed in 125 ng/kg/min group. Vomiting frequently occurred during the first three days. Water to mucoid diarrhea was seen over days 2 through 4. Bloody stools were observed in one female dog on day 4. Thrombocytopenia was observed in both 40 and 125 ng/kg/min dose groups. Thrombocytopenia started on day 4 and remained throughout the treatment. Leukopenia was found mainly in 125 ng/kg/min dose group. The no-effect dose was 12.5 ng/kg/min.

In the other 30-day toxicity study in dogs (7205/82/7263/006), FLOLAN was intravenously infused at 125 ng/kg/min for 30 days to study the reversibility of its hematological effects seen in the earlier study (7205/82/7263/005). The thrombocytopenia and other hematological effects were rapidly reversed after discontinuing the FLOLAN treatment. The decrease in the platelet count was totally recovered within 5 days after discontinuing the treatment. Vomiting, diarrhea and hypoactivity were observed in the treatment group in this study.

In the 2-week toxicity study in monkeys (*E. Patas*) (BPAT 78/16), FLOLAN was intravenously infused at 10, 100 and 1000 ng/kg/min for 60 min, 3 times per week for 2 weeks. The major signs of toxicity were vomiting and diarrhea observed in one of the four monkeys in the 1000 ng/kg/min group. Autopsy revealed papillary necrosis of the heart muscle in one of the four monkeys in the 1000 ng/kg/min group. The no effect dose was 100 ng/kg/min. Some pharmacological responses observed in this study included lowering blood pressure, increasing heart rate and anti-platelet aggregation.

In the other 2-week toxicity study in monkeys (*E. patas*) (BPAT 79/04), 6-oxo-PGF_{1 α} , the major metabolite of epoprostenol, was intravenously infused at 1000 ng/kg/min for 60 minutes, 3 times per week for 2 weeks. In the agreement with the results obtained with FLOLAN, 6-oxo-PGF_{1 α} at this concentration induced necrotic lesions in the hearts in 3/6 monkeys. These lesions included one small lesion in the papillary muscle, two small lesions in the atrial wall and one small mixed infiltrate perivascular focus in the ventricular wall.

In the Segment I fertility and general reproductive study in rats (7205/81/7263/006), FLOLAN at 10, 30 and 100 $\mu\text{g}/\text{kg}/\text{day}$ was subcutaneously given to male rats for 60 days prior to mating and during 14-day breeding period and to female rats for 14 days prior to mating, during breeding and throughout gestation and lactation. Fertility and the reproductive performance were not impaired in this study.

In the Segment II. teratogenicity study in rats (BPAT 78/27), FLOLAN at 1, 10 and 100 $\mu\text{g}/\text{kg}/\text{day}$ was subcutaneously given to pregnant rats on days 6-16 of pregnancy. No teratogenic effects were observed in rats in this study.

In the two Segment II fetal and teratogenicity studies in rabbits (BPAT 78/31 and BPAT 79/21), FLOLAN at 1, 10 and 100 $\mu\text{g}/\text{kg}/\text{day}$ was subcutaneously given to pregnant rabbits on days 6-18 of pregnancy. No teratogenic effects were observed in these two studies.

In the Segment III perinatal and postnatal study in rats (7205/81/7263/004), FLOLAN at 10, 30 and 100 $\mu\text{g}/\text{kg}/\text{day}$ was subcutaneously given to pregnant rats on gestation day 15 through day 21 post-partum. FLOLAN did not produce any toxic effects on parturition, lactation and pup survival in this study. However, the length of gestation was slightly but statistically significantly increased in the 30 and 100 $\mu\text{g}/\text{kg}/\text{day}$ groups. The maximum prolongation (~ 12 hour compared to the control) was found in the 100 $\mu\text{g}/\text{kg}/\text{day}$ group. The 95% confidence intervals for the length of gestation were 21.72-22.1, 21.74-22.18, 21.99-22.49 and 22.00-22.78 days for the control, 10, 30 and 100 $\mu\text{g}/\text{kg}/\text{day}$, respectively (pair comparison) and they overlap. Therefore, this slight prolongation may not be biologically significant.

The mutagenicity studies revealed that there were no evidence for mutagenic potential in all three tests including Ames test, micronucleus test in rats and DNA damage/alkaline elution assay in cultured Chinese hamster lung V-79 cells. However, the Ames test and DNA damage/alkaline elution assay were not interpretable because of lack of data concerning the stability and concentration of epoprostenol, its inherent nature and instability, rapid metabolism and extremely short *in vitro* half life ($\sim 1-3$ minutes).

The labelling should be revised as suggested in the labelling portion.

The toxicity studies submitted in this submission include acute toxicity studies in mice and rats and short term (2-week and 30-day) toxicity studies in rats, dogs and monkeys. In the short term toxicity studies, the following target organs of toxicity were identified: cardiovascular, gastrointestinal and central nervous systems. These were reflected by cardiac lesions, hypotension, leukopenia and thrombocytopenia, vomiting, diarrhea and bloody stools, and hypothermia. These changes except myocardial lesions were reversible. Leukopenia and thrombocytopenia were observed in both rats and dogs. The gastrointestinal disturbances were observed in both dogs and monkeys. The cardiac lesions were seen in both rats and monkeys. Hypothermia and hypotension were found in all species tested. The 2-week toxicity studies in rats and monkeys revealed that both FLOLAN and its metabolite, 6-oxo-PGF_{1 α} , induced

myocardial lesions. FLOLAN is proposed to be marketed for long term (indefinite) treatment of primary pulmonary hypertension in adults and children. Long term toxicity studies were not conducted. Therefore, it is necessary to conduct long term toxicity studies to assess the long term effects of FLOLAN in the rat and monkey.

There were no carcinogenicity studies available to support the safety of the long term use of this drug. FLOLAN is the sodium salt of epoprostenol, a synthesized prostacyclin. Due to the similarity between FLOLAN and the naturally occurring prostacyclin, it is not necessary to conduct the carcinogenicity studies.

RECOMMENDATION:

From a preclinical standpoint, this NDA is approvable. Sponsor should be asked to revise the labelling as recommended and to conduct postmarketing long term toxicity studies with FLOLAN. These toxicity studies should include 1-year toxicity studies in a rodent (rat) and a nonrodent (monkey).

Ke Zhang, 12/21/94
Ke Zhang, Ph.D

- cc:
- NDA
- HFD-180
- HFD-181/CSO
- HFD-180/Dr. Choudary
- HFD-180/Dr. Fredd
- HFD-180/Dr. Zhang
- HFD-345/Dr. James
- HFD-502/Dr. Taylor

KZ/hw/12/21/94
C:\WPFILES\PHARM\N20444410.0KZ

- ① Concur
- ② Even though flolan is the sodium salt of endogenous prostacyclin, its long term impact on cardiac tissue needs to be assessed since it is proposed to be administered at levels much higher than the endogenous levels of prostacyclin for an indefinite period.

Ke Zhang
12/21/94

Chem

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG
PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

NDA:# 20-444 CHEM REVIEW # 4 REVIEW DATE: August 22, 1995

<u>DOCUMENT TYPE</u>	<u>DOCUMENT</u>	<u>CDER</u>	<u>DATES</u> <u>ASSIGNED</u>	<u>REVIEW</u>
ORIGINAL	28-Feb-94	01-Mar-94	07-Mar-94	1
AMENDMENT	10-Apr-95	12-Apr-95	14-Apr-95	2
	09-Jun-95	12-Jun-95	13-Jun-95	3
	24-Jul-95	26-Jul-95	31-Jul-95	Current

NAME & ADDRESS OF APPLICANT :

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park

AUG 25 1995

DRUG PRODUCT NAME:

Proprietary: Flolan
Nonproprietary/USAN: epoprostenol sodium
Code Name/#: 4AU76
Chem.Type/Ther.Class: 1P V

PHARMACOLOGICAL CATEGORY anti-platelet

INDICATION: Long-term, intravenous treatment of NYHA Class III and Class IV patients with Primary Pulmonary Hypertension (PPH)

DOSAGE FORM: Freeze-dried powder for Injection

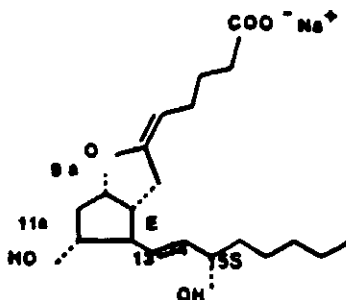
STRENGTHS: 0.5 and 1.5 mg/vial

ROUTE OF ADMINISTRATION: Intravenous Injection

HOW DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

epoprostenol sodium
prostaglandin I₂, sodium salt
Sodium 5Z,9α,11α,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-
dienoate (IUPAC)
C₂₀H₃₁O₅Na MW=374.45 CAS 61849-14-7



SUPPORTING DOCUMENTS: DMFs

DMF

DMF

RELATED DOCUMENTS: IND

CONSULTS: See Review #2, April 28, 1995

REMARKS/COMMENTS: The deficiencies in the DMF for the drug substance have been addressed satisfactorily. There are a number of outstanding minor questions but they may be answered in an Annual Report and will not delay approval of the NDA.

There are some suggested revisions to the Package Insert (see attached memo dated August 10, 1995).

CONCLUSIONS & RECOMMENDATIONS: The application may be approved from a CMC standpoint.

Arthur B. Shaw 8/25/95
Arthur B. Shaw, Ph. D.
Chemist, HFD-180

John J. Gibbs 8/25/95
John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

CC:
NDA 20-444
HFD-180/SFredd
HFD-180/Division File
HFD-181/CSO
R/D Init by: JGibbs/8-24-95
ABS/dob F/T 8-25-95\WP: c:\wpfiles\chem\n\20444508.4AS

DMF:

Title: Epoprostenol Sodium

1. CHEM REVIEW # 5 2. REVIEW DATE: July 26, 1995

3. DMF INFORMATION REVIEWED:

<u>Type of Submission</u>	<u>Date of Submission</u>	<u>Location of Information</u>
Amendment	21-Jul-95	Volume 3.1

4. PREVIOUS DOCUMENTS

<u>Type of Document</u>	<u>Date of Document</u>	<u>Comment</u>	AUG 11 1995
ORIGINAL	16-May-85		
Review	01-Oct-86	Deficiency letter	01-Oct-86
Response to letter	26-Jan-89		
Review	19-Jul-89	Deficiency letter	19-Jul-89
Response to letter	20-Apr-90	Not reviewed	
Annual Report	06-Nov-91		
Annual Report	17-Nov-92		
Annual Report	08-Oct-93		
Review	03-Aug-94	Deficiency letter	03-Aug-94
Response to letter	01-Feb-95		
Annual Report	01-Feb-95		
Review	27-Mar-95	Deficiency Letter	27-Mar-95
Telecon	13-Jul-95		
Telecon	27-Jul-95		

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE:

NAME:

ADDRESS:

6. ITEM REVIEWED: epoprostenol sodium
See Chem Review #4 for chemical name and structure.

7. DMF REFERENCED FOR:

NDA: 20-444

APPLICANT NAME: Burroughs Wellcome Company

LOA DATE: 07-Dec-93

DRUG PRODUCT NAME: Flolan

DOSAGE FORM: Lyophilized Powder for Injection

ROUTE OF ADMINISTRATION: Intravenous

8. SUPPORTING DOCUMENTS: None

9. CURRENT STATUS OF DMF:

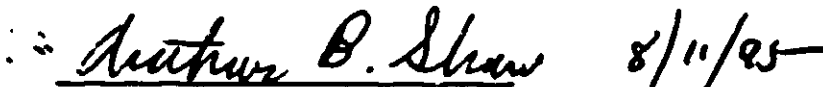
DATE OF LAST UPDATE OF DMF: July 21, 1995

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED:
February 1, 1995

10. CONSULTS: None

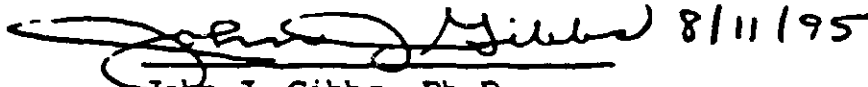
11. REMARKS/COMMENTS: The holder has provided a completed batch record for review but this was not filed with the DMF. There are a number of commitments for assays and validation to be provided by the end of 1995.

12. CONCLUSIONS & RECOMMENDATIONS: ADEQUATE There are a number of minor questions and commitments for information to be provided.

 8/11/95

Arthur B. Shaw, Ph.D.

Review Chemist, HFD-180

 8/11/95

John J. Gibbs, Ph.D.

Supervisory Chemist, HFD-180

cc:

DMF

HFD-180/Division File NDA 20-444

HFD-180/SFredd

HFD-181/CSO

HFD-180/AShaw

R/D Init by: JGibbs/8-9-95

ABS/dob F/T 8-9-95\WP: c:\wpfiles\chem\D\06065507.3AS

C. W. W.

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-444 CHEM REVIEW #3 REVIEW DATE: June 21, 1995

JUN 23 1995

<u>DOCUMENT TYPE</u>	<u>DOCUMENT</u>	<u>CDER</u>	<u>DATES</u> <u>ASSIGNED</u>	<u>REVIEW</u>
ORIGINAL	28-Feb-94	01-Mar-94	07-Mar-94	1
AMENDMENT	10-Apr-95	12-Apr-95	14-Apr-95	2
	09-Jun-95			Current

NAME & ADDRESS OF APPLICANT :

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park

DRUG PRODUCT NAME:

Proprietary: Flolan
Nonproprietary/USAN: epoprostenol sodium
Code Name/#: 4AU76
Chem.Type/Ther.Class: 1P V

PHARMACOLOGICAL CATEGORY anti-platelet

INDICATION: Long-term, intravenous treatment of NYHA Class III and Class IV patients with Primary Pulmonary Hypertension (PPH)

DOSAGE FORM: Freeze-dried powder for Injection

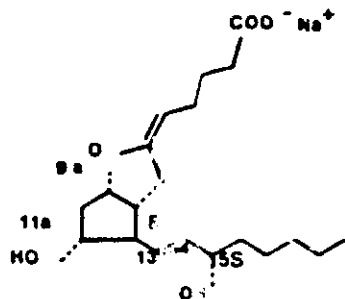
STRENGTHS: 0.5 and 1.5 mg/vial

ROUTE OF ADMINISTRATION: Intravenous Injection

HOW DISPENSED: X Rx _ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

epoprostenol sodium
prostaglandin I₂, sodium salt
Sodium 5Z,9α,11α,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dienoate (IUPAC)
C₂₀H₃₁O₅Na MW=374.45 CAS 61849-14-7



SUPPORTING DOCUMENTS: DMFs

DMF

DMF

RELATED DOCUMENTS: IND

CONSULTS: See Review #2, April 28, 1995

REMARKS/COMMENTS: There are still a number of deficiencies in the DMF for the drug substance

CONCLUSIONS & RECOMMENDATIONS: The application is approvable pending a satisfactory response to the deficiencies in DMF for the synthesis of the drug substance.

Arthur B. Shaw 6/22/95

Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

John J. Gibbs 6/23/95

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

CC:

ADA 20-444

HFD-180/SFredd

HFD-180/Division File

HFD-181/CSO

R/D Init by: JGibbs/6-22-95

AS/dob F/T 6-22-95\Wp: c:\wpfiles\chem\n\20444506.3AS

C11102
APR 28 1995

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-444 CHEM REVIEW:#2 REVIEW DATE: April 25, 1995

<u>DOCUMENT TYPE</u>	<u>DOCUMENT</u>	<u>CDER</u>	<u>DATES</u>		<u>REVIEW</u>
			<u>ASSIGNED</u>		
<u>ORIGINAL</u>	28-Feb-94	01-Mar-94	07-Mar-94		1
<u>AMENDMENT</u>	10-Apr-95	12-Apr-95	14-Apr-95		Current

NAME & ADDRESS OF APPLICANT :

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park

DRUG PRODUCT NAME:

Proprietary: Flolan
Nonproprietary/USAN: epoprostenol sodium
Code Name/#: 4AU76
Chem.Type/Ther.Class: 1P V

PHARMACOLOGICAL CATEGORY anti-platelet

INDICATION: Long-term, intravenous treatment of NYHA Class III and Class IV patients with Primary Pulmonary Hypertension (PPH)

DOSAGE FORM: Freeze-dried powder for Injection

STRENGTHS: 0.5 and 1.5 mg/vial

ROUTE OF ADMINISTRATION: Intravenous Injection

HOW DISPENSED: Rx OTC

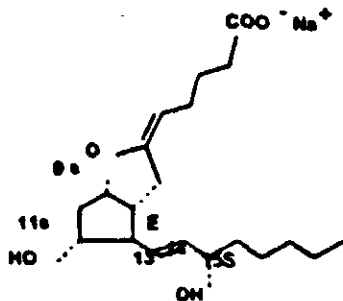
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

epoprostenol sodium

prostaglandin I₂, sodium salt

Sodium 5Z, 9α, 11α, 13E, 15S)-6, 9-epoxy-11, 15-dihydroxyprosta-5, 13-dienoate (IUPAC)

C₂₀H₃₁O₅Na MW=374.45 CAS 61849-14-7



SUPPORTING DOCUMENTS: DMFs

DMF

, DMF

RELATED DOCUMENTS: IND

CONSULTS:

Statistics: Consult received Dec 13, 1994

Environmental Assessment: FONSI issued October 17, 1994

Trademark Review: Acceptable July 22, 1994

Establishment Inspection: Acceptable (see Chem Review #1, February 23, 1995)

Microbiology: Acceptable Review Dated April 18, 1995

REMARKS/COMMENTS: The application is acceptable. The questions in the draft letter may be answered post-approval. There are still a number of deficiencies in the DMF for the drug substance

. Since the applicant has adequate controls for the specifications for acceptance of the drug substance, it is possible to approve the NDA without a complete resolution of all the issues in the DMF.

CONCLUSIONS & RECOMMENDATIONS: The application may be approved if the applicant commits to answering the questions in the draft letter, post-approval, and commits to ensuring that the holder of DMF provides adequate responses to the questions in our letter dated March 27, 1995.

Arthur B. Shaw 4/8/95

Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

John J. Gibbs 4/28/95

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

CC:
NDA 20-444
HFD-180/SFredd
HFD-180/Division File
HFD-181/CSO
HFD-180/AShaw
R/D Init by:4-27-95
ABS/dob F/T 4-27-95\WP: c:\wpfiles\chem\N\20444504.2AS

oliver

MAR 27 1995

DMF:

Title: Epoprostenol Sodium

1. CHEM REVIEW # 4

2. REVIEW DATE: March 20, 1995

3. DMF INFORMATION REVIEWED:

<u>Type of Submission</u>	<u>Date of Submission</u>	<u>Location of Information</u>
Amendment	01-Feb-95	Volume 2.1
Annual Report	01-Feb-95	Volume 2.1

4. PREVIOUS DOCUMENTS

<u>Type of Document</u>	<u>Date of Document</u>	<u>Comment</u>
ORIGINAL	16-May-85	
Review	01-Oct-86	Deficiency letter 01-Oct-86
Response to letter	26-Jan-89	
Review	19-Jul-89	Deficiency letter 19-Jul-89
Response to letter	20-Apr-90	Not reviewed
Annual Report	06-Nov-91	
Annual Report	17-Nov-92	
Annual Report	08-Oct-93	
Review	03-Aug-94	Deficiency letter 03-Aug-94

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE:

NAME:

ADDRESS:

6. ITEM REVIEWED:

NAME: epoprostenol sodium (prostaglandin I₂, sodium salt)

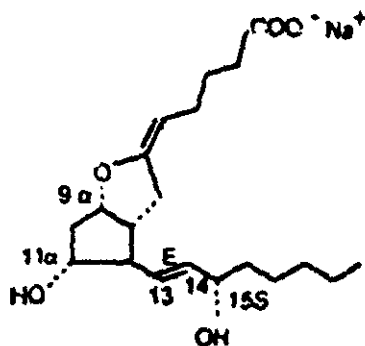
CHEMICAL NAME: Sodium 5Z,9α,11α,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-oate

CAS NUMBER: 61849-14-7

MOLECULAR WEIGHT: 374.45

CHEMICAL FORMULA: C₂₀H₃₁O₉Na

STRUCTURAL FORMULA:



7. DMF REFERENCED FOR:

NDA: 20-444

APPLICANT NAME: Burroughs Wellcome Company

LOA DATE: 07-Dec-93

DRUG PRODUCT NAME: Flolan

DOSAGE FORM: Lyophilized Powder for Injection

ROUTE OF ADMINISTRATION: Intravenous

8. SUPPORTING DOCUMENTS: None**9. CURRENT STATUS OF DMF:**

DATE OF LAST UPDATE OF DMF: February 1, 1995

DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE BEEN PROVIDED:
February 1, 1995**10. CONSULTS: None****11. REMARKS/COMMENTS:** The holder has committed to providing more information regarding validation of a number of assays either under development or already being used. A number of deficiencies remain.**12. CONCLUSIONS & RECOMMENDATIONS:** The holder should be sent an Information Request letter.

Arthur B. Shaw 3/24/95 -
Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

John J. Gibbs 3/27/95
John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

cc:

DMF

HFD-180/Division File NDA 20-444

HFD-180/SFredd

HFD-181/CSO

HFD-180/AShaw

R/D Init by: JGibbs/3-23-95

ABS/dob P/T 3-24-95\WP: c:\wpfiles\chem\D\06065502.2AS

01/16/92

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA:# 20-444 CHEM REVIEW # 1 REVIEW DATE: February 16, 1995

<u>DOCUMENT TYPE</u>	<u>DOCUMENT</u>	<u>CDER</u>	<u>DATES</u> <u>ASSIGNED</u>	<u>REVIEW</u>
<u>ORIGINAL</u>	28-Feb-94	01-Mar-94	07-Mar-94	Current

FEB 23 1995

NAME & ADDRESS OF APPLICANT :

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park

DRUG PRODUCT NAME:

Proprietary: Flolan
Nonproprietary/USAN: epoprostenol sodium
Code Name/#: 4AU76
Chem.Type/Ther.Class: 1P V

PHARMACOLOGICAL CATEGORY anti-platelet

INDICATION: Long-term, intravenous treatment of NYHA Class III and Class IV patients with Primary Pulmonary Hypertension (PPH)

DOSAGE FORM: Freeze-dried powder for Injection

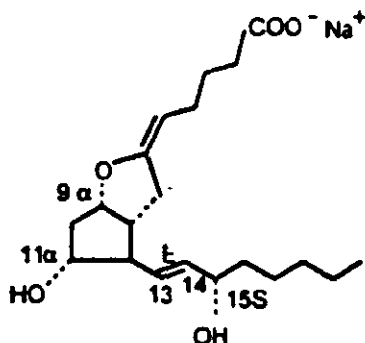
STRENGTHS: 0.5 and 1.5 mg/vial

ROUTE OF ADMINISTRATION: Intravenous Injection

HOW DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT.:

epoprostenol sodium

prostaglandin I₂, sodium saltSodium 5Z,9 α ,11 α ,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dienoate (IUPAC)C₂₀H₃₁O₅Na MW=374.45 CAS 61849-14-7**SUPPORTING DOCUMENTS:** DMFs

DMF

DMF

RELATED DOCUMENTS: IND**CONSULTS:**

Statistics: Consult received Dec 13, 1994

Environmental Assessment: FONSI issued October 17, 1994

Trademark Review: Acceptable July 22, 1994

Establishment Inspection: Acceptable

REMARKS/COMMENTS: The application is, in general, acceptable. None of the questions in the draft deficiency letter are major. The DMF for the drug substance is deficient in a number of ways.

CONCLUSIONS & RECOMMENDATIONS: The application is approvable pending an adequate reply to the deficiencies in the DMF for the drug substance and a satisfactory reply to the questions in the draft letter.

Arthur B. Shaw 2/22/95

Arthur B. Shaw, Ph.D.
Review Chemist, HFD-180

John J. Gibbs 2/23/95

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

CC:

NDA 20-444

HFD-180/SFredd

HFD-180/Division File/

HFD-181/CSO

R/D Init by:JGibbs/2-18-95

ABS/dob F/T 2-21-95\WP: c:\wpfiles\chem\N\20444408.1AS#

JUL 30 1994

**DIVISION OF GASTROINTESTINAL AND COAGULATION
DRUG PRODUCTS**

Review of Chemistry, Manufacturing, and Controls

DMF:# **CHEM REVIEW # 3 REVIEW DATE:** July 26, 1994

<u>SUBMISSION TYPE</u>	<u>DATES</u>					
	<u>DOCUMENT</u>	<u>CDER</u>	<u>REVIEW</u>	<u>NUM</u>	<u>LETTER</u>	<u>ST</u>
ORIGINAL	16-May-85	22-Oct-85	01-Oct-86	1	01-Oct-86	DE
AMENDMENT						
1	26-Jan-86	01-Feb-89				
2	01-Jun-89	06-Jun-89	19-Jul-89	2	19-Jul-89	DE
3	20-Apr-90	27-Apr-90	Response to 19-Jul-1989 letter			
4	06-Nov-91	13-Nov-91	Annual Report			
5	17-Nov-92	27-Nov-92	Annual Report			
6	08-Oct-93	19-Oct-93	Annual Report			

NAME & ADDRESS OF HOLDER:

DRUG PRODUCT NAME:

Proprietary:

Nonproprietary/USAN: epoprostenol sodium

Code Name/#: U-53,217A

Chem.Type/Ther.Class: 1P

ANDA Suitability Petition/DESI/Patent Status: N/A

APPLICANT FOR NDA FOR WHICH DMF IS IN SUPPORT:

Burroughs Wellcome Company

NDA #: 20-444

CONTACT PERSON AT COMPANY APPLYING FOR NDA:

DATE OF LETTER OF AUTHORIZATION: 07-Dec-93

Pharmacological Category: Vasodilator

Dosage Form:

Drug substance to be used in iv injections

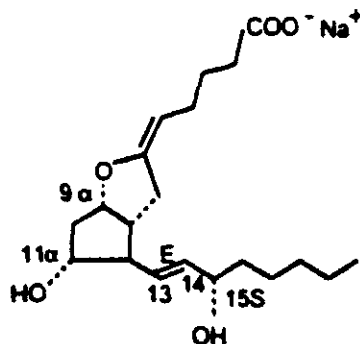
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

prostaglandin I₂, sodium salt

Sodium 5Z, 9 α , 11 α , 13E, 15S) -6, 9-epoxy-11, 15-dihydroxyprosta-5, 13-dien-oate

C₂₀H₃₁O₅Na

MW=374.45



SUPPORTING DOCUMENTS: N/A

RELATED DOCUMENTS (if applicable): N/A

CONSULTS: N/A

REMARKS/COMMENTS: The original review is not included in the DMF, but the "deficiency letter" dated October 1, 1986 is in the jacket. The January 26, 1989 amendment responds to this letter and includes a complete resubmission. The June 1, 1989 amendment contains a revision to correct a typographical error. The review dated July 19, 1989 (erroneously dated June 26, 1988 in the review itself) responds to these amendments. A deficiency letter was sent on July 19, 1989. The holder responded in the April 20, 1990 amendment. There have been subsequent annual reports. The changes reported are summarized in the attached table. This review will follow the review outline as if this were a new DMF and first review.

CONCLUSIONS & RECOMMENDATIONS: The DMF is deficient in many aspects, including the structure proof and the validation of the assays.

SUMMARY FOR CDR: DMF inadequate for structure proof, validation of assays, description of reference standard.

Arthur B. Shaw 7/29/94

Arthur B. Shaw, Ph. D.
Chemist, HFD-180

John J. Gibbs 7/30/94

John J. Gibbs, Ph.D.
Supervisory Chemist, HFD-180

CC:

DMF

HFD-180/SFredd

HFD-82/Lipov

HFD-180/

HFD-180/Division File/ NDA 20-444

HFD-181/CSO

R/D Init by: JGIBBS/7-29-94

abs/F/T/ 7-29-94 filename: Wp #c:\wpfiles\a\db\06065406.1AS

Amicus

APR 18 1995

CONSULTATIVE REVIEW TO HFD-180
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 2
April 12, 1995



Review Microbiologist: Carol K. Vincent

A. 1. NDA No.: 20-444

PRODUCT NAME: Floian
(Epoprostenol sodium for injection, 0.5 mg or 1.5 mg / vial)

APPLICANT: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

MANUFACTURING SITE:

Lyophilized drug product: Wellcome Foundation, LTD.
Dartford, England

Sterile diluent for Floian: Burroughs Wellcome Co.,
Greenville, NC

2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Sterile, lyophilized powder in glass vial with rubber stopper and aluminum seal; intravenous. To be reconstituted with Sterile Diluent for Floian, 50 mL vial

3. METHOD(s) OF STERILIZATION: Aseptic fill for lyophilized drug product, Floian for injection, and terminal steam sterilization for Sterile Diluent for Floian.

4. PHARMACOLOGICAL CATEGORY AND / OR PRINCIPAL INDICATION:

Long term intravenous treatment of adults and children with NYHA Class III and Class IV patients with primary pulmonary hypertension (PPH). Drug product is delivered continuously on an ambulatory basis through a permanent indwelling central venous catheter via a small, portable infusion pump.

5. DRUG PRIORITY CLASSIFICATION: 1 P

B. 1. AMENDMENT: 01-27-95 (Subject of this review)

2. RELATED DOCUMENT: DMF

C. REMARKS:

This 01-27-95 amendment responds to the Information Request letter for additional information concerning microbiological quality and sterilization process validation that HFD-180 issued October 17, 1994. The original February 28, 1994 application and April 29, 1994 amendment lacked sufficient sterilization process validation information and the Microbiology group did not recommend approval for sterility assurance and microbiological quality for the application at that time [See CONSULTATIVE REVIEW TO HFD-180, MICROBIOLOGIST'S REVIEW NO. 1 DATED SEPTEMBER 29, 1994 FOR NDA 20-444]

NDA 20444

6 OF 8

This 01-27-95 amendment to NDA 20-444 satisfies all outstanding requests for additional information.

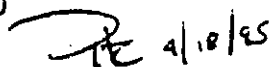
We do, however, request that the applicant provide, as a post-approval commitment, adequate sterilization process validation information for the filter sterilization of the drug product. This information was very briefly described by the applicant in Volume 1.5, p 1021, in section IV.B.1.c entitled "Summary of Filter Validation".

D. CONCLUSION and RECOMMENDATION: We recommend approval for sterility assurance and microbiological quality for the application provided that the applicant commits to amend the application with adequate and appropriate sterilization process validation information for the filter sterilization of the drug product.

See "E. REVIEW NOTES:" and DRAFT OF LETTER TO APPLICANT, below.



Carol K. Vincent
Reviewing Microbiologist, HFD-160



Orig. NDA 20-444
HFD-180/Fredd/Gibbs/Shaw/Oliver
HFD-160/Consult file/CKVincent
Drafted by: CKVincent/04-11-95
R/D Init by: PHCooney/04-17-95

007 9 1994

CONSULTATIVE REVIEW TO HFD-180
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 1
September 29, 1994

Review Microbiologist: Carol K. Vincent

A. 1. NDA No.: 20-444

PRODUCT NAME: Flolan
[Epoprostenol sodium for injection,
0.5 mg or 1.5 mg / vial]

APPLICANT: Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

MANUFACTURING SITE:

Lyophilized drug product: Wellcome Foundation, LTD.
Dartford, England

Sterile diluent for Flolan: Burroughs Wellcome Co.,
Greenville, NC

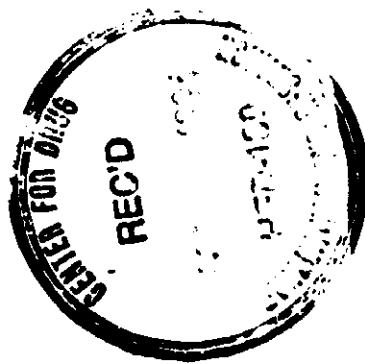
- 2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile, lyophilized powder in glass vial with rubber stopper and aluminum seal; intravenous. To be reconstituted with Sterile Diluent for Flolan, 50 mL vial
- 3. METHOD(s) OF STERILIZATION: Aseptic fill for lyophilized drug product, Flolan for Injection, and terminal steam sterilization for Sterile Diluent for Flolan.
- 4. PHARMACOLOGICAL CATEGORY AND / OR PRINCIPAL INDICATION:
Long term intravenous treatment of adults and children with NYHA Class III and Class IV patients with primary pulmonary hypertension (PPH). Drug product is delivered continuously on an ambulatory basis through a permanent indwelling central venous catheter via a small, portable infusion pump.
- 5. DRUG PRIORITY CLASSIFICATION: 1 P

- B. 1. INITIAL APPLICATION DATE: 02-28-94
- 2. APPLICATION RECEIVED FOR CONSULT REVIEW: 03-15-94
- 3. AMENDMENT: 04-29-94

C. REMARKS:

The applicant has formatted the Sterilization Process Validation information section to correspond with the June 1, 1993 "Recommendations for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products". This "Recommendations . . ." document, with minor modifications, was subsequently issued in the Federal Register (58 FR 63996, Docket No. 93D-0312 dated December 3, 1993).

Sterile Diluent for Flolan manufactured in Greenville, NC is filter sterilized, aseptically filled, and terminally sterilized by steam autoclave. We consider the filtration and aseptic fill as a bicburden reduction process because the terminal sterilization that follows provides a greater sterility



assurance level. This review of the Greenville, North Carolina facility is therefore for the terminal sterilization process, only. Manufacturing activities that would solely be intended for an aseptic fill manufacturing process are not reviewed at this time.

D. **CONCLUSION** and **RECOMMENDATION**: We do not recommend approval for sterility assurance and microbiological quality for the application.

Carol K. Vincent 9-29-94

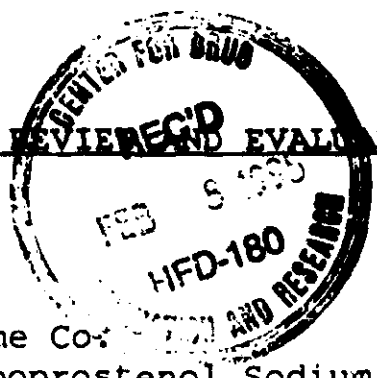
Carol K. Vincent
7/10/94

Orig. NDA 20-444
HFD-180/Fredd/Gibbs/Shaw/Oliver
HFD-160/Consult file/CKVincent
Drafted by: CKVincent/04-04-94/09-29-94
R/D Init by: PHCooney/09-30-94

5fot5

Older

STATISTICAL REVIEW AND EVALUATION



Date: FEB 7 1995

NDA # : 20-444
 Applicant: Burroughs Wellcome Co.
 Name of the Drug: Flolan (Epoprostenol Sodium)
 Indication: Treatment of Primary Pulmonary Hypertension (PPH).
 Documents reviewed: One volume dated April 6, 1994; one volume dated May 6, 1994; one volume dated May 27, 1994; one volume dated August 23, 1994; one volume dated October 28, 1994; one volume dated October 4, 1994; one volume presented at the FDA meeting on December 5, 1994; one volume dated December 9, 1994; one volume dated December 12, 1994; one volume dated December 19, 1994; one volume dated January 24, 1995 and one volume dated January 25, 1995.

The issues in this review have been discussed with the medical reviewer Eugenie Triantas, M.D., Ph.D.

This is an addendum to two previous statistical reviews for this NDA. The addendum is related to the Statistical Review of Study #46, dated September 6, 1994, by this reviewer (here referred to as previous review).

A. Introduction

The previous review for Study # 46 raised concern about the proper execution of the randomization in this open trial. This review addresses the following points regarding randomization for this trial.

- i) Sponsor's randomization program.
- ii) Comments on the sponsor's comparison of the modified adaptive randomization, the so-called 'Wold method', versus the Random Block Design method.
- iii) Comments on the statistics which the sponsor submitted during the December 25, 1994 meeting concerning baseline comparability.
- iv) Additional analysis for the primary endpoints as suggested

by Dr. Triantas, the medical officer.

I. Sponsor's Randomization Program:

The sponsor used the so-called 'Wold method', a modified version of the adaptive randomization method of Pocock and Simons [Biometrics(1975), 31:103-115], to achieve, as claimed, baseline balance with respect to NYHA class, vasodilator use and study site (center).

In a response to the FDA request on May 4, 1994, the sponsor submitted the randomization program used in Study 46. In running this program for treatment assignments, the sponsor used information in addition to the three variables intended for balancing. The sponsor claimed on the December 5, 1994 meeting that the purpose of this additional information is to ensure that all data needed are collected and these additional information does not influence the treatment assignments.

This reviewer's experience with the randomization program indicated that one could enter more patients to the already entered 81 patients, but could not verify the validity of the treatment assignment for the 81 patients in the study. To validate this a copy of the program before entering any patients in the study along with baseline measurements for the NYHA class, vasodilator use and site was needed.

Consequently, an additional request was made for a copy of the randomization program before entering any patients to the program. A copy of the randomization program, called 'PPH.EXE', was provided by the sponsor on January 25, 1995. This copy, according to Leland Pierce, M.D., from the Division of Scientific

Investigations, was retrieved from crashed hard disk. On using this program this reviewer was able to make treatment assignments to patients from the beginning as the sponsor claimed.

Also, this reviewer tried the random number generator 'RANDOM.EXE' program provided by the sponsor. This program generated the random numbers used in the randomization as claimed by the sponsor. However, both of these programs (i.e. PPH.EXE and RANDOM.EXE) are in machine language, not readable by the user. Therefore, this reviewer could not validate the programs.

In addition, one of the files which the randomization program uses, called PAF46.DBF, was created on 9/7/94, i.e., after the end of the study. The sponsor in the January 25, 1995 submission claimed the need for this change so that 'this file is as it was for the start of the trial'.

B.II. Randomization Method: The Sponsor's Comparison of 'Wold Method' Versus the Permuted Block Design Method:

The sponsor in the December 5, 1994 meeting justified the use of the so-called 'Wold method' by stating that it controls for more levels of stratification than the Permuted Block Design method. To support this claim the sponsor provided distributions of the treatment imbalances with respect to baseline variables, under the two randomization schemes(see Table 1, attachment 2). These imbalances were based on simulation with 200 replications for each design. For each simulation, the imbalance(Flolan-Conventional) was computed and presented for each combination of NYHA Class and vasodilator use as well as for each study site. An overall distribution of treatment imbalance was also given by the sponsor.

In this reviewer's opinion, the sponsor's preference for the 'Wold method' over the Permuted Block Design method, claiming that it achieves better balance with respect to the baseline variables is not established since:

- i) No test statistics is presented to show any significance difference between the two procedures of randomization.
- ii) As can be seen from Table 1, The magnitude of imbalance of the Wold method exceeds that of the Permuted Block Design for each combination of NYHA Class and vasodilator use.

The magnitude of imbalance of the two methods can also be seen in Table 2, below, which presents a comparison of 'total score' for imbalance for each NYHA Class and vasodilator use combination. Since, in comparing the imbalance one would be interested in the magnitude not the direction of imbalance, therefore this 'total score' is computed as:

$$\text{Total score} = \sum \text{imbalance}(i) * \text{Frequency of the imbalance}(i).$$

Table 2
Comparison of Total Imbalance Score for 'Wold Method' and the Permuted Block Design Method

Baseline variables	No Patients	Total Score of Treatment Imbalance	
		Permuted Block	Wold method
NYHA Class III & Vasodilator use	43	200	290
NYHA Class IV & Vasodilator use	9	200	262
NYHA Class III & no Vasodilator use	15	200	268
NYHA Class IV & no Vasodilator use	14	134	224

Table 2, shows that Permuted Block Design method has numerically less total imbalance score for each NYHA Class and vasodilator use combination. Comparison of treatment imbalance with respect

to each site should not be given much weight since:

- (i) As the sponsor acknowledged NYHA Class and vasodilator use are more important for creating treatment balance than sites, and
- (ii) Most of the sites contain small number of patients as shown below:

Site #	4	5	6	7	8	9	10	11	13	14	15	16	17	18
Patients #														

In practice any randomization method used will create treatment imbalance in such small centers.

Finally, the distribution of the overall treatment imbalance is driven to large extent by the imbalances in small sites, since most of the sites are small in size and no adjustment was made to take into account the number of patients in each site.

In summary, the results of the comparison in Tables 1 and 2 show that the total score of treatment imbalance of the 'Wold Method' numerically exceeds that of the Permuted Block Design for each combination of variables presented in Table 2. Therefore, the sponsor's simulation experiment does not establish the point that the 'Wold method' is superior to the standard Permuted Block Design method.

III. Randomization Results: Pattern of Unexpected Treatments Assignments

Based on the so-called 'Wold method' the sponsor's treatment assignments had the following steps:

- i) The probability, $p(F)$, that the next patient will be assigned to the Flolan treatment [] was calculated based on the previous imbalances in the randomization, and consequently this probability $p(F)$ changed from one assignment to the next.
- ii) A random number from the range 0 to 32767 was selected,
- iii) If this random number was less than $p(F) * 32768$ then the patient receive Flolan, otherwise the patient receive conventional therapy.

In the above algorithm, a patient may be more likely to receive Flolan than conventional therapy [because $p(F) > 0.5$]. However, depending on the value of the random number generated, the patient may receive the other treatment. Similarly, a patients may have a small value for $p(F)$ and be assigned to Flolan and not to the conventional therapy. However, these, which I call 'unexpected assignments' should occur in a random manner, i.e. without forming a certain pattern over time.

Table 3, below, presents the unexpected treatment assignments sequentially over time for Study # 46.

Table 3 shows there is a total of 21 such unexpected assignments of the total 81 assignments, that is more than 25% of the assignments were unexpected. Furthermore, these assignments form a clear pattern over time. The first 9 were assigned to the conventional therapy and the remaining 13 to Flolan therapy. Application of the run test to the assignments in Table 3 shows that the probability that this event occurs due to chance alone is practically zero.

Table 3

List of patients with unexpected treatment assignments

<u>Patients</u> <u>Sequence</u>	<u>Site/</u> <u>Patient</u>	<u>Prob.Flolan</u> <u>Assignment</u>	<u>Treatment</u> <u>Received</u>	<u>Remarks</u>
4	02/	0.67	C	
8	08/	0.67	C	
15	01/	0.67	C	patient died
22	07/	0.67	C	
23	03/	0.67	C	
31	07/	0.67	C	patient died
32	07/	0.67	C	
37	03/	0.60	C	
40	07/	0.71	C	patient died
48	10/	0.33	F	
49	06/	0.29	F	
52	15/	0.17	F	
55	09/	0.25	F	
59	16/	0.40	F	
63	15/	0.14	F	
68	17/	0.43	F	
72	03/	0.40	F	
73	16/	0.40	F	
74	07/	0.33	F	
76	11/	0.25	F	
78	01/	0.13	F	

Table 3 shows that for site 7, 5 out of the total 7 treatment assignments were unexpected treatment assignments and the first 4 patients received the 'less likely' conventional therapy.

This remark about the treatment assignment in center 7 is in agreement with the remark made in the previous statistical review about the randomization in this particular center(see p.8 and Tables 11 and 12 of that review).

IV. Baseline Walk Distance Comparability Revisited: The Sponsor's Comparison

The issue of baseline walk distance comparability was addressed in the previous review. Here, this reviewer addresses the sponsor's response to this issue on December 25, 1994.

The sponsor presented a frequency table for the walk distance called 'distribution analysis of baseline walk' (see Table 4; attached). Based on this table the sponsor concluded that Fisher's Exact test does not support a difference in distribution of baseline walk between the two treatment groups ($p=0.41$).

This reviewer's comments about this table are:

i) Interval of varying length were used in constructing the frequency table. The width of the interval ranges from 1 meter, to 49 meters, to 100 meters to 160 meters for the last interval. This is too far from well-known statistical practice and it is misleading.

ii) the p-value presented by the sponsor is contaminated by the use of these varying length intervals. Having given the original data, this reviewer's preference is to use this original data for comparison instead of grouped data; since by grouping one loses information about the actual measurements.

Table 5 presents the walk distance in frequency form, avoiding the limitation in the sponsor's table.

Table 5
Frequency Table for Day1 and Day2 Walk Distance

Distance (meter)	Frequency		Frequency %		% Cumulative Frequency	
	Flolan	Standard	Flolan	Standard	Flolan	Standard
i) Day1 Walk Distance						
0, <50	2	8	4.9	20.0	4.9	20.0
90, <180	3	6	7.3	15.0	12.2	35.0
180, <270	11	12	26.8	30.0	39.0	65.0
270, <360	14	4	34.2	10.0	73.2	75.0
360, <450	6	9	14.6	22.5	87.8	97.5
>540 ¹	5	1	12.2	2.5	100.0	100.0
p-value (Fisher's Exact Test)=0.018						
ii) Day2 Walk Distance						
0, <90	2	3	4.9	7.5	4.9	7.5
90, <180	3	9	7.3	22.5	12.2	30.0
180, <270	5	8	12.2	20.0	24.4	50.0
270, <360	18	7	43.9	17.5	68.3	67.5
360, <450	8	10	19.5	25.0	87.8	92.5
450, <540	3	3	12.2	7.5	100.0	100.0
p-value (Fisher's Exact Test)=0.086						
¹ In comparison with Day2 walk distance frequency Table this interval is left open as one observation with value 569.6 falls outside the upper limit of the interval.						

The findings from this table are in agreement with baseline comparability presented in the previous statistical review. It can be seen from the % cumulative frequency column in Table 5, that for walk distance less than 270 meters the difference between the treatment assignment for the two drugs is about 25% (for Day1 measurement: 39% vs 65%, and for Day2 measurement 24.4% vs 50%). Then, in the next interval more patients assigned to Flolan than the standard therapy (14 vs 4 for Day1 measurement and 18 vs 7 for Day2 measurement) so that balancing is reached by

the end of the study. The message conveyed from Table 5 concerning the distributions of the baseline walk distance of the two treatments is in agreement with that based on the rank histogram presented in previous review(see Histogram 1, p.10).

V. Quality of the data:

V.a. Sites 7 and 11 Data Revisited:

The previous Statistical Review, dated September 6,1994 raised concern about the randomization in sites 7 and 11(see p.8 p.11 Tables 11 and 12 of that review). Consequently, to check the sensitivity of the analysis to patients from these centers an additional analysis was carried out by excluding patients from these centers(see Tables 14, 15 and 16 of that review).

The sponsor's data, provided in the December submission, showed the following misplaced base walk distance for three patients:

Table 6
Misplaced Baseline walk Distance

<u>Site/ Patients</u>	<u>Treatment</u>	<u>6-minute Walk Distance(feet)</u>			<u>Difference Basewalk-Day2</u>
		<u>Day1</u>	<u>Day2</u>	<u>Basewalk</u>	
11/	Flolan	1177.59	1425	475	-950
11/	Standard	510	513	1539	1026
02/	Standard	1363	1386	1368	18

The effect of these misplaced baseline walk distance are:

i) Since they give rise to a lower average walk distance for Flolan and higher average walk distance for the standard, they make the treatments more comparable in terms of baseline walk

distance than actually they are.

ii)As a consequence of (i) there will be greater improvement in walk distance for Flolan and less improvements for the standard therapy.

However, these differences in baseline walk distance do not affect the results of the analyses in Tables 9 through 16 of the previous review, since in these analyses, this reviewer computed baseline measurements directly from Day1 and Day2 measurements (without using the sponsor's baseline measurements).

V.b. Varying Length of Time Exit Between Study Day1 and Day2:

The time difference between Study Day1 and Study Day2 range from 0 to 48 days. Similarly for the time difference for the time difference between the entry of Study 46 and the start of Study 46, where the difference range from 0 day to 55 days. However, comparison of the two treatments on the bases of these time differences shows that the differences are not statistically significant.

IV. Medical Reviewer's Requested Analysis

IV.a. Primary Endpoint(Improvement in Walk Distance):

Dr. Triantas, the medical reviewer, suggested that for efficacy evaluation, one might consider the improvements in walk distance for the survivals only, i.e. to disregard deaths from the analysis, or one might assign 0 final walk distance for those who died. Results of efficacy analysis with 0 walk distance assigned for missing data due to death were stated in the previous review(p.14). For completeness, Table 7 presents the results of

the efficacy analysis for the following 2 cases:

- i) assigning 0 final walk distance to those who died.
- ii) excluding from the analysis those who died

Table 7

Re-Analysis Results of 6-minute Walk Distance by assigning zero walk distance for those who died and by excluding deaths.

	<u>Treatment</u>		2-sided p-value	
	<u>Flolan</u>	<u>Standard</u>	<u>t-test</u>	<u>Wilcoxon Ranks Test</u>
i) Zero walk distance for deaths				
Number of patients	41	40		
Mean baseline walk distance	315.743	272.194	0.1344	0.1664
Mean 'WK 12' final walk distance	349.881	227.037	0.0004	0.0014
Mean change from base walk dist.	34.138	-45.156	0.0023	0.0013
ii) Excluding deaths				
Number of patients	41	32		
Mean baseline walk distance	315.743	291.560	0.4013	0.3563
Mean 'WK 12' final walk distance	349.881	283.797	0.0460	0.0433
Mean change from base walk dist.	34.138	-7.763	0.0563	0.0201

Comparison of the results of this table with those of Table 13.a in the previous review, shows that by assigning zero walk distance to those who died, one obtain more significant results for Flolan in comparison to the analysis in which the last observation was carried forward. This is to be expected. Excluding deaths from the analysis the results remain significant at the 0.05 level. This last analysis is conservative compared to other analyses because: (i) all deaths occurred in the standard therapy and (ii) other methods of analyses would record, for each patient excluded, an improvement in walk distance, either 0 or negative value, depending on who one treat their missing values.

IV.b. Secondary Endpoint(Mortality Benefit):

Dr. Triantas , The medical reviewer, raised question about comparability of the survival rates of Flolan and standard therapy based on data from the continuation studies 37 and 47 and from the NIH Registry(see previous review p.17).

Table 8 addresses the survival rates comparability for Studies 46 and #47, for the following three data sets: i) all centers/ . patients (81 patients), ii) all centers except centers 7 and 11 (70 patients) and iii) all patients except the 11 patients with the lowest baseline walk distance (70 patients).

Table 8
Testing Results For Equality of The Survival Curves For Flolan
Versus Standard Treatment, Study 46/47

	2-sided p value		
	All patients	Excluding Sites 7&11 pat.	Lowest walk 11 pat.
Number of patients (Flolan:Standard)	41/40	36/34	38/32
<u>Statistical test</u>			
Log-Rank	0.0074	0.0249	0.1042
Wilcoxon	0.0038	0.0128	0.0587
-2 Log (LR)	0.0017	0.0112	0.1135
Rank test for Association of Surv.			
With Baseline Walk	0.0102	0.0044	(n.s.)

The results of Table 8 show that when analyzing the total study population all three tests indicate significant difference among the survival curves in favor of the Flolan. This conclusion

remains even if one exclude sites 7 and 11 patients from the analysis. However, by excluding the 11 patients with the lowest walk distance the results become non-significant.

The differences in the p-values for the 3 tests given are due to different assumption used in these tests. The likelihood ratio test assumes the data are exponentially distributed while the other 2 tests, based on ranks, do not. In addition, the rank test indicate a difference at larger survival time because the logrank test places more weight on larger survival times. On the other hand, the Wilcoxon test places more weight on early survival times.

For comparing the survival curves for the two treatments by using data from Study 46/47 and the NIH Registry one needs to consider the following:

i) Patients of the NIH Registry, total 194, are NYHA classes I II, III and IV whereas patients of Study 46 are of classes III and IV. Consequently an adjustment for the NYHA Class need to be considered when making this comparison.

ii) Patients of Study 46, due to the termination of this study were subjected to more censoring than those of the NIH Registry. On the other hand, some survival times for NIH registry patients, due to the relatively large sample size, extend much beyond those in Study 46/47. The effect of these points on the statistical tests was discussed following Table 8 above.

Table 9 presents the results of comparing the survival curves for the Flolan and the standard therapy for the following two sets of data:

- i) all patients in Study 46/47 and the NIH Registry and
- ii) excluding from the patients in (i) patients with NYHA class I and II from the NIH Registry as well as patients from sites 7 and 11 in Study 46/47.

Table 9
Testing Results For Equality of The Survival Curves For Flolan Versus Standard Treatment, Study 46/47 and the NIH Registry

	2-sided p value	
	All patients in Study#46/47 &NIH Registry	Excl. NYHA(II)pat. &Sites 7&11 pat
Number of Patients (Flolan:Standard)	41/234	36/175
<u>Statistical test</u>		
Log-Rank	0.0095	0.0119
Wilcoxon	0.0043	0.0056
-2 Log (LR)	0.1612	0.1196
Rank test for Association of Survival With NYHA class	0.0001	0.0001

The results of Table 9 shows that Flolan have significant benefit in terms of mortality for the two rank tests, but the results is not significant for the likelihood ratio test.

IV. Summary and Comments:

The sponsor used a variation of the adaptive randomization method of Pocock and Simons, called the 'Wold method' to assure, as claimed, balance for the NYHA class, vasodilator use and site. The results of implementing the 'Wold method' in making treatment assignment raises concern about the proper execution of the randomization in this open trial.

The results of the simulation experiment which the sponsor presented in support of the claim that the 'Wold method' achieves better balances than the Permuted Block Design, for the NYHA Class, vasodilator use and site, does not establish that claim. A numerical comparison of total imbalance score for the two methods shows that the Permuted Block Design has lower imbalance score than the Wold method for each NYHA Class and vasodilator use combination. These two prognostic factors are more important for creating treatment balance than sites, as the sponsor stated.

The sponsor's results of the adaptive randomization showed that:

i) There were 21 patients, out of total 81 patients , assigned to the less probable treatment. The first 9 of these 'unexpected assignments' were made to the conventional therapy and the last 13 were made to the Flolan therapy.

ii) The first 4 patients in center 7 (total 7 patients) were assigned to the standard therapy and the last 3 to the conventional therapy. The individual probabilities for the first 4 patients to receive conventional treatment are: 0.33, 0.33, 0.33 and 0.29 respectively.

iii) The distributions of the Day1 and Day2 walk distance show more sicker patients (and consequently leading to more death) were assigned to the conventional therapy than the Flolan.

This reviewer tried the randomization program, provided by the sponsor on January 25,1995, and was able to make treatment assignments to patients as those claimed by the sponsor. However, the program is in machine language not readable by the user. Consequently this reviewer could not validate the program.

The results of the re-analyses of the 6-minute walk distance are in favor of the Flolan treatment. The results are still significant in favor of Flolan even on excluding all deaths from the efficacy data analyzed.

Comparisons of the Flolan and conventional therapy survival curves indicate mortality benefit in favor of Flolan. This benefit, however, does not reach the significant level on excluding the 11 patients with the lowest walk distance from Study 46/47 analysis in order to adjust for the baseline imbalance. Similarly, the mortality benefit is not significant for the likelihood ratio test for Study 46/47 and NIH Registry data analysis.

IIIV. Overall Comments:

The results of the randomization in Study #46 show an unexpected pattern in treatment assignments in addition to an imbalance in baseline walk distance.

Concerning treatments assignments, there were 21 patients, out of total of 81 patients, assigned to the less probable treatment. The first 9 of these 21 'unexpected assignments' were made to the conventional therapy and the last 13 were made to the Flolan therapy. The probability that this pattern might occur among these 21 assignments due to chance alone is practically zero. This raises concern about the proper execution of the randomization in this open trial.

The randomization program provided by the sponsor makes the same treatment assignments claimed. However, the program is in machine language not readable by the user. Consequently this reviewer

cannot validate the program.

The results of the re-analyses of the 6-minute walk distance are in favor of the Flolan treatment even in the conservative analysis which excludes all deaths. In addition, Flolan has mortality benefit over the standard therapy. This benefit, however, is not as robust as that of the 6-minute walk distance.

M. Al Osh 2/6/95

M. Al Osh, Ph.D.

Mathematical Statistician

This review consists of 18 pages of text and 24 pages of tables.

Concur: Dr. M. Huque
Dr. S. Dubey

Huque 2/6/95
O 2-7-95

cc:

Orig. NDA 20-444

HFD-180/ Dr. Fredd

HFD-180/ Dr. Triantas

HFD-180/ Ms. Oliver

HFD-713/ Dr. Dubey [File DRU 1.3.2 NDA]

HFD-713/ Dr. Huque

HFD-713/ Dr. Al Osh

MAlosh/x4594/SERB/Alosh/02/6/94

BASELINE EXERCISE

Agency's Specific Issue

Significantly more patients who could not walk more than 200 meters at baseline were randomized to standard treatment (14 vs 6 p<0.05). Five of these patients died during the study.

Sponsor's Response

- FLOLAN patients walked 315±116 meters (mean ± Sd.) at baseline while standard therapy patients walked 272 ± 142 meters, p=0.13.
- Distribution analysis of baseline walk

Distribution Analysis of Baseline Walk

<u>Distance</u>	<u>FLOLAN</u>	<u>Standard</u>	<u>Deaths</u>
0	0 (0%)	1 (2.5%)	1
1-49	1 (2.4%)	1 (2.5%)	1
50-99	1 (2.4%)	3 (7.5%)	1
100-149	2 (4.9%)	5 (12.5%)	2
150-199	2 (4.9%)	4 (10.0%)	0
200-299	12 (29.3%)	8 (20.0%)	0
300-399	15 (36.6%)	8 (20.0%)	1
400+	8 (19.5%)	10 (25.0%)	2

- Three patients died having walked in excess of 300 meters, while three patients died who walked less than 100 meters.
- A Fisher's Exact analysis does not support a difference in distribution of baseline walk between the two treatment groups (p=0.41).
- Analyses of exercise capacity used baseline exercise as a covariate.

Conclusion:

There is no evidence that there is a difference in baseline walk between the two treatment groups

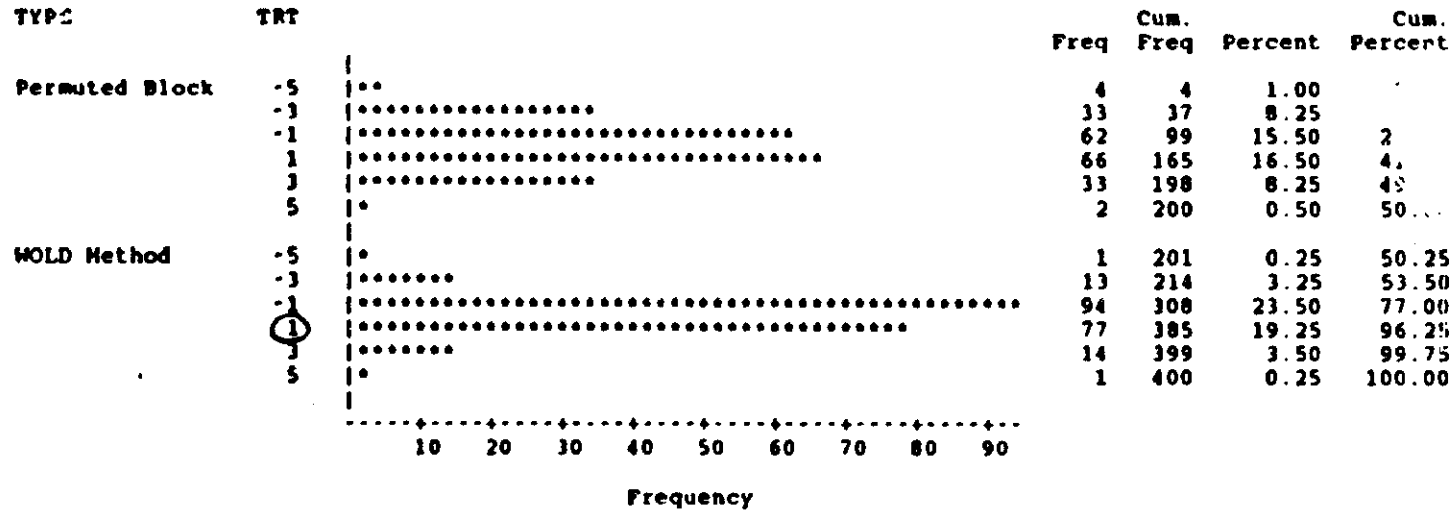
Table 1

ATTACHMENT 2

**GRAPHICAL SUMMARIES OF SIMULATIONS COMPARING
PERMUTED BLOCK RANDOMIZATION TO WOLD RANDOMIZATION**

Comparison of two randomization methods
Wold method used in Study 46 vs Permuted Block Design

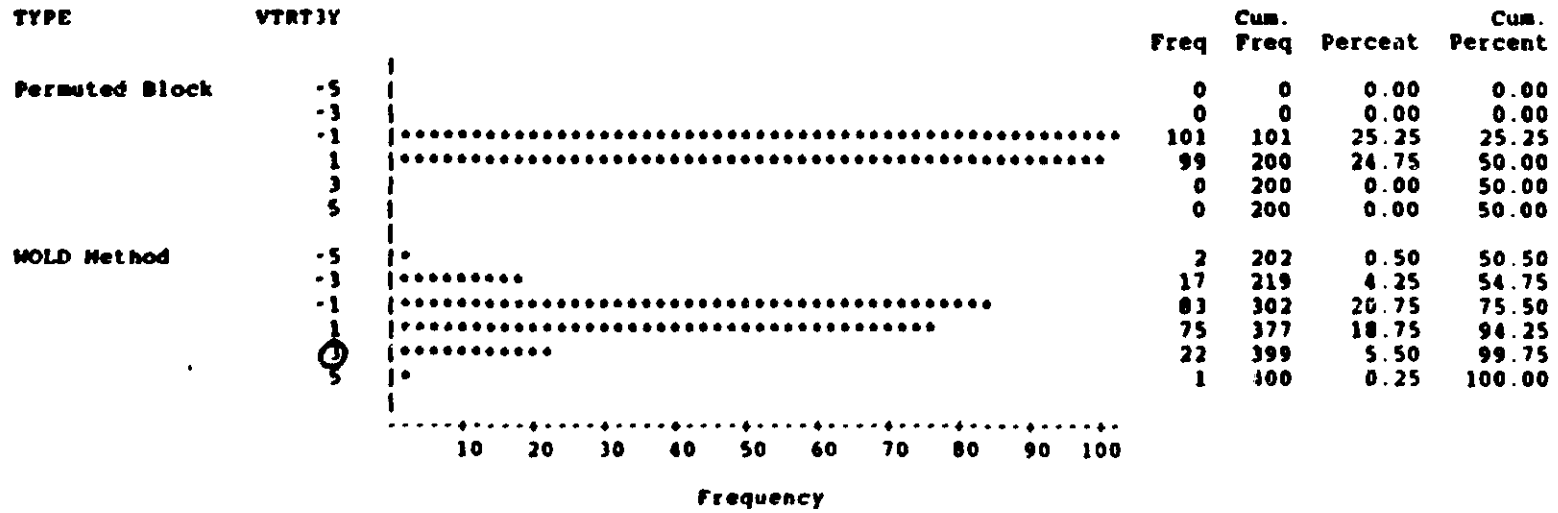
Distribution of Overall Treatment Imbalance (Flolan-Conventional)
Total Patients = 81



17-4

Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design

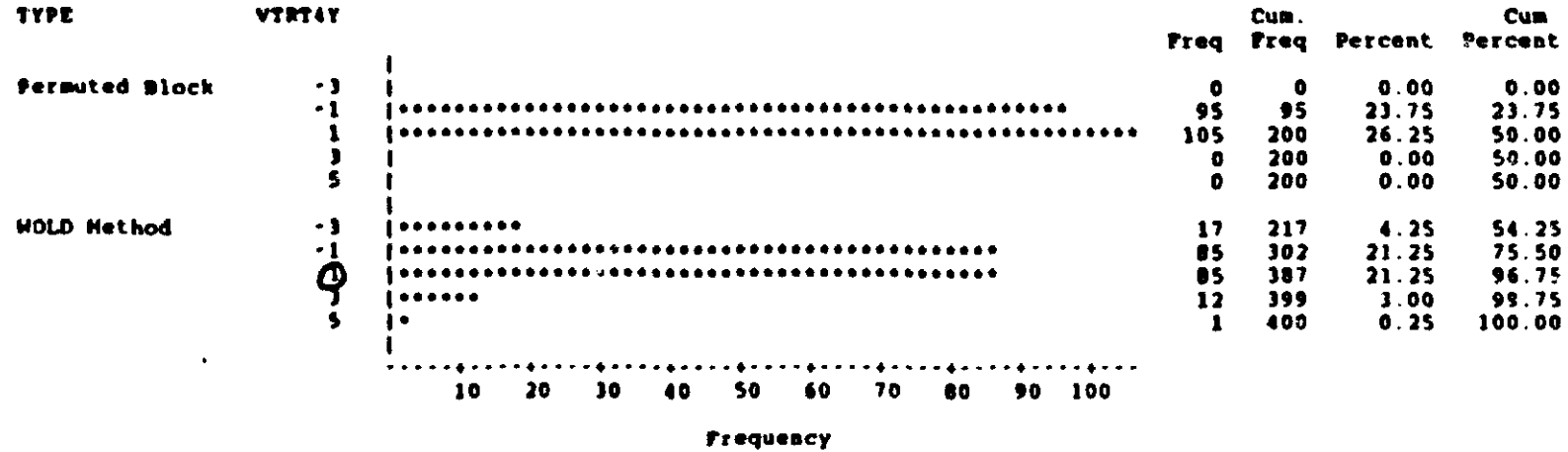
Distribution of NYHA Class III & Vasodilator Use Imbalance (Flolan-Conventional)
 Total Patients = 43



R.22

Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design

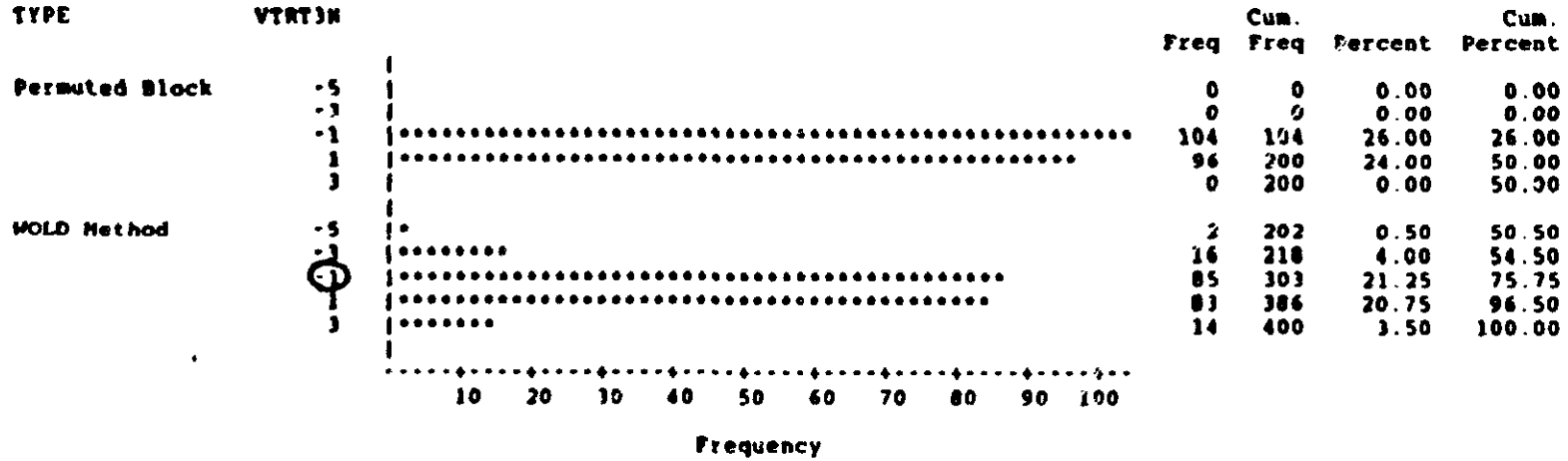
Distribution of NYBA Class IV & Vasodilator Use Imbalance (Piolan-Conventional)
 Total Patients = 9



1-23

Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design

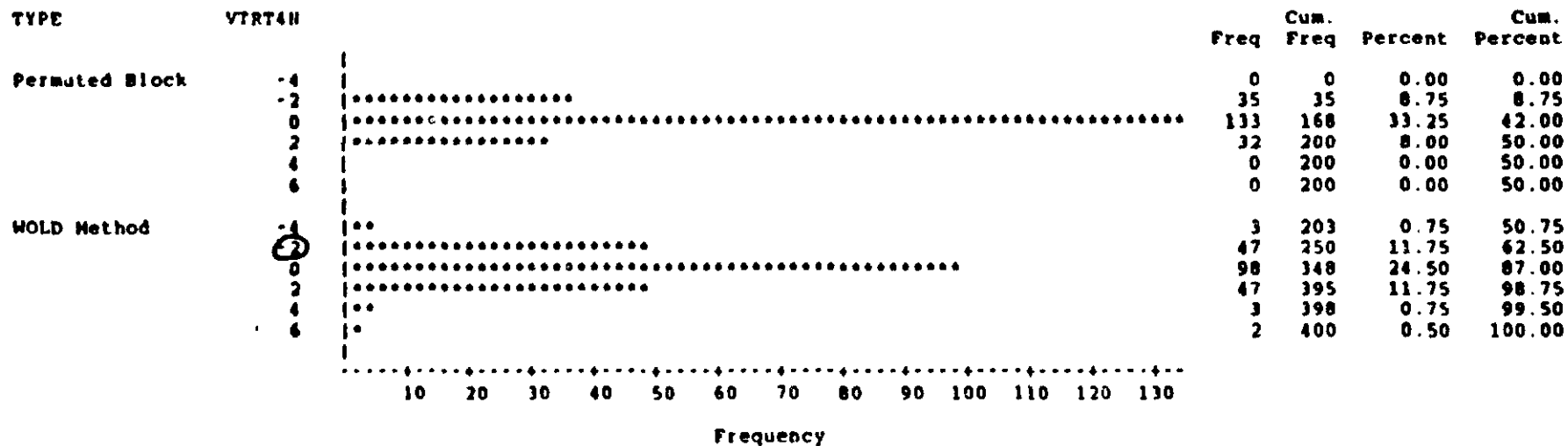
Distribution of NYMA Class III & No Vasodilator Use Imbalance (Flolan-Conventional)
 Total Patients = 15



42-24

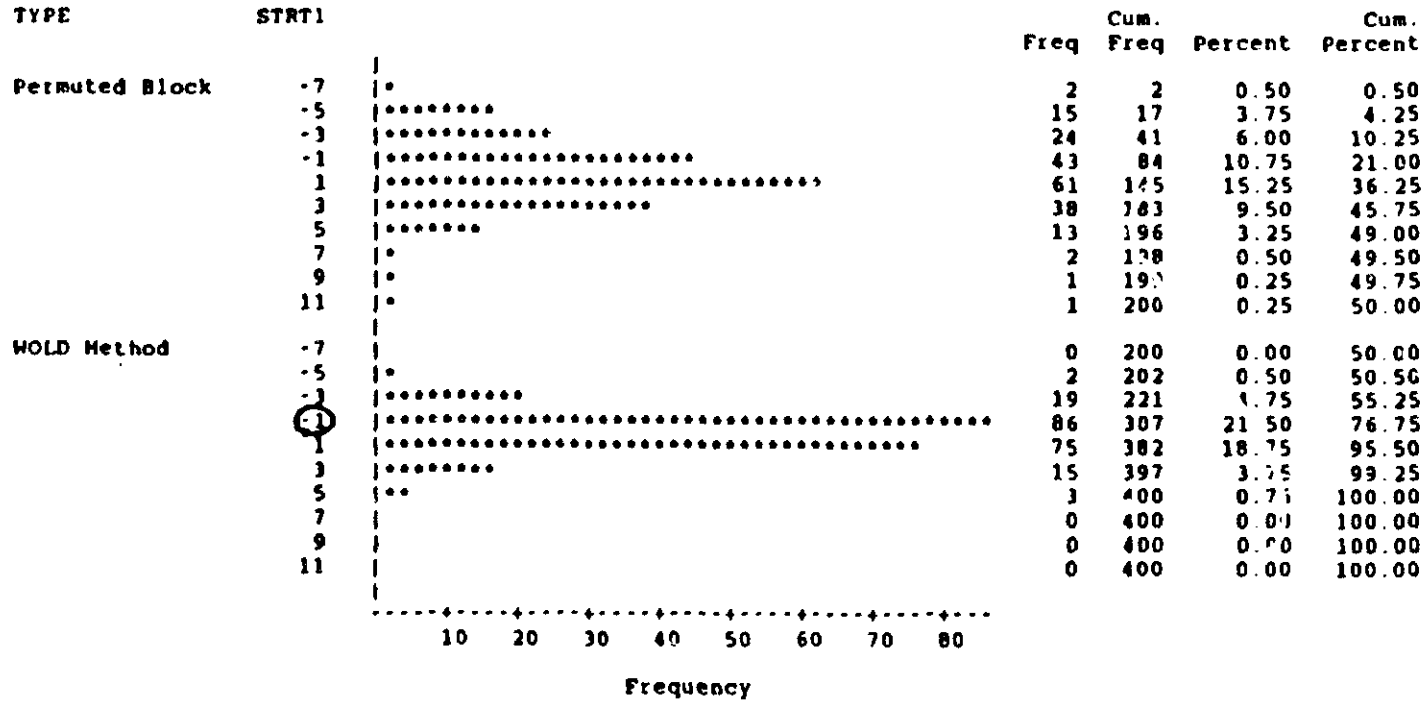
Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design

Distribution of NYHA Class IV & No Vasodilator Use Imbalance (Fioian-Conventional)
 Total Patients = 14



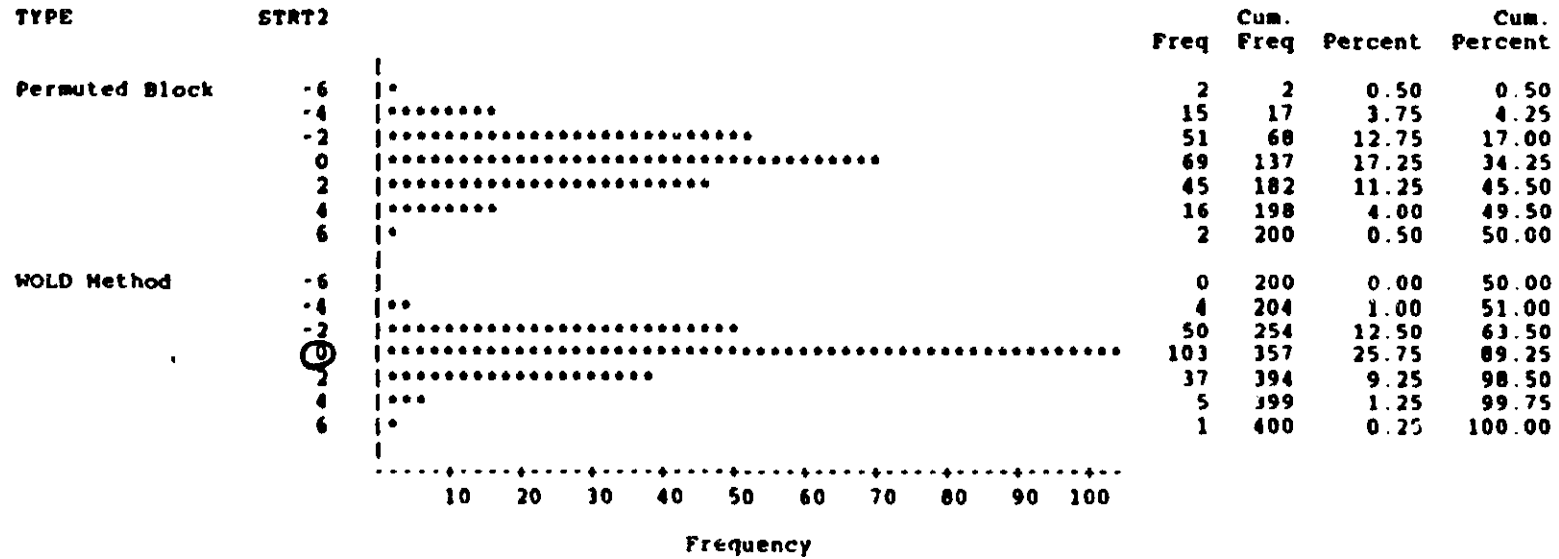
11-1

Comparison of two randomization methods
Wold method used in Study 46 vs Permuted Block Design
Distribution of Site 1 Imbalance (Flolan-Conventional)
Total Patients = 13

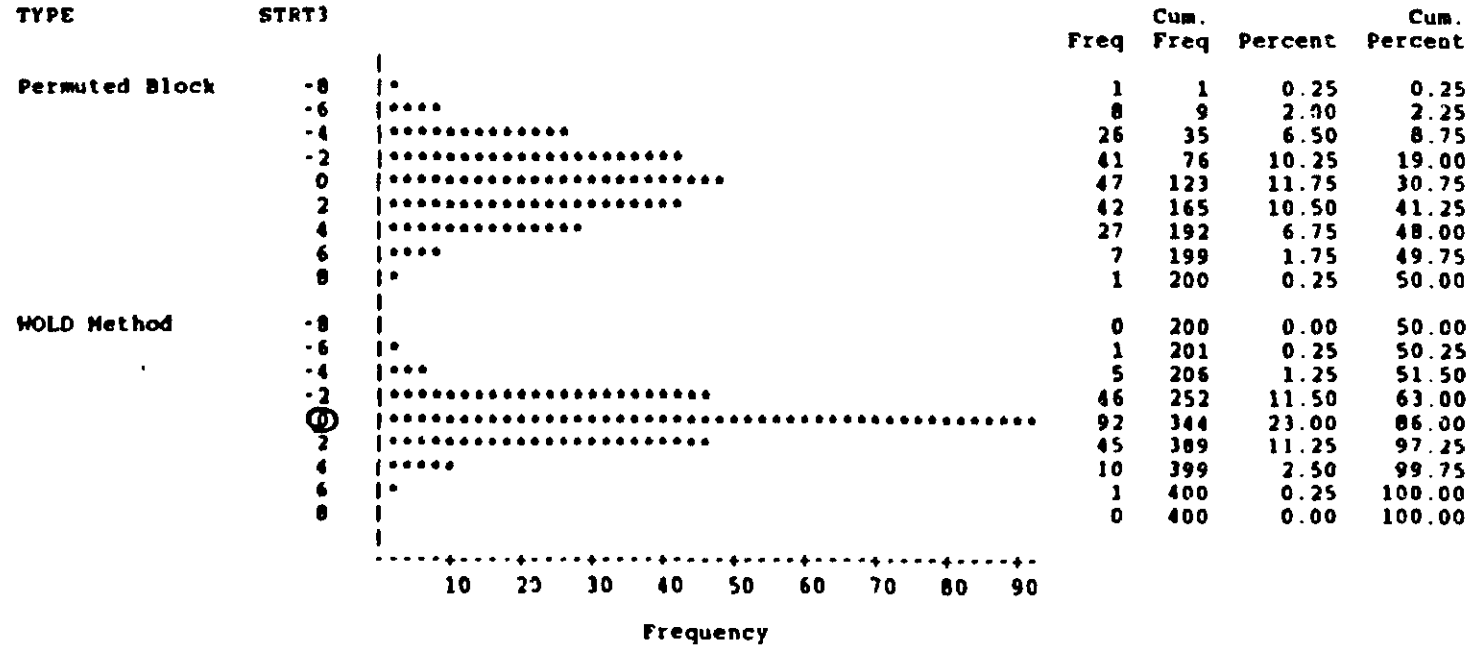


K-22

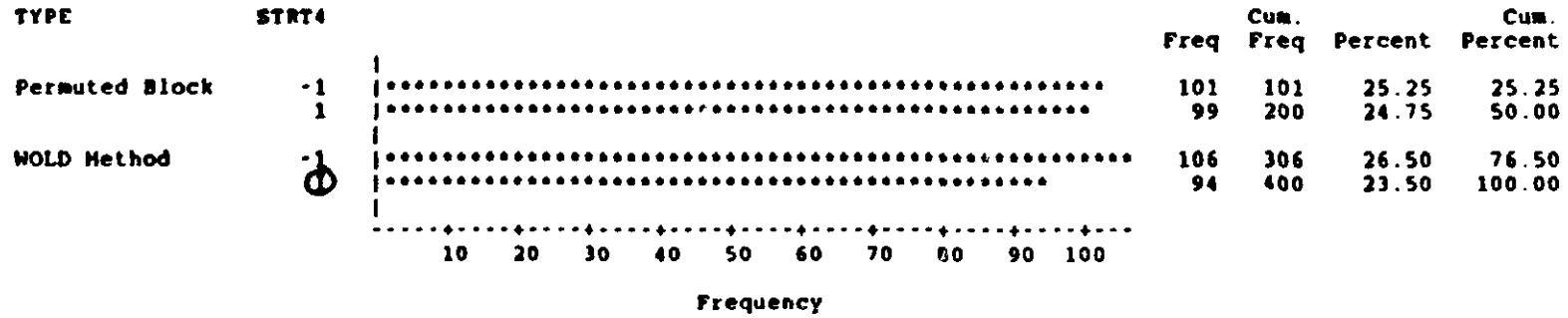
Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 2 Imbalance (Flolan-Conventional)
 Total Patients - 9



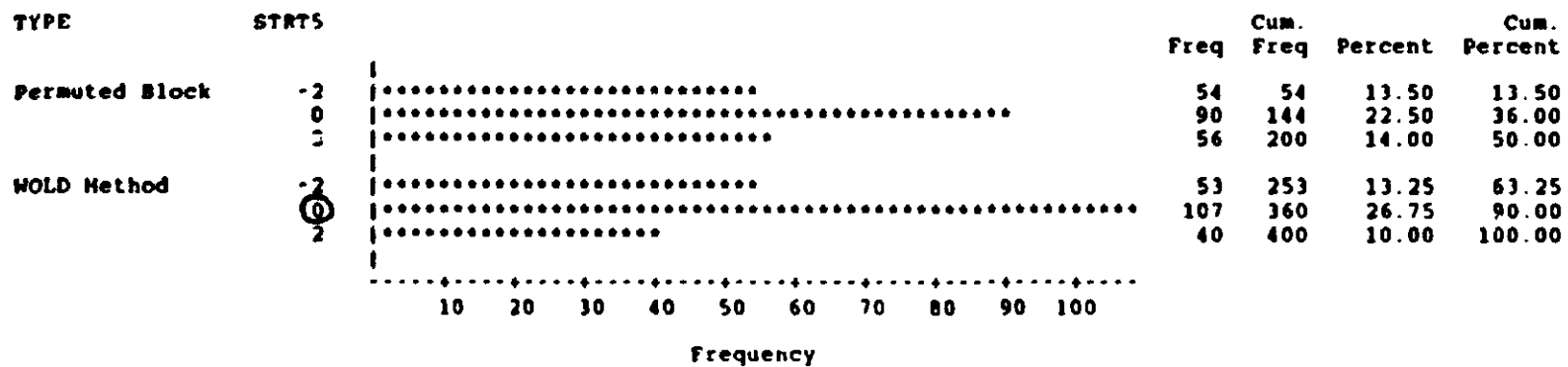
Comparison of two randomization methods
Wold method used in Study 46 vs Permuted Block Design
Distribution of Site 3 Imbalance (Flolan-Conventional)
Total Patients = 12



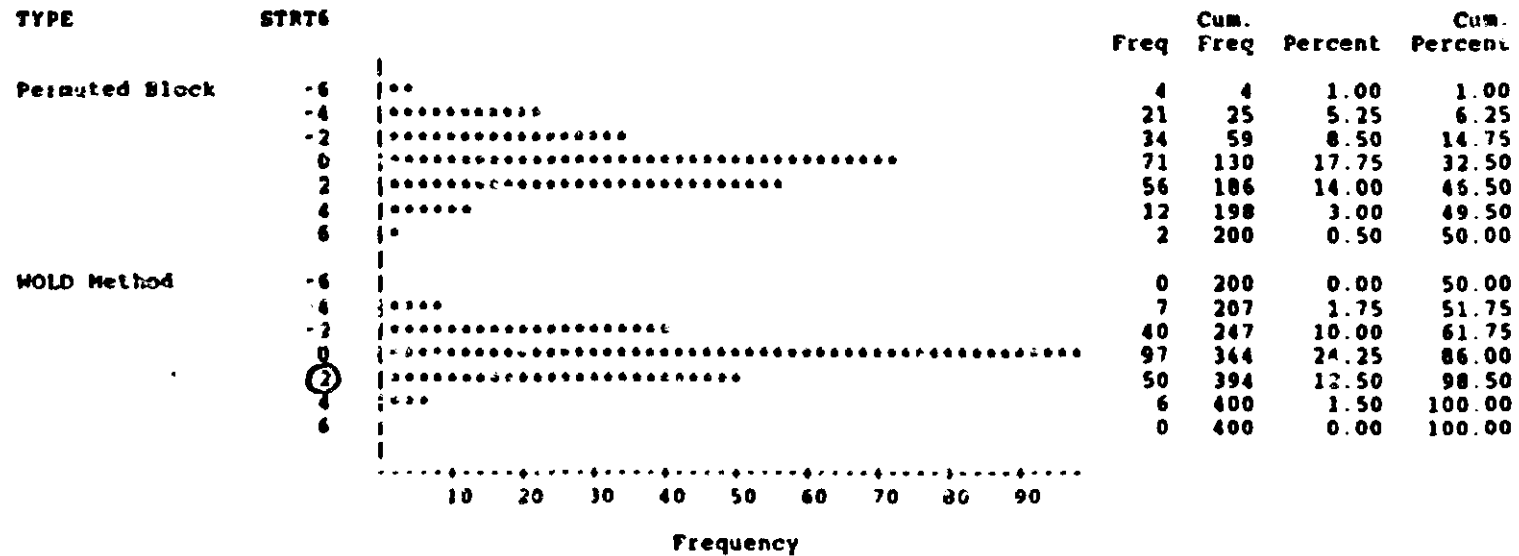
Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 4 Imbalance (Flolan-Conventional)
 Total Patients = 1



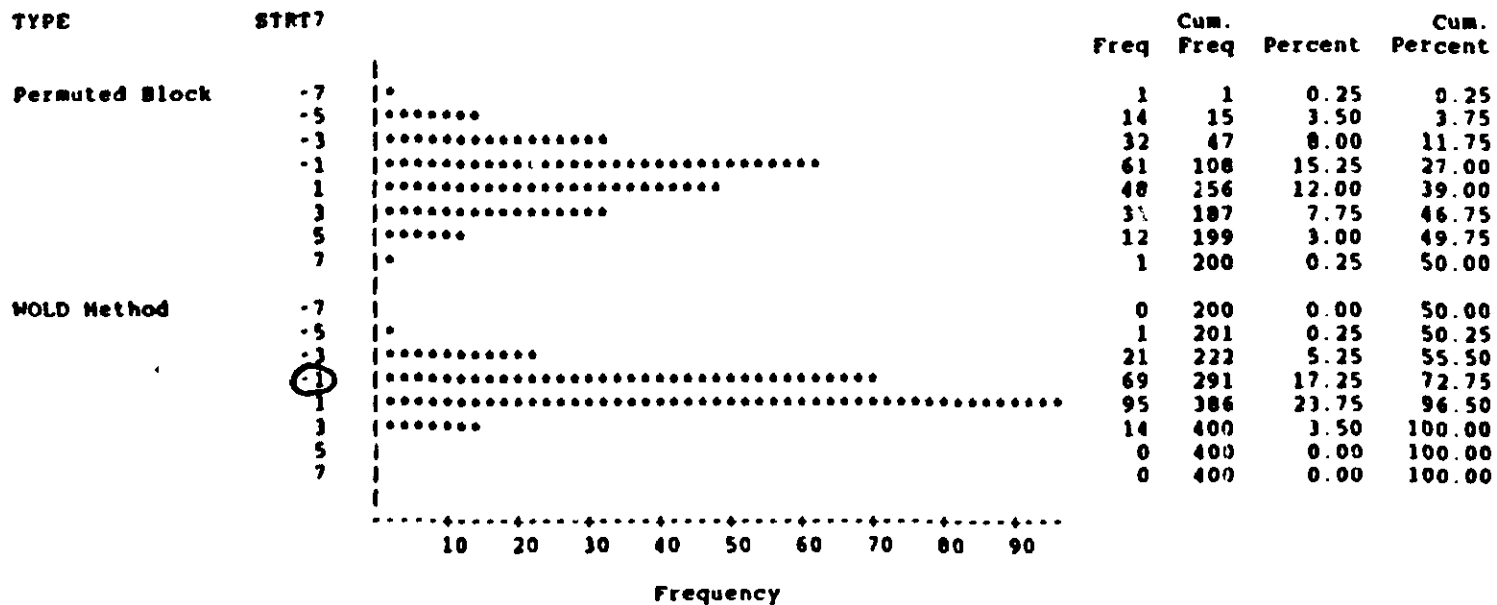
Comparison of two randomization methods
 Hold method used in Study 46 vs Permuted Block Design
 Distribution of Site 5 Imbalance (Flolan-Conventional)
 Total Patients = 2



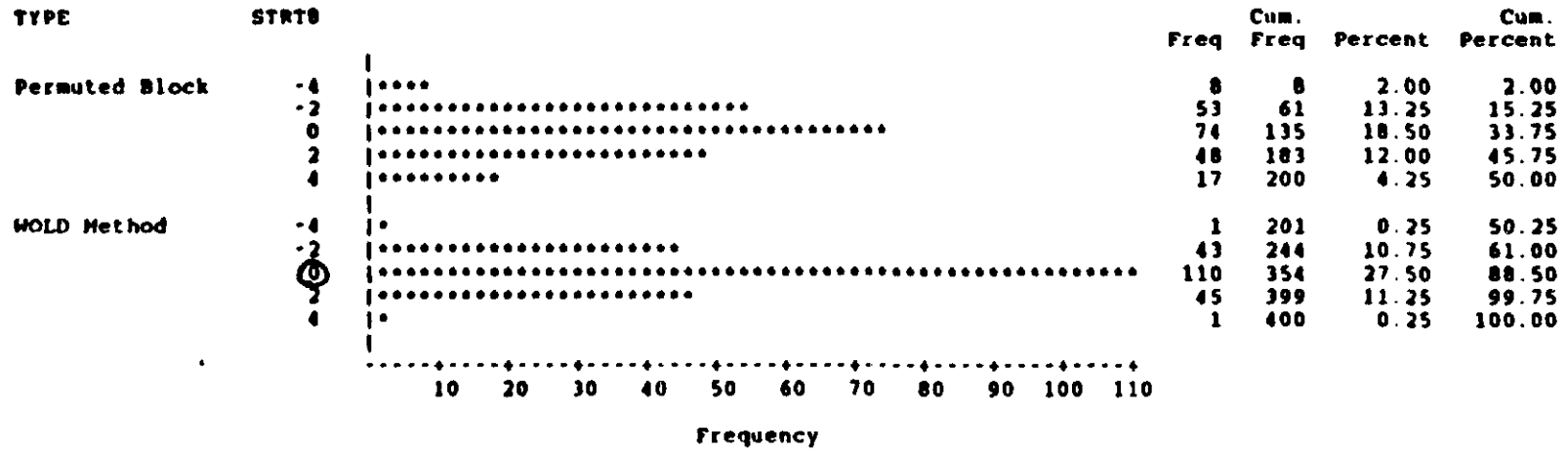
Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 6 Imbalance (Violan-Conventional)
 Total Patients = 6



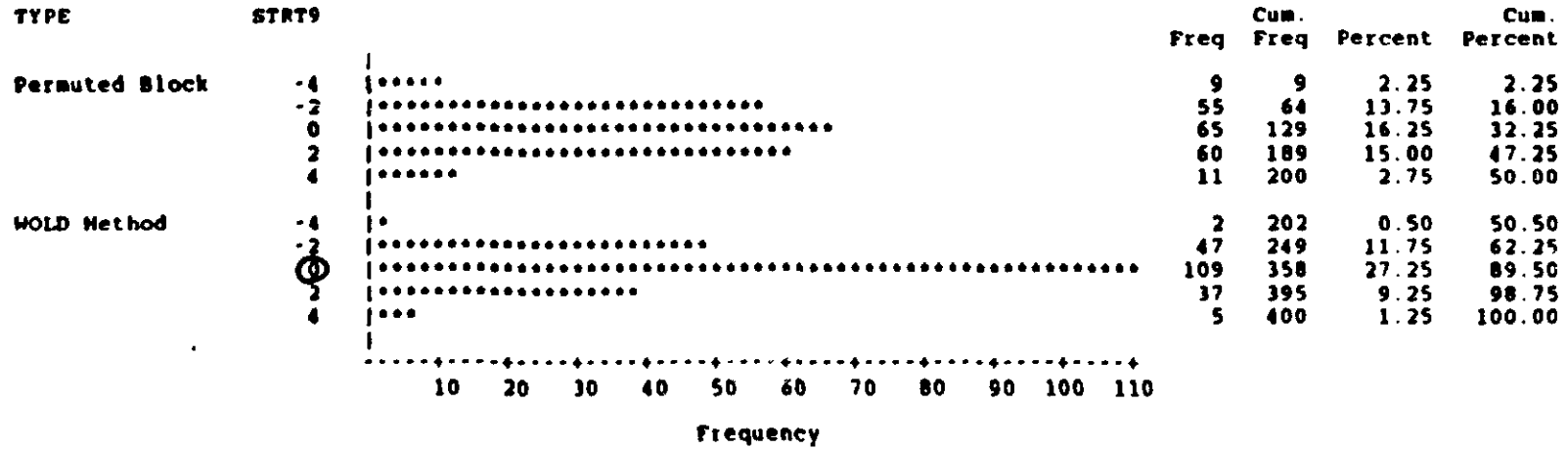
Comparison of two randomization methods
Wold method used in Study 46 vs Permuted Block Design
Distribution of Site 7 Imbalance (Flolan-Conventional)
Total Patients = 7



Comparison of two randomization methods
 Hold method used in Study 46 vs Permuted Block Design
 Distribution of Site # Imbalance (Flolan-Conventional)
 Total Patients = 4

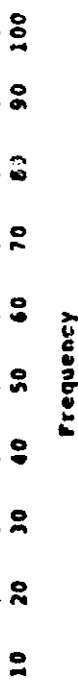


Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 9 Imbalance (Flolan-Conventional)
 Total Patients - 4

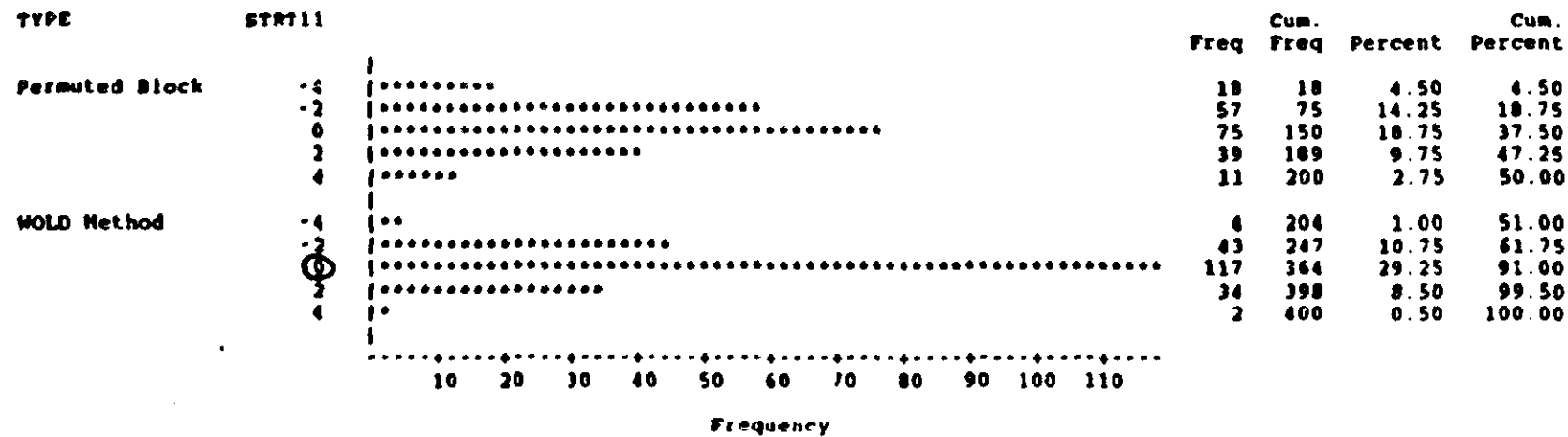


Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 10 Imbalance (Piolan-Conventional)
 Total Patients = 1

TYPE	STAT10	Freq	Percent	Cum. Freq	Percent	Cum. Percent
Permuted Block	-1	103	25.75	103	25.75	25.75
	1	97	24.25	200	24.25	50.00
WOLD Method	-1	99	24.75	299	24.75	74.75
	1	101	25.25	400	25.25	100.00



Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 11 Imbalance (Flolan-Conventional)
 Total Patients = 4



Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 13 Imbalance (Folian-Conventional)
 Total Patients = 3

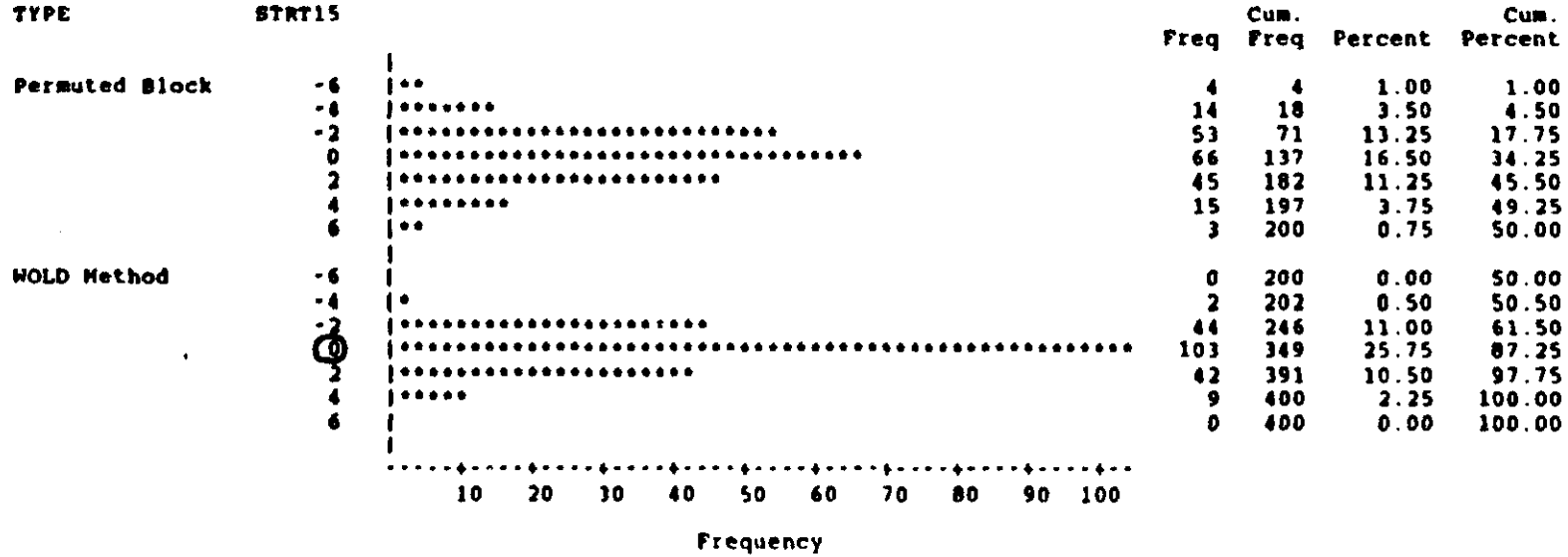
TYPE	STRT13		Freq	Cum. Freq	Percent	Cum. Percent
Permuted Block	-3		27	27	6.75	6.75
	-1		70	97	17.50	24.25
	1		75	172	18.75	43.00
	3		28	200	7.00	50.00
WOLD Method	-3	...*	6	206	1.50	51.50
	-1		88	294	22.00	73.50
	1		95	389	23.75	97.25
	3		11	400	2.75	100.00

.....
 10 20 30 40 50 60 70 80 90
 Frequency

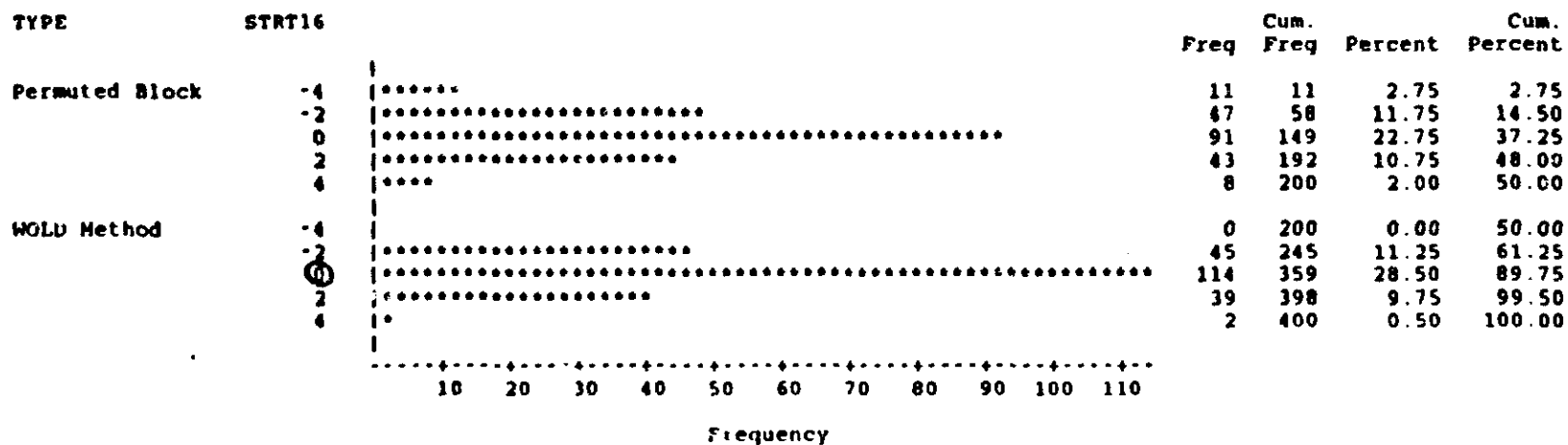
Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 14 Imbalance (Flolan-Conventional)
 Total Patients = 1

TYPE	STRAT14		Freq	Cum. Freq	Percent	Cum. Percent
Permuted Block	-1		97	97	24.25	24.25
	1		103	200	25.75	50.00
WOLD Method	-1		105	305	26.25	76.25
	1		95	400	23.75	100.00

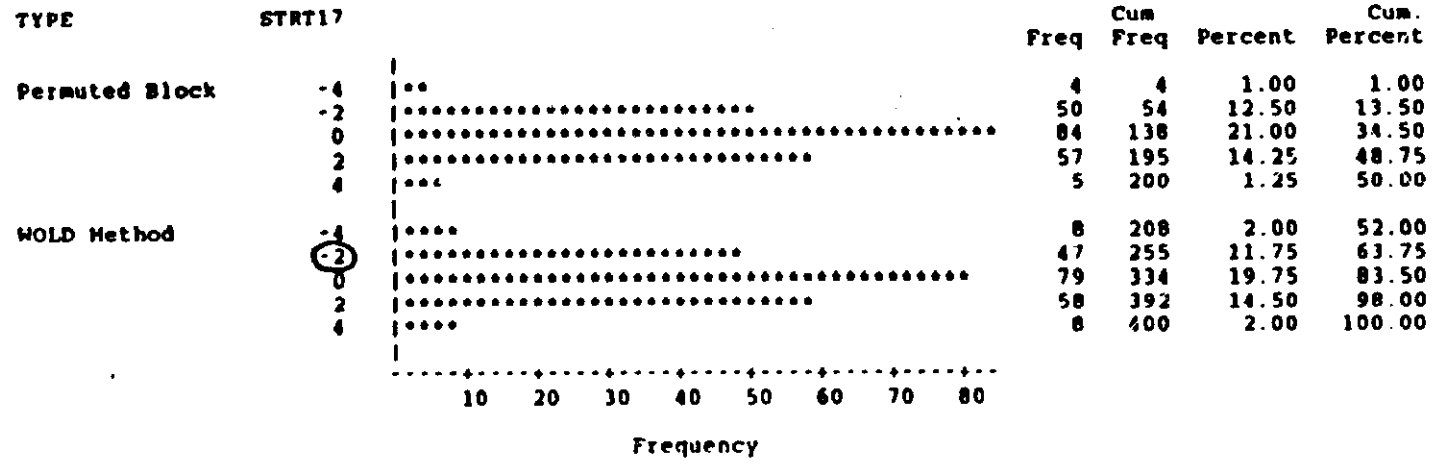
Comparison of two randomization methods
Wold method used in Study 46 vs Permuted Block Design
Distribution of Site 15 Imbalance (Flolan-Conventional)
Total Patients = 6



Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 16 Imbalance (Flolan-Conventional)
 Total Patients = 4



Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 17 Imbalance (Flolan-Conventional)
 Total Patients = 4



Comparison of two randomization methods
 Wold method used in Study 46 vs Permuted Block Design
 Distribution of Site 18 Imbalance (Flolan-Conventional)
 Total Patients = 1

TYPE	STR18		Freq	Cum. Freq	Percent	Cum. Percent
Permuted Block	-1		104	104	26.00	26.00
	1		96	200	24.00	50.00
WOLD Method	-1		101	301	25.25	75.25
	①		99	400	24.75	100.00

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STATISTICAL REVIEW AND EVALUATION

Date: **SEP 6 1994**

NDA # : 20-444
Applicant: Burroughs Wellcome Co.
Name of the Drug: Flolan (Epoprostenol Sodium)
Indication: Treatment of Primary Pulmonary Hypertension (PPH).
Documents reviewed: Volumes 1.1, 1.56-1.68 (14 volumes)
Dated: February 28, 1994

The issues in this review have been discussed with the medical officer Eugenie Triantas, M.D.

I. INTRODUCTION

This review addresses Study # 46 that the sponsor has submitted for claiming safety and efficacy of Flolan (epoprostenol sodium) infusions plus conventional therapy in patients with severe Primary Pulmonary Hypertension (PPH).

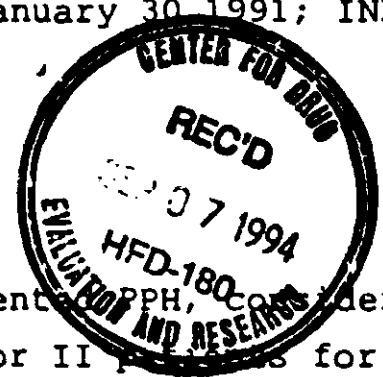
The sponsor's claim for this study is that patients treated with continuous Flolan infusions plus conventional therapy will have, in comparison to patients treated with conventional therapy alone,

- a) improved exercise capacity (6-minute walk distance) and
- b) prolonged survival.

This review also briefly mentions Study 35/36 as a background; this study was reviewed by Dr. Harrison (January 30, 1991; IND review).

II. STUDY # 35/36

Studies 35 and 36, for patients with documented PPH, considered NYHA (New York Heart Association) Class I or II, were for



Study 35 and Class III or IV patients for Study 36. Patients who met inclusion/exclusion criteria were randomized to receive either 8 weeks of Flolan plus conventional therapy (Flolan treatment) or conventional therapy alone (standard treatment). However, because of the occurrence of serious adverse events in the first two Flolan patients in Study 36 (the death of the first and the experience of life-threatening adverse events for the second) and the death of a third patient in Study 37 (continuation study of 35/36) Study 35 was discontinued after the enrollment of only two patients. Data from Studies 35 and 36 were combined and analyzed together as Study 35/36.

For a complete statistical review of this study, please see Dr. Harrison's statistical review of IND #16459, dated January 30, 1991.

III. STUDY # 46

3.1 Design

Study 46 is a multicenter, open-label, randomized, parallel groups, controlled clinical trial. Eighty-one (81) patients with NYHA Class III or IV PPH were randomized to receive either Flolan plus conventional therapy (Flolan treatment) or conventional therapy alone (standard treatment) for 12 weeks. Conventional therapy, as stated by the sponsor, included diuretics, digoxin/other inotropes, oxygen, oral vasodilators and anticagulants.

The study consisted of a screening phase, a baseline and a treatment phase. The treatment phase contained two segments: an initial dose-ranging segment followed by a 12-week treatment segment.

Patients who met all inclusion/exclusion criteria during the screening phase entered the baseline phase. During the baseline phase, two 6-minute walk tests were performed: a practice walk test on Study Day 1 of the baseline phase, and a second walk test on Study Day 2. The baseline 6-minute walk test value used in the statistical analysis is the Study Day 2 value; the Study Day 1 value is imputed for Study Day 2 value if the later is missing.

After baseline hemodynamic measurements were obtained, all patients in both treatment groups entered the dose-ranging segment of the treatment phase and received increasing doses of Flolan. Upon completion of this segment patients were randomized to start their treatment.

During the 12-week treatment segment, 6-minute walk tests were performed on weeks 1, 6 and 12. The walk distance measurements were used in the statistical analysis to evaluate the effect of Flolan on exercise capacity.

Study Population:

The study population was recruited from patients who had a diagnosis of severe symptomatic PPH. Patient included were to:

1. Be between 6 months and 70 years of age; have a diagnosis of severe symptomatic PPH and remain NYHA Class III or IV despite the attempted use of vasodilators for at least one month,
2. Have a chest radiograph and pulmonary function tests consistent with the diagnosis of PPH; have an echocardiogram, cardiac catheterization at baseline consistent with the diagnosis of PPH,
3. If female, be physiologically incapable of childbearing or

practicing an acceptable method of birth control.

Patients excluded were to:

1. Have any PPH medications, excluding anticoagulants, discontinued within the last week, .
2. Have a new type of chronic therapy for PPH added within the last month, excluding anticoagulants,
3. Receiving an investigational drug or have participated in an investigational drug study within the past 30 days, .
4. pregnant women.

Randomization: For each patient, following completion of the dose-ranging segment, study personnel contacted Burroughs Wellcome Co. and received the randomization assignment. Central randomization was performed at Burroughs Wellcome Co. via a portable computer using an adaptive randomization program. The sponsor's randomization procedure used is a variation of the adaptive randomization method by Pocock and Simons [Biometrics (1975), 31:103-115]. According to this adaptive randomization method the probabilities of each of the treatment allocation are adjusted so that balance within and across desired strata are more likely. The stratification variables chosen for balancing purpose in this study are: NYHA Class, vasodilator use at baseline, and study site(center).

Patients were randomized (1:1) to receive either Flolan plus conventional therapy or conventional therapy alone. A total of 81 patients were randomized at 18 centers, 41 to Flolan and 40 to standard treatment.

The primary endpoint was improvement in exercise capacity, defined as the maximum distance a patient could walk on the level

surface in 6 minutes. This walk test viewed to correspond closely to the demands of everyday activity and has reproducible results. The secondary endpoint is death.

All patients who completed Study 46 had the option of receiving Flolan in a continuation study (Study 47). In the continuation studies (37 and 47) Flolan was administered to each patient until death, transplantation or until the patient elected to discontinue therapy. Survival continued to be monitored in both uncontrolled studies; exercise capacity continued to be evaluated in Study 37 only.

3.2 Sponsor's Analysis Methods / Study # 46

The sponsor analyzed data on all randomized patients by an intent-to-treat principle. Treatments comparison was based on analysis of the 6-minute walk distance for Week 1, Week 6, and Week 12. Two methods were applied for the analysis: 1) a nonparametric analysis of covariance and 2) a parametric analysis of variance. Two approaches were considered for handling dropouts because of PPH severity or death. These dropouts were assigned: i) a value of zero meter (or equivalently the lowest rank when analyzing ranks), ii) the last available observation carried forward to Week 12.

The sponsor compared the two treatments by applying the one-way analysis of variance to the 6-minute walk distance. In addition, changes of the walk distance from baseline values were compared for the two treatments.

The sponsor also analyzed the 6-minute walk data by nonparametric analysis of covariance method of Quade [J. of the Amer. Stat.

Assoc., 62, (1967), 1187-1200]. Missing values were assigned the lowest rank. Appropriateness of Quade method for this type of data is discussed in the reviewer's evaluation and comments section.

The sponsor analyzed the mortality data using: i) patient's survival until death or end of the study, ii) survival data were censored at the time of transplant. The statistical methods applied are the log-rank test and Kaplan-Meier estimate of survival curves.

3.3 Sponsor's Efficacy Results / Study # 46

Table 1 displays patients disposition data. There were eight (8) deaths in the standard therapy group as compared to none in the Flolan group.

Table 2 shows baseline comparability of treatment groups with regard to patient characteristics and demographic information. Comparative p-values for this table, calculated by this reviewer, show there are no significant differences between the two treatments for the listed variables. The smallest p-value is that for comparing baseline walk distance ($p = .1344$), the validity of this comparison is addressed in reviewer's evaluation and comments section.

Results for 6-Minute Walk Exercise Test

Table 3 shows sponsor's results of treatment comparisons based on analysis of the 6-minute walk test by the 1-way analysis of variance. In this analysis all randomized patients were included, with last observation carried forward for missing values. The

results shows that the mean walk distance for Flolan patients is significantly higher than that of the standard treatment. This reviewer has reanalyzed this efficacy data set after adjusting for the baseline imbalance (see reviewer's evaluation and comments section).

Table 4 presents sponsor's results for the same data as for Table 3, after adjusting for baseline walk and vasodilator use at baseline by using Quade's nonparametric analysis of covariance method. This reviewer has concern about the appropriateness of this method. The Quade's method assumes that the distribution of the baseline measurements is the same for the two treatments. In addition, as vasodilator use was one of the stratification variables chosen for balancing purpose, which led to treatment comparability with respect to this variable ($p=0.61$, Table 2), therefore, no further adjustment is needed. The results of another statistical analysis is presented in the reviewer's evaluation and comments section.

Tables 5 and 6 show descriptive statistics and within group comparisons of the cohort excluding patients who died, had a transplant or discontinued Flolan prematurely. Surprisingly, the sponsor did not report the between group comparisons for this efficacy subset. Table 6 (last column) indicates that within group 95% confidence intervals overlap.

Results for the Mortality End-point

Tables 7.a and 7.b shows the sponsor's results for comparing the estimated probabilities of survival in the two treatments by applying the log-rank test. In Analysis 1 (Table 7.a) patient's survival are followed until death or until the end of the study.

In Analysis 2 (Table 7.b) patients are censored at transplant time. Figures 1.a and 1.b show Kaplan-Meier curves for the analyses in Tables 7.a and 7.b.

3.4 Reviewer's Evaluation & Comments / Study #46

Observed Imbalances in the Baseline Walk Distance:

One of the purposes of randomization is to have balance in the cohorts with respect to known and unknown variables at the baseline. The review of the data indicates the following imbalances:

Center 7 contributed 7 patients to the trial; the first 4 patients in chronological order were assigned to the standard treatment and the last three to the Flolan treatment giving the following treatment allocation sequence for this specific center:

S S S S F F F

More patients who walked smaller baseline 6-minute walk distance were allocated to the standard therapy than to the Flolan therapy. Ordering the baseline 6-minute walk distances of the 81 patients in an ascending order gives the following treatment allocation sequence:

SFSSFSSSSSFSFSSFFSSSFSSFSFSSFSFSSFFSSFFFFFFFFFFEFFFFSSSFSFFFSFFSSFFFS
SSSSFFSSFSFSFFFS

This sequence shows that, among the 11 lowest baseline 6-minute walk distance patients, there were only 2 patients assigned to the Flolan treatment compared to 9 for the standard treatment.

Taking the distance of 120 meters, close to the one walked by the 11th patient in the above sequence, as a cut-off point, the allocation of patients between the two treatments is given in Table 8.

Table 8

Baseline Imbalance (Walking Distance)

Baseline walk distance	Treatment	
	Flolan	Standard
< 120	2/41 (4.9%)	9/40 (22.5%)
> 120	39/41 (95.1)	31/40 (77.5)

Two-sided p-value Fisher's exact test= .0255

Table 9 presents the baseline (Day 2) 6-minute walk test for the 11 patients with the lowest test value along with other characteristics. It can be seen from this table that out of the 9 patients assigned to the standard treatment 5 died. In one patient (patient _____), the dates of both first and second day tests is taken 11/21/91. The patient was too ill to perform any test, was allocated to the standard treatment and died the following day (11/22/91).

Imbalance in the baseline 6-minute walk distance is caused not only by the allocation of the weakest 11 patients between the two treatments but there is an overall baseline difference between the two treatment groups. This can be seen from Histogram 1, which presents the allocation of patients, ranked by their baseline walk distance, between the two treatments.

Histogram 1

Stem-and-leaf plots of the ranks of baseline walk distances of Flolan and standard treatments

Ranks, Flolan treatment						Ranks, standard treatment					
012	5					011	3	4	6.5	6.5	8
112	4	7	8			110	1	3	5	6	9
212	4	6	8.5			210	1	3	5	7	8.5
311	4	5.5	5.5	7	8 9	310	2	3			
410	1	2	4	5	6.5 6.5	413	8	9			
511	3	4	5	7	8.5 8.5	510	2	6			
612	3	4				610	1	5	6	8	8 8
710	1	4	6.5	8	9	712	3	5	6.5		
810						811					

Comparison of the first line of each histogram (bold underlined rank numbers) shows that out of the 9 patients with the lowest baseline walk distance only 2 (their baseline walk distances ranked 2 and 5) were allocated to the Flolan treatment. Similarly out of the 29 patients (bold rank numbers) with lowest-baseline walk distance only 9 (their baseline walk distances ranked 2,5,12,14,17,18, 22,24,26 and 28.5) were in the Flolan group. This pattern of patients' allocation is reversed for the next 30 ranks before another change take place for patients whose baseline walk distance ranked 60 and higher.

In the standard treatment, the frequency distribution of the patients' walk distances has a U-shape. Consequently, as large baseline (Day 2) values compensate for some of the small values, comparison between the two groups means (or medians) does not show significant difference.

The baseline imbalance is also indicated by the significant difference in the mean of Day 1 6-minute walk distance, as well as by combining Day 1 and Day 2 walk distances. This can be seen from Table 10 (below) which shows baseline comparability with

respect to Day 1, Day 2, and Day 1 and Day 2 combined.

Table 10

Baseline Comparability With Respect to Baseline Day 1 & Day 2

Measurement	<u>Treatment</u>		2-sided p-value
	Flolan	Standard	
Day 1			
Number of patients	41	38*	
Mean	306.752	245.697	0.0337 (t-test) - 0.0362 (Wilcoxon)
Median	307.848	240.792	
Day 2			
Number of patients	41	40	
Mean	315.743	272.194	0.1344 (t-test) 0.1644 (Wilcoxon)
Median	314.554	269.596	
Day 1 & Day 2 Combined			0.0462 (Repeated Measures ANOVA)

* Two patients did not have Day 1 value

The data indicate that, in comparison to other centers, Center 7, and to a less extent Center 11, contributes most to the imbalance in the baseline 6-minute walk distance (see Table 11). Table 12 shows baseline characteristics of patients in these centers and their allocation to the two treatment groups. The influence of these two centers on the results of the analysis can be judged by the change in the p-value for comparing the mean final walk distances in two treatments. This p-value increased from 0.0051 (for all centers) to .0440 when centers 7 and 11 are excluded from the analysis. A more detailed discussion about adjustment for the imbalance in baseline is given in the reviewer comments (see also Tables 13.a-13.d, attached).

As efficacy endpoints are associated with the baseline walk distance (see Tables 13.a-13.d, 14 and 16), such an imbalance in the baseline walk distance is likely to cause bias in favor of Flolan.

Because of the above imbalances this reviewer has concern regarding the proper execution of the randomization of this trial given that the trial is an open trial.

Efficacy With Respect to 6-minute Walk Test Distance:

The sponsor analyzed the intent-to-treat data set by using a nonparametric analysis of covariance method of Quade [J. of the Amer. Stat. Assoc., 62, (1967), 1187-1200]. However this is not the appropriate method to apply given the different shapes of the baseline measurements in the two treatments (see Histogram 1).

This reviewer has re-analyzed the data with purpose of checking robustness of the reported Flolan's efficacy results to adjustments for the baseline imbalance. This re-analysis can be classified according to the data set and measurements analyzed, and further, the statistical method used.

Data Set Re-analyzed:

Since imbalance was more obvious for some centers/patients the following three data sets are considered for re-analysis:

- i) all patients/centers,
- ii) patients of all centers but excluding centers 7 & 11, and
- iii) all patients but excluding 11 patients with the lowest baseline walking distance (see Table 9).

Measurements analyzed:

- i) final walk distance,
- ii) Change from baseline walk distance, and
- iii) Adjusted change from baseline walk distance.

Statistical method used:

- i) parametric method (t-test),
- ii) non-parametric method (Wilcoxon rank sum test and analysis of covariance applied to the ranks of the walk distances).

For each data set analyzed comparison of mean baseline walk distance for the two treatments is presented to show baseline comparability. Analysis of the adjusted mean change is considered in addition to analysis of the change, to account for the correlation between the change and baseline walk distance.

Table 13.a presents results of the re-analysis of the 6-minute walk distance for all centers/patients. This reviewer analyzed the walk distance for Week 1, Week 6, and Week 12 to check results' consistency. It can be seen from Table 13.a that the results of the comparison are consistently in favor of Flolan. The mean change in the final 'Week 12' walk distance, is 34.1376 meters for Flolan compared to -8.428 meters for the standard treatment, with 2-sided p-value 0.0137 in favor of Flolan. The conclusion from the analysis of the adjusted mean change is similar.

Table 13.b presents results of the re-analysis of the 6-minute walk distance after excluding centers 7 and 11 data. It can be seen from this table that, though the p-value for comparing the final walk distance increased from 0.0051, in table 13.a, to 0.0440; the results still in favor of Flolan. The p-value for

comparing the mean change in the final walk distance is 0.0103, which is comparable to that in Table 13.a.

Table 13.c presents results of the re-analysis after excluding the weakest 11 patients. Here, the p-value for comparing the raw treatment means of final walk distance increased to 0.1003. But, the treatment comparisons with respect to the mean changes from baseline and the adjusted mean changes remain statistically significant in favor of Flolan .

In a discussion with Dr. Triantas, the medical reviewer, expressed concern that some of the deaths in the standard treatment may not be caused by the progression of the disease. To investigate how the allocation of these patients would influence the previous conclusion about the walk distance, this reviewer re-analyzed the data after excluding the patients who died or had transplant. The results of this analysis are presented in Table 13.d. The conclusion is that, though the p-value increases to .0253, it is statistically significant in favor of Flolan. This reviewer re-analysis in Table 13.c takes account of the influence of some of those died on the walk distance, because 5 deaths occurred among the excluded patients.

The analyses in Tables 13.a-13.c were based on the intent-to-treat principle in which the last observation was carried forward for missing data. This reviewer done similar analyses in which 0 walk distance assigned for missing data due to death. The results, not presented here, still significantly in favor of Flolan.

The Wilcoxon rank sum test, presented in Tables 13.a-13.c, were applied to guard against the non-symmetry of the baseline walk

distance (see Histogram 1). This reviewer applied also analysis of covariance to the ranks of the 'final' and 'baseline' walk distances. This method was advocated by Conover and Iman [Analysis of Covariance Using the Rank Transformation, Biometrics, 38, (1982), 715-724].

Table 14 shows the results of the analysis of covariance. It can be seen from this table that the 2-sided p-value of Flolan increased from .0048, for all patients, to .0104 when centers 7 and 11 are excluded from the analysis. Furthermore, it increased to 0.0210 when the lowest 11 patients are excluded. But, despite these increases, the results of the comparison are statistically significant in favor of Flolan.

The results of the re-analysis presented in Tables 13.a-13.d and 14, shows that the 6-minute walk distance of Flolan patients, in this trial, is significantly higher than that of the standard treatment. This finding hold for the parametric as well as the non-parametric analyses considered. Exclusion of some centers/ patients from the analysis led to increase in the p-value for comparing the two treatments, but the results were still in favor of Flolan.

Mortality Benefit:

Because of the baseline imbalance in walk distance concern, this reviewer reanalyzed the survival rates by the proportional hazard (Cox-regression) model (with baseline walk distance as covariate) for three data sets: i) all centers/ patients (81 patients), ii) all centers except centers 7 and 11 (70 patients) and iii) all patients except the 11 patients with the lowest baseline walk distance (70 patients).

Table 15 presents the results of proportional hazard regression model as applied to the survival rates for the three sets of data. It can be seen from this table the 2-sided p-value for testing drug effect increased from .0154 (for all patients/centers) to .0221 when centers 7 and 11 are excluded from the analysis. Furthermore, this p-value increased to .0520 when the lowest 11 patients are removed from the analysis. This change is to be expected since 5 deaths, out of total 8 deaths, occurred among these 11 excluded patients (see Table 9). These changes in the p-values shows how sensitive the mortality benefit of Flolan to the imbalance in the baseline walk distance.

This reviewer also tested for equality of the survival curves of Flolan and standard treatments for the three data sets discussed above. The results of this analysis are given in Table 16. Here also, the p-values for testing equality of the survival curves increase as one move across the three data sets analyzed.

Exclusion of the lowest 11 patients from the analyses led to increase in the p-value from 0.0035 to 0.0586 for the Wilcoxon rank test, and from 0.0016 to 0.0413 for the likelihood ratio test. That is to say these p-values increased by about 17 and 26 folds respectively.

Table 16 shows also significant association between the survival rates and the baseline walk distance (for all patients the p-value= 0.0407). However, as 5 deaths occurred among the lowest 11 patients, this association become non-significant, when these 11 patients are removed from the analysis.

The findings from Table 16 are consistent with those of Table 15. Analyses in both tables show that the mortality benefit of Flolan is highly sensitive, in comparison to the walk distance, to the

exclusion of some centers/patients from the analysis.

Comparison with the NIH Registry data:

Dr. Triantas, the medical officer, expressed concern about the sponsor's comparison of the survival rates of Flolan, standard therapy and those of the NIH Registry. These sponsor calculated rates for 24 months period are presented in Table 17 attached.

As the period of the controlled studies 35/36 and 46 are 8 weeks and 12 weeks respectively, survival rates beyond the controlled study periods were based on the continuation, uncontrolled, studies. However, based on the information supplied by the sponsor it is difficult to verify the sponsor's claim about comparison of these survival rates. Table 18 summarizes patients election of treatment in the continuation studies.

For validating/estimating survival rates for the continuation studies(# 37 and # 47) the reviewer would need the following information:

- i) The dates when patients entered these studies.
- ii) The time-to-death from the time patients entered into the study, the actual dates for the deaths, and the cause for each death.
- iii) The time-to-censoring from the time patients entered into the study, the actual dates for censoring, and the cause for each censoring.

For Study # 47, the patient enrollment dates in this study are not given. A patient could enroll in this study within 3 months from the completion date of study # 46. Similarly, nothing is

mentioned about the enrollment dates for Study # 37.

The absence of these data along with lack of information about times and types of censoring makes it impossible to follow and validate the number of patients in the cohort which the sponsor listed and are shown in Table 17. Thus survival rates beyond the control study periods should not be considered unless the sponsor provide additional information justifying their computation.

Table 18

Summary of Patient's Election of Treatment in The Continuation Studies after Completion of The Controlled Studies

Controlled Study #	35/36	46
Approximate period	8 weeks	12 weeks
No. patients enrolled	25(11 F:14 S) ^{1,2}	81(41 F:40 S)
No. of patients received transplant	0(0 F:0 S)	3(1 F:2 S)
No. of patients died	4(1 F:3 S)	8(0 F:8 S)
No. of patients discontinue	0(0 F:0 S)	2(2 F:0 S)
No. patients completed Study	21(10 F:11 S)	68(38 F:30 S)
Continuation Study #	37	47
No. patients on Flolan	38(10 FF:9 SF) ^{3,4}	64(38 FF:26 SF)
No. patients declined entry	3(0 F:3 S)	4(0 F: 4 S)

¹ F: Flolan treatment, S: Standard treatment.

² includes two NYHA Class I/II patients from Study #35(1F 1S)

³ FF:Patient was on Flolan in the control study and continued on Flolan thereafter, SF:Patient was on standard treatment in the control study and switch to Flolan thereafter

⁴ Study # 37 description states 8 patients switched from the standard therapy to Flolan, but patient's listing (Table 18, Vol. 1.56) shows 9 such patients.

3.5 Summary and Comments / Study #46:

The sponsor used the adaptive randomization method of Pocock and Simons to achieve balance in the allocation of patients with respect to 3 selected factors: NYHA Class, vasodilator use at baseline, and study site (center). However, as i) the purpose of randomization is to have balancing with respect to the variable(s) affecting the outcome, and ii) as it was known from previous study (Study 35/36) that baseline walk is associated with the 'Final' walk distance, therefore, baseline walk distance should also have been considered (along with the other variables) in the application of the adaptive randomization procedure.

The baseline walk data indicate that, in general, more sicker patients (and consequently leading to more deaths) were assigned to the standard therapy than the Flolan treatment. This imbalance at the baseline would affect the comparison of the mean walk distances and the mortality benefits in the two treatments.

To adjust for the observed imbalance at the baseline, this reviewer re-analyzed, by the intent-to-treat principle, the efficacy data on:

- i) all patients/centers,
- ii) all patients but excluding those of centers 7 & 11, for which the imbalance was obvious, and
- iii) all patients but excluding the weakest 11 patients, since only two of them assigned to Flolan; furthermore, 5 deaths occurred among the 9 assigned to the standard therapy,
- iv) all patients but excluding those who died or had transplant.

The results of these re-analyses of the 6-minute walk distance shows that, when adjustments for the imbalance in the baseline is made, the p-value for comparing the two treatments increases in some cases by as much as 20 fold; depending on the adjustment made, the measurement analyzed and the method of analysis used. Similarly, comparison of the survival rates of the two treatments shows even more sensitivity to adjustments for the imbalance in the baseline. However, despite the changes in the p-values, the overall conclusion from the analysis is in favor of Flolan. .

3.6 Information Request

For validating/estimating survival rates for the continuation studies (# 37 and # 47) the reviewer would need the following information:

- i) The dates when patients entered these studies.
- ii) The time-to-death from the time patients entered into the study, the actual dates for the deaths, and the cause for each death.
- iii) The time-to-censoring from the time patients entered into the study, the actual dates for censoring, and the cause for each censoring.

3.7 Overall Conclusion / Study # 46

Various re-analyses were done for checking the sensitivity of the results on adjusting for the observed baseline imbalance. These re-analyses results suggest that exercise capacity, measured in term of 6-minute walk distance, and survival rates are significantly higher for Flolan patients compared to those of standard therapy. However, the fact that the trial is not blinded

raises concern about the possibility of selection bias.

M. Al Osh 8/30/94
M. Al Osh, Ph.D.
Mathematical Statistician

This review consists of 21 pages of text and 14 pages of tables.

Concur: Dr. Huque
Dr. Dubey

Huque 8/30/94
9-1-94

cc:

Orig. NDA 20-444
HFD-180/ Dr. Fredd
HFD-180/ Dr. Triantas
HFD-180/ Ms. Oliver
HFD-713/ Dr. Dubey [File DRU 1.3.2 NDA]
HFD-713/ Dr. Huque
HFD-713/ Dr. Al Osh

Aloshm/x4594/SERB/Alosh/08/6/94

Table 1
Patient's Disposition Data

	<u>Study</u>			
	35/36 (n=25)		46 (n=81)	
	Flolan	Standard	Flolan	Standard
No. patients				
Randomized	11	14	41	40
Received Transplant	0	0	1	2
Dead	1	3	0	8
Alive	10	11	41	32

Table 2

Comparison of Baseline Characteristics of Patients Who Died to Survivors

Parameter	Flolan (N=41)		Standard (N=40)		Total	2-Sided P-value Flolan vs. Standard		
	Treatment	Statistic or Level	Death?					
			No	Yes				
Age	Flolan	N	41		41	0.98		
		Mean	39.88		39.88			
		Std.Dev.	16.74		16.74			
		Minimum	6.00		6.00			
		Median	41.00		41.00			
		Maximum	70.00		70.00			
	Standard	N	32	0	40			
		Mean	39.63	40.63	39.83			
		Std.Dev.	12.38	12.87	12.52			
		Minimum	9.00	14.00	9.00			
		Median	41.00	42.50	41.50			
		Maximum	59.00	63.00	63.00			
	Sex	Flolan	N	41			41	0.59
			Female	31 (75.6%)			31 (75.6%)	
Male			10 (24.4%)		10 (24.4%)			
Standard		N	32	0	40			
		Female	23 (71.9%)	5 (62.5%)	28 (70.0%)			
		Male	9 (28.1%)	3 (37.5%)	12 (30.0%)			
Baseline vasodilator	Flolan	N	41		41	0.61		
		No	14 (34.1%)		14 (34.1%)			
		Yes	27 (65.9%)		27 (65.9%)			
	Standard	N	32	0	40			
		No	13 (40.6%)	3 (37.5%)	16 (40.0%)			
		Yes	19 (59.4%)	5 (62.5%)	24 (60.0%)			
NYHA class	Flolan	N	41		41	0.75		
		III	31 (75.6%)		31 (75.6%)			
		IV	10 (24.4%)		10 (24.4%)			
	Standard	N	32	0	40			
		III	25 (78.1%)	4 (50.0%)	29 (72.5%)			
		IV	7 (21.9%)	4 (50.0%)	11 (27.5%)			
Baseline walk	Flolan	N	41		41	0.13		
		Mean	315.74		315.74			
		Std.Dev.	115.98		115.98			
		Minimum	0.61		0.61			
		Median	314.55		314.55			
		Maximum	521.21		521.21			
	Standard	N	32	0	40			
		Mean	291.56	194.73	272.19			
		Std.Dev.	128.19	177.04	142.22			
		Minimum	60.05	0.00	0.00			
		Median	273.86	188.97	269.60			
		Maximum	534.93	438.00	534.93			
	Mixed venous saturation (%)	Flolan	N	38			38	0.23
			Mean	62.48			62.48	
Std.Dev.			12.64		12.64			
Minimum			42.00		42.00			
Median			63.00		63.00			
Maximum			92.00		92.00			
Standard		N	31	0	39			
		Mean	60.78	51.65	58.91			
		Std.Dev.	13.08	13.99	13.60			
		Minimum	26.60	31.18	26.60			
		Median	61.00	58.05	60.00			
		Maximum	88.00	68.00	88.00			
PAPs (mm Hg)		Flolan	N	41		41	0.48	
			Mean	60.54		60.54		
	Std.Dev.		11.97		11.97			
	Minimum		39.00		39.00			
	Median		59.00		59.00			
	Maximum		89.00		89.00			
	Standard	N	32	0	40			
		Mean	58.00	61.38	58.68			
		Std.Dev.	14.52	11.04	13.83			
		Minimum	23.00	49.00	23.00			
		Median	59.50	61.50	60.00			
		Maximum	95.00	79.00	95.00			

Table 2

Comparison of Baseline Characteristics of Patients Who Died to Survivors (Continued)

Parameter	Fleolan (N=41)		Standard (N=40)		Total	2-sided p-value Fleolan vs Standard
	Treatment	Statistic or Level	Death?			
			No	Yes		
RAPs (mm Hg)	Fleolan	N	41		41	0.75
		Mean	12.59		12.59	
		Std.Dev.	7.27		7.27	
		Minimum	1.00		1.00	
		Median	12.00		12.00	
		Maximum	26.00		26.00	
	Standard	N	31	8	39	
		Mean	11.76	13.25	12.06	
		Std.Dev.	7.00	6.50	7.51	
		Minimum	1.00	3.00	1.00	
		Median	10.00	13.50	12.00	
		Maximum	29.00	21.00	29.00	
Cardiac output (L/min)	Fleolan	N	41		41	0.55
		Mean	3.52		3.52	
		Std.Dev.	1.59		1.59	
		Minimum	1.60		1.60	
		Median	3.00		3.00	
		Maximum	9.34		9.34	
	Standard	N	32	8	40	
		Mean	5.01	3.47	3.75	
		Std.Dev.	2.01	1.40	1.90	
		Minimum	1.00	2.30	1.00	
		Median	3.25	2.00	3.20	
		Maximum	11.90	6.00	11.90	
PVR (Wood u)	Fleolan	N	34		34	0.65
		Mean	13.71		13.71	
		Std.Dev.	6.39		6.39	
		Minimum	4.10		4.10	
		Median	15.60		15.60	
		Maximum	36.00		36.00	
	Standard	N	24	5	29	
		Mean	16.45	16.00	16.17	
		Std.Dev.	7.67	5.00	7.32	
		Minimum	1.70	7.30	1.70	
		Median	10.05	15.60	10.00	
		Maximum	30.90	20.90	30.90	
TPR (Wood u)	Fleolan	N	41		41	0.61
		Mean	19.09		19.09	
		Std.Dev.	8.35		8.35	
		Minimum	5.10		5.10	
		Median	20.00		20.00	
		Maximum	43.50		43.50	
	Standard	N	32	8	40	
		Mean	10.60	20.22	10.92	
		Std.Dev.	8.04	8.29	8.65	
		Minimum	4.00	8.20	4.00	
		Median	19.75	19.45	19.75	
		Maximum	36.00	32.90	36.00	
SVR (Wood u)	Fleolan	N	41		41	0.55
		Mean	25.05		25.05	
		Std.Dev.	8.77		8.77	
		Minimum	7.30		7.30	
		Median	26.30		26.30	
		Maximum	47.30		47.30	
	Standard	N	31	8	39	
		Mean	23.67	23.52	23.64	
		Std.Dev.	8.43	8.16	8.27	
		Minimum	8.00	12.00	8.00	
		Median	23.70	24.05	23.70	
		Maximum	44.00	32.90	44.00	

Table 3

Between Treatment Comparison of the 6-minute Walk Exercise Test
(Carrying Forward Results for Missing Values or Results After a
Transplant, Analysis of Variance)

Week	N	Flolan		N	Standard		Analysis of Variance (two-sided test)
		Baseline mean (meters)	Mean (meters)		Baseline mean (meters)	Mean (meters)	
1	41	315.7	331.1	40	272.2	248.5	0.0103
6	41	315.7	370.9	40	272.2	263.9	0.0005
12	41	315.7	348.1	40	272.2	257.2	0.0029

Table 4

Between Treatment Comparison of the 6-minute Walk Exercise Test
Adjusting for the Baseline Walk and Vasodilator Use at Baseline
(Nonparametric Analysis of Covariance)

Week	N	Flolan		N	Standard		Nonparametric Analysis of Covariance (two-sided test)
		Baseline median (meters)	Median (meters)		Baseline median (meters)	Median (meters)	
1	40	312.0	332.4	40	269.6	254.4	0.0030
6	40	312.0	385.3	40	269.6	268.1	0.0010
12	41	314.6	362.4	40	269.6	203.5	0.0020

Table 5

Summary of the 6-minute Walk Exercise Test Results Excluding
Patients Who Died, Had a Transplant or Discontinued Flolan
Prematurely

Period	Treatment	N	Mean	S.E.	Min	25-th X-ile	Median	75-th X-ile	Max
Day 1	Flolan	38	313.7	19.7	2.1	248.4	327.3	376.4	559.6
	Standard	28	268.2	23.8	36.6	182.8	263.4	364.8	534.9
Day 2	Flolan	37	319.8	19.5	8.6	278.1	314.6	394.1	521.2
	Standard	29	282.3	23.4	68.8	192.6	266.7	390.1	487.4
Wk 1	Flolan	38	335.4	16.1	8.8	292.6	333.8	401.7	518.2
	Standard	30	268.8	23.8	49.4	181.1	258.2	348.1	511.2
Wk 6	Flolan	38	374.7	17.7	39.6	331.3	385.3	451.7	554.3
	Standard	30	293.4	26.7	75.8	151.8	302.8	412.1	572.1
Day 80	Flolan	38	358.9	17.9	24.4	286.2	372.6	426.7	543.2
	Standard	30	284.4	26.3	79.2	160.6	265.5	402.3	558.7

Table 6

Comparison of Changes From The Baseline in The 6-minute Walk Exercise Test Results, Excluding Patients Who Died, Had a Transplant or Discontinued Flolan Prematurely

Period	Treatment	N ²	Mean	S.E.	Min	25-th %-ile	Median	75-th %-ile	Max	N-L ³ Est.	Nonparametric 95% Confidence Interval ⁴
Wk 1	Flolan	38	15.2	9.6	-139	-8.2	18.9	47.9	150.0	17.1	(-2.3,33.5)
	Standard	30	-23.9	14.4	-309	-46.3	-17.2	15.5	149.4	-17.1	(-35.7,0.5)
Wk 6	Flolan	38	54.5	14.9	-81.4	-7.0	47.4	84.7	424.6	46.0	(21.6,70.0) *
	Standard	30	2.7	10.8	-182	-30.2	-0.3	23.8	129.2	0.0	(-20.1,21.6)
Day 88	Flolan	38	30.8	11.3	-122	-14.6	28.8	71.3	212.8	30.8	(9.3,50.9) *
	Standard	30	-6.3	13.4	-172	-42.1	-7.9	39.0	133.5	-8.2	(-33.4,22.3)

Table 7.a

Summary of Patient Survival(Patients are Followed to The Time of Study Discontinuation) With The Lowest Baseline Walk Test

N	Flolan			Standard Therapy			Logrank two-sided p-value
	# of deaths	Percent censored ¹	Mean ² Median ³	# of deaths	Percent censored ¹	Mean ² Median ³	
41	0	100.0		40	8	80.0 64.15	0.0027

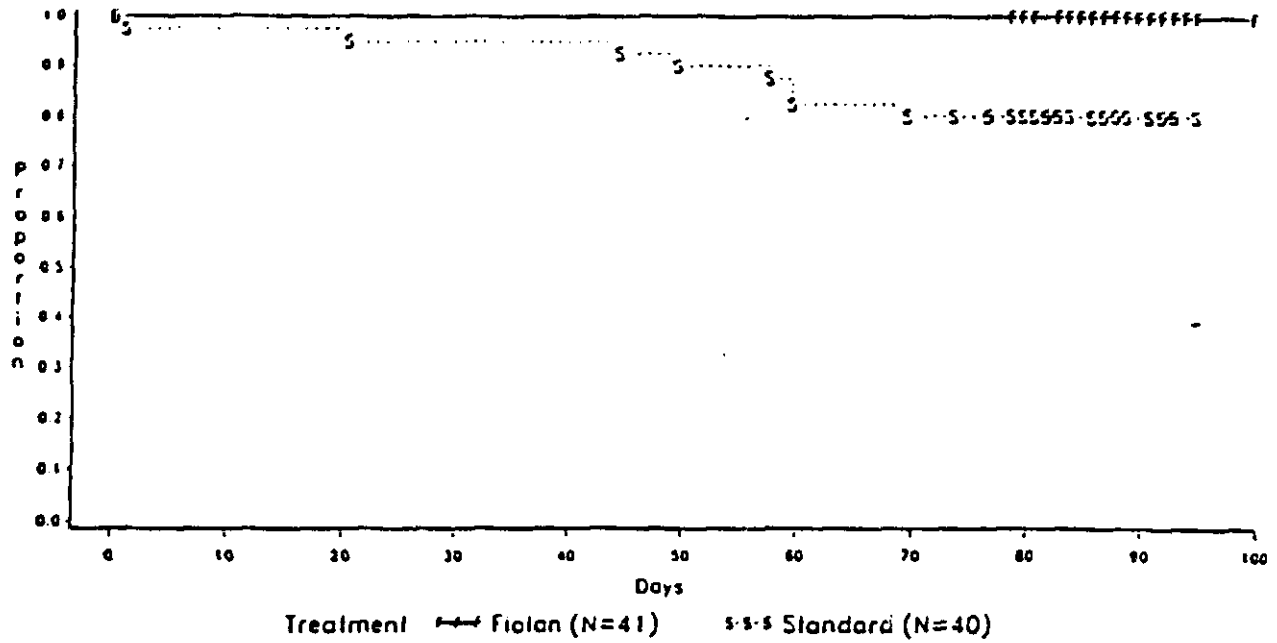
Table 7.b

Summary of Patient Survival(Patients are Censored at the Time of Transplant

N	Flolan			Standard Therapy			Logrank two-sided p-value
	# of deaths	Percent censored ¹	Mean ² Median ³	# of deaths	Percent censored ¹	Mean ² Median ³	
41	0	100.0		40	8	80.0 64.15	0.0029

Figure 1.a

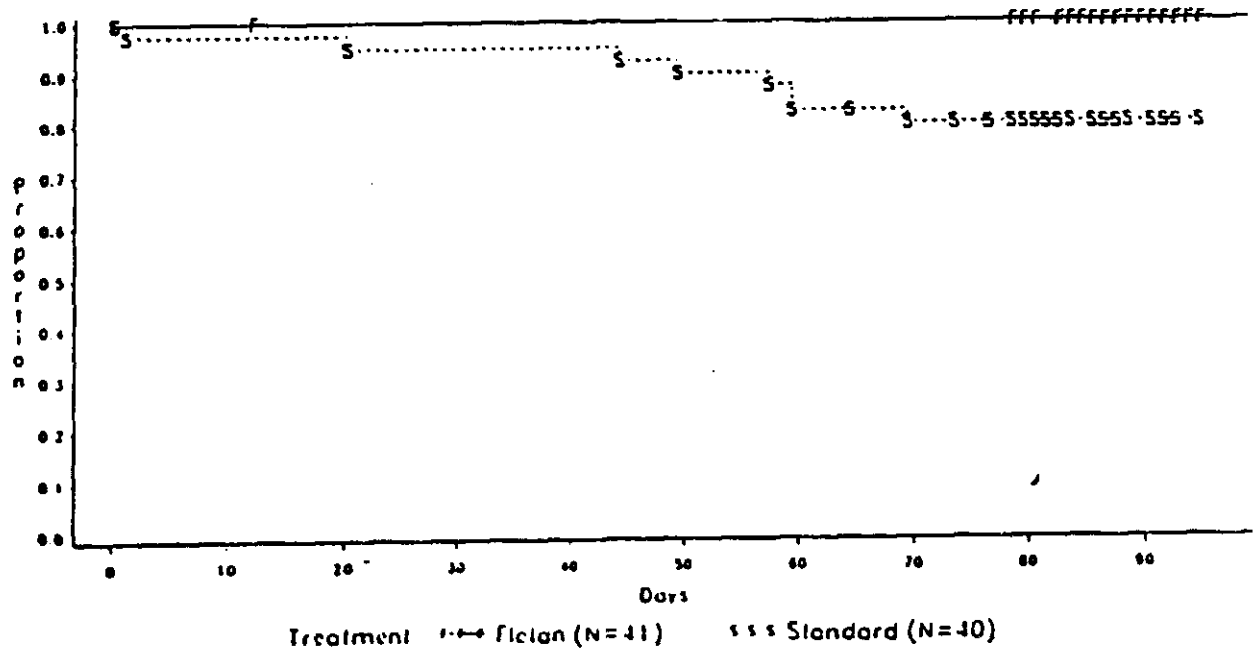
Proportion of Patients Surviving (Patients are Followed to The Time of Study Discontinuation)



Two-sided p-value from the logrank test=0.0027

Figure 1.b

Proportion of Patients Surviving (Patients are Censored at The Time of Transplant)



(Estimates made using the Kaplan-Meier product-limit method
Two-sided p-value from the logrank test=0.0027)

Table 9
 Characteristics of The 11 Patients With The Lowest Baseline Walk
 Test

Patient's Number	Treatment	Date of Study initiation	baseline 6- minutes walk	Remarks
	Standard	11/22/91	0.0	died 11/22/92
	Flolan	4/3/92	0.6	
	Standard	5/15/92	45.72	died 7/01/92
	Standard	1/28/92	60.05	
	Flolan	1/9/92	68.28	
	Standard	5/13/91	91.44	
	Standard	4/1/92	91.44	died 5/29/92
	Standard	11/15/92	100.5	died 12/4/92
	Standard	4/21/92	114.30	
	Standard	2/25/92	117.35	died 4/18/92
	Standard	5/4/92	118.87	

Table 11
Influence of Centers 7 & 11 on Baseline Walk Distance
Comparability

	<u>Treatment</u>		p-value
	Flolan	Standard	
<u>Center 7</u> n=	3	4	
Day 1 Mean =	323.596	146.495	0.0232
Median =	307.848	120.396	
Day 2 Mean =	327.152	168.173	0.0865
Median =	306.324	137.922	
Day 1 & Day 2 Combined			0.0303 (Repeat Measures ANOVA)
<u>Centers 7&11</u> n=	5	6	
Day 1 Mean =	298.491	147.650	0.0085
Median =	307.848	149.962	
Day 2 Mean =	339.121	157.226	0.0059
Median =	306.324	136.855	
Day 1 & Day 2 Combined			0.0043 (Repeat Measures ANOVA)
<u>All Centers</u> <u>except 7&11</u> n=	36	34	
Day 1 Mean =	307.899	264.081	0.1656
Median =	308.762	251.612	
Day 2 Mean =	312.496	292.483	0.3454
Median =	323.240	293.065	
Day 1 & Day 2 Combined			0.2398 (Repeat Measures ANOVA)

Table 12
Centers 7 and 11 Patients Walk Distance and Their Allocation to
Treatments

Patient number	Treatment	Day 1 Walk Distance	Day 2 Walk Distance	Receive Oxygen?	Remarks
	Standard	79.1	158.5	yes	
	Standard	265.9	336.8	yes	died 3/19/92
	Standard	82.3	60.0	yes	
	Standard	158.5	117.3	yes	died 4/8/92
	Flolan	307.8	384.0	yes	
	Flolan	297.2	396.3	yes	
	Flolan	365.8	291.1	yes	
	Flolan	358.9	434.3	no	
	Standard	155.4	156.4	yes	
	Standard	144.5	114.3	yes	
	Flolan	162.8	279.8	no	

Table 13.a

Re-Analysis Results of 6-minute Walk Distance for All Centers/Patients (Last Observation Carried Forward Analysis by the Intention-to-Treat Principle)

	<u>Treatment</u>		2-sided p-value	
	Flolan	Standard	t-test	Wilcoxon Ranks Test
Number of patients	41	40		
Mean baseline walk distance	315.743	272.194	0.1344	0.1664
Mean 'WK 1' walk distance	331.149	248.519	0.0020	0.0026
Mean change from base walk dist.	15.406	-23.675	0.0103	0.0038
Adjusted mean change	20.391	-28.786	0.0005	
Mean 'WK 6' walk distance	373.239	264.986	0.0005	0.0014
Mean change from base walk dist.	57.496	-7.209	0.0004	0.0004
Adjusted mean change	60.889	-18.687	0.0001	
Mean 'WK 12' final walk distance	349.881	263.766	0.0051	0.0067
Mean change from base walk dist.	34.138	-8.428	0.0137	0.0029
Adjusted mean change	36.977	-11.338	0.0052	

Table 13.b

Re-Analysis Results of 6-minute Walk Distance Excluding Centers 7 and 11 (Last Observation Carried Forward Analysis by the Intention-to-Treat Principle)

	<u>Treatment</u>		2-sided p-value	
	Flolan	Standard	t-test	Wilcoxon Ranks Test
Number of patients	36	34		-
Mean baseline walk distance	312.496	292.482	0.5250	0.6092
Mean 'WK 12' final walk distance	351.511	282.550	0.0440	0.0554
Mean change from base walk dist.	39.014	-9.933	0.0103	0.0018
Adjusted mean change	40.131	-11.115	0.0069	

Table 13.c

Re-Analysis Results of 6-minute Walk Distance Excluding the Weakest 11 Patients (Last Observation Carried Forward Analysis by the Intention-to-Treat Principle)

	<u>Treatment</u>		2-sided p-value	
	Flolan	Standard	t-test	Wilcoxon Ranks Test
Number of patients	39	31		
Mean baseline walk distance	330.169	327.355	0.9102	0.9340
Mean 'WK 12' final walk distance	362.485	313.914	0.1003	0.1065
Mean change from base walk dist.	32.317	-13.441	0.0113	0.0031
Adjusted mean change	32.519	-13.696	0.0152	

Table 13.d

Re-Analysis Results of 6-minute Walk Distance Excluding Deaths/Transplant Patients (Last Observation Carried Forward Analysis by the Intention-to-Treat Principle)

	<u>Treatment</u>		<u>2-sided p-value</u>	
	Flolan	Standard	t-test	Wilcoxon Ranks Test
Number of patients	40	30		
Mean baseline walk distance	319.926	290.698	0.3256	0.2990
Mean 'WK 12' final walk distance	353.179	284.429	0.0255	0.0264
Mean change from base walk dist.	33.254	-6.269	0.0253	0.0182
Adjusted mean change	35.098	-8.728	0.0109	

Table 14

Re-Analysis Results of the 6-minute Walk Distance (Last Observation Carried Forward Analysis by The Intention-to-Treat Principle), Analysis of Covariance

	All Cts/pats.	<u>2-sided p value</u>	
		Excl. Cts. 7&11	Excl. low. 11 pts
Number of Patients	81	70	70
<u>Source of variation:</u> (test for homogeneity of slope)			
Drug*baseline	0.5955	0.7010	0.7028
Drug (Flolan vs Std.)	0.0048	0.0104	0.0210
Baseline walk distance	0.0001	0.0001	0.0001

Table 15
 Re-Analysis Results of The Survival Rates, Proportional Hazard
 Regression Model

	All Cts/pats.		<u>2-sided p value</u>		Excl. low.11 pts	
	Event	Censored	Event	Censored	Event	Censored
Number of Patients	11	70	9	61	6	64
Variables in the model						
Drug	0.0154		0.0221		0.0520	
Baseline	*		0.0163		*	
Drug's Risk Ratio	0.078		0.086		0.117	

* p -value is not significant when the variable included in the model

Table 16
 Results of Testing For Equality of The Survival Curves For Flolan
 Versus Standard Treatment

	All Cents/pats.		<u>2-sided p value</u>	
	81	70	Exclude Cts.7&11	Exclude low.11 pts
Number of Patients	81	70	70	
<u>Statistical test</u>				
Log-Rank	0.0018		0.0042	0.0207
Wilcoxon	0.0035		0.0115	0.0586
-2 Log (LR)	0.0016		0.0061	0.0413
Rank test for Association of Surv. With Baseline Walk	0.0407		0.0090	0.7440

Table 17

Estimated Probabilities of Survival for Patients Randomized to Flolan or Standard Therapy in Studies 35/36 and 46 and Patients Enrolled in the NIH Registry*

Follow-up Time (months)	FLOLAN		Standard Therapy		NIH Registry	
	Number of Patients Followed	Estimated Probability of Survival	Number of Patients Followed	Estimated Probability of Survival	Number of Patients Followed	Estimated Probability of Survival
0	51	1.00	53	1.00	138	1.00
2	49	0.98	40	0.81	114	0.84
3	48	0.98	10	0.71	110	0.81
6	44	0.96	3	0.71	97	0.72
12	15	0.86	1	0.71	85	0.64
18	5	0.80	1	0.71	73	0.56
24	5	0.80	0	-	68	0.52

* Calculated by the sponsor

JAN 6 1995

Memorandum of Consultation



Date: January 5, 1995
From: M. Al Osh, Ph.D.
Mathematical Statistician/ HFD-713

To: Stephen Fredd, M.D.
Director, Division of Gastrointestinal and Blood
Coagulation Drug Product, HFD-180

Subject: Request for additional information for Studies #49, and #50 of NDA 20-444 of Flolan injection in the treatment of primary pulmonary hypertension (PPH), submitted by Burroughs Wellcome Co.

Information Requested:

- A. Please, provide the following information on 3.5" diskettes as SAS data sets and in hard copy, with codes for study number, patient number, center, treatment group, date treatment administered and indicator variables for dropouts. These information should cover studies 49 and 50 and should include:
- i) The dates when patients entered these studies.
 - ii) The time-to-death from the date patients entered into the study, the actual dates for deaths, and the cause for each death.
 - iii) The time-to-censoring from the date patients entered into the study, the actual dates for censoring, the cause for each censoring.
- B. How baseline characteristics of patients in studies #49 and #50 (individually and combined) are comparable with those of patients in the NIH Registry and with those of studies

#35/36 and #46? Please explain this comparability and provide baseline data along with events and censoring data, as described in A above, for each patient in studies #49 and #50 on a 3.5" diskettes as SAS data set and in hard copy.

- C. Please indicate whether Study # 50 is a continuation of Study #49, and if this is so please state the reason for termination of study 49. In case Study #50 is a continuation of Study #49 please identify the patients who were transferred to Study #50 and whether the patient continued the same treatment assigned in the original study.
- D. Please provide a disk copy of the protocol for studies#49 and #50.

M. Al Osh

M. Al Osh, Ph.D.

Mathematical Statistician

Concur:

Dr. M. Huque

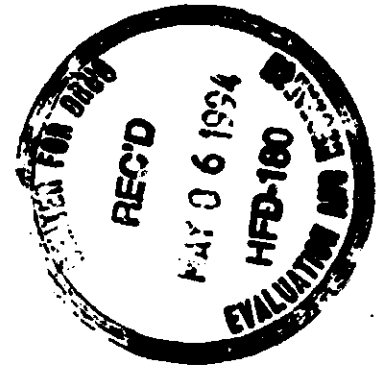
Huque
1/5/95

cc: Orig. NDA 20-444

HFD-180
HFD-180/ Dr.Fredd
HFD-180/ Dr.Triantas
HFD-180/ Ms.Oliver
HFD-713/ Dr.Dubey [File:1.3.2, NDA]
HFD-713/ Dr.Huque
HFD-713/ Dr.Al Osh

Aloshm/x4594/SARB/1/5/95

Memorandum of Consultation



Date: May 4, 1994
From: M. Al Osh, Ph.D.
Mathematical Statistician/ HFD-713

To: Stephen Fredd, M.D.
Director, Division of Gastrointestinal and Blood
Coagulation Drug Product, HFD-180

Subject: Request for additional information for Study #46 of NDA 20-444 of Flolan injection in the treatment of primary pulmonary hypertension (PPH), submitted by Burroughs Wellcome Co.

Background:

The sponsor used a dynamic adaptive randomization procedure which is a modification of the adaptive randomization method by Pocock and Simon (Biometrics 31:103-115, 1975). The purpose of this randomization procedure was to balance with respect to three baseline stratification variables: NYHA class, the use of vasodilators at baseline, and study site (center).

Imbalances:

A preliminary review of the data indicates the following imbalances:

1. In center # 7 (David B. Badesch, MD. and Bertron M. Groves, MD. investigators) 4 patients were assigned to the standard treatment and 3 to Flolan. The date of assignment indicates that the first 4 patients (in chronological order) were assigned to the standard treatment and the remaining 3 to Flolan. In addition, all the 4 standard treatment patients consistently have

lower baseline 6-minutes walking distance relative to the Flolan patients (see Table 1, attached).

Furthermore in center #1 (Robyn J. Barst, MD investigator) 3 out of the 7 patients assigned to the standard treatment did not attempt exercise first day as compared to none of the 6 patients assigned to the Flolan treatment.

2. There appears to be imbalance with respect to the 6-minutes baseline walking distance between the standard and the Flolan groups (see Table 2).

3. There are 14 patients with 6-minutes baseline walking distance of 150 meters or less. Of these, 11 are assigned to the standard treatment and only 3 to the Flolan treatment (see Table 3).

Information Requested:

Given the above imbalances, the following information is needed to continue the statistical review for Study #46:

1. Please, provide details of the execution of the randomization method and how the patients were assigned to treatment to provide balance for prognostic factors such as baseline walking distance.

2. Given that the trial is an open trial, provide details regarding methods used to minimize bias in the conduct of the trial.

3. Please, provide relevant computer printouts of the statistical analysis done including residuals from the fitted analysis of covariance models provided in the NDA.

M. Al Osh

M. Al Osh

Mathematical Statistician

Concur:

Dr. M. Huque *Huque*
5/4/94

This report contains 3 pages of text and 2 pages of tables.

cc: Orig. NDA 20-444

HFD-180

HFD-180/ Dr. Fredd

HFD-180/ Dr. Triantas

HFD-180/ Ms. Oliver

HFD-713/ Dr. Dubey [File:1.3.2, NDA]

HFD-713/ Dr. Huque

HFD-713/ Dr. Al Osh

Table 1

Assignment of patients of Center #7 to different treatments

Patient's number	Admission date	Treatment	1st day 6-minutes walking distance	walked the entire 6 minutes	Remarks
	12/13/91	standard	79.2	no	
	01/22/92	standard	265.9	yes	died 01/23/92
	01/27/92	standard	82.3	no	
	02/10/92	standard	158.5	no	died 04/8/92
	03/30/92	Flolan	307.8	yes	
	04/06/92	Flolan	297.2	yes	
	05/11/92	Flolan	365.8	yes	

Table 2

Comparison of baseline 6-minutes walking distance

Treatment	No. of patients	Mean baseline walking distance	Standard Error
Standard	40	255.997	21.281
Flolan	41	306.748	18.903

2-sides p-value for testing the equality of baseline means walking distance:

t-test: .0780

Wilcoxon rank test: .0856

Table 3

Listing of patients with baseline walking distance of less than 150 meter according by treatment group

Standard treat.	Baseline walking distance	Event's date	Flolan treat.	Baseline walking distance	Event's date
	0	09/10/91	06003	63.8	01/08/92
	141.1	10/14/91	05002	100.2	03/09/92
	62.3	11/14/91 death 12/4/91	16002	2.1	04/02/92
	0	11/21/91 death 11/21/91			
	79.2	12/13/91			
	not done	1/14/92			
	82.5	1/27/92			
	119.2	3/30/92 death 5/29/92			
	36.6	4/02/92			
	144.8	4/16/92			
	49.5	5/14/92			

STATISTICAL REVIEW & EVALUATION

Date: JAN 30 1991

IND #:

Applicant: Burroughs Wellcome Co.

Drug Name: FLOLAN (Epoprostenol Sodium)

Pharmacologic Category of the Drug: Vasodilator

Indication: Treatment of Primary Pulmonary Hypertension

Documents Reviewed: N(GC)063 with disks, dated September 5, 1990,
and Volumes 1-4, dated September 18, 1990.

I. Introduction

These studies are to provide evidence warranting a treatment IND in patients with primary pulmonary hypertension. Such patients commonly await lung or heart-lung transplants. The purposes are to

a) prolong survival

b) improve exercise capacity (six minute walk distance)

in New York Heart Association (NYHA) Class III and Class IV patients with Primary Pulmonary Hypertension.

II. Description of Studies and Sponsor's Analyses and Results

As shown in Table 1, five studies are submitted. Studies 35, 36 and 37 were undertaken by Burroughs Wellcome Co. (B.W.Co.) Study 35 was for NYHA class I and II patients, and was aborted due to risks. Study 36 was for NYHA class III and IV patients. Treatment was to be given for eight weeks in studies 35 and 36. Unrandomized study 37 is an extension of studies 35 and 36, with patients opting to receive FLOLAN or no FLOLAN on their choice, after completing studies 35 or 36.

A historical control was included in this IND, consisting of 194 patients not treated with FLOLAN. The historical control patients were enrolled in the U.S. National Registry of Patients, a study sponsored by NIH. The last study submitted is the Papworth Hospital study, conducted in the

The sponsor consistently used one tailed p-values, apparently testing at the .05 significance level. This is equivalent to using two tailed p-values, testing at the .10 significance level. The conventional approach is to use two tailed p-values, testing at the .05 significance level. Consequently, the sponsor and this reviewer disagree on the statistical significance of several results.

Study 35, U.S., B.W.Co., Description of the Study

Only two (2) patients were randomized in study 35. This study was a three center unblinded, parallel, randomized clinical trial undertaken by B.W.Co. of NYHA Class I and II patients. Otherwise the entry and exclusion criteria are the same as in Study 36, described next. The study was aborted on risk to benefit considerations, based on data from studies 35 and 36. Patients could remain in this protocol for eight weeks. By implication, the indication for NYHA Class I and II patients was withdrawn.

Study 36, U.S., B.W.Co., Description of the Study

Study 36 was a three center open, parallel, randomized clinical trial undertaken by B.W.Co. of NYHA Class III and IV patients. Ten (10) of the total of 23 patients enrolled were treated with FLOLAN. Patients could remain in this protocol for eight weeks. Conventional therapy was at the investigator's discretion, including diuretics, vasodilators, inotropes, anticoagulants and oxygen. Different randomization schedules were employed depending on whether or not the patient was receiving oral vasodilators at the time of screening.

FLOLAN was administered by a positive pressure infusion pump via an intravenous catheter. Due to the pharmacokinetics and safety considerations, the dosing scheme is somewhat sophisticated. Each dose-ranging segment was conducted in a cardiac lab, to find the dose giving the greatest hemodynamic improvement and largest tolerated dose. The dose-ranging segments were to be conducted at baseline, at the end of the eight-week treatment phase (end of studies 35, 36) and at the end of the post-treatment phase (end of study 37.) The long-term infusion rate was to be the lesser of the maximum tolerated dose or the dose which elicited the greatest reduction in pulmonary vascular resistance without reductions in systemic oxygen transport below baseline values. Dosage adjustments were allowed throughout the long-term infusion segment.

The primary endpoint is all deaths, treating lung and heart-lung transplants as censoring. Another analysis was performed using all deaths and transplants as the primary endpoint. No patients withdrew or were lost to follow up in the B.W.Co. studies. The

secondary endpoint seems to be improvement in exercise capacity, measured as the distance a patient can walk on a level surface in six minutes. Quality of life was also assessed using the Nottingham Health Profile.

The study population was recruited from patients for whom a diagnosis of PPH was clinically suspected or had been confirmed by cardiac catheterization. Each patient must have:

1. been six months to 70 years of age; been either not receiving any therapy for PPH or have received current therapy for 60 days;
2. had a medical history and physical exam consistent with diagnosis of PPH, NYHA Class III or IV; had evidence of right ventricular hypertrophy on 12-lead ECG and echocardiogram within the previous month; had a chest radiograph not inconsistent with diagnosis of PPH within past 6 months;
3. given written informed consent;
4. had mean pulmonary arterial pressure ≥ 25 mm Hg, total pulmonary resistance ≥ 5 mm Hg/liter/min, or pulmonary vascular resistance ≥ 3 mm Hg/liter/min; had at least a 10 mm Hg gradient between mean pulmonary arterial pressure and mean pulmonary capillary wedge pressure if available;
5. received an echocardiogram within the past month revealing normal mitral valve (excluding mitral stenosis) and normal left ventricular function; and been practicing a method of birth control acceptable to the investigator.

Exclusion criteria include:

1. pregnant or breast feeding, or clinically significant arrhythmias, or abnormal clinical values indicating a disease other than PPH;
2. had supine systemic blood pressure outside range of 80-150 mm Hg and 50-100 mm Hg diastolic; heart rate outside range of 60-120 beats per minute; or evidence of pulmonary embolism by V/Q scan or angiogram;
3. received FLOLAN within 60 days prior to study, or had any change in PPH therapy within 14 days prior to entering study.

Protocol Violations

This reviewer found three protocol violations especially interesting (volume 2, pages 16-17.)

"1. The original protocol was intended to enroll patients sequentially who presented at each site with PPH, irrespective of their clinical response to other therapies. However, due to the complexity in delivering and maintaining FLOLAN infusions, only patients who were clearly not responding clinically to other medications were enrolled in Study 36."

By implication, there is an empirically defined change in the patient population during the trial, restricting to non-responders to conventional therapy.

"3. Each evaluation of exercise was to be composed of a practice evaluation in the morning followed that evening by a second evaluation which was to be considered primary data to be used in all events. In general, patients did not undergo a practice evaluation and only one test was performed at each evaluation time. When exercise capacity was evaluated twice (according to the protocol), the evening or second assessment was used."

This may imply bias in favor of the drug showing an exaggerated improvement, i.e. a modest improvement in a patient might inspire using a practice exercise for that patient, yielding a larger improvement for the measured exercise. The exaggeration can be removed by the Wilcoxon rank-sum test, shown in Table 7. The p-values come out about the same.

"5. The first patient (101) was a class III patient who was not receiving oral vasodilator therapy. This patient entered the study before the randomization schedule was available; patient 101 was assigned independent of the official randomization schedule to receive FLOLAN for the eight week treatment. All other patients were randomized according to the appropriate schedule."

This 21 year old patient received the drug, and died in 15 days. This protocol violation did not bias the study in favor of the drug.

Study 37, U.S., U.S., B.W.Co.

All patients completing studies 35 and 36 were offered the opportunity to participate in study 37, in which patients were treated with FLOLAN. There is no randomization in study 37, and only three (3) conventional therapy patients. A historical control is used to evaluate the combined results of studies 35, 36, and 37 with respect to mortality and transplant endpoints. This historical control contained 194 patients not treated with FLOLAN. The historical control patients were enrolled in the U.S. National Registry of Patients.

Serious adverse reactions in study 37 (open label long term treatment of 18 patients under B.W.Co., table 36 vol 1,) are listed in Table 2.

Studies 35, 36 and 37, U.S., B.W.Co. Sponsor's Analysis and Results

This reviewer addresses these trials together because the remaining studies are uncontrolled.

Two (2) patients entered study 35, both NYHA Class II, one randomized to FLOLAN. Twenty three (23) patients entered study 36. The distribution of NYHA classes is given in the following table.

**Distribution of Patients by NYHA Class at Baseline
Studies 35 and 36**

Class	Conventional Therapy	FLOLAN
I	0	0
II	1	1
III	7	8
IV	6	2
<u>Total</u>	<u>14 patients</u>	<u>11 patients</u>

Combining studies 35 and 36 (for the 8 week treatment period) yielded a two tailed log rank test $p=0.392$, not significant. However, the numeric difference is in favor of FLOLAN, with 1 out of 11 deaths in the FLOLAN group as compared to 3 out of 14 deaths in the conventional therapy group.

**Patients enrolled in Studies 35 and 36, n=25
(8 week period)**

<u>FLOLAN Therapy</u>			<u>Conventional Therapy</u>			2 tail Log rank $p=0.392$
Died	Completed	Total	Died	Completed	Total	
1	10	11	3	11	14	

There was a 26th patient who experienced an embolic event during dose ranging; this patient was not randomized and received no further FLOLAN. From this point onward, which patient went where and what happened to him becomes somewhat complicated; the complete data for the primary endpoint are arrayed in Table 3 for the convenience of the reader.

With respect to the following counts of patients in study 37, note the advantages for FLOLAN in terms of deaths after 8 weeks. The three patients who declined to enter study 37 had originally been randomized to conventional therapy; however, these patients were followed up to the death.

Patients Eligible for Study 37, n=21
(Patients who completed 8 weeks, followed up to about 2 years)

<u>Entered, Received FLOLAN</u>				<u>Did not Enter</u>	
Survived	Transplanted	Died	Total	Died	Total
10	5	3	18	3	3

On pooling the mortality events of study 37 with those of studies 35 and 36, crossing the 8 patients over at the time of change of therapy from conventional to FLOLAN, the survival probability (using transplants as censoring) were as follows. The sponsor's statistical method is not specified. The reviewer's statistical method is Kaplan-Meier. Also, see Figure 1.

Probability of Survival, Studies 35, 36 and 37 (combined)

Time	Agreed FLOLAN 11 patients	Sponsor Conventional 14 patients	Reviewer Conventional 14 patients
0.5 Year	91%	58%	53%
1.0 Year	91%	29%	26%
1.5 Year	81%	29%	26%
2.0 Year	81%	0%	0%

* Eight of the 14 patients assigned to conventional therapy initially, and were censored when they went to FLOLAN at the end of the eight week period.

On an intent-to-treat basis, comparing patients originally randomized to FLOLAN versus patients originally randomized to conventional therapy, the two sided p-value from the log rank test is 0.018, censoring transplants. Treating transplants as deaths, two tail p=.032 by the log rank test. However, these results may be biased because uncontrolled study 37 drives the overall result.

U.S. National Registry Study (NIH)

The National Institutes of Health conducted a multicenter, observational study of patients with PPH on July 1, 1981. Enrollment ended on September 30, 1985, and patients were followed until August 8, 1988. A total of 194 patients were enrolled, all receiving conventional care (not chronically on FLOLAN.) All patients were followed at six-month intervals. In the event of a heart-lung or single-lung transplant, the date of transplant was recorded; follow-up data after transplant surgery was not found.

In this study, (pg 6/114, vol 3) survival time after baseline diagnosis was not associated with patient gender, smoking history, the presence or absence of serum antinuclear antibody

titre, a family history of PPH, a history of oral contraceptive medication or pregnancy. However, survival time after baseline was associated with NYHA functional class, as shown in the following table of tests chosen for their low p-values. Patients on a chronic drug therapy other than FLOLAN showed no significant difference in survival time from those patients who were not on a chronic drug therapy.

**U.S. National Registry (NIH) Study:
Cox Regression Analysis
Association of Survival Time with Baseline Variables**

Variable	2-tail p-value
NYHA Functional Class I-II vs III-IV	0.0068
NYHA Functional Class I-II-III vs IV	0.0004
Right Atrial Mean Vascular Pressure	0.0001
Cardiac Index	0.0008
Pulmonary Indexed Vascular Resistance	0.0001

Combined Analysis: Burroughs Wellcome Co. and
U.S. National Registry Study (NIH) Studies

The baseline patient demographics seem reasonably comparable, although the trials are not parallel (the periods overlap by about a year.) Also, the U.S. National Registry study had (approximately) four years enrollment and three years minimum follow up, versus B.W.Co. three years enrollment and half year minimum follow up. Due to the early stopping of study 35, there is a clear imbalance in the numbers of class I and II patients between B.W.Co. studies and the NIH study. So this reviewer does not address class I and II patients from this combination of studies. Otherwise the patient populations seem similar; their baseline characteristics are shown in Table 4.

The two tailed p-values are .062 for Wilcoxon, and .116 for log rank tests restricted to Class III and IV patients. Summaries of the mortality, transplant and exercise capacity are in Tables 5 to 7.

If covariates are taken into account one at a time, some weaker p-values are obtained. The effects of covariates on the comparison of FLOLAN versus conventional treatment follows.

**Two tailed p-values for FLOLAN with Covariates
Proportional Hazards Models for Survival, Classes III. IV
National Registry and B. W. Co.**

Age	0.128	Sex	0.126
NYHA	0.100	Cardiac Index	0.104
Pulmonary Art. Press.	0.150	Mixed Venous Oxygen.	0.428
Right Atrial Press.	0.378	Total Pulmonary Press.	0.378
Race	0.128	Pulmonary Vasc. Res.	0.434
Total Sys. Res.	0.130		

This result is to be interpreted considering that there is a historical control and there could be bias because of imbalances at baseline (yielding a strong lack of orthogonality in the design.) Such imbalances would normally be controlled by randomization.

Next, the estimated magnitude of the improvement, measured in probability of survival (method not specified.) Also, see Figure 2.

**Probability of Survival
National Registry and B.W.Co., classes III, IV**

Time	Conventional Therapy	Flolan
	National Registry	B.W.Co.
	n=138	n=18
0.5 Year	72%	95%
1.0 Year	64%	95%
1.5 Year	55%	88%
2.0 Year	51%	65%

Log Rank 2 tail p=.116
Wilcoxon 2 tail p=.062

The sponsor's analysis may have excluded the five B.W.Co. patients receiving conventional therapy. This reviewer wonders why these patients, all of whom died, would be excluded.

Papworth Hospital Study, United Kingdom

In this study, 25 out of 44 patients were treated with FLOLAN, but the study was not randomized, had serious selection biases and a different (more ill) population as discussed below. The complete primary endpoint data for the Papworth study are given in Table 8.

For class III and IV patients, the sponsor gave the two tailed p-values 0.0186 for Wilcoxon and 0.030 for the log rank test, in

favor of FLOLAN over conventional therapy, censoring transplants. This reviewer obtained $p=.0211$ for the log rank test on the same basis, using the asymptotic approximation. There were five NYHA class II patients, none of whom took FLOLAN and all of whom survived. From the data, the advantage for FLOLAN is in the first two years, when most patients were at risk, as shown in Figure 3.

Five patients were not offered FLOLAN treatment due to either poor psychological background or living at too great a distance from the hospital. Fourteen patients were unable to obtain the necessary funding for drug and supplies; to quote volume 4, page 10, "Patients received long-term FLOLAN therapy if their district of residence was willing to pay for FLOLAN, otherwise they received conventional therapy." So conditional on the NYHA class, the patients with poorer prognoses or less access to medical facilities, would tend to not receive FLOLAN. This could bias the results in favor of FLOLAN.

Due to treatment selection bias, the results need to be confirmed by well controlled studies.

Reasons for not pooling:

Between 1982 and 1987, patients with severe PPH were referred to Papworth Hospital for heart-lung transplantation. The initial diagnosis of PPH averaged 42 months before the initial catheterization at the hospital. So these patients were more ill than the patients in the B.W.Co. and NIH populations, making it hazardous to combine the five studies. This reviewer does not attempt to combine the data from the study with the other studies.

For hypothesis generating purposes, the probabilities of survival on FLOLAN observed in the Papworth and B.W.Co. FLOLAN patients may be of use. The probabilities of survival on FLOLAN given by the sponsor are in the following table.

Probability of Survival on FLOLAN
Hospital and B.W.Co., classes III, IV

Time	Hospital		B.W.Co.	
	n=25	FLOLAN	n=18	FLOLAN
0.5 Year		95%		84%
1.0 Year		95%		69%
1.5 Year		88%		51%
2.0 Year		65%		27%

III. Reviewer's Comments and Conclusions
(which may be conveyed to the sponsor)

The FDA customarily uses two sided tests at the .05 significance level. The use of one sided tests at the .025 significance level might be accepted, but the acceptance of one sided tests at the .05 significance level would entail a (tacit) change in the regulatory practice.

The pooled mortality data from studies 35, 36, and 37 which had some patients on conventional therapy indicate a mortality benefit of about 20 to 30 percent in favor of FLOLAN, which needs to be verified by adequate, well controlled trial(s). The two sided log rank p-value comparing survival up to three years was $p=.018$ on an intent to treat basis. This result is suspect since it is driven by uncontrolled study 37, and is not confirmed by the reviewer's calculations. The exact two tailed p-values for the log rank test without any blocking or covariates obtained by the reviewer are:

Definition of Censoring

Censoring transplant and transfer to FLOLAN	.0220
Ignore transplant, Censor transfer	.0402

Although the p-values remain statistically significant, the lack of concordance is of some concern.

Also, see Figure 1. Statistical benefit in favor of FLOLAN was not achieved by the eight (8) week data from the controlled studies 35 and 36 alone.

There was no statistical benefit in favor of FLOLAN based on the eight (8) week change in exercise capacity, with two tailed $p=.083$ and $p=.096$ for the t-test and Wilcoxon rank-sum test respectively. However, there seems to be a trend in favor of FLOLAN. A better randomized trial is needed to confirm these results.

The softness of the current exercise capacity endpoint is a cause for concern. From *Annals of Internal Medicine*, (1990, 112:7, pp 485-491): "we found no correlation between improvement in the 6-minute walk and any hemodynamic variable in either group. ... It appears that this test may be too dependent on other factors, such as the degree of motivation of the patient or physician, to be useful as a variable with which to judge clinical response." The development of a harder but similar endpoint would be helpful.

In this reviewer's assessment, pooling the B.W.Co. and NIH studies for the primary endpoint is appropriate for class III, IV patients. As shown in Table 4, the groups compare reasonably well with respect to key baseline prognostic factors. The survival

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7 OF 8

curves (see Figures 1, 2, 3) of FLOLAN versus conventional therapy shows separation early but closing up of the curves later. The two sided p-value by the log rank test was not significant, at $p=.116$. The Wilcoxon test, which by comparison is more sensitive to differences in mortality early in time, has a two tail $p=.062$. More data needs to be collected to confirm the trend in favor of FLOLAN.

In comparison with the historical control, the covariate adjusted proportional hazard analyses need to be done more carefully. The covariate analyses should include parameter estimates, tests of the goodness of fit (testing the proportional hazards assumption) and residual plots.

Some statisticians such as Richard Peto suggest that a historical control comparison (or a meta-analysis comparison) could be convincing only if the estimated treatment is greater than three (3) times its standard error. This yields a two tailed test at the .001 level, or a one tailed test at the .0013 significance level. This might be kept in mind in designing the size and number of future studies to obtain the desired power and significance level.

Some Suggestions for Analyses and Design

1. This reviewer suggests that transplantation be analyzed more closely and some transplants regarded as success depending on patient condition, with death as failure. Whether the patient improved or deteriorated might be based on tests conducted immediately before transplant, or on the curve from tests conducted at regular intervals. The choice of test and regime would primarily be based on clinical considerations.

Statistical analysis of transplants considered successes might include not censoring the improved patient at the time of transplant, or the use of bivariate life statistics. The case of a patient deteriorating and receiving a transplant would be treated as death at the time of transplant.

2. The sponsor might conduct a new analysis, taking into account the apparent difference in transplant based censoring regimes. Such an analysis might be based on Kalbfleisch and Prentice, *The Statistical Analysis of Failure Time Data*, page 135 onward.

3. For future studies the computer readable data needs to be submitted in a better format, to make it easier to review. Such a formatting would be discussed with the statistical reviewer before submitting the data.

4. The exercise capacity endpoint might be improved by a similar, alternate endpoint, or by additional tests. An

alternate endpoint might be chosen on clinical considerations. Additional tests (based on clinical considerations) might clarify the situation when a patient walks only once or a short distance.

IV. Conclusion

In summary, there is a trend in mortality and exercise capacity in favor of treatment with FLOLAN for primary pulmonary hypertension. The trend is not shown to be statistically significant in well controlled studies. Additional work is needed to design and conduct future studies.

Ferrin Harrison

Ferrin Harrison, Ph.D.
Mathematical Statistician

This review consists of 12 pages of text, 9 pages of tables, and 3 pages of figures.

Concur: Dr. Huque *Huque 1/28/91*

Dr. Dubey *Dubey 1-30-91*

cc: orig. IND 9
HFD-180
HFD-180/ Dr. Fredd
HFD-180/ Dr. Triantis
HFD-180/ Mr. Hassall
HFD-713/ Dr. Dubey [File DRU 1.3.2 Treatment IND]
HFD-713/ Dr. Huque
HFD-713/ Dr. Ferrin Harrison
Chron.

FHarrison/4434594/SERB/harrison/ 1990

**Table 1a/FLOLAN:PPH
Studies of Primary Pulmonary Hypertension Submitted**

Study	Population	Study Type	Study State	Dosing	Randomized?
Burroughs Wellcome Co.					
35	Class I, II	Treatment	Aborted	Dose Ranging	Yes
36	Class III, IV	Treatment	Concluded	Dose Ranging	Yes
37	Survivors of 35, 36	Continuation	Continuing	Dose Ranging	No
NIH National Registry	All NYHA Classes	Observational	Concluded	no dosing	No
Papworth Hospital, UK	All NYHA Classes, awaiting transplant	Treatment	Concluded	Dose Ranging ¹	No

¹The dose ranging schemes differ slightly between studies. The dose is tailored to the needs of each patient during each period. No information was given on the actual doses given.

Table 1a/FLOLAN:PPH, continued

Study	Number of Centers	Maximum follow up time	First Enrollment	Last Enrollment	Last Followup
Burroughs Wellcome Co., US					
35	3	8 weeks \	>--- Apr 10 87	Jan 4 90	Feb 28 90
36	3	8 weeks /			
37	3	3 years	Aug 25 87	Feb 2 90	May 31 90
NIH National Registry, US	32	7 years	Jul 1 81	Sep 30 85	Aug 8 88
Papworth Hospital, UK	1	4 years	1982	(information not available)	1987

Table 1b/FLOLAN:PPH
Studies of Primary Pulmonary Hypertension Submitted

Study	Total Number of Patients								
	Total	on FLOLAN	no FLOLAN	On FLOLAN:			Not on FLOLAN:		
				Lived	Died	Transplant	Lived	Died	Transplant
Burroughs Wellcome Co. 35, 36	25	11	14	10	1	0	11	3	0
37	21 ²	18	3 ²	10	3	5	0	3 ²	0
NIH National Registry	194	none	194	none	none	none	76	106	12
B.W.Co, NIH on III,IV only	156	18	138	10	5 ³	3	44	86	8
Papworth Hospital, UK	44	25	19	9	13	3	7	9	3

In this table, "transplant" patients are those patients who received a transplant and survived the study.

²These three patients were classified as having declined entry into study 37. For the sake of having two arms in study 37, this reviewer prefers to regard these patients as declining to take drug but being in the study.

³One patient received a transplant and died, classified as a "death" here.

**Table 2/FLOLAN:PPH
Serious Adverse Events Associated with FLOLAN
or FLOLAN delivery**

Bacteremia	1 delivery
"Bolus Syndrome": chest pain, lightheaded	2 delivery
Central venous catheter clot	2 delivery
Dyspnea/light headedness	1 delivery
<u>Infection (at catheter site)</u>	4 delivery
<u>"Infusion Interruption Syndrome:" lightheaded, increased shortness of breath, malaise</u>	2 delivery
Pallor	1 delivery
Anorexia	1 drug
Dizziness and/or paresis (episodic)	1 drug
Edema	2 drug
<u>Fatigue/decreased strength</u>	4 drug, 1
drug/lack	
GI upset: diarrhea, abdominal pain,	2 drug
<u>constipation, vomiting, nausea</u>	
Hypotension	1 drug
<u>Hypoxia</u>	
<u>Interstitial Lung Disease: shortness of breath, cough, hypoxemia</u>	1 drug
<u>Pain: neck/shoulder, musculoskeletal</u>	1 drug, 1 delivery
<u>Photosensitivity: headache, pain, "color flashing" syndrome; skin blotchy, burned</u>	1 drug

"Catheter Flush Syndrome": hypotension, bradycardia, nausea, back pain, tinnitus, whole body reddening, left forearm numbness, blurred vision right eye, faintness: one life threatening and fatal reaction. Three "other" reactions, all reactions associated with the FLOLAN delivery system.

Progression of PPH vs Tachyphylaxis: fatigue, increased supplemental oxygen requirement, dyspnea on exertion, loss of consciousness, absence of respirations, cyanosis, seizure activity. One life threatening, nonfatal reaction and seven "other" reactions.

Key:

delivery: event was associated with the drug delivery system.
 drug: event was associated with the drug itself.
 lack: event was associated with lack of drug, FLOLAN.

Table 3/FLOLAN:PPH
Combined Burroughs Wellcome Co. Studies: Primary Endpoint Data

Patient Numbers	NYHA Class	Enrolled to drug	Transferred to drug	Time in Days from Enrollment to "event":		
				Transplant	Death	End of Follow Up
	4	0	0		2	2
	3	0	0		5	5
	4	0	0		49	49
	4	0	0		89	89
	2	0	0		266	266
	4	0	0		632	632
	3	0	1			147
	4	0	1			164
	3	0	1	355		546
	4	0	1			547
	3	0	1			553
	3	0	1			630
	3	0	1		659	659
	3	0	1			1081
	3	1	0		15	15
	3	1	0		372	372
	3	1	0			444
	3	1	0			450
	3	1	0	164	525	525
	4	1	0			532
	3	1	0			687
	3	1	0	391		751
	4	1	0	497		806
	2	1	0	822	855	855
	3	1	0		963	963

Key: NYHA classes are identified by their arabic numerals instead of roman numerals, 0=no, 1=yes. A blank for time means the event did not occur. The leftmost patient number is an index number for this table.

Number of Patients	Description
3	Enrolled to conventional therapy, died before week 8
3	Enrolled to and continued conventional therapy, died after week 8
8	Enrolled to conventional therapy, switched to FLOLAN
1	Had an embolic event during dose ranging, not enrolled
1	Enrolled to FLOLAN, died before week 8
10	Enrolled to and continued FLOLAN, survived week 8
0	Enrolled to FLOLAN, switched to conventional therapy
26	Total number of patients

Table 4/FLOLAN:PPH
Baseline Patient Characteristics and Conditions
National Registry and B.W.Co.

	Conventional Therapy NIH, n=194		Flolan B.W.Co, n=19	
<u>Demographic Variables</u>				
Mean Age	36		35	
Male vs. all	73/194	38%	7/19	37%
White vs. all	149/194	77%	19/19	100%
<u>Hemodynamic Variables</u>				
Cardiac index (l/min/m ²)	2.2		1.9	
Mixed venous oxygenation	56		59	
Pulmonary Arterial Pressure (mm Hg)	61		61	
Right Atrial Pressure (mm Hg)	10		9	
Pulmonary Vascular Resistance (Wood Units)	16		19	
<u>New York Heart Association (NYHA) Class</u>				
NYHA Class I	3	2%	0	0%
NYHA Class II	53	27%	1	5%
NYHA Class III	109	56%	14	74%
NYHA Class IV	29	15%	4	21%
NYHA Class III vs Classes III, IV	29/138	78%	4/18	78%

**Table 5/FLOLAN:PPH
Summary of results by Fatalities**

Study	Approximate Period	Flolan		No Flolan		Log rank 2 tail p-value
		#died, total	%	#died, total	%	
B.W.Co. 35,36	8 week	<u>1</u> 11	9.0%	<u>3</u> 14	21.4%	.392
B.W.Co. 37	3 year	<u>4</u> 18	16.7%	<u>3</u> 3	100.0%	Combined, ITT .018 ¹
NIH Registry	5 year	--	----	<u>106</u> 194	54.6%	-----
B.W.Co, NIH for NYHA classes III, IV	5 year	<u>4</u> 18	44.4% (2 year)	<u>65</u> 138	47.1% (2 year)	.116 (overall)
		<u>5</u> 18	27.8% (3 year)	<u>76</u> 138	55.0% (3 year)	
Papworth, U.K. for classes III, IV	4 year	<u>13</u> 25	52%	<u>9</u> 14	64.3%	.030

¹For the combination of studies 35, 36, 37, treating transplants and transfer to FLOLAN of 8 patients originally enrolled to conventional treatment as censoring. This p-value may have bias since it is driven by uncontrolled study 37. The reviewer obtained p=.022 by recalculation (also subject to bias.)

**Table 6/FLOLAN:PPH
Summary of results by Transplants**

Study	Approximate Period	<u>FLOLAN</u>		<u>No FLOLAN</u>	
		<u>#trans- plant</u> #total	, %	<u>#trans- plant</u> #total	, %
B.W.Co. 35,36	8 week	<u>0</u> 11	0%	<u>0</u> 14	0%
B.W.Co. 37	2 year	<u>5</u> 18	27.8%	<u>0</u> 3	0%
NIH Registry	5 year	--	-----	<u>12</u> 194	6.1%
B.W.Co, NIH for NYHA classes III, IV	5 year	<u>3</u> 18	16.7%	<u>1</u> 138	0.7%
	(2 year)			(2 year)	
		<u>3</u> 18	16.7%	<u>3</u> 138	2.2%
				(3 year)	
Papworth, U.K.	5 year	<u>3</u> 25	12%	<u>3</u> 19	15.8%

The purpose of this table is to show a difference in transplants, supporting the case for more detailed analysis of transplants.

Table 7/FLOLAN:PPH
Exercise Capacity in meters in 6 minutes, Studies 35, 36

Patient ID number	NYHA Class	Patients who took FLOLAN		
		Exercise Capacity Baseline	8 week	Differences
	II	320	447	127
	III	251.7	300	48.3
	III	194.4	280	85.6
	IV	110	408.6	298.6
	III	482	400	-82
	III	261.3	386	124.7
	III	109	0	-109
	III	458	462	4
	III	81	323	242
	IV	0	346	346
	III	316.8	428	111.2
Mean change				108.764

Patient ID number	NYHA Class	Patients who did not take FLOLAN		
		Exercise Capacity Baseline	8 week	Selected Differences
	IV	3.6	203	199.4
	IV	0	0	0
	IV	108.9	369.2	260.3
	III	342	450	108
	IV	315	1	-314
	III	353	371	18
	III	420	448	28
	III	78	106	28
	IV	63	0	-63
	II	264.6	300	35.4
	III	278	293.3	15.3
	III	476	408	-68
	IV	110	124	14
	III	244	0	-244
Mean Change				1.243

	Statistic:	2 tail p:
t-test, df=23	1.8116	.083
Wilcoxon rank-sum test	174	.096

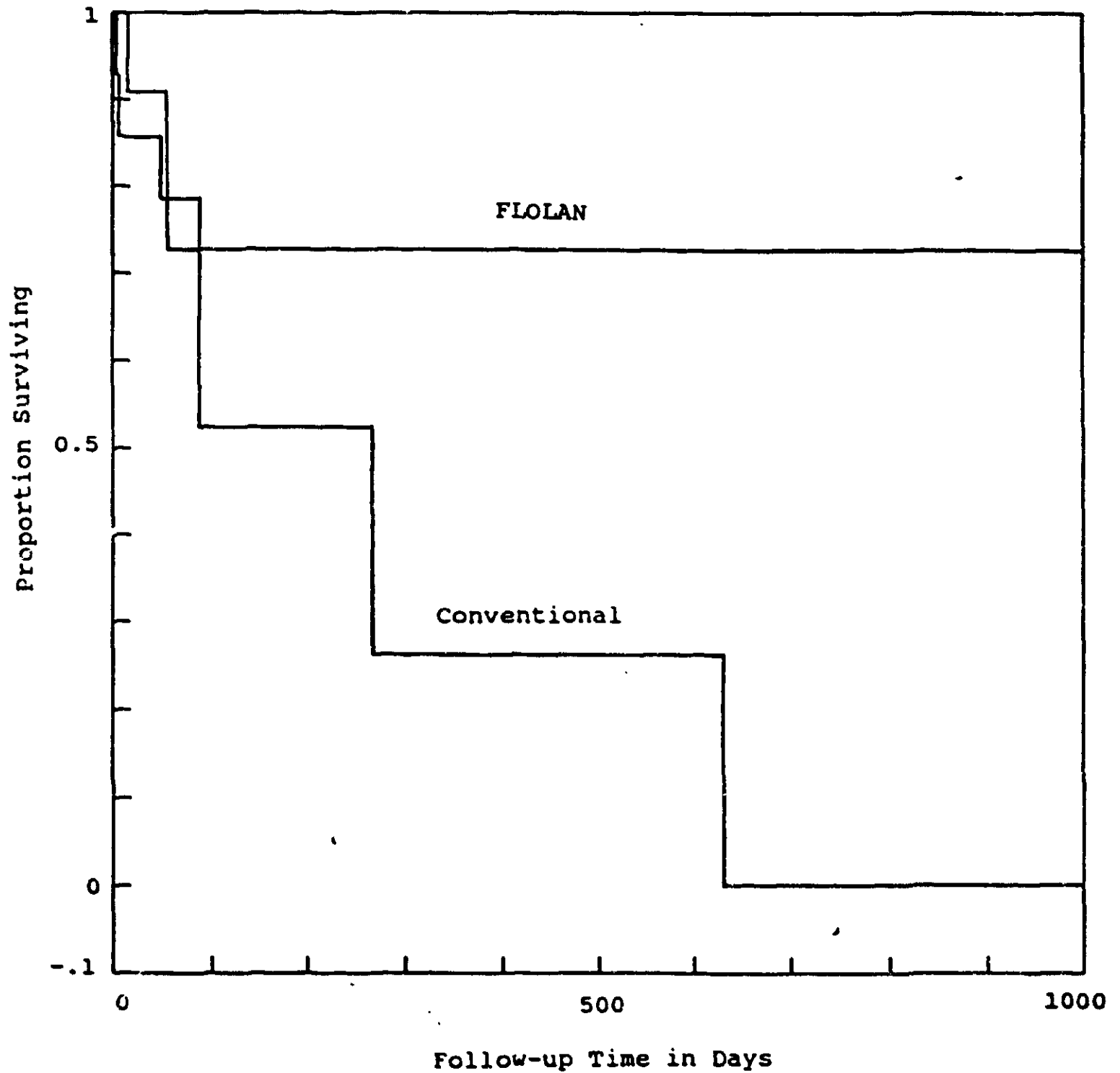
Both tests favor FLOLAN. The p-value for the Wilcoxon rank sum test was obtained by 76 million simulations, observing p=.09557. By the normal approximation to the Wilcoxon test statistic, two tailed p=.0897.

Table 8/FLOLAN:PPH
Papworth, UK data for the primary endpoint

Index, Patient Number	NYHA Class	FLOLAN Flag	Trans- plant	Death Flag	Time in days to	
					Transplant or other	Death or end of follow up
	4	0	0	1	5	5
	3	0	0	1	9	9
	3	0	0	1	15	15
	4	0	0	1	45	45
	3	0	0	1	76	76
	3	0	0	1	100	100
	4	0	0	0	136	136
	2	0	0	0	163	163
	3	0	0	1	195	195
	2	0	0	0	198	198
	3	0	0	1	245	245
	3	0	0	0	261	261
	4	0	1	0	359	380
	2	0	0	0	394	394
	4	0	1	0	75	491
	3	0	0	1	757	757
	4	0	1	0	242	790
	2	0	0	0	896	896
	2	0	0	0	1031	1031
	4	1	0	1	12	12
	4	1	0	1	14	14
	4	1	0	1	31	31
	3	1	0	1	144	144
	3	1	0	0	191	191
	3	1	0	0	232	232
	3	1	0	0	254	254
	4	1	0	1	264	264
	3	1	0	1	279	279
	4	1	1	1	267	306
	3	1	0	0	387	387
	3	1	1	0	100	408
	4	1	0	1	449	449
	4	1	1	1	398	451
	3	1	0	0	510	510
	4	1	0	1	585	585
	3	1	0	0	678	678
	3	1	0	0	682	682
	4	1	0	1	684	684
	4	1	1	0	445	757
	3	1	0	0	854	854
	3	1	1	0	882	919
	4	1	1	1	693	1106
	3	1	0	0	1378	1378
	4	1	1	1	518	1422

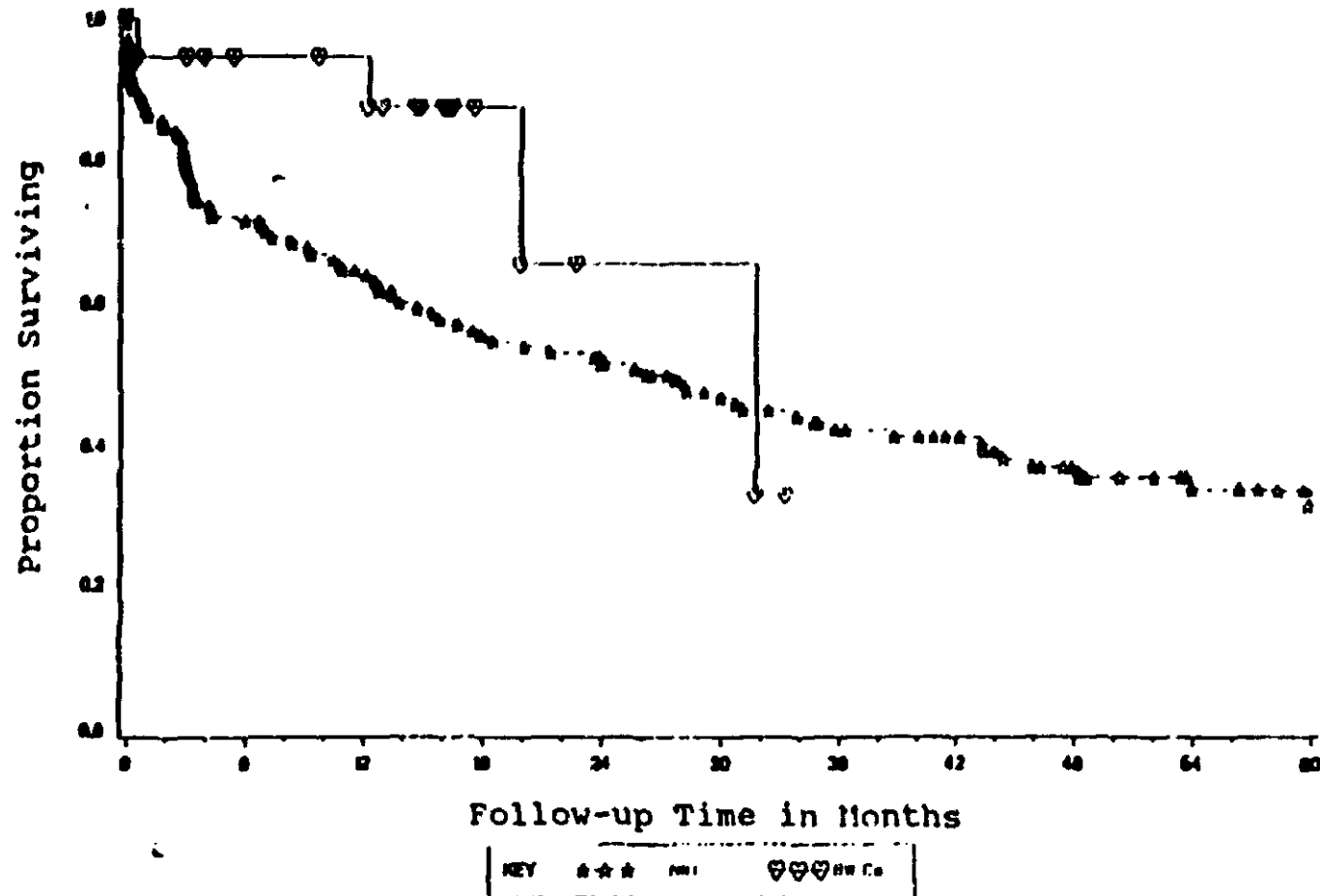
Key: NYHA classes are identified by their arabic numerals instead of roman numerals. 0=no, 1=yes.

Figure 1/FLOLAN:PPH
Conventional Treatment versus FLOLAN (B.W.Co.) Survival Curve



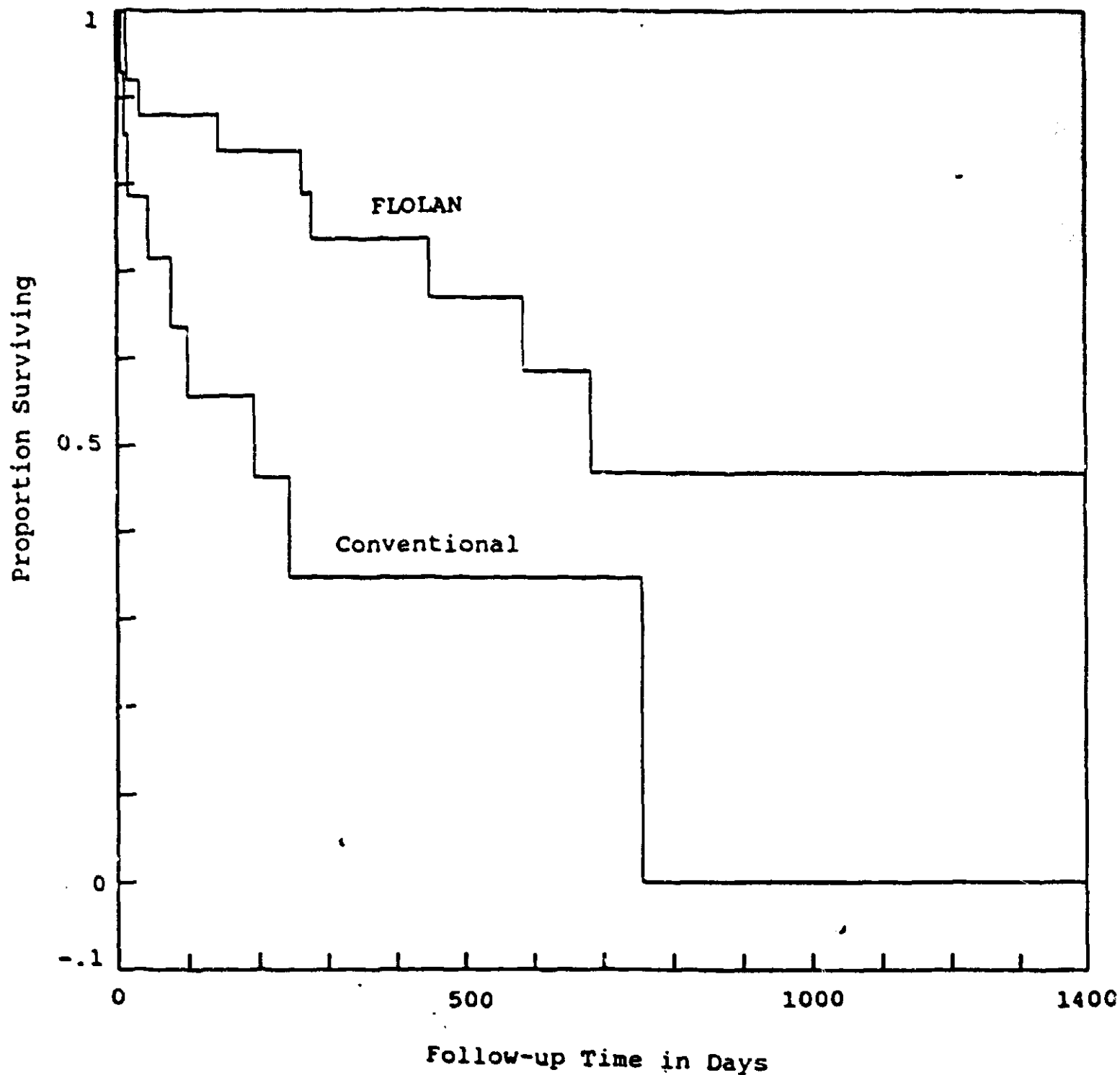
Transplants and transfers from conventional therapy to FLOLAN are censored
Follow-up times greater than 1000 days are not shown

Figure 2/FLOLAN:PPH
 National Registry (NIH) versus FLOLAN (B.W.Co.) Survival Curve
 New York Heart Association (NYHA) Class III, IV Patients Only



Transplants are censored
 Follow-up times greater than 60 months are not shown

Figure 3/FLOLAN:PPH
Conventional therapy versus FLOLAN (Papworth, UK) Survival Curve



Transplants are censored
Only New York Heart Association class III, IV patients are used
Follow-up times greater than 1400 days are not shown

U/11

Statistical Review and Evaluation
(Part II)

IND #:

Date: MAR 13 1995

Applicant: Burroughs Wellcome Co.

Name of Drug: Flolan (Epoprostenol Sodium) for Injection

Documents Reviewed:

NDA Submission Amendment "Response to FDA Letter Dated February 1, 1994", Date of Document, Feb. 17, 1994.

Introduction

Burroughs Wellcome Co. has provided some statistical analyses in response to the FDA comments contained in the February 1, 1994 letter. The reviewing chemist, Dr. Shaw, HFD-180, has requested the Division of Biometrics to perform a statistical review and evaluation of the sponsor's statistical analyses.

Sponsor's Designs and Analyses

The following are the sponsor's responses to FDA comments:

Comment: You have provided no statistical analysis to support the claim that the 1.5 mg strength behaves the same as the 0.5 mg strength. Please provide the analysis of variance to demonstrate that all three 0.5 mg batches have the same slope. Then provide the analysis to show that the 1.5 mg strength batch has the same slope.

Sponsor's Response: The statistical procedures described in the FDA Guideline (February, 1987) were applied to the stability data of epoprostenol assay, moisture content, 3AU76 assay, and PH.

The stability data included three batches of 0.5 mg studies (16249, 16250, and 16252) and one batch of 1.5 mg study (16486). For each test study (epoprostenol assay, moisture content, 3AU76 assay, and PH), the sponsor tested the similarities in slopes among four batches. The test results showed that similarities in slope existed for epoprostenol assay, but not for pH, moisture, and 3AU76 assay. Figures 1-4 summarized the above results. Figure 5 suggests that all the 0.5 mg strength studies have similar slopes. Figure 6 suggests that the strengths between 0.5 mg studies and 1.5 mg study do not differ with respect to epoprostenol assay over 36 months. Figure 7 shows that there is a significant difference in slopes in 3AU76 assay in the 0.5 mg strength study. Figure 8 suggests that the strengths between 0.5 mg studies and 1.5 mg study do not differ with respect to 3AU76 assay over 36 months.

With the exception of pH, which had a shortest estimated dating period of 55 months, all other stability tests had estimated dating

periods greater than 60 months.

Comment: The differences between the 24 month and zero time points for the data shown on page 3 and 4 are significantly different between the two strengths, indicating a more rapid decay for the 1.5 mg strength.

Sponsor's Response: There are four pairs of initial and repass data points for the epoprostenol assay and 3AU76 assay. Each pair of the data points, initial and repass, could not be compared for similarity of slope statistically, since there are only two data points available from each batch. All 0.5 mg data points were pooled and compared to the pooled 1.5 mg data points for similarity in stability characteristics. Based on the analyses, the sponsor concluded that "the data suggests that the 0.5 and 1.5 mg strengths had coincidental least squares fit lines ($p > 0.25$). The statistically insignificant ($p > 0.05$) rate of coincidental degradation was estimated to be -0.06% per month or an average change of -2.2% over 36 months based on the epoprostenol data." Figures 9 and 10 summarize the above results.

Reviewer's Comments and Analyses

(1) With respect to the sponsor's response to the first comment, the reviewer applied two methods to analyze the data. First, the data of epoprostenol assay and 3AU76 assay at 0.5 mg and 1.5 mg were fitted to the following model.

$$Y_{ij} = \mu + \text{Strength}_i + \text{Month}_j + \text{Strength}_i * \text{Month}_j + e_{ijk}$$

where Y_{ij} is the observed epoprostenol assay or 3AU76 assay of the i th strength and the j th month. There are two different strengths (0.5mg and 1.5mg) and three to seven different months (0, 3, 6, 9, 12, 24, and 32) in this model.

For both epoprostenol assay and 3AU76 assay, the results of analysis showed that there is no significant difference in slope between 0.5 mg and 1.5 mg strengths. However, there is a significant difference in intercepts ($p = 0.0001$) between 0.5 mg and 1.5 mg strengths. Tables 1 and 2 revealed the results of epoprostenol assay and 3AU76 assay, respectively. Noted that there is only one batch at the 1.5 mg strength studied. The test may not have enough power to detect possible true differences.

Second, the reviewer also applied the statistical procedures described in the FDA Guideline (February, 1987) to the stability data of epoprostenol assay. Data of three batches at 0.5 mg were analyzed first, then the combined data of 0.5 mg and 1.5 mg studies were used in the analyses. The specification limits for assay of epoprostenol were 90% to 110% of label claim. The statistical analyses and results are as follows:

(a) The assay of epoprostenol at 0.5 mg strength.

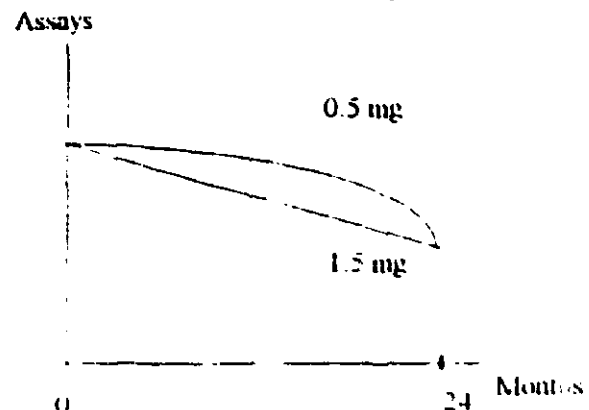
Table 3 presents the data of studies 16249, 16250, and 16252 and the analysis of variance table of the data. Based on the p-values of the statistical tests for selection of degradation curve models, the models of separate intercepts and common slope were selected. The 95% lower confidence bounds for the three individual regression lines were calculated. Noted that the slope of three regression lines is -0.004546.

(b) The assay of epoprostenol at 0.5 mg and 1.5 mg strengths. .

Table 4 presents the data of studies 16249, 16250, 16252 and 16486 and the analysis of variance table of the data. Based on the p-values of the statistical tests for selection of degradation curve models, the models of separate intercepts and common slope were selected. The 95% upper confidence bounds for the four individual regression lines were calculated. Noted that the slope of four regression lines is 0.00225718.

Based on the above analyses, the reviewer agrees with the sponsor's conclusions that all the 0.5 mg strength studies have similar slopes and the combined studies of 0.5 mg and 1.5 mg strengths have similar slopes. However, there is a significant difference in intercepts ($p = 0.0001$) between the 1.5 mg studies and the 0.5 mg studies. The slope of the 0.5 mg studies was changed from a negative value (-0.004546) to a positive value (0.00225718) when data of 1.5 mg and 0.5 mg studies were compared. As mentioned previously, there is only one batch at 1.5 mg strength studied. The test may not have enough power to detect possible true differences.

(2) With respect to the sponsor's response to the second comment, the reviewer did not agree with the method the sponsor used. Since there are only two time points available from each strength, there are not enough data to test the similarity in stability characteristics between 0.5 mg and 1.5 mg strengths. The following graph shows that the stability characteristics between 0.5 mg and 1.5 mg strengths are different, however, the assays of 0.5 mg and 1.5 mg strengths at time 0 and 24 months are all the same.



The reviewer has compared the means of loss of activity between 0.5 mg and 1.5 mg strengths. The t statistics based on the assumption that the variances of the two strengths are equal and the Wilcoxon rank-sum test (nonparametric test) were used in the comparison. The results of the analyses showed that there is a significant difference in loss of activity between 0.5 and 1.5 mg strengths in the t test ($p = 0.0147$) but not in the Wilcoxon rank-sum test ($p = 0.0606$). It is noted that there are only four pairs of assay data for each strength, and that the power of the test may not be enough to detect true differences.

In summary, with only four pairs of assay data for each product strength, there is not enough information to evaluate the similarity in stability characteristics between 0.5 and 1.5 mg strengths.

Summary

Burroughs Wellcome Co. has provided some statistical analyses in response to the FDA comments contained in the February 1, 1994 letter.

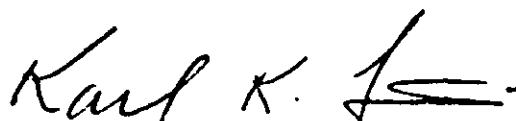
With respect to the sponsor's response to the first comment, the reviewer applied two methods to analyze the data. Based on the results of the analyses, the reviewer agrees with the sponsor's conclusions that all the 0.5 mg strength studies have similar slopes and the combined studies of 0.5 mg and 1.5 mg strengths have similar slopes. However, there is a significant difference in intercepts ($p = 0.0001$) between the 1.5 mg studies and the 0.5 mg studies. The slope of the 0.5 mg studies was changed from a negative value (-0.004546) to a positive value (0.00225718) when data of 1.5 mg and 0.5 mg studies were compared. It is noted that there is only one batch at 1.5 mg strength studied and that the power of comparison may not be enough to detect possible true differences.

With respect to the sponsor's response to the second comment, the reviewer does not agree with the method the sponsor used. With only four pairs of assay data for each product strength, there is not enough information to evaluate the similarity in stability characteristics between 0.5 and 1.5 mg strengths.



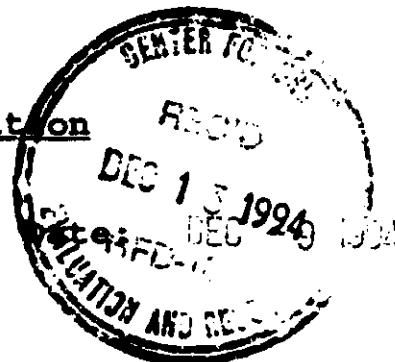
Daphne Lin, Ph.D.
Mathematical Statistician

Concur:

 3/10/95
Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original IND
HFD-180/Dr. Fredd
HFD-180/Dr. Gibbs
HFD-180/Dr. A. Shaw
HFD-180/Ms. K. Oliver
HFD-710/Chron
HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-715/Chron (SARB)
HFD-715/DRU 2.1.1, Flolan, Burroughs Wellcome Co.

Statistical Review and Evaluation



NDA #: 20-444

Applicant: Burroughs Wellcome Co.

Name of Drug: Flolan (Epoprostenol Sodium) for Injection

Documents Reviewed:

NDA Submission, Amendment Chemistry, Manufacturing, and Controls, "Amendment-Updated Stability Data", Date of Document, Sept. 19, 1994.

Introduction

Burroughs Wellcome Co. has submitted eight batches of updated stability data of Flolan for Injection, 0.5 mg and 1.5 mg epoprostenol per vial, as committed in the April 20, 1994 telephone conference and subsequent submission dated April 29, 1994. The reviewing chemist, Dr. Shaw, HFD-180, has requested the Division of Biometrics to perform a statistical review and evaluation of the sponsor's stability data.

Sponsor's Designs and Analyses

In support of both strengths of Flolan for Injection, three batches of the 0.5 mg potency and five batches of the 1.5 mg potency were placed on stability study. Noted that batch numbers AM3415G (0.5mg), AM3558H (0.5mg), AM3106 (1.5mg), and AM3142R (1.5mg) were tested according to the stability protocol 1 of April 29, 1994 submission. Batch numbers 3T2781 (1.5 mg) and 4M2796 (1.5 mg) were tested according to the stability protocol 2 of April 29 1994 submission. Batch numbers A2883B (0.5 mg) and A3077A (1.5 mg) were tested according to the development protocol of original NDA, Vol. 1.3, pages 505 and 521. Appendix 1 listed the stability protocol 1, stability protocol 2, and the development protocol. The test methods used in this study included appearance, assay for epoprostenol, assay for related substances, total related substances, pH, sterility and bacterial endotoxins. Tables 1 and 2 listed the detailed information of dosage strengths, manufacturing sites, packaging, and test conditions for these batches.

No statistical analysis was performed on these updated stability data for Flolan injection. Based on the actual observed stability data, the sponsor indicated that "both the Flolan (epoprostenol sodium) for Injection, 0.5 mg and 1.5 mg epoprostenol per vial, formulations demonstrated suitable stability to date. No adverse effects on stability were observed."

Reviewer's Analyses

The statistical procedures described in the FDA Guideline (February,

1987) were applied to the stability data provided by the sponsor. The reviewer analyzed the assays for epoprostenol of 0.5 mg and 1.5 mg stored at 25°C. Data of three batches for 0.5 mg and five batches for 1.5 mg formulations were used in the analyses. The specification limits for assay of epoprostenol were 90% to 110% of label claim. The statistical analyses and results are as follows:

a. Statistical analyses

(1) The assay of epoprostenol of 0.5 mg stored at 25°C.

Table 3 presents the data of batches AM3415G, AM3558H, and A2883B stored at 25°C and the analysis of variance table of the data. Based on the p-values of the statistical tests for selection of degradation curve models, the models of separate intercepts and common slope were selected. The 95% upper confidence bounds for the three individual regression lines were calculated.

(2) The assay of epoprostenol of 1.5 mg stored at 25°C.

Table 4 presents the data of batches 3T2781, 4M2796, AM3106, AM3142R, and A3077A stored at 25°C and the analysis of variance table of the data. Based on the p-values of the statistical tests for selection of degradation curve models, the models of separate intercepts and separate slopes were selected. The 95% upper and lower confidence bounds for the five individual regression lines were calculated.

b. Results of analyses

Based on the above analyses, we found that the assay for epoprostenol of 0.5 mg was stable after 36 months storage at 25°C. The assay for epoprostenol of 1.5 mg was stable after 8 months storage at 25°C. However, for assay of epoprostenol of 0.5 mg, two batches had sample assay data only up to 3 months, one batch had sample assay data up to 9 months. Hence, the reviewer recommends that a 15 month expiry date be granted for Flolan for injection, 0.5 mg, and a 8 month expiry date for Flolan for injection, 1.5 mg stored at 25°C.

Noted that the above estimated expiration dating period was based on the data extrapolation beyond the range of storage time actually observed.

Summary

Burroughs Wellcome Co. has submitted eight batches of updated stability data of Flolan for Injection, 0.5 mg and 1.5 mg epoprostenol per vial, as committed in the April 20, 1994 telephone conference and subsequent submission dated April 29, 1994.

The reviewer analyzed the assays for epoprostenol of 0.5 mg and 1.5 mg stored at 25°C. Data of three batches for 0.5 mg and five batches for 1.5 mg formulations were used in the analyses. The statistical procedures described in the FDA Guideline (February, 1987) were applied to the stability data. The specification limits for assay of

epoprostenol were 90% to 110% of label claim.

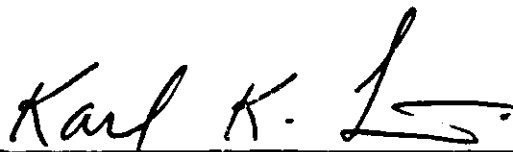
The above analyses results showed that the assay for epoprostenol of 0.5 mg was stable after 36 months storage at 25°C. The assay for epoprostenol of 1.5 mg was stable after 8 months storage at 25°C. However, for assay of epoprostenol of 0.5 mg, two batches had sample assay data only up to 3 months, one batch had sample assay data up to 9 months. Hence, the reviewer recommends that a 15 month expiry date be granted for Flolan for injection, 0.5 mg, and a 8 month expiry date for Flolan for injection, 1.5 mg stored at 25°C.

Noted that the above estimated expiration dating period was based on the data extrapolation beyond the range of storage time actually observed.



Daphne Lin, Ph.D.
Mathematical Statistician

Concur:

 12/08/94

Karl K. Lin, Ph.D., Group Leader, SARB

cc: Original NDA 20-444
HFD-180/Dr. Fredd
HFD-180/Dr. Gibbs
HFD-180/Dr. A. Shaw
HFD-180/Ms. K. Oliver
HFD-710/Chron
HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-715/Chron (SARB)
HFD-715/DRU 2.1.1, Flolan, Burroughs Wellcome Co.

Bio

FEB 10 1995

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NDA: 20-444

SUBMISSION DATE: Feb. 28, 1994
Apr. 22, 1994

Epoprostenol Sodium for Injection (Flolan®)
0.5 mg and 1.5 mg, Freeze-dried powder
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

REVIEWER: Hae-Ryun Choi, Ph.D.

TYPE OF SUBMISSION: Original NME

PRIORITY: 1 P



REVIEW OF REQUEST FOR WAIVER OF THE HUMAN PHARMACOKINETICS AND BIOAVAILABILITY REQUIREMENTS

SYNOPSIS:

NDA 20-444 for FLOLAN (epoprostenol sodium) for Injection was submitted by Burroughs Wellcome Co. on February 28, 1994. Epoprostenol is an endogenous prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation. FLOLAN for Injection is indicated in adults and children for the long-term intravenous treatment of primary pulmonary hypertension (PPH) in NYHA Class III and Class IV patients.

The sponsor has requested a waiver of the human pharmacokinetics and bioavailability requirements for this application.

RECOMMENDATION:

Please convey the General Comments and Labelling Comments, as appropriate, to the sponsor.

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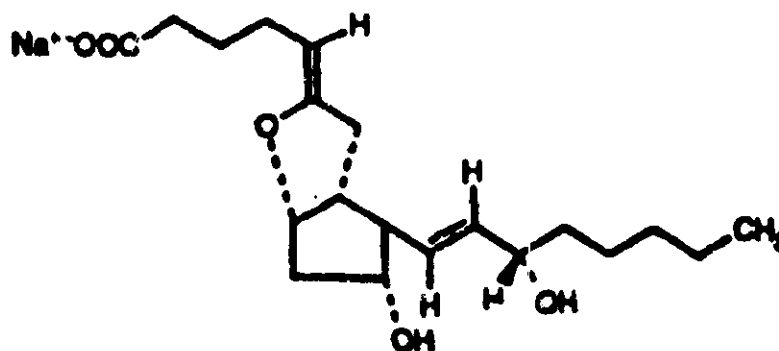
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BACKGROUND:

Epoprostenol, a metabolite of arachidonic acid, is an endogenous prostaglandin with vasodilatory activity and inhibitory activity of platelet aggregation. It is a potent but extremely labile compound. FLOLAN for Injection is indicated in adults and children for the long-term intravenous treatment of primary pulmonary hypertension (PPH) in NYHA Class III and Class IV patients to improve survival, exercise capacity, and aspects of quality of life. FLOLAN is proposed to be administered in combination with standard therapy (including anticoagulants, digitalis glycosides, oral vasodilators, diuretics and oxygen) to PPH patients. FLOLAN is designated under 21 CFR, Part 312 Subpart E as a drug intended to treat life threatening and severely-debilitating illness, and also an orphan drug for this indication.

Epoprostenol is (5Z,9α,11α,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid with the following structure:



Epoprostenol sodium is a white to off-white powder with a molecular weight of 374.45 and a molecular formula of $C_{20}H_{31}NaO_5$. It is readily soluble in water and ethanol and sparingly soluble in acetonitrile. Epoprostenol is unstable in acid, and is somewhat labile at room temperature. However, it can be stabilized as its sodium salt at -20°C for greater than 6 months.

The sponsor originally submitted

an NDA for FLOLAN for Injection (NDA
This NDA was subsequently

withdrawn and resubmitted for hemodialysis indication only. However, the application was not approved.

FLOLAN has been submitted in 16 European countries and New Zealand, Singapore and Cuba, for marketing approval as a heparin substitute for renal hemodialysis in patients who have an increased risk of bleeding. Applications have been approved in 8 countries, 2 applications were withdrawn, 2 applications were rejected, and others are pending.

FORMULATION:

1. Strengths: 0.5 mg and 1.5 mg
2. Dosage forms: freeze-dried powder for injection
3. Market formulation: Each vial contains 0.5 mg or 1.5 mg epoprostenol as the sodium salt.

	mg Per Vial	
Epoprostenol as the sodium salt ^a	0.531	1.593
Glycine, EP/USP		
Sodium Chloride, EP/USP		

Sodium Hydroxide Solution
Water for Injection, EP/USP^b

g

g

^a These are typical values. Potency is expressed in terms of anhydrous active moiety. The actual weight of epoprostenol sodium is calculated from a lot specific factor.

^b Removed during manufacture.

4. FLOLAN must be reconstituted with Sterile Diluent for Flolan. Sterile Diluent for Flolan is supplied in 50 mL glass vials containing 94 mg glycine, 73.5 mg sodium chloride, sodium hydroxide (added to adjust pH of 10.2-10.8), and water for injection, USP.

5. The formulation used in clinical trials was formulated with % overage of (epoprostenol, mg epoprostenol). Its quantitative composition was identical to the formulation for marketing except epoprostenol.

DOSAGE AND ADMINISTRATION:

FLOLAN is proposed to be delivered chronically through a permanent indwelling central venous catheter using a portable infusion pump.

The initial chronic infusion rate of FLOLAN for Injection is determined by acute dose-ranging with increasing infusion rates. During dose-ranging, infusions are initiated at ng/kg/min and increased at increments of ng/kg/min after minutes at each infusion rate until dose-limiting symptoms occur. During acute dose ranging in clinical trials, the mean ($\pm$ S.E.M.) maximal infusion rates which did not elicit dose-limiting pharmacologic effects in adult PPH patients and children (less than 16 years old) were and ng/kg/min, respectively.

During chronic use, infusion is supposed to be initiated at ng/kg/min less than the maximum-tolerated rate determined during acute dose-ranging. During clinical trials, the mean initial chronic infusion rate for adults was 5 ng/kg/min. The mean chronic infusion rates for children were only slightly higher than for adults.

Multivariate analyses of variance were used to test demographic, disease, concomitant medication effects on epoprostenol dosing. Only age and gender were predictive of the maximum infusion rate achieved during the initial acute dose-ranging procedure. But none of the factors were predictive of chronic infusion rate at the end of controlled studies.

PHARMACOKINETICS OF EPOPROSTENOL:

The firm claimed that no definitive information about the pharmacokinetics of epoprostenol in human is available because of the lack of a sensitive, specific, and precise analytical method for epoprostenol in biological fluids.

Most of the information in this section were obtained from the literature. The appendix of this review contains the references cited in this section.

I. ANIMAL PHARMACOKINETICS:

The ADME of epoprostenol in animals has been extensively studied. Many investigators have assayed total radioactivity, 6-keto PGF1-alpha, and other metabolites of epoprostenol as surrogate indicators of the concentrations of epoprostenol in biological samples. Such studies, performed in rats, cats, and dogs, have indicated that epoprostenol is rapidly and extensively metabolized, and that elimination is rapid.

Studies performed in rats, dogs, and monkeys in vivo indicate that epoprostenol is converted initially either to the 6-keto-PGF1-alpha or enzymatically to a 13,14-dihydro-6,15-diketo PGF1-alpha, with beta and omega or omega-1 oxidation reactions occurring as subsequent steps in a complicated metabolic pathway.

Rats: After i.v. or s.c. administration, 33%-49% of the radiolabel was excreted in urine, and 35%-61% was excreted in feces. Rapid and extensive biliary excretion of drug-related material has been demonstrated in rats.

Dogs: All of the radiolabel were excreted in urine.

Monkeys: At least 45% of the radiolabel was excreted in urine (recovery in feces was not determined).

Rabbits: After IV bolus administration of radiolabelled epoprostenol to rabbits, epoprostenol showed two compartment pharmacokinetics, with a very high clearance (mL/min/kg), small volume of distribution (mL/kg), and short half-life (min). During IV infusion, steady-state plasma concentrations were achieved after minutes of infusion and increased proportionally with increasing infusion rates (2).

II. HUMAN PHARMACOKINETICS/PHARMACODYNAMICS:

Epoprostenol degrades quickly and spontaneously in blood or plasma at physiological pH to two primary metabolites; 6-keto-PGF₁-alpha (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-PGF₁-alpha (enzymatically formed). These two metabolites have pharmacological activity which is orders of magnitude less than epoprostenol using animal tests. The in-vitro half-lives of epoprostenol in human blood and plasma at °C are about minutes, respectively.

Metabolism: Epoprostenol is stable at pH 10 or greater. However, it is rapidly hydrolyzed at physiological pH to a fold less potent compound, 6-keto-PGF₁-alpha. Epoprostenol undergoes enzymatic reactions commonly seen with prostaglandins in general: dehydrogenation of the C-15 hydroxyl group, reduction of the 13,14 double bond, beta oxidation, and omega or omega-1 oxidation.

Several studies identified the major metabolites of epoprostenol in human in plasma or urine. The major plasma metabolite was 6-keto-PGF₁α; the major urinary metabolite was 2,3-dinor-6-keto-PGF₁α.

After a 10-hour intravenous infusion of tritiated epoprostenol at ng/kg/min to 4 healthy male subjects, 42% of the radioactivity recovered from plasma was 6-keto-PGF₁α; two other metabolites, 2,3-dinor-6,15-diketo-13,14-dihydro-PGF₁α and its 20-carboxylated analogue, constituted 17% of radioactivity recovered.

After 24-hour infusion of radiolabelled epoprostenol at ng/kg/min to 3 healthy male subjects, 82% and 4% were recovered in urine and feces within 7 days, respectively (1). At least 16 metabolites were found in urine and 10 metabolites were characterized. All identified metabolites retained the 6-keto-PGF structure characteristic of epoprostenol hydrolysis. The major urinary metabolites (mean values expressed as % of administered dose) were 2,3-dinor-6-keto-PGF₁α (8.3%), 2,3-dinor-6,15-diketo-13,14-dihydro-PGF₁α (6.6%), 6-keto-PGF₁α (5.9%), and 6,15-diketo-13,14-dihydro-PGF₁α (2.5%).

Elimination: After a 24-hour intravenous infusion of tritiated epoprostenol at ng/kg/min to 3 healthy male volunteers, the total radioactivity in plasma continued to increase throughout the entire infusion period (1). After discontinuation, total plasma radioactivity declined in a biphasic manner with half-lives of 53 and 246 minutes.

Effect on Hepatic Blood Flow: During epoprostenol infusion at 5 ng/kg/min to 8 healthy volunteers, apparent liver blood flow (as measured by indocyanine green clearance 10 minutes after start of epoprostenol or placebo infusion) increased by 41% on average.

Enzyme Induction: Preliminary study results showed that epoprostenol might induce hepatic microsomal enzyme activity. A decrease in half-life of antipyrine (a model compound used to assess the cytochrome P-450 activity) was noted on Day 2 during 5 ng/kg/min infusions of epoprostenol, which returned toward baseline levels after termination of the infusions.

Protein Binding: The protein binding of epoprostenol is about 55% in a 4% human serum albumin solution and 52% in human plasma by using ultrafiltration technique.

Pharmacodynamics: Hemodynamic changes due to epoprostenol (e.g., increased heart rate, facial flushing) returned to baseline within 10 minutes of termination of 60-minute infusions at 1 to 16 ng/kg/min.

III. ANALYTICAL METHODS:

Various analytical methods have been tried for the measurements of epoprostenol in systemic circulation. These included the bioassay techniques, GC/MS methods, and HPLC/UV methods, and radioimmunoassay methods. However, no assay is successfully sensitive, specific and precise to quantify epoprostenol in plasma.

Chromatographic methods for epoprostenol with concentrations in the pg/ml range might be restricted to GC/MS or LC/MS methods. Because of instability of epoprostenol at high temperature used in GC/MS, LC/MS might be the preferred technique of measuring epoprostenol. However, information regarding LC/MS method is not available.

For the measurement of metabolites, the capillary-column GC/MS/NICI (negative-ion chemical-ionization) method appears to be the most sensitive and specific to quantify the 6-keto-PGF1-alpha in plasma.

One investigation which used GC/MS/NICI to quantify 6-keto-PGF1-alpha found plasma concentrations of _____ ng/ml for this metabolite in 4 healthy volunteers after _____ minute infusions of epoprostenol at _____ ng/kg/min.

REQUEST FOR WAIVER OF IN VIVO BIOAVAILABILITY AND PHARMACOKINETIC STUDIES:

The sponsor requests a waiver of the human pharmacokinetics and bioavailability requirements based on the following seven arguments:

1. The active component of FLOLAN (epoprostenol sodium) for Injection, epoprostenol, is an endogenous substance undergoing continuous biosynthesis and extremely rapid catabolism.

2. FLOLAN for injection is administered intravenously after reconstitution; therefore, bioavailability is not an issue.
3. A sensitive, specific, and precise analytical method for the determination of epoprostenol plasma concentrations after treatment with FLOLAN for Injection does not exist, making conventional pharmacokinetic analyses not feasible.
4. The possible conduct of a pharmacokinetic study using radiolabelled epoprostenol is not appropriate due to the size of the required dose and the possibility of tissue incorporation of radioactivity, given the endogenous nature of the compound.
5. The hemodynamic effects of FLOLAN for Injection (e.g., increased heart rate, facial flushing) end within minutes of terminating the infusion, suggesting that epoprostenol has an extremely short half-life and a rapid clearance.
6. Because of the apparently rapid clearance of the compound, continuous infusion is required in order to maintain effective concentrations in patients; therefore, accumulation of epoprostenol is not a concern.
7. In the clinical sections of the New Drug Application, efficacy has been demonstrated in patients with primary pulmonary hypertension, a relatively rare and fatal disease with no approved medical therapy, in two well-controlled trials. Safety has also been shown in over 8000 patients.

GENERAL COMMENTS:

1. The Division of Biopharmaceutics requests that the sponsor submit raw data for the pharmacodynamic response with regards to platelet aggregation, obtained from the clinical studies (Study # 1059, 1066, 1067, 1099, and BW 01) for further review.
2. The arguments (see 'Request for waiver.....studies') presented by the sponsor for a request of waiver for the human pharmacokinetics and bioavailability requirements for FLOLAN for Injection are not convincing for the following reason:
 - a. Although epoprostenol is an endogenous compound, there is no data which support that the endogenous levels are so high and/or variable that they would interfere with the assay or interpretation of the data.
 - b. While demonstration of bioavailability is not needed for a drug given intravenously, pharmacokinetic characterization of the drug is necessary, as outlined in 21 CFR 314.50 (d) (3), for the approval of an NDA.

c. Even if accumulation is not thought to be an issue for a drug with short half-life and rapid clearance, the pharmacokinetics of the drug and/or its metabolites still need to be characterized, if possible.

d. The conduct of radiolabelled studies in human is feasible since there are such studies reported in the literature.

3. In view of the difficulties in developing a sensitive, specific and precise analytical method for measurement of epoprostenol concentration in plasma, the Division of Biopharmaceutics, at the present time, recommends that a deferment be granted for the Human Pharmacokinetics and Bioavailability Section of NDA 20-444, FLOLAN for Injection, under the auspices of 21 CFR 320.22(e). However, the Division requests that the sponsor continue its endeavors to develop an appropriate assay for epoprostenol. Upon development of adequate assay and sampling methodologies, the firm is required to submit sufficient data that characterize the pharmacokinetic disposition of epoprostenol after intravenous administration. If further attempts to characterize the pharmacokinetics of epoprostenol is unfruitful, measurement of a metabolite or metabolites that adequately reflect the parent drug should be investigated.

LABELLING COMMENTS:

The statement in the labelling
should be replaced by the following:

'the in vitro functional half-lives of epoprostenol in plasma, based on.....respectively'.

The statement in the labelling
be replaced by the following: should

'At this time, no assay is sufficiently sensitive.....epoprostenol'.

Hae-Ryun Choi 02/09/95
Hae-Ryun Choi, Ph.D.
Division of Biopharmaceutics

pharm day on 11/01/94 (Collins, Ludden, Malinowski, M. Chen, Fleischer, Gillespie, and Choi)

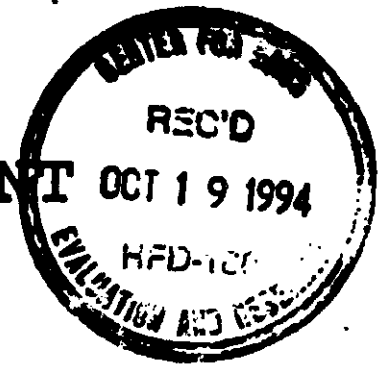
initialed by Mei-Ling Chen, Ph.D. MLC 2/9/95

NDA 20-444, HFD 180, HFD 426 (Fleischer), HFD 427 (M. Chen, Choi), HFD 340 swanathan), Chron, Drug, FOI (HFD 19), Reviewer.

E.A. +

Fonsi

01/152



ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

**FLOLAN[®]
(Epoprostenol Sodium)**

FOR INJECTION

NDA 20-444

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION HFD-180

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-444

FLOLAN®
(Epoprostenol Sodium)

For Injection

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for FLOLAN®, Burroughs Wellcome Co. has prepared an abbreviated environmental assessment under 21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Epoprostenol Sodium is a synthetically produced drug substance which will be administered parenterally for the treatment of primary pulmonary hypertension. The drug substance is also a naturally occurring prostaglandin which has been found present in multiple mammalian species. FLOLAN® has been granted orphan and Subpart E status by the FDA and its use will be limited to a small patient population. The drug substance will be manufactured at _____ the drug product will be manufactured by The Wellcome Foundation Limited (Temple Hill; Dartford, Kent, United Kingdom) and the Sterile Diluent for FLOLAN® will be manufactured at Burroughs Wellcome Co. (Greenville, NC). The finished drug product will be used in hospitals and homes.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging.

Waste drug substance generated at _____ will be destroyed by licensed on-site high temperature incineration. At The Wellcome Foundation Limited rejected drug substance will either be returned to _____ or destroyed at a licensed high temperature incineration facility, small quantities of surplus drug substance will be directed to a licensed landfill and rejected drug product will either be directed to a licensed landfill or licensed high temperature incineration facility. In the United States expired, rejected or returned FLOLAN® and Sterile Diluent for FLOLAN® will be destroyed either by shredding or rinsing followed by wastewater treatment or by licensed on-site high temperature incineration.

At U.S. hospitals, empty or partially empty packages will be disposed according to hospital regulations; while empty or partially empty containers will be disposed as trash by consumers, destroyed by the community's solid waste management system, and disposed in an approved sanitary landfill.

Epoprostenol Sodium readily degrades in aqueous environments and is not expected persist in the environment.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

10-14-94

Nancy B. Sager

 DATE Prepared By

Nancy B. Sager
 Review Chemist

Center for Drug Evaluation and Research

OCT 17 1994

DATE

Phillip G. Vincent

 Approved

Phillip G. Vincent, Ph. D.
 Environmental Assessment Officer

Center for Drug Evaluation and Research

OCT 17, 1994

C. Kumkumian

 DATE Concurred

Charles S. Kumkumian, Ph. D.
 Assistant Director (Chemistry)
 Office of Drug Evaluation I

Center for Drug Evaluation and Research

Attachments: Environmental Assessment
 Material Safety Data Sheets
 Curricula Vitae
 Facility Compliance Statements

CC: Original NDA 20-444/KOliver copy to NDA/HFD-180
FONSI File 20-444/HFD-102
P. Vincent/HFD-102
Docket File 20-444/HFD-102

20444.FON
F/T by NBS/10/13/1994

BURROUGHS WELLCOME CO.
Research Triangle Park, NC, USA



Abbreviated Environmental Assessment for FLOLAN® (epoprostenol sodium) for Injection

B B Franklin
Chemical Development Laboratories, Greenville, NC, USA

T Henderson
Chemical Development Laboratories, Research Triangle Park, NC, USA

S Alston
Environmental Services, Greenville, NC, USA

R Thompson
Environmental Management Centre, Dartford, UK

8 September 1994

Brenda Bunch Franklin
B B Franklin

8 September 1994
Date

Thomas R Henderson
T Henderson

9 September 1994
Date

Sarah R. Alston
S Alston

9 September 1994
Date

R Thompson
R Thompson

9 September 1994
Date

FLOLAN FOR INJECTION ABBREVIATED ENVIRONMENTAL ASSESSMENT INFORMATION

1. DATE:

21 June 1994

2. APPLICANT/PETITIONER:

Burroughs Wellcome Co.

3. ADDRESS:

3030 Cornwallis Rd.
Research Triangle Park, NC 27709

4. DESCRIPTION OF PROPOSED ACTION

4.a Describe the requested approval

Burroughs Wellcome has filed a new drug application for approval to manufacture, package, and market FLOLAN®¹ (epoprostenol sodium) for Injection and Sterile Diluent for FLOLAN for the treatment of primary pulmonary hypertension (PPH).

4.b Describe the need for the action

PPH is a rare disease with approximately 400 new patients diagnosed each year in the US. Approximately 65% of adult patients are female; the disease is more common in young adults, although patients greater than age 50 are also afflicted. FLOLAN has been granted orphan and Subpart E status by FDA.

The natural history of PPH is characterized by progressive loss of the pulmonary vascular bed, which causes right ventricular strain and eventually right ventricular failure. Progressive compromise in cardiac output limits exercise capacity initially, followed by syncope and/or symptoms at rest.

Following diagnosis, the median survival of patients with mild to moderate symptoms is six years, compared to two and one half years in sicker Class III patients and to only six months in severely ill Class IV patients.

No treatment has been established as safe and effective in treating patients with PPH. However, given the high mortality of PPH, it is not surprising that a number of different treatments are employed empirically including oral vasodilators, anticoagulants, inotropic agents, diuretics, oxygen, heart-lung transplantation, and single lung transplantation. Regardless of therapy, most patients with PPH travel an inexorable downhill course of syncope, right heart failure, and death.

¹ This is a Trade Mark of the Wellcome Group of Companies.

FLOLAN®, infused at increasing doses for short periods of time, has been associated with dose related decreases in mean pulmonary arterial pressure and pulmonary vascular resistance and an increase in cardiac output.

FLOLAN has been infused safely in patients with severe PPH in uncontrolled trials for up to seven years and has been infused chronically into severely ill patients with PPH in two controlled trials for 8 and 12 weeks. In both trials, the hemodynamic profile was improved in patients who received FLOLAN acutely. After chronic treatment for 12 weeks in one trial and eight weeks in another, exercise capacity was significantly improved in patients who received FLOLAN compared to those who received standard therapy, alone. Quality of life appeared to improve more in patients randomized to FLOLAN than those randomized to standard therapy. Survival, though not the primary endpoint in either trial, was improved significantly in patients who received FLOLAN for 12 weeks in one trial. In a meta-analysis, survival in all PPH patients who have ever received FLOLAN was compared to survival in patients with PPH who enrolled in the US National Registry of patients with PPH. No patient enrolled in the US Registry received FLOLAN. Though not a controlled trial, survival appeared improved in Class III and Class IV patients who received FLOLAN.

In summary, these results clearly demonstrate that exercise capacity, hemodynamics, and quality of life are improved in critically ill patients with PPH who receive FLOLAN chronically. Survival is also improved. No other therapy has been established as safe and effective in treating these patients.

4.c Describe location(s) where the product(s) are to be

(1) *Produced*

The drug substance, epoprostenol sodium, will be synthesized at

FLOLAN for Injection will be formulated at the Wellcome Foundation Limited, Temple Hill, Dartford, Kent, DA1 5AH, UK.

The Sterile Diluent for FLOLAN will be formulated at Burroughs Wellcome Co., P.O. Box 1887, Greenville, NC, 27834, NC, USA.

(2) *Used*

FLOLAN is intended for use in patients with primary pulmonary hypertension. This product will be used in hospitals and in homes throughout the US.

(3) *Disposed*

Lots of the drug substance that are off-specification will be either recovered by chemical means or destroyed by on-site incineration.

The incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #MID000820381 in compliance with 40 CFR 264, Subpart O requirements. Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets certain conditions until final administrative disposition of the owner's and operator's permit application is made.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F, the secondary chamber, where final destruction of the product and off-gasses occurs, operates at 1,800°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a Venturi scrubber, an entrainment separator, an induced draft fan and an exhaust stack.

A hazardous waste RCRA Part B/Act 64 permit application has been submitted to the Waste Management Division of the _____ facility is operating under interim status provisions until action is taken on the permit application. _____ action on the Act 64 permit is expected in 1994. The State air permit issued on 15 July 1980 (#242-80) was revised to incorporate the Act 64 requirements and was approved on 26 May 1993. There is no expiration date for this permit at this time.

All necessary permits are in place for manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of Act 64 licensing requirements.

The Wellcome Foundation Limited

Rejected bulk drug substance which is not waste will be returned to the _____ Rejected drug product and small quantities of surplus drug substance will be directed to a landfill site licensed by the Waste Regulation Authority. The landfill site normally used is the Mucking Landfill site in the neighboring County of Essex operated by Cory Environmental Limited and licensed by the Essex Waste Regulation Authority, license number 72/79.(Control of Pollution Act 1974). There is no expiration date for this license. All landfill site used are engineered to allow biodegradation of the waste with gas and leachate controls. Alternatively, rejected drug substance or drug product will be directed, off-site, to an appropriate high temperature incineration facility, licensed by Her Majesty's Inspectorate of Pollution. Authorizations granted by Her Majesty's Inspectorate of Pollution will not expire but will be reviewed on a regular basis (every 4 years). Waste solutions containing drug substance are directed to the on-site liquid incineration facility or are disposed of off site by a licensed contractor with agreement from the appropriate Waste Regulation Authority.

Burroughs Wellcome Co. (USA)

Disposal of expired, rejected, or returned sterile powder and diluent will be accomplished through on-site waste management procedures which minimize threats to human health or the environment. Material is destroyed either by shredding or rinsing followed by wastewater treatment or by incineration.

The shredder facility combines shredding of the material through a Milpac shredder with a water wash of the shredded material. Wastewater from the wash operation is discharged to an on-site activated sludge biological pretreatment facility and then discharged to the Greenville Utilities Publicly Owned Treatment Works under Pretreatment Permit BW 01-98 (expiration date, 3 May 1998). Solids generated during the shredding process are incinerated on site or disposed off site at the Pitt County Landfill under local County ordinances.

Alternatively, the material may be destroyed by an on-site controlled air incinerator which operates at temperatures ranging from 1200°F in the primary chamber to 1850°F in the secondary chamber. The incinerator operates under N.C. Division of Solid Waste Permit No. 74-03-1 (subject to review on 7 July 1997). Inert material such as glass and foil wrap remains with the ash residue, which is managed according to specified permit conditions; cardboard packaging is destroyed and remains mostly as ash material; and volatile emissions from PVC packaging are released into the secondary chamber and converted to water, carbon dioxide, and hydrogen chloride. The gases are further treated in a fluxed force collision scrubber which removes particulate and hydrogen chloride contaminants. The incinerator and ancillary equipment (scrubber and waste feed components) have all been designed to meet Federal and State air emission standards for particulates, hydrogen chloride, and metal compounds.

4.d Describe the type of environment present at and adjacent to production and disposal sites.

The drug substance will be manufactured at site facility, located in the northern portion of the _____ is in the southwest corner of the state, approximately 140 miles equidistant from _____ The facility is approximately 1.7 miles northeast of the center of the _____ approximately 5.4 miles south of the center of the _____ and directly to the south of the _____

The area in the immediate vicinity of the _____ facility is a mix of zoning including heavy and light industry, general business, and single- and multiple-family residences. _____ is on land zoned for heavy industry. The site is directly bordered by airport property, land used by an subsidiary for crop testing and seed development, residences and undeveloped land. The climate is temperate.

The complex consists of approximately 80 buildings including chemical and pharmaceutical manufacturing operations, offices, laboratories, utility operations and various other support buildings. The plant site occupies a portion of approximately 810 hectares lying south of
. and

The Wellcome Foundation Limited

The Wellcome Foundation Limited site, where the product will be formulated, is located in an industrial area adjacent to the town of Dartford, Kent, UK. Dartford is in the Thames estuary region in a temperate zone. The on-site liquid incinerator is located in the Environmental Management Centre at - Wellcome Foundation Limited.

The Mucking Landfill site, operated by Cory Environmental Limited, occupies an area of 800 Ha. (1976 acres) in the County of Essex to the north of the River Thames. Some 300 Ha. (889 acres) are allotted to landfill, of which some 60 Ha. (148 acres) have been filled and restored. The landfill receives waste primarily from London and the County of Essex.

Burroughs Wellcome Co. (USA)

The United States production site where sterile diluent preparation and packaging will take place is located on the outskirts of Greenville, North Carolina. Greenville, North Carolina, is in a coastal plain region in a temperate zone. The production site in Greenville is in an industrial park surrounded by mostly rural areas.

Treatment and/or disposal of rejected or returned goods will take place both on site at the Burroughs Wellcome Co. wastewater pretreatment plant and solid waste incineration facility, and off site at the Greenville Utilities Commission (GUC) Wastewater Treatment Plant, and the Pitt County Landfill.

The Burroughs Wellcome Co. on-site waste water pretreatment facility is located in the northeastern section of the plant, within the Environmental Complex. Unit operations consist of first and second stage aeration tanks for biological stabilization, second clarifiers for removal of sludge solids, a neutralization tank, surge tanks, and effluent discharge with flow monitoring equipment. The pretreatment facility is designed to handle a maximum sustained daily flow rate of gallons. Flexibility to operate within a wide range of organic and hydraulic loadings is provided by a system of surge tanks for high strength wastewater or hydraulic surges in excess of the design capacity. Effluent from the pretreatment plant is discharged to the GUC wastewater treatment plant. The plant operates under a permit granted by GUC, No. BW 01-98 (expiration date, 3 May 1998).

The on-site incineration facility is also located in the Environmental Complex and houses a lb/hr controlled air solid waste incinerator, flux forced

collision scrubber, automatic waste feed through a rotary shear shredder, and nearly 2000 sq. ft. of storage space. The incinerator/scrubber combination has been designed to meet or exceed Federal and State air quality limitations on particulates and chlorides. The facility is owned and operated under permits granted by both the N.C. Division of Solid Waste, Permit No. 74-03-1 (subject to review on 7 July 1997), and the N.C. Air Quality Management Section, Permit No. 5754R48 (expiration date, 1 January 1996).

The GUC Wastewater Treatment Plant is situated in an area of mixed industrial and rural settings. The treatment plant serves the city of Greenville and contiguous areas. Treated wastewater from the plant is discharged into the Tar River, which empties into the Pamlico Sound. GUC operates the wastewater treatment plant under authority granted by the North Carolina Division of Environmental Management, NPDES Permit No. NC0023931.

The Pitt County Landfill is located just outside the city of Greenville in a rural area surrounded by farmland and forested land. It encompasses approximately 115 acres with 52 acres remaining as useful fill area. The County of Pitt manages the landfill in accordance with N. C. Department of Environment, Health and Natural Resources Permit No. 74-01.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THE PROPOSED ACTION

5.a NOMENCLATURE

Drug Substance:

Generic Name:	Epoprostenol sodium
Chemical Name {IUPAC}:	Sodium (5Z, 9 α , 11 α , 13E, 15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid monosodium salt
Chemical Name {Chem. Abstr.}	(5Z, 9 α , 11 α , 13E, 15S)-6,9-Epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid monosodium salt

Hydrolysis Product:

(9 α , 11 α , 13E, 15S)-6-oxo-9,11,15-trihydroxyprosta-13-enoic acid
also referred to as: (6-oxo-PGF1 α)

Drug Product:

FLOLAN® for Injection
Sterile Diluent for FLOLAN

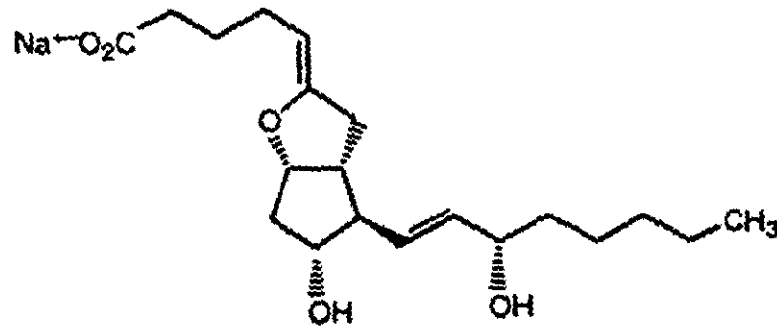
5.b CAS Registration Number(s),
[61849-14-7]: Epoprostenol sodium
[58962-34-8]: 6-oxo-PG1 α

5.c Molecular Weight(s) and Formula(s)

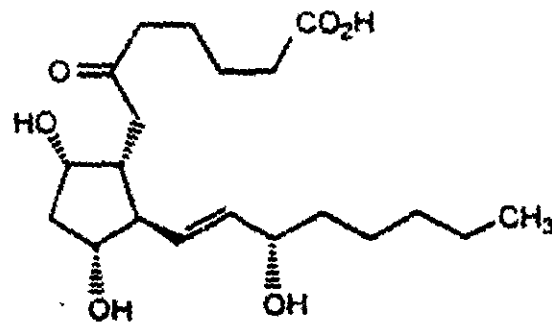
Epoprostenol sodium
 $C_{20}H_{31}NaO_5$
MW = 374.45

6-oxo-PG1 α
 $C_{20}H_{34}O_6$
MW = 370.49

5.d Structural Formula(s)
Epoprostenol Sodium



6-oxo-PGF1 α



5.e Physical and Chemical Characteristics

Drug Substance

A white or off-white freeze-dried powder

Solubility: >96mg/ml in phosphate buffer at pH 10

Hydrolysis: Readily hydrolyzes in aqueous solutions.

Hydrolysis Product

A semi-translucent crypto-crystalline solid

Soluble in water - 1%

Soluble in methanol - 1%

5.f Additives and impurities

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.a For the production site -

(1) *Substances expected to be emitted*

A list of materials used in the manufacture of epoprostenol sodium is furnished in _____ Chemical Abstract Service (CAS) numbers are provided in _____ to facilitate acquisition of Material Safety Data Sheets for OSHA regulated materials.

(2) *Controls exercised*

The drug substance, epoprostenol sodium, is not expected to be introduced into the environment through transportation and storage. Epoprostenol sodium will be shipped in Department of Transportation (DOT) specification packaging. Epoprostenol sodium is not regulated as a hazardous material under current DOT regulations. Material ready for shipment will be stored in the manufacturing facility, which maintains security through limited access.

Portions of the materials listed in _____ may be released to the environment as a result of the proposed action. These would be generated from the manufacturing site in the form of air emissions, liquid waste streams and solid wastes as follows.

Air/Particulate Emissions

There will be no particulate emissions during the manufacture of epoprostenol sodium. Protection is provided to employees by preventing unnecessary exposure. All packaging operations take place in nitrogen glove bags which are disposed of after use in an on-site approved incinerator. See Section 4.d. for a description of the incinerator.

Air/Solvent Emissions

is operating under an air consent judgment with the
This consent judgment was effective 15 March 1991, and all aspects of this consent judgment are scheduled to expire 1 August 1996. The air consent judgment required that an inventory be taken by 1 July 1991, of all equipment with either the potential to emit or to control an air contaminant, and that completed permits be in place for this equipment in accordance with the schedule set forth in the consent judgment. That inventory was submitted to on 1 July 1991. Where applicable, LAER (lowest achievable emissions rate) controls must be installed on the VOC (volatile organic compound) portion of the processes by 1 September 1995.

The production facilities for epoprostenol sodium are part of the Chemical Division's Region IV. The process will be run in the pilot plant, with the exception of small quantity steps, which will be run in the commercial products laboratory. The permit application for all subject equipment in Region IV was submitted to the under permit No. 929-92 in compliance with the 1 July 1992, scheduled submission date for this region.

Solvent emissions in the pilot plant operations have brine-cooled condensers on reactors and also have brine-cooled condensers on vacuum sources (Huckepack pumps). Laboratory operations use water-cooled condensers on distilling operations. Plans call for the installation of a thermal oxidizer for Region IV VOC emissions. Any solvent emissions from the pilot plant that would not be condensed in the brine-cooled condensers would go to the regional system. The removal efficiency of the thermal oxidizer is guaranteed by the manufacturer to be 98% or greater.

Aqueous Waste Streams

Aqueous waste streams resulting from epoprostenol sodium processes will be disposed on site by a chemical process water management (CPWM) injection system in accordance with this facility's Underground Injection Control (UIC) permits granted pursuant to the Safe Drinking Water Act.

The CPWM injection operations are conducted in accordance with this facility's Underground Injection Control permit Nos. MI-077-1W-0001 and MI-077-1W-0002 granted by Region 5 of the U.S. Environmental Protection Agency (USEPA) pursuant to the Safe Drinking Water Act. The permits are both dated 9 July 1993, with an expiration date of 27 October 1996.

Only those aqueous streams not permitted to be discharged to the sanitary sewer are sent to the CPWM.

With respect to the permits to dispose of liquid waste by the CPWM system, the Federal UIC permits restrict the types and concentrations of contaminants in the injected fluid. The contaminants are the same contaminants which is allowed to handle under the hazardous waste permit

application. These permits require that the concentration and type of contaminants listed in the permits be monitored on a monthly basis and reported to the USEPA, Region 5. In addition, groundwater is protected through the construction and design of the CPWM injection system, the operating procedures employed and the continuous monitoring program, all of which are described in the permit. A steam stripper was recently added to the CPWM to further reduce contaminants in the injected fluid. Volatile contaminants are now removed from this waste stream by steam stripping and recovered by the solvent recycling and distribution process.

With respect to the permit application terminology, wells are identified as "class 1" by USEPA. Class 1 wells are used to inject hazardous wastes below the deepest underground source of drinking water or aquifer. A confining formation consisting of an impermeable geologic strata prevents any upward migration of injected fluid into underground sources of drinking water.

has completed and received approval of a no-migration petition and demonstration for both UIC wells. The no-migration petition is a requirement of the USEPA Land Ban Restrictions which state that wastes may not be placed in a land disposal unit unless an approved petition is in place. The petition must show that there will be no migration of any waste constituent from the injection zone for as long as the waste remains hazardous or for 10,000 years. A monitoring and containment system using a pressurized annulus prevents the leakage of injected fluid from the injection wells into any formation outside of the injection zone.

A further description of EPA's requirements for the issuance of UIC permits is contained in 40 CFR Part 144.

Solvent Recycling and Distribution (SRD)

Used solvents from the epoprostenol sodium process at are collected at the production areas and conveyed via pipeline to a solvent recovery and distribution (SRD) facility within the plant site.

The SRD system receives the various solvents into holding tanks and then feeds them into one of five distillation/reclamation columns that fractionate the constituents through the application of heat. At the different temperatures various solvent species are recovered and sent to a clean or virgin tank where they are then distributed to the various production operations located throughout the plant site.

Those portions of the fractionation process that do not result in a product that is usable in production operations are sent off-site for disposal. The vast majority of this material is used as a waste-derived fuel that replaces or enhances other fossil fuels burned for energy. Other disposal options are the local waste water treatment plant and high temperature incineration dependent upon the chlorine and water content of an individual stream.

Spent Solvents

Spent solvent mixtures from the epoprostenol sodium process are sent to an approved off-site facility as part of a waste-derived fuels program where the

waste is blended at permitted facilities with other solvents for incineration or directly injected for incineration.

Waste spent solvents from the epoprostenol sodium process sent off site are transported using the Uniform Hazardous Waste Manifest form. All facilities that receive the spent solvents are permitted by the USEPA and/or the state environmental agency where the facility is located. These facilities are audited periodically by

Solid Waste

Spent silica gel and sodium sulfate from the epoprostenol sodium process are disposed of by incineration, as described in Section 4.d.

(3) ***Citation of and statement of compliance with applicable emission requirements.***

states it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the chemical processing of epoprostenol sodium at its facilities in as well as emission requirements set forth in federal, state, and local statutes and regulations applicable to the chemical processing of epoprostenol sodium at its facilities in

See Attachment III for the formal, signed Statement of Compliance for this facility.

Federal

The following federal regulations or standards are cited as applicable to the proposed action.

1. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended.
2. Clean Air Act PL 91-604, as amended.
3. Clean Water Act PL 95-217, as amended.
4. Safe Drinking Water Act PL 93-523.
5. Resources Conservation and Recovery Act (RCRA) of 1976 PL 94-580, as amended.
6. Occupational Safety and Health Act of 1970, as amended.
7. Hazardous Materials Transportation Act of 1975, as amended.
8. Standards from the American National Standards Institute.
9. National Fire Protection Agency Standards.
 - a National Electrical Code Standards
 - b Life Safety Requirements

State

The following state regulations or standards are cited as applicable to the proposed action:

1. Act 348 of 1965 as amended
2. Act 245 of 1929 as amended
3. Act 399 of 1976, as amended
4. Act 136 of 1969, amended as
5. Act 315 of 1969, as amended
6. Act 641 of 1978
7. Act 64 of 1979, as amended
8. Act 368 of 1978,

Local

The following local regulations or standards are cited as applicable to the proposed action:

1. Chapter 28 of the (Services and Wastewater) as amended by ordinance No. 1190
2. regulation applicable to the state of as amended (local)

(4) *Effect of the action upon compliance with current emissions requirements.*

Waste streams resulting from the processing of epoprostenol sodium will include solvent emissions, aqueous waste streams, spent solvents and solid waste.

Air/Particulate Emissions

No particulate air emissions are expected to occur during the processing of epoprostenol sodium.

Air/Solvent Emissions

is operating under an air consent judgment with the
This consent judgment was effective March 15, 1991, and all aspects of this consent judgment are scheduled to expire August 1, 1996. The production facilities for epoprostenol sodium are part of the Chemical Division's Region IV. The process will be run in the pilot plant, with the exception of small quantity steps, which will be run in the commercial products laboratory. The permit application for all subject equipment in Region IV was submitted to the under permit No. 929-92 in compliance with the July 1, 1992, scheduled submission date for this region.

Solvent emissions in the pilot plant operations have brine-cooled condensers on reactors and also have brine-cooled condensers on vacuum sources (Huckepack pumps). Laboratory operations use water-cooled condensers on distilling operations. Plans call for the installation of a thermal oxidizer for Region IV VOC emissions. Any solvent emissions from the pilot plant that would not be condensed in the brine-cooled condensers would go to the regional system. The removal efficiency of the thermal oxidizer is guaranteed by the manufacturer to be 98% or greater.

Projecting to the fifth year production figure all solvent emissions from the production of epoprostenol sodium have been included under permit No. 929-92 submitted to the Discharges from this process will not exceed the limits applied for under this permit.

Aqueous Waste Streams

Aqueous waste streams resulting from epoprostenol sodium processes will be disposed on site by a chemical process water management (CPWM) injection system in accordance with this facility's Underground Injection Control (UIC) permits granted pursuant to the Safe Drinking Water Act. The CPWM injection operations are conducted in accordance with the facility's Underground Injection Control permit Nos. MI-077-1W-0001 and MI-077-1W-0002 granted by Region 5 of the U.S. Environmental Protection Agency (USEPA) pursuant to the Safe Drinking Water Act. The permits are both dated July 9, 1995, with an expiration date of October 27, 1996.

Only those aqueous streams not permitted to be discharged to the sanitary sewer are sent to the CPWM.

Projecting to the fifth year production figure solvent discharges to the CPWM from the production of epoprostenol sodium will represent 0.00009% of the total allowed under the UIC permits granted pursuant to the Safe Drinking Water Act.

Solvent Recycling and Distribution (SRD)

Used solvents from epoprostenol sodium processes at are collected at the production areas and conveyed via pipeline to a solvent recovery and distribution (SRD) facility within the plant site.

The SRD system receives the various solvents into holding tanks and then feeds them into one of five distillation/reclamation columns that fractionate the constituents through the application of heat. At the different temperatures various solvent species are recovered and sent to a clean or virgin tank where they are then distributed to the various production operations located throughout the plant site.

The portions of the fractionation process that do not result in a product that is usable in production operations are sent off-site for disposal. The vast

majority of this material is used as a waste-derived fuel that replaces or enhances other fossil fuels burned for energy. Other disposal options are the local waste water treatment plant and high temperature incineration dependent upon the chlorine and water content of an individual stream.

Spent Solvents

Spent solvent mixtures from the epoprostenol sodium process are sent to an approved off-site facility as part of a waste-derived fuels program where the waste is blended at permitted facilities with other solvents for incineration or directly injected for incineration.

All facilities that receive the spent solvents are permitted by the USEPA and/or the state environmental agency where the facility is located. These facilities are audited periodically by Upjohn.

Projecting to the fifth year production figure all discharges from the production of epoprostenol sodium will not impact the limits imposed under the off-site facility's USEPA and/or state environmental agency's permit.

Solid Waste

Spent silica gel and sodium sulfate from the epoprostenol sodium process are nonhazardous and disposed of by incineration.

The incinerator is operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #MID000820381 in compliance with 40 CFR 264, Subpart O requirements. Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets certain conditions until final administrative disposition of the owner's and operator's permit application is made.

A hazardous waste RCRA Part B/Act 64 permit application has been submitted to the Waste Management Division of the facility is operating under interim status provisions until action is taken on the permit application. action on the Act 64 permit is expected in 1994. The State air permit issued on July 15, 1980 (#242-80) was revised to incorporate the Act 64 requirements and was approved on May 26, 1993. There is no expiration date for this permit at this time

All necessary permits are in place for manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 64 licensing requirements.

Projecting to the fifth year production figure solid wastes from the production of epoprostenol sodium will represent less

than 0.00008% of the limits imposed under the RCRA Part B/ Act 64 permit application for the on-site incinerator.

6.b For the production site – The Wellcome Foundation Limited (UK)

(1) *Substances expected to be emitted*

A list of materials used in the formulation of FLOLAN® for Injection is furnished in numbers are provided in to facilitate acquisition of Material Safety Data Sheets for OSHA regulated materials.

(2) *Controls exercised*

Air Emissions:

No air emissions are expected to occur during formulation of FLOLAN for Injection.

Waste water:

Waste water is treated at the Wellcome Foundation's effluent plant and then discharged to the sewers under the consent of the local water company, Thames Water Utilities, consent license numbers LS73008A and 73003P (Waste Industry Act 1991). There is no expiration date for these licenses.

Liquid Waste

Liquid wastes containing epoprostenol sodium are incinerated on site in a facility authorized by Her Majesty's Inspectorate of Pollution, Authorization No. AG9264 (Environmental Protection Act 1990), as issued by Her Majesty's Inspectorate of Pollution. Authorizations granted by Her Majesty's Inspectorate of Pollution will not expire but will be reviewed on a regular basis (every 4 years). Alternatively material will be directed off site for disposal by a licensed contractor with agreement from the appropriate Waste Regulation Authority

Solid Waste

General factory waste is incinerated on site in a facility authorized by Her Majesty's Inspectorate of Pollution, Authorization number AG9264 (Environmental Protection Act 1990). Alternatively material will be directed off site to a landfill site licensed by the Waste Regulation Authority or to a high temperature incineration facility authorized by Her Majesty's Inspectorate of Pollution. Authorizations granted by Her Majesty's Inspectorate of Pollution will not expire but will be reviewed on a regular basis (every 4 years)

Process materials are directed off site to a landfill site licensed by the Waste Regulation Authority or to an appropriate high temperature incineration facility authorized by Her Majesty's Inspectorate of Pollution. Authorizations granted by Her Majesty's Inspectorate of Pollution will not expire but will be reviewed on a regular basis (every 4 years).

(3) *Citation of and statement of compliance with applicable emission requirements*

The Wellcome Foundation Limited states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in authorizations, consents and regulations applicable to the formulation of FLOLAN® for Injection at its facilities at Dartford, Kent, the United Kingdom.

See Attachment III for the formal, signed Statement of Compliance for this facility.

<u>Facility/Governing Authority</u>	<u>Authorization Number</u>	<u>Expiration Date</u>
The Wellcome Foundation Limited Wastewater Treatment Plant discharge to Sewer Her Majesty's Inspectorate of Pollution: Environmental Protection Act 1990 and	AK 6853	No Expiration Date Subject to Regular review
Thames Water Utilities: Waste Industry Act 1991	LS73008A & 73003P	No Expiration Date Subject to Regular review
The Wellcome Foundation Limited On Site Waste Incineration facilities. Her Majesty's Inspectorate Of Pollution: Environmental Protection Act 1990	AG 9264	No Expiration Date Subject to Regular review

(4) *Effect of the action upon compliance with current emissions requirements*

The Wellcome Foundation Limited is licensed to discharge effluent waste to the sewer by the Thames Water Utilities and Her Majesty's Inspectorate of Pollution, to discharge cooling/surface water to controlled waters by the National Rivers Authority, and to operate certain processes by Her Majesty's Inspectorate of Pollution.

Air Emissions

No air emissions are expected to occur during the formulation of FLOLAN for Injection

Wastewater

Trade effluent (wastewater) is discharged to the sewer under a license granted by the Thames Water Utilities, consent license numbers LS73008A and 73003P

(Waste Industry Act 1991). The formulation of FLOLAN will result in small volumes of water from cleaning operations and is not expected to have an adverse impact on the current compliance situation.

Liquid Waste

Liquid waste from the formulation of FLOLAN®, directed to the on-site liquid incinerator (authorization number AG9264), is not expected to have an adverse impact on the current compliance situation. The amount of rejected product from formulation processes is expected to be kept to a minimum acceptable reject standard and will contribute less than 0.001% of liquid waste directed for incineration.

Solid Waste

Solid waste generated from the formulation of FLOLAN for Injection will contribute a small volume to that already dealt with and is not expected to have an adverse impact on the current compliance situation. The amount of rejected product from formulation processes is expected to be kept to a minimum acceptable reject standard and will contribute less than 0.01% of solid waste directed to landfill.

6.c For the production site – Burroughs Wellcome Co. (USA)

(1) *Substances expected to be emitted*

A list of materials used in the manufacture of epoprostenol sodium is furnished in CONFIDENTIAL Appendix B. The Occupational Exposure Limits and a discussion of controls exercised within the process designed to prevent their emission into the environment are also included. Chemical Abstract Service numbers are provided in CONFIDENTIAL Appendix B to facilitate acquisition of Material Safety Data Sheets for OSHA regulated materials

(2) *Controls exercised*

Air Emissions

No air emissions are expected to occur during formulation of the Sterile Diluent for FLOLAN (epoprostenol sodium).

Wastewater

Wastewater generated from formulation of the diluent is discharged to the Burroughs Wellcome Co. Wastewater Pretreatment Facility. The facility is operated in accordance with Discharge Permit, BW01-98 (expiration date, 3 May 1998), which permits the discharge of pharmaceutical wastewater to

the Greenville Utilities Commission (GUC) treatment plant. Limitations of this permit cover conventional wastewater pollutants, and heavy metals. Procedures for operating the Wastewater Treatment facilities are covered in an SOP titled "Wastewater Pretreatment Plant and Wastewater Monitoring Operations, Inspection/Corrective Actions."

Solid Waste

Solid waste generated from formulation of the Sterile Diluent is nonhazardous and will be treated on site through incineration or an alternative shredding/rinsing process. Solid waste includes expired, rejected, or returned product and packaging material. The on site solid waste incinerator is operated under a permit granted by the N.C. Division of Solid Waste, Permit No. 74-03-1 (subject to review on 7 July 1997). Procedures for operating the solid waste incinerator are covered in an SOP titled "Operation of the Solid Waste Incinerator." The shredding operation uses a Milpac shredder followed by water wash of the shredded material. Wastewater from the wash operation is discharged to the on-site wastewater pretreatment facility and then discharged to the Greenville Utilities Publicly Owned Treatment Works under Pretreatment Permit BW01-98 (expiration date, 3 May 1998). Shredded packaging material, glass, and plastic is incinerated on site or may be disposed off site at the Pitt County Landfill under local County ordinances. Shredder operations are covered in SOP's titled "Labeling, Disposition, and On-site Destruction of Product-Related Waste," and "Waste Destruction Area Daily Inspection" and "Waste Destruction Area Daily Inspection."

(3) *Citation of and statement of compliance with applicable emission requirements*

Burroughs Wellcome Co states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the formulation of the Sterile Diluent for FLOLAN[®], at its facilities in the United States, as well as emission requirements set forth in federal, state, and local statutes and regulations applicable to the formulation of the Sterile Diluent for FLOLAN, at its facilities in the United States.

All the following applicable emissions requirements are complied with on a daily basis for the formulation of the Sterile Diluent for FLOLAN, at Burroughs Wellcome Co's Greenville, North Carolina, facility. See Attachment III for the formal, signed Statement of Compliance for this facility.

Federal

Direct point source discharges from the manufacturing facility are governed by 40 CFR 122 - The National Pollutant Discharge Elimination System (NPDES). Wastewater generated at the manufacturing facility, or during

destruction of off-specification or returned product are governed by 40 CFR 403 - EPA Standards, and 40 CFR 439 - Guidelines and Standards for Pharmaceutical Manufacturing. Both the NPDES program and wastewater management programs are authorized by the Federal Water Pollution Control Act, PL 92-500 (also known as the Clean Water Act). The objective of this act is to restore and maintain the chemical, physical and biological integrity of the nation's waters.

Air emissions from the facility are governed by the general provisions of 40 CFR 60 - EPA Regulations on Standards and Performance for New Stationary Sources. Air Quality Management Programs are authorized by the Clean Air Act, PL 90-128. The purpose of the act is to protect and enhance the quality of the Nation's air resources, develop and maintain a program to achieve the prevention and control of air pollution and to encourage reasonable governmental actions for pollution prevention.

Hazardous wastes generated and treated at the manufacturing facility are governed by the general provisions of 40 CFR 260-280 - Hazardous Waste Management System. Hazardous Waste Management Programs are authorized by the Resource Conservation and Recovery Act of 1976, PL 94-580. The objectives of the act are to promote the protection of health and the environment and to conserve valuable material and energy resources.

State

The North Carolina Department of Environment, Health and Natural Resources requires permits covering the operation of air pollution abatement facilities and/or emission sources from manufacturing operations; point source discharges to surface waterways; and the generation and treatment of Hazardous Waste. Burroughs Wellcome Co.'s Greenville facility has received an AQ-22 Permit No. 5754R48 for air emissions from production and manufacturing operations. This permit expires on January 1, 1996. Burroughs Wellcome Co.'s Greenville facility has received a permit, NCD047373766, to operate a hazardous waste treatment and storage facility, and permit No. 74-03-1 for operation of a solid waste incinerator. The hazardous waste management permit expires on 15 October 1999. The solid waste incinerator permit comes up for review on 7 July 1997 (every five years). Burroughs Wellcome Co. has received an NPDES Discharge Permit, NC001058, for noncontact cooling water point source discharge to Parker's Creek, North Carolina. The NPDES permit is currently expired however Burroughs Wellcome Co. has applied for a new permit. Until the new permit is issued, the current (expired) permit remains effective, in accordance with the provisions contained in 40 CFR 122.6, Continuation of Expiring Permits.

Local

All wastewater from the Burroughs Wellcome Co. manufacturing facility is discharged to the Greenville Utilities Commission's Publicly Owned

Treatment Works under a Pretreatment Discharge Permit No. BW01-98. This permit expires on 3 May 1998.

(4) *Effect of the action upon compliance with current emissions requirements*

A production estimate is included as CONFIDENTIAL information in Appendix B.

Waste streams resulting from the formulation of the Sterile Diluent for FLOLAN will include wastewater and nonhazardous solid waste.

Air Emissions

No air emissions are expected to occur during formulation of the Sterile Diluent for FLOLAN.

Wastewater

Wastewater will be generated during formulation of diluent and from waste disposal processes using the crusher facility's shredding and rinsing procedure [see 6.a(2)]. The only potential area of impact on emissions limitations is the local Pretreatment Discharge Permit No. BW01-98, specifically flow limitations. However, because the equipment to be used for production and disposal processes is currently in place, no increase in flow is anticipated, therefore no impact on the permit is expected.

Modifications which will significantly impact the hydraulic or pollutant loading require notification to the local Publicly Owned Treatment Works (POTW). Depending on the impact, negotiations with the local authority to allow permit modifications may be required. As described above, all modifications are reviewed and evaluated in-house by the Environmental Services Department. Formulation of drug product is not expected to trigger notification or modification of the permit.

Solid Waste

Nonhazardous solid waste is generated as rejected raw materials during formulation of the Sterile Diluent for FLOLAN®. This waste will be treated on site either through use of the crusher facility or the solid waste incinerator [see 4.c(3)]. The amount of rejected product from formulation processes is expected to be minimal and thus the capacity of the waste treatment systems will not be affected. Treatment of the nonhazardous solid waste through the on-site treatment facilities would consume less than 0.0004 % per hour of the unit's waste handling capacity. Applicable permits are the local Pretreatment Discharge Permit No. BW01-98 for the crusher facility and N.C. Division of Solid Waste Permit No. 74-03-1 for the solid waste incinerator. Neither of these permits will be impacted by the formulation of the Sterile Diluent for FLOLAN.

- 6.d **Through use of calculations and/or direct measures, estimate to the extent possible quantities and concentrations of substances expected to enter the environment as a result of use and/or disposal of products affected by the action.**

Calculation of the Maximum Expected Emitted Concentrations (MEEC) and the Expected Environmental Concentration (EEC) are included in CONFIDENTIAL Appendices B. and C. These environmental concentrations are less than the criterion concentrations of 1% of the lowest toxicity measure available and thus will not adversely affect the environment.

The amounts of drug produced will not result in significant introductions from use of the product into the environment. Epoprostenol sodium will be administered infrequently and in limited amounts to patients in a hospital setting. The small amounts of parent compound or metabolites excreted in urine or feces would be discharged into sanitary sewer systems. Product end-use does not present a potential for significant environmental release.

Therefore, should there be a release of epoprostenol sodium according to the definition found at 21 CFR 25.5(c)(6), epoprostenol sodium can reasonably be expected to be non-toxic.

- 7.-11. **THIS DOCUMENT IS AN ABBREVIATED ENVIRONMENTAL ASSESSMENT. FORMAT ITEMS 7 THROUGH 11 ARE NOT REQUIRED FOR AN ABBREVIATED ENVIRONMENTAL ASSESSMENT**

12. **LIST PREPARERS OF THE ASSESSMENT (CURRICULA VITAE ARE INCLUDED IN ATTACHMENT II)**

NAME	EXPERTISE	EXPERIENCE	PROFESSIONAL DISCIPLINE
T Henderson	Chemical Development	19 years	Organic Chemistry
S. Alston	Environmental Engineering	9 years	Engineering
R. Thompson	Environmental Chemistry	17 years	Chemical Sciences
B. B. Franklin	Environmental Assessment	12 years	Environmental Chemistry

13. CERTIFICATION

The undersigned representatives of Burroughs Wellcome Company certify that the information presented is true, accurate, and complete to the best of the knowledge of the firm or agency responsible for preparation of this environmental information.

Date: 9-Sep-94

Signature of responsible official: Roy A. Swaringen

Name: Roy A. Swaringen

Title: Director, Chemical Development Laboratories

Date: 9/9/94

Signature of responsible official: Michael L. Esarey

Name: Michael L. Esarey

Title: Manager, Environmental Services

14. REFERENCES

1. Environmental Assessment for Epoprostenol Sodium, Drug Master File
2. Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA Vol. 7, Pharmaceutical Manufacturers Association, 1991
3. "Technical Assistant Document (TAD)," FDA Environmental Assessment Technical Assistance Handbook. NTIS PB87-175345.
4. U.S. Environmental Protection Agency, CFR Part 40 § 122, The National Pollutant Discharge Elimination System (NPDES).
5. U.S. Environmental Protection Agency, CFR Part 40 § 403, EPA Standards
6. U.S. Environmental Protection Agency, CFR Part 40 § 439, Guidelines and Standards for Pharmaceutical Manufacturing
7. U.S. Environmental Protection Agency, CFR Part 40 § 60, EPA Regulations on Standards and Performance for New Stationary Sources

10. Federal Water Pollution Control Act, P.L. 92-500
11. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended.
12. Clean Air Act PL 90-128.
13. Clean Air Act PL 91-604, as amended.
14. Clean Water Act PL 95-217, as amended.
15. Safe Drinking Water Act PL 93-523.
16. Resources Conservation and Recovery Act (RCRA) PL 94-580 of 1976, as amended.
17. Occupational Safety and Health Act of 1970, as amended.
18. Hazardous Materials Transportation Act of 1975, as amended
19. Standards from the American National Standards Institute.
20. National Fire Protection Agency Standards.
 - a. National Electrical Code Standards
 - b. Life Safety Requirements
21. Act 348 of 1965, , as amended
22. Act 245 of 1929, as amended
23. Act 399 of 1976, as amended
24. Act 136 of 1969, as amended
25. Act 315 of 1969, as amended
26. Act 641 of 1978,
27. Act 64 of 1979 as amended
28. Act 368 of 1978,
29. Chapter 28 of the (Services and Wastewater) as amended by ordinance No. 1190.
30. 1970, as amended
(Local regulation applicable to the State of
31. Environmental Protection Act, Parts I & II, United Kingdom, 1990.
32. Water Resources Act, United Kingdom, 1991.
33. Water Industry Act, United Kingdom, 1991.
34. Control of Pollution Act, United Kingdom, 1994

15a. **This document is an abbreviated Environmental Assessment. Data summary charts and test reports are not required for an abbreviated Environmental Assessment.**

15b. **NON-CONFIDENTIAL Attachments**

ATTACHMENT I-Material Safety Data Sheets for Epoprostenol Sodium, 6-oxo-PGF1 α

ATTACHMENT II-Curricula Vitae of Contributors

ATTACHMENT III-Facility Compliance Statements

ATTACHMENT IV-Hydrolysis Report

15c. CONFIDENTIAL Appendices

CONFIDENTIAL APPENDIX A- Identification of Chemical Substances

**CONFIDENTIAL APPENDIX B-Introduction of Substances into The
Environment**

**CONFIDENTIAL APPENDIX C- Environmental
Assessment**

**ATTACHMENT I:
MATERIAL SAFETY DATA SHEETS
EPOPROSTENOL SODIUM
6-OXO-PGF_{1α}**

Sigma Chemical Co. P.O. Box 14508 St. Louis, MO 63178 Phone: 314-771-5765	Aldrich Chemical Co., Inc. 1001 West St. Paul Milwaukee, WI 53233 Phone: 414-273-3850	Fluka Chemical Corp. 980 South Second St. Ronkonkoma, NY 11779 Phone: 516-467-0980 Emergency Phone: 516-467-3535

SECTION 1. - - - - - CHEMICAL IDENTIFICATION- - - - -
PRODUCT #: K2626 NAME: 6-KETOPROSTAGLANDIN F1A

SECTION 2. - - - - - COMPOSITION/INFORMATION ON INGREDIENTS - - - - -
CAS #: 58962-34-8
MF: C20H34O6
RTECS DATA AND SYNONYMS SUPPLIED ARE FOR A CLOSELY RELATED COMPOUND.
SYNONYMS
PGF 1-ALPHA * PROSTAGLANDIN F1 ALPHA * PROTAGLANDIN F1 * PROST-13-EN-
1-OIC ACID, 9,11,15-TRIHYDROXY-, (9-ALPHA,11-ALPHA,13E,15S) (9CI) *

SECTION 3. - - - - - HAZARDS IDENTIFICATION - - - - -
LABEL PRECAUTIONARY STATEMENTS
HARMFUL
HARMFUL BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
REPRODUCTIVE HAZARD.
TARGET ORGAN(S):
SMOOTH MUSCLE
DO NOT BREATHE DUST.
WEAR SUITABLE PROTECTIVE CLOTHING.

SECTION 4. - - - - - FIRST-AID MEASURES- - - - -
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS.
CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER
FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND
SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT,
CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER
FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING
THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

SECTION 5. - - - - - FIRE FIGHTING MEASURES - - - - -
EXTINGUISHING MEDIA
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROPRIATE FOAM.
SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO
PREVENT CONTACT WITH SKIN AND EYES.

SECTION 6. - - - - - ACCIDENTAL RELEASE MEASURES- - - - -
WEAR RESPIRATOR, CHEMICAL SAFETY GOGGLES, RUBBER BOOTS AND HEAVY
RUBBER GLOVES.
SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.
AVOID RAISING DUST.
VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

SECTION 7. - - - - - HANDLING AND STORAGE- - - - -
REFER TO SECTION 8.

SECTION 8. - - - - - EXPOSURE CONTROLS/PERSONAL PROTECTION- - - - -
NIOSH/MSHA-APPROVED RESPIRATOR.
USE ONLY IN A CHEMICAL FUME HOOD.
COMPATIBLE CHEMICAL-RESISTANT GLOVES.

CHEMICAL SAFETY GOGGLES.
STORE IN THE DARK.
STORE WITH DESICCANT.

SECTION 9. - - - - - PHYSICAL AND CHEMICAL PROPERTIES - - - - -
APPEARANCE AND ODOR

SOLID.
MELTING POINT: 79 TO 82°C
SOLUBILITY: WATER-INSOLUBLE ACETONE-SOLUBLE

SECTION 10. - - - - - STABILITY AND REACTIVITY - - - - -
STABILITY

STABLE.
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
TOXIC FUMES OF:
CARBON MONOXIDE. CARBON DIOXIDE
HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.

SECTION 11. - - - - - TOXICOLOGICAL INFORMATION - - - - -
ACUTE EFFECTS

HARMFUL IF SWALLOWED, INHALED, OR ABSORBED THROUGH SKIN.
THE TOXICOLOGICAL PROPERTIES HAVE NOT BEEN THOROUGHLY
INVESTIGATED.

CHRONIC EFFECTS

REPRODUCTIVE HAZARD.
TARGET ORGAN(S):
SMOOTH MUSCLE

RTECS DATA AND SYNONYMS SUPPLIED ARE FOR A CLOSELY RELATED COMPOUND.

RTECS NO: GY4569700

CYCLOPENTANEHEPTANOIC ACID, 3,5-DIHYDROXY-2-(3-HYDROXY-1-OCTENYL)-

TARGET ORGAN DATA

PATERNAL EFFECTS (SPERMATOGENESIS)
PATERNAL EFFECTS (PROSTATE, SEMINAL VESICLE, COWPER'S, ACCESSORY GLANDS)
EFFECTS ON FERTILITY (PRE-IMPLANTATION MORTALITY)
EFFECTS ON FERTILITY (POST-IMPLANTATION MORTALITY)
EFFECTS ON FERTILITY (OTHER MEASURES OF FERTILITY)
EFFECTS ON EMBRYO OR FETUS (EXTRA EMBRYONIC STRUCTURES)
EFFECTS ON EMBRYO OR FETUS (FETOTOXICITY)
EFFECTS ON EMBRYO OR FETUS (FETAL DEATH)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES
(RTECS) DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR
COMPLETE INFORMATION.

SECTION 12. - - - - - ECOLOGICAL INFORMATION - - - - -
DATA NOT YET AVAILABLE.

SECTION 13. - - - - - DISPOSAL CONSIDERATIONS - - - - -
DISSOLVE OR MIX THE MATERIAL WITH A COMBUSTIBLE SOLVENT AND BURN IN A
CHEMICAL INCINERATOR EQUIPPED WITH AN AFTERBURNER AND SCRUBBER.
OBSERVE ALL FEDERAL, STATE AND LOCAL ENVIRONMENTAL REGULATIONS.

SECTION 14. - - - - - TRANSPORT INFORMATION - - - - -
CONTACT SIGMA CHEMICAL COMPANY FOR TRANSPORTATION INFORMATION.

SECTION 15. - - - - - REGULATORY INFORMATION - - - - -
RTECS DATA AND SYNONYMS SUPPLIED ARE FOR A CLOSELY RELATED COMPOUND.

SECTION 16. - - - - - OTHER INFORMATION - - - - -

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO
BE ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA, ALDRICH,
FLUKA SHALL NOT BE HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING

Product #: K2626 Name: 6-KETOPROSTAGLANDIN F1A
Material Safety Data Sheet
Printed 06/28/1994 09:59:19

Page 3
ValidD

OR FROM CONTACT WITH THE ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR
PACKING SLIP FOR ADDITIONAL TERMS AND CONDITIONS OF SALE.
COPYRIGHT 1994 SIGMA CHEMICAL CO., ALDRICH CHEMICAL CO., INC.,
FLUKA CHEMIE AG
LICENSE GRANTED TO MAKE UNLIMITED PAPER COPIES FOR INTERNAL USE ONLY



Wellcome

Cables & Telegrams
Tabloid Greenville, N.C.
TWX 5109291618
Tel. 919 758-3436

Burroughs Wellcome Co.

Intersection U.S. 13 & S.R. 1590
Post Office Box 1887
Greenville, North Carolina 27835-1887

PRELIMINARY MATERIAL SAFETY DATA SHEET

Because this is a project compound, extensive safety data concerning its safe handling in the work-place is not available; therefore, treat this compound with appropriate care.

GXSE88/0006

SECTION I: IDENTIFICATION

Wellcome Product Name: Flolan

Chemical Name: Sodium (5Z,9,11,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oate

Formula: C₂₀H₃₁NaO₅

Generic Name: Epoprostenol Sodium

For Information on Health Hazards Call: Ext. 7014

Information Effective: 2/6/89

SECTION II: HAZARDOUS INGREDIENTS OF MIXTURES

Principal Hazardous Component(s): Flolan

Toxicity:

Intravenous LD₅₀ (Rat) = 66.3 mg/kg¹ Rapidly hydrolysed under physiological conditions.

SECTION III: PHYSICAL DATA

Boiling Point: N.A.

Vapor Pressure: N.A.

Vapor Density: N.A.

Solubility in Water: N.D.

Specific Gravity (H₂O=1): N.A.

Percent Volatile by Volume (%): N.A.

Evaporation Rate: N.A.

Melting Point: N.D.

Appearance and Odor: A white or off white freeze-dried powder.

SECTION IV: FIRE AND EXPLOSION DATA

Flash Point (Method Used): N.D.

Flammable Limits: LEL: N.D.
UEL: N.D.

Special Fire Fighting Procedures: Self-contained breathing apparatus

Unusual Fire and Explosion Hazards: May emit toxic or irritant fumes when heated.

Extinguishing Media: Use agent appropriate to the nature of the fire and other materials involved

SECTION V: HEALTH HAZARD DATA

Threshold Limit Value: None established.

Effects of Overexposure: Paralysis, hypoactivity, ataxia, labored breathing and ptosis was observed in rats given lethal doses of Flolan intravenously.²

Adverse reactions associated with medical use have occurred in some cases, including headache, severe hypotension, facial flushing, nausea and diarrhea. Other symptoms of side effects include skin reddening, abdominal pain, skin rash, shortness of breath and dizziness, loss of consciousness. Some prostaglandins are irritating to the skin and eyes. Contact with broken skin must be avoided.³

Emergency and First Aid Procedures:

If in Eyes:

Flush immediately with large quantities of water. Contact Health Center

If Swallowed:

Induce vomiting. Contact Health Center. Support respiratory and cardiovascular functions as needed.

If Inhaled:

Remove person to fresh air. Contact Health Center. Support respiratory and cardiovascular functions as needed.

In Contact with Skin:

Flush exposed skin with water and wash with soap and water. If irritation develops, contact Health Center

SECTION VI: REACTIVITY DATA

Stability: N.D.

Conditions to Avoid: N.D.

Incompatibility (Materials to Avoid): N.D.
N.D.

Hazardous Decomposition Products:

Hazardous Polymerization: N.D.

SECTION VII: SPILL OR LEAK PROCEDURES

Steps to be Taken if Material is Spilled or Leaked

Wear suitable protective clothing. Treat spillage with dilute acetic acid for three to five minutes, followed by a 3% (half strength household bleach) sodium hypochlorite in water solution for one hour. Small quantities of neutralised material may be washed down the drain.³

SECTION VII: SPECIAL PROTECTION INFORMATION

Respiratory Protection: Toxic dust mask eg. 3M 8710

Ventilation: Fume hood or local exhaust

Protective Gloves: Neoprene or PVC

Eye Protection: Goggles

Other Protective Equipment: Tyvek jumpsuit if dust is generated.

SECTION IX: SPECIAL PRECAUTIONS

Precautions to be Taken in Handling and Storage: Protect from heat and moisture.

Other Precautions: Wash hands after using.

SECTION X: REFERENCES

¹ An Acute Single-dose Intravenous Toxicity Study with Prostacyclin Sodium in Rats. BPAT 80.22.

² Information for Clinical Investigators Prostacyclin Sodium. THIB/79/0026.

³ Substance Safety Information Sheet. GSS No: 1/1242/83.

N.A = Not Applicable

N.D.= Not Determined

**ATTACHMENT III:
FACILITY COMPLIANCE STATEMENTS**



Burroughs Wellcome Co.

Intersection U.S. 13 & S.R. 1590
Greenville North Carolina 27834-1887

cables & telegrams
cable: Greenville N.C.
TWX 5109291618
tel 919 758 3436

June 22, 1994

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

To Whom It May Concern:

Burroughs Wellcome Co. states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to its facilities in the United States, as well as emission requirements set forth in federal, state, and local statutes and regulations applicable to its facilities in the United States.

All applicable emissions requirements are complied with on a daily basis at Burroughs Wellcome Co.'s Greenville, North Carolina, facility. The specific environmental regulations, along with permit numbers and expiration dates, are summarized in the attached table.

In summary, Burroughs Wellcome Co. states that it is in compliance with all federal, state, and local environmental regulations for its manufacturing facility in Greenville, North Carolina, USA.

Sincerely,

Michael L. Esarey
Manager,
Environmental Services Department
Burroughs Wellcome Co.
Greenville, NC 27834-1887

/bbf

Attachment

PERMIT INDEX

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Permit	North Carolina Department of Environment, Health and Natural Resources Division of Environmental Management	5754R48	08/10/93	01/01/96
National Pollutant Discharge Elimination System ^a (NPDES)	North Carolina Department of Environment, Health and Natural Resources Division of Environmental Management	NC0001058	05/01/88	04/30/93
RCRA Hazardous Waste Management Permit (EPA)	US Environmental Protection Agency, Region IV Waste Management Division	NCD047373766	10/23/93	10/15/99
RCRA Hazardous Waste Management Permit (NC)	North Carolina Department of Environment, Health and Natural Resources Division of Solid Waste Management	NCD047373766	06/25/92	10/15/99
Wastewater Discharge Permit	Greenville Utilities Commission	BW01-98	05/03/93	05/03/98
Solid Waste Permit	North Carolina Department of Environment, Health and Natural Resources Division of Solid Waste Management	74-03-1	07/07/92	^b

^a NPDES permit (NC0001058) is currently expired however Burroughs Wellcome Co. has applied for a new permit. Until the new permit is issued, the current (expired) permit remains effective, in accordance with the provisions contain in 40 CFR 122.6, Continuation of Expiring Permits

^b Subject to review every five years



Wellcome

The Wellcome Foundation Ltd

Tripartite Hill, Dartford
Kent DA11 5AB

telex 913770
fax 01822 291831
teletext 0322 227486

crh25w.mh

27/06/94

Centre for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville
MD 20857

TO WHOM IT MAY CONCERN

The following information is provided in relation to the formulation of FLOLAN for injection.

The Wellcome Foundation Limited states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements in authorisations, licences, consents and regulations applicable to its facilities at Dartford, Kent, United Kingdom.

In summary, the Wellcome Foundation Limited states that it is in compliance with all environmental laws, including regulations, for its manufacturing facility at Dartford, Kent, United Kingdom, for the formulation of FLOLAN injection.

Yours faithfully

C R Heap
Environment Manager
Environmental Management Centre

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, MI 49001-0199

Environmental Quality Division
Randal S. Senger
Manager, Environmental Affairs
6602-306-1
Telephone No. (616) 323-5341

August 15, 1994

Drug Master File Staff
Food and Drug Administration
12420 Parklawn Drive, Room 2-14
Rockville, MD 20852

re: **DMF 6065**
Epoprostenol Sodium

Sir/Madam:

The Upjohn Company states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees or administrative orders applicable to the manufacture of epoprostenol sodium at its facilities in Kalamazoo, Michigan, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the manufacture of epoprostenol sodium at its facilities in Kalamazoo, Michigan.

The specific environmental regulations, along with permit numbers and expiration dates where applicable, are summarized in the table attached.

Sincerely,



Randal S. Senger

enc.

:dr usis@edr.com

TERRA™

Terra Environmental Resources
Regulated Air

Product of Terra Environmental Resources, Inc. 10000 Terra Blvd. Kalamazoo, MI 49001

**THE UPJOHN COMPANY
PERMIT INDEX**

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Consent Judgment	Michigan Department of Natural Resources, Air Quality Division		03/15/91	03/01/96
National Pollutant Discharge Elimination System (NPDES)	Michigan Department of Natural Resources Michigan Water Resources Commission	MI0002941	09/20/90	10/01/95
RCRA/Michigan Hazardous Waste Management Act 64 (On-site Incinerator)	Michigan Department of Natural Resources Waste Management Division	Incinerator being operated as a RCRA Interim Status Treatment Storage and Disposal Facility under #MID 00082038; pending action on Part B/Act 64 permit application.		
Michigan Air Pollution Act 38 (On-site Incinerator)	Michigan Department of Natural Resources Air Quality Division	242-80	07/15/80 (revised to incorporate the Act 64 requirements) approved 05/26/93	non-expiring until modified
Wastewater Discharge Permit	City of Kalamazoo Industrial Pretreatment Program	The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations/Industrial Control Document	03/25/94	03/31/99
Chemical Process Water Management (CPWM) Injection System (Class I wells) Underground Injection Control Permit	U.S. EPA, Region 5 Safe Drinking Water Act	MI-077-1W-0001 MI-077-1W-0002	07/09/93	10/27/96

8/15/94

**ATTACHMENT IV:
HYDROLYSIS REPORT**

The hydrolysis report consisting of a summary of readily available published data and copies of the publications used (pages 43-118 of the environmental assessment) have been excluded from the Finding of No Significant Impact (FONSI) by the FDA. An example reference is:

Cho, M.J.; Allen, M.A.; "Chemical Stability of Prostacyclin (PGI₂) in Aqueous Solutions;" Prostaglandins; Vol 15; No. 6; 943-954; 1978

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 28, 1994
FROM: Glen Jon Smith, HFD-102
THROUGH: Phillip G. Vincent, Ph.D.
Environmental Assessment Officer, HFD-102
SUBJECT: Environmental Concerns - NDA 20-444 Flolan®
(epoprostenol sodium) Injection
TO: Karen Oliver, HFD-180



The Center has reviewed the environmental assessment for the subject NDA.

Action: INADEQUATE

Please transmit the following to the firm and copy HFD-102.

Your environmental assessment has been carefully reviewed. Please address the following deficiencies.

1. Regarding Item 4:
 - A. Please submit complete and accurate addresses for each manufacturing site (drug substance, sterile powder and diluent).
 - B. Environmental Assessment END-0093 from submitted for the bulk drug substance is dated June 14, 1990. This EA is outdated and inadequate. Please submit an updated environmental assessment for the manufacture of the drug substance by Note that the confidential and non-confidential sections of the assessment must be incorporated into the respective sections of your environmental assessment.
 - C. Please submit certification from all appropriate foreign regulatory agencies that waste disposal within those countries will be in accordance with current environmental laws or regulations.
 - D. Please revise the description of the methods used for waste disposal to include all applicable permit

numbers, issuing agents and expiration dates. Do not submit entire copies of each permit.

2. Regarding Item 5:

- A. Please revise Item 5 to include a physical description of the drug substance.
- B. You have indicated that the drug substance is subject to rapid hydrolysis, especially in non-alkaline conditions. Please submit a copy of the hydrolysis study and testing results. Note that the submission should be a stand-alone document and meet all criteria as defined in Technical Assistance Document 3.09 of the Environmental Assessment Technical Handbook.
- C. The rapid hydrolysis of the drug substance indicates that hydrolysis products will be emitted into the environment rather than drug substance. Please identify the hydrolysis product(s) and submit with any additional information (e.g. CAS numbers, toxicity).
- D. The Material Safety Data Sheets submitted for the drug substance and drug product are public documents and cannot be submitted in confidential appendices. Please revise your EA accordingly.

3. Regarding Item 6:

This section of the environmental assessment did not contain sufficient information to allow for accurate analysis. Please revise this section taking into consideration the following comments.

- A. Item 6 should be formatted on a per facility or on a per process basis. All information regarding substances emitted, controls exercised, permitted emission levels and the effect the approval will have on compliance with current emissions requirements for a specific site/process should be contained in a single, continuous section. Do not group information regarding several different facilities or process steps in a single section (e.g. controls exercised).
- B. Each list of substances expected to be emitted contained statements indicating that inclusion in the list does not necessarily indicate that the materials are emitted into the environment. Please remove this type of statement. Since the lists must include all substances which are expected to be emitted, inclusion of statements of this nature are contradictory.
- C. The description of the controls exercised did not contain sufficient detail to allow for adequate

evaluation. Please revise these descriptions to include the type of waste processed, the basis of operation for the control system, and the efficiency for each control.

- D. Please revise your description of applicable emission requirements to include the identification of the regulation, the regulatory authority, the permit number, the expiration date and applicable limits for each emission allowed by the permit.
- E. Please submit formal, signed statements of compliance for each facility. Note that a separate document must be submitted for each facility.
- F. Please submit calculations to support your conclusion for the effects of the approval of the proposed action. These calculations should use the expected emission levels of all substances, the efficiencies of the applicable controls, permit levels and current emission levels to estimate the effect of the approval of the proposed action will have upon current emission requirements at each production site. Analysis must be conducted for each facility, and analysis for individual process steps for the manufacturing process may be necessary depending upon the nature and complexity of process. Note that the level of detail needed should be sufficient to support any conclusions regarding the effect on emission requirements.

Note that when submitting information for production in foreign countries, you may find that it is more convenient to obtain a letter or letters from the appropriate officer(s) of the foreign government stating that the manufacture of the product(s) that is the subject of the application has been evaluated by that government and that it meets their requirements for emissions and occupational controls. Provided that the letter(s) has some specificity about the drug substance and/or the drug product that would be manufactured under the NDA and the government's requirements, such a letter can be used in lieu of the information requested in section 6 of the EA format. Note that the letters must include the names and signatures of the appropriate officials, dates of signing and confirmatory seals or insignia where applicable. Letters written in a language other than English must be accompanied by a certified English translation. All documents submitted must be clear and legible.

- G. Since the drug product is indicated for a rare disease, calculations of Maximum Expected Emitted Concentrations using a constant based on the entire population of the

U.S. does not appear to be appropriate. A more realistic estimate should be based on the number of patients with the condition for which the drug substance is indicated. In addition, the apparently rapid hydrolysis of the drug substance in neutral to acid solutions suggests that MEEC and EEC values should be calculated for the hydrolysis products rather than the drug substance. Please submit new estimates for MEEC and EEC values taking these points into consideration.

4. Item 12: The Curricula Vitae for the preparers should be part of the Environmental Assessment and cannot be placed in a confidential appendix. Please add the CVs for each preparer to the EA.
5. Item 13: The certification submitted failed to include the word "accurate" as shown in 21 CFR 25.31a. Please revise. Note that all sign-off sheets in the EA must have the name of the signing individual(s) typed as well as the signature.
6. Item 14: Please submit a complete list of all referenced materials. The EA for _____ and federal, state and local regulations should be included in this section. Note that this does not require inclusion of the actual text or copies of the regulations. Do not supply copies of regulations unless requested.

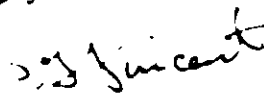
Please note that the abbreviation of certain requirements of the environmental assessment format per 21 CFR 25.31a(b)(3) appears to be appropriate at this time. However, the Agency reserves the right to request additional information as needed to reach a final determination regarding the proposed action.

Endorsements:

HFD-102/GJSmith

HFD-102/PGVincent

 4/29/97

 4-29-97

cc: Original NDA 20-444
EA File 20444.REV
Division File/HFD-180
Supervisory Chemist/HFD-180

20444E00.LGS/GJSEA#01

F/T by GJS/ 4 2 1 97.

Integrated Summ.

No Pages
Are missing

9.7 Integrated Summary Of Efficacy In Patients With Primary Pulmonary Hypertension

9.7.1 Survival

9.7.1.1 Introduction and Analysis Plan

In this section, the effect of FLOLAN[®] (epoprostenol sodium) on survival was analyzed separately for Study 35/36 and Study 46. A proportional hazards model was used. Though not formally analyzed, only descriptive survival statistics were calculated for Studies 35/36 and 37, combined. Similar descriptive statistics were calculated for data from Studies 46 and 47, combined. In each case, data were censored for patients who were originally randomized to standard therapy in Study 35/36 or 46 and who elected FLOLAN in Study 37 or 47. Data were censored at the time of entry into Study 37 or Study 47. Data were also censored in each trial at the time of transplant for patients that received a transplant during the observation period.

In addition to these analyses, the effect of FLOLAN on survival was also analyzed using the combined data from all 104 Class III/IV patients enrolled in Studies 35/36, 37, 46, and 47 in a proportional hazards model. The two Class II patients enrolled in Study 35/36 were not included in this analysis. As above, data were censored for patients originally randomized to standard therapy who elected to receive FLOLAN in Study 37 or 47. Censoring occurred at the time of entry into these trials. Data also were censored at the time of transplant in appropriate patients. In an effort to evaluate determinants of survival other than FLOLAN, survival was analyzed using proportional hazards models that analyzed the impact on survival of FLOLAN and each of the following covariates individually:

1. Demographics and baseline variables: gender, NYHA classification, race, age, exercise capacity and body weight.
2. Baseline hemodynamic response to the maximum tolerated dose of FLOLAN for the following variables: CI, PAPm, RAPm, TPR, TSR and mixed venous saturation. Response was expressed as percent change-from-baseline
3. Baseline use of digoxin, calcium-channel blockers, all vasodilators (combined) and diuretics.

Because of censoring in this analysis, only 8 patients were included in the long-term follow-up of the control group.

To further evaluate the effect of FLOLAN on survival that was observed in studies sponsored by Burroughs Wellcome Co., a comparison with a historical control was made. Survival in 138 Class III/IV patients who were treated with standard therapy (no FLOLAN) and enrolled in the NIH

Registry was summarized and compared to survival in Class III/IV patients treated with FLOLAN® (epoprostenol sodium) in Studies 35/36, 37, 46 and 47, combined. As discussed below in Section 9.7.1.5, a time-dependent analysis of covariates was used. As in the combined analysis of Studies 35/36, 37, 46, and 47, determinants of survival, other than FLOLAN, were evaluated. However, since the acute response to FLOLAN of selected hemodynamic variables was not available for patients enrolled in the NIH Registry, baseline hemodynamic measurement values, not their response to FLOLAN during dose-ranging, were used in this analysis. In addition to baseline hemodynamic variables other covariates used in this analysis were gender, NYHA classification, race, and age. These covariates were selected based on their availability in the NIH Registry.

9.7.1.2 *Trials Sponsored by Burroughs Wellcome Co.*

Study 35/36 and Study 37

Survival was followed for 8 weeks in the 25 patients enrolled in Study 35/36. Overall demographics and baseline hemodynamic parameters were similar between the 11 patients treated with FLOLAN and the 14 treated with standard therapy (Section 9.5 and Section 9.7.4).

The distribution of NYHA functional class for both treatment groups is summarized below. The imbalance in distribution of Class IV patients was addressed by including baseline NYHA Classification as a covariate in the overall analysis of survival described in Section 9.7.1.3.

Class	Standard Therapy, n (%)	FLOLAN, n (%)
I	0 (0%)	0 (0%)
II	1 (7%)	1 (9%)
III	7 (50%)	8 (73%)
IV	6 (43%)	2 (18%)

Patient disposition through Study 35/36 is summarized in Table 3. During the eight-week treatment period, one patient of the 11 randomized to FLOLAN died; three patients of the 14 randomized to standard therapy died. The Kaplan-Meier survival analysis is shown in Figure 1. This difference in mortality did not reach statistical significance ($p = 0.39$; two-tailed log rank test).

Patient progression and deaths through 1 December 1992 are summarized in Table 4. The number of patients followed in both treatment groups and the estimated probability of survival in Studies 35/36 and 37 is summarized in Table 31. The Kaplan-Meier analysis for Study 35/36 and 37 is presented in Figure 2. All ten patients randomized to FLOLAN who survived the eight week treatment elected to continue FLOLAN; eight of the 11 randomized to standard therapy who survived elected to receive FLOLAN in Study 37. The median survival was 40.5 months in the FLOLAN therapy group versus

8.8 months in the standard therapy group. It is important to note that only three standard therapy patients who were enrolled in Study 35/36 did not elect FLOLAN® (epoprostenol sodium) in Study 37. Analysis of survival longer than 8 weeks contains only these 3 standard therapy patients, making survival beyond eight weeks difficult to interpret.

Study 46 and Study 47

Survival was followed for 12 weeks in 81 patients randomized in Study 46. Overall demographics and baseline hemodynamics were similar between the 41 patients treated with FLOLAN and the 40 patients treated with standard therapy (Section 9.5, Section 9.7.4). Approximately 75% of patients in both treatment groups were NYHA Class III; the remainder were NYHA Class IV. During the 12-week treatment period in Study 46, three patients received transplants and their data were censored at the time of transplant. Two patients elected to withdraw from FLOLAN therapy during the treatment period. These patients remained in the analysis as randomized.

Patient disposition through Study 46 is summarized in Table 3. Figure 3 displays the Kaplan-Meier survival analysis for Study 46. During the twelve-week treatment period, eight patients randomized to standard therapy died; no FLOLAN patient died. The difference in survival was significant ($p = 0.003$; two-sided log rank test).

Patient disposition in Study 47 through 1 December 1992 for both treatment groups is summarized in Table 4. The number of patients followed and the probability of survival are summarized in Table 32. The Kaplan-Meier survival analysis for these data is shown in Figure 4. Sixty-four patients entered Study 47. Thirty-eight of the 40 patients randomized to FLOLAN who survived the 12-week treatment and did not receive a transplant elected to continue FLOLAN; 26 of the 30 patients, who were randomized to standard therapy and survived and did not receive a transplant, elected to receive FLOLAN in Study 47. Of the six patients who declined entry into Study 47, one was lost to follow-up (data censored at patient's dismissal from Study 46), two were transplanted and three remained alive. Median survival could not be calculated since neither treatment group reached 50% mortality.

Combined Analysis: Studies 35/36, 37, 46, and 47

Survival was followed until 1 December 1992 in the 104 Class III/IV patients enrolled in all studies sponsored by Burroughs Wellcome Co. Overall demographics and baseline hemodynamics were similar between the patients who received FLOLAN and the patients who received standard therapy (Section 9.5, and Section 9.7.4). As in the general population of patients with PPH, patients in both treatment groups were predominantly young (average age 38 years), white (approximately 84%), and female (approximately 72%). The baseline distribution of NYHA Class for patients in these trials is summarized below.

Class	Standard Therapy, n (%)	FLOLAN [®] , n (%)
I	0 (0%)	0 (0%)
II	0 (0%)	0 (0%)
III	36 (67%)	39 (75%)
IV	17 (31%)	12 (23%)

The number of patients followed and the estimated probability of survival are shown in Table 33. The Kaplan-Meier summary is presented in Figure 5. In this analysis, data from the one patient lost to follow-up after being dismissed from Study 46 were censored at the end of Study 46. Survival was significantly improved ($p = 0.0001$) in patients receiving FLOLAN[®] (epoprostenol sodium). The median survival of FLOLAN therapy patients was 40.4 months compared to 8.8 months in patients treated with standard therapy.

The effect of FLOLAN on survival was analyzed using 18 different proportional hazards models (Table 34). Each model included FLOLAN and one of the covariates described previously (Section 9.4). Because this analysis is exploratory, adjustment to the level of significance for multiple comparisons was not made. As shown below, FLOLAN treatment remained a strong determinant of survival in each model. Other than baseline walk, none of the demographic or baseline variables or the acute hemodynamic response to FLOLAN were significant predictors of survival. Although baseline walk may be related to survival ($p = 0.02$), the importance, based on relative risk, is small. Similarly, after correcting for the effect of FLOLAN therapy, the use of concomitant medications at baseline were not significant determinants of survival, although the use of digoxin, calcium channel blockers and diuretics at baseline may have been associated with decreased survival in patients treated with FLOLAN. The use of these agents with FLOLAN may be indicative of a sicker group of patients with higher mortality.

Model Number	Baseline Covariate	FLOLAN® effect p-value	Relative Risk
1	No covariate	0.0012	0.16
2	Gender	0.0013	0.16
3	NYHA classification	0.0024	0.18
4	Race	0.0023	0.17
5	Age	0.0015	0.16
6	Change in CI	0.0012	0.14
7	Change in PAPm	0.0011	0.15
8	Change in RAPm	0.0034	0.15
9	Change in SVO ₂	0.0277	0.20
10	Change in TPR	0.0008	0.11
11	Change in TSR	0.0004	0.12
12	Ideal body weight	0.0012	0.15
13	Actual/Ideal body weight	0.0010	0.14
14	Exercise	0.0098	0.23
15	Digoxin	0.0086	0.21
16	Calcium channel blocker	0.0034	0.20
17	All vasodilators	0.0013	0.15
18	Diuretics	0.0007	0.13

9.7.1.3 FLOLAN® (epoprostenol sodium) Versus Standard Therapy (U.S. National Registry)

The National Institutes of Health initiated a prospective, multicenter, observational study of patients with PPH on 1 July 1981; enrollment was discontinued on 30 September 1985 and patients were followed until 8 August 1988. A total of 194 NYHA Class I-IV patients were enrolled; 138 patients were Class III or IV and survival in these Class III and IV patients was compared to survival in Class III and IV patients who received FLOLAN in studies sponsored by Burroughs Wellcome Co. All patients in the NIH Registry were treated with standard therapy; no patient was treated with chronic FLOLAN therapy. A diagnostic right heart catheterization was performed in each patient prior to entry, and each patient was classified as to NYHA Class. All patients were followed at six-month intervals. For each death, the cause of death was recorded. In the event a patient received a heart-lung or single lung transplant, the date of transplant was recorded; data were censored at the time of transplant.

As shown in Table 35, the demographics and baseline hemodynamics were similar between Class III/IV patients randomized to FLOLAN and standard therapy in studies sponsored by Burroughs Wellcome Co. and Class III/IV patients enrolled in the NIH Registry. Of the 242 patients, most were young

(mean age 38–39), white (76%–84%), and female (67%–73%). The majority were NYHA Class III (68%–79%).

The number of Class III/IV patients followed and the estimated probability of survival in patients randomized to FLOLAN® (epoprostenol sodium) or standard therapy in Burroughs Wellcome Co. trials and patients enrolled in the NIH Registry are summarized in Table 36. As shown in the Kaplan-Meier survival summary (Figure 6), survival profiles were similar during the first 12 weeks in patients randomized to standard therapy in the Burroughs Wellcome Co. trials and patients enrolled in the NIH Registry. After this time only 4 standard therapy patients were followed in Burroughs Wellcome Co. trials; no meaningful comparisons can be made between control groups beyond 12 weeks.

As shown, the difference in survival between FLOLAN patients and the patients enrolled in the NIH Registry appears relatively constant for the first 30 months of follow-up; only 4 FLOLAN patients were followed beyond 30 months in the Burroughs Wellcome Co. trials. Survival estimates become very unstable and imprecise under these circumstances. These data did not meet the proportional hazards assumption necessary for Cox regression. Inspection of the curves shows that mortality in the standard therapy group decreased after the first two to three months, while mortality in the FLOLAN group increased after the first six to eight months. Because of this nonproportionality, an analysis with time-dependent covariates was undertaken. This analysis has the additional advantage that makes use of data from standard therapy patients who began FLOLAN therapy after completing the controlled trial. In this analysis, as in other analyses, patients' data were censored at the time of transplant. Patient data were censored at the end of Study 46 for the single patient lost to follow-up after completing Study 46. Using this analysis, survival was improved significantly ($p = 0.0001$) in patients who were receiving FLOLAN compared to those who were not receiving FLOLAN.

As in the preceding combined analysis of Studies 35/36, 37, 46, and 47, the ability of covariates to predict survival was evaluated. A summary of the effect of FLOLAN on survival in 12 models using time-dependent covariate analyses is presented in Table 37. Characteristics of each model and the p -value for the effect of FLOLAN on survival are summarized below. The use of FLOLAN is associated with a significant improvement in survival after adjusting for each baseline covariate. Based on the relative risk statistic, the risk of dying while receiving FLOLAN is less than 24% of the risk of dying while not receiving FLOLAN.

Model Number	Covariate	FLOLAN® effect p-value	Relative Risk
1	None	0.0001	0.24
2	NIH	0.0002	0.18
3	NIH, Gender	0.0002	0.18
4	NIH, NYHA Class (baseline)	0.0004	0.19
5	NIH, Race	0.0003	0.18
6	NIH, Age (baseline)	0.0002	0.18
7	NIH, CI (baseline)	0.0001	0.16
8	NIH, PAPm (baseline)	0.0001	0.17
9	NIH, RAPm (baseline)	0.0002	0.15
10	NIH, TPR (baseline)	0.0001	0.16
11	NIH, PVR (baseline)	0.0057	0.20
12	NIH, TSR (baseline)	0.0002	0.17

Table 37 summarizes the impact of baseline covariates on survival after adjusting for the use of FLOLAN® (epoprostenol sodium). As in the NIH Registry, baseline NYHA classification, cardiac index, mean pulmonary artery pressure, mean right atrial pressure, total peripheral resistance, and pulmonary vascular resistance remain significantly important predictors of survival.

Adjusting for baseline covariates of mean right atrial pressure, pulmonary vascular resistance and total systemic resistance combined, in a multivariate time-dependent analysis, survival remained significantly improved ($p = 0.006$, Table 38) in patients receiving FLOLAN.

9.7.1.4 Discussion

Data from two different sources were used to assess the effect of FLOLAN on survival in Class III/IV patients with PPH: (1) trials sponsored by Burroughs Wellcome Co. and (2) data from the U.S. National Registry of Patients with PPH, which was used as an historical control. Analyses compared survival in Class III/IV patients who received long-term continuous infusion of FLOLAN to survival in Class III/IV patients treated with any other therapy which included single or combined use of calcium channel blockers, angiotensin converting enzyme inhibitors, other vasodilators, diuretics, and/or digoxin.

In Study 46, FLOLAN significantly improved the survival of Class III/IV patients who received FLOLAN compared to those who did not. When data from all studies sponsored by Burroughs Wellcome were combined and analyzed, survival was significantly improved in patients who received FLOLAN. Survival data from Class III/IV patients enrolled in trials sponsored by Burroughs Wellcome Co. were combined and compared to

survival of Class III/IV patients enrolled in the NIH Registry. Survival was significantly improved in patients who were receiving FLOLAN® (epoprostenol sodium). When NYHA Class was used as a covariate with FLOLAN, the use of FLOLAN remained a strong and important predictor of survival. This analysis indicates that survival was improved in Class III and in Class IV patients who received FLOLAN. Though not shown, there was no evidence of a significant interaction between FLOLAN use and NYHA classification, indicating that FLOLAN has a similar magnitude of effect on survival in Class III and Class IV patients.

In conclusion, a consistent benefit in survival was demonstrated across all studies sponsored by Burroughs Wellcome Co. in patients with NYHA Class III and NYHA Class IV PPH who received FLOLAN. Survival was also significantly improved in Class III/IV patients who received FLOLAN in studies sponsored by Burroughs Wellcome Co. compared to similar patients enrolled in the NIH Registry who did not receive FLOLAN. The effect of FLOLAN on survival was demonstrated both in NYHA Class III and in NYHA Class IV patients.

9.7.2 *Exercise Capacity*

9.7.2.1 *Introduction*

The effects of FLOLAN® (epoprostenol sodium) therapy on exercise capacity were analyzed using two different methods. The first, or preferred, analysis was an intent-to-treat, non-parametric analysis of covariance, adjusted for distance walked at baseline and oral vasodilator use at baseline. Distances walked at Week 8 or 12 for patients who died or did not perform the walk were assigned lowest rank for the purpose of calculating the test statistic. Patients who received a transplant during the study, returned at the conclusion of the study and exercise capacity was evaluated; these data were used in the analysis. If patients discontinued FLOLAN therapy, exercise capacity was evaluated at Week 8 or 12, as appropriate; these assessments were included in the analyses. In two instances in Study 35/36, patients walked longer than 6 minutes; these distances were corrected by prorating each distance to six minutes.

A second analysis was performed. This analysis was an intent-to-treat, parametric analysis of variance. The last assessment of exercise was carried forward to Week 8 or 12 for patients who died during the chronic treatment phase. For patients who received a transplant, the last pre-transplant assessment of exercise was carried forward to Week 8 or 12, as appropriate.

Using these analyses and conventions, the effect of FLOLAN therapy on exercise capacity has been summarized by comparing between-treatment changes from baseline to Week 8 in Study 35/36 and Week 12 in Study 46, separately. Exercise capacities at Week 8, in Study 35/36, were combined with those at Week 12, in Study 46, and changes from baseline to last visit were compared for the two treatment groups.

In addition to these two primary analyses, descriptive statistics were calculated comparing baseline exercise to exercise capacity at Week 1 in Studies 35/36 and 46, combined. The effect of long-term FLOLAN therapy was also summarized descriptively by comparing exercise capacity at baseline in Study 35/36 to exercise assessments determined at six month intervals for up to 30 months in Study 37.

In an effort to evaluate other determinants of improvement in exercise, exercise capacity was analyzed using a multivariate parametric linear model, adjusting for baseline walk. In this analysis, exercise assessments at Weeks 8 and 12 were combined. Covariates were baseline age, gender, race, and acute hemodynamic response of TPR, CO, PAPm and RAIPm to FLOLAN. The chronic use of concomitant medications (i.e., diuretics, digoxin, calcium-channel blockers and all vasodilators) was also a covariate.

9.7.2.2 *Individual Study Analyses*

Study 35/36: Baseline vs. Week 8

Demographics and oral vasodilator use at baseline (Section 9.5) were similar for the two treatment groups. As shown in the individual study report, the

hemodynamic effects of acute administration of FLOLAN® (epoprostenol sodium) were similar for the two groups, suggesting similar residual pulmonary vasoreactivity at baseline. Baseline mean exercise capacity was slightly less in patients randomized to FLOLAN therapy than in patients randomized to standard therapy (213 meters vs. 254 meters); fewer Class IV patients were randomized to FLOLAN therapy (2 vs. 6).

Three patients (1 FLOLAN; 2 Standard therapy) died during the treatment phase. No patient underwent transplantation and no patient discontinued FLOLAN therapy prematurely. As discussed previously, two patients walked longer than six minutes; patient 35001 walked 320 meters during 9 minutes and patient 35020 walked 293 meters during 10 minutes. One other standard therapy patient could not walk at Week 8. The underlying reason for his inability to walk is unclear. Though the patient was suspected of having gout at his Week 8 assessment, the diagnosis of gout was not confirmed, nor was the patient receiving treatment for gout. Data for the Week 8 assessment were assigned lowest rank.

As shown in Table 39 and summarized below, median change from baseline in exercise capacity in patients treated with FLOLAN for 8 weeks was +111 meters compared to +17 meters in standard therapy patients. The difference between treatments in improvement in exercise capacity was significant ($p = 0.045$). At the end of Week 8, patients in the FLOLAN group walked 386 meters (median) and the standard therapy patients walked 248 meters (median).

Summary of Between-Treatment Comparison of Exercise Capacity
Study 35/36

FLOLAN therapy				Standard therapy				p value
Baseline Median N	Week 8 Median (meters)	Change from Baseline Median (meters)		Baseline Median N	Week 8 Median (meters)	Change from Baseline Median (meters)		
11	213	386	111	14	254	248	17	0.045

Using the parametric analysis of variance (Table 40), exercise capacity improved more in FLOLAN-treated patients (mean: +139 meters) at Week 8 than in standard therapy patients (mean: +28 meters). The difference was significant ($p = 0.043$).

Study 46: Baseline vs. Week 12

As in Study 35/36, baseline demographics and oral vasodilator use were similar between the two treatment groups (Section 9.5). Baseline distribution on NYHA classification was similar between the two treatment groups. As shown in the study report, the hemodynamic effects of acute administration of FLOLAN were similar between the two groups, suggesting similar residual pulmonary vasoreactivity at baseline. In contrast to Study 35/36 where

patients randomized to standard therapy walked further at baseline, patients randomized to FLOLAN® (epoprostenol sodium) walked further at baseline in Study 46 (315 meters vs. 270 meters).

Eight patients (0 FLOLAN, 8 Standard therapy) died during the treatment phase. Three patients (1 FLOLAN, 2 Standard therapy) underwent transplantation during the chronic treatment phase; exercise capacity was evaluated in these patients at Week 12 and was included in this analysis.

As shown in Table 39 and summarized below, median change from baseline exercise capacity in patients treated with FLOLAN for 12 weeks was +31 meters compared to -29 meters for standard therapy patients. Using the nonparametric analysis of covariance, the between-treatment difference was significant ($p = 0.002$). As in Study 35/36, after 12 weeks patients in the FLOLAN group walked 362 meters (median); standard therapy patients walked 204 meters (median).

Summary of Between-Treatment Comparison of Exercise Capacity
Study 46

FLOLAN therapy				Standard therapy				p value
Baseline Median (meters)	Week 12 Median (meters)	Change from Baseline Median (meters)	N	Baseline Median (meters)	Week 12 Median (meters)	Change from Baseline Median (meters)	N	
315	362	31	41	270	204	-29	40	0.002

Using the parametric analysis of variance (Table 40), the between-treatment improvement in exercise capacity after 12 weeks was greater in FLOLAN patients (mean: +32 meters) than standard therapy patients (mean: -15 meters). The difference was significant ($p = 0.003$).

9.7.2.3 *Integration of Studies 35/36 and 46*

As shown above, two multicenter, open-label, randomized, parallel, and well controlled trials have independently demonstrated that patients who received FLOLAN chronically had significantly greater improvement in exercise capacity than patients who did not receive FLOLAN. Data from Weeks 8 and 12 in these two trials were combined and compared to the combined baseline evaluation. As in each study, the preferred analysis used for these composite data was an intent-to-treat, nonparametric analysis of covariance.

The preferred analysis of composite data used the conventions noted in the individual study preferred analyses for patients who died, underwent transplantation, were discontinued prematurely from FLOLAN or did not walk during the treatment phase or at the last visit.

Baseline vs. Weeks 8 and 12 combined

Between-treatment comparisons of the distances walked at baseline and at Weeks 8 and 12, combined, using the preferred analysis are listed in Table 39

and summarized below. Median change from baseline exercise capacity in patients treated with FLOLAN® (epoprostenol sodium) was +49 meters compared to -4 meters for standard therapy patients. The between-treatment difference was significant (p = 0.001). As in each individual trial, patients walked further after chronic treatment with FLOLAN compared to standard therapy patients (373 meters vs. 204 meters).

Week 8 and 12 Combined Summary of Between-Treatment Comparisons of 6-Minute Walk - Nonparametric Analysis of Covariance

FLOLAN therapy				Standard therapy				p value
Baseline Median (meters)	Weeks 8 and 12 Median (meters)	Change from Baseline Median (meters)	N	Baseline Median (meters)	Weeks 8 and 12 Median (meters)	Change from Baseline Median (meters)	N	
301	373	49	52	266	204	-4	54	0.001

As shown in Table 40 and summarized below, exercise capacity, analyzed using the parametric analysis of variance, was significantly improved (p = 0.001) after patients received FLOLAN (mean: +55 meters) compared to patients who received only standard therapy (mean: -4 meters).

Weeks 8 and 12 Combined Summary of Between-Treatment Comparisons of 6-Minute Walk - Analysis of Variance

FLOLAN® therapy				Standard therapy				p value
Baseline Mean (meters)	Weeks 8 and 12 Mean (meters)	Mean Change from Baseline (meters)	N	Baseline Mean (meters)	Weeks 8 and 12 Mean (meters)	Mean Change from Baseline (meters)	N	
297	351	55	52	257	253	-4	54	0.001

Baseline vs Weeks 1, 4, and 6

A 6-minute walk test was performed during the first week of therapy and at the midpoint of each study. As shown in Table 40 and below, mean change from baseline exercise capacity in patients treated with FLOLAN for one week was +30 meters, compared to -16 meters for standard therapy patients. As shown in individual study reports, improvement in exercise capacity that was apparent at Week 1 appeared to be maintained at Week 4 and at Week 6 in patients receiving FLOLAN compared to patients receiving standard therapy (Sections 4.2 and 4.3).

**Summary of Week 1 Between-Treatment Comparisons of
6-Minute Walk – Analysis of Variance**

FLOLAN® therapy				Standard therapy			
	Baseline Mean (meters)	Week 1 Mean (meters)	Change from Baseline Mean (meters)	N	Baseline Mean (meters)	Week 1 Mean (meters)	Mean Change from Baseline (meters)
52	297	326	30	54	257	241	-16

Effect of Long-term FLOLAN® (epoprostenol sodium) Therapy on Exercise Capacity

The effect of chronic FLOLAN infusions on exercise capacity was assessed at 6-month intervals in Study 37 (Table 41). Of the 18 patients electing to receive FLOLAN in this study, 6 have been followed for up to 30 months. As shown in Table 41 and summarized below, there was no obvious deterioration in exercise capacity in these patients during 30 months of FLOLAN therapy.

Six Minute Walk – Chronic Infusion

	N	Mean Change from Baseline (meters)
6 months	15	113
12 months	12	67
18 months	11	111
24 months	7	119
30 months	6	101

Exercise capacity has been evaluated for up to 42 months in three patients. One patient continues to walk over 150 meters more than at baseline (442 meters vs. 278 meters); another patient continues to walk over 100 meters further (214 meters vs. 109 meters). Exercise capacity was transiently improved over 18 months in a third patient, but was reduced from 110 meters at baseline to 60 meters at 42 months.

9.7.2.4 Drug-Demographic, Drug-Drug and Drug-Hemodynamic Interactions

As shown below and in Table 42, baseline age, race or gender were not predictors of improvement in exercise capacity:

Covariate	p-value
Age	0.954
Race	0.568
Gender	0.435

As expected, baseline walk was highly predictive of final walk in an individual patient. However, none of the baseline or concomitant medication variables demonstrated a statistically significant association with final walk.

9.7.2.5 *Summary*

Two multicenter, open-label, randomized, parallel, and well controlled clinical trials in severely ill (NYHA Class III/IV) patients with PPH receiving FLOLAN® (epoprostenol sodium) plus standard therapy as compared to patients receiving standard therapy alone were conducted to assess FLOLAN's effect on exercise capacity. The primary analysis for these trials assessed the improvement in exercise capacity from baseline to the end of the chronic treatment phase (Week 8 or 12).

Analyses of exercise capacity were confounded by unequal survival in the two treatment groups. In Study 35/36, one of 11 FLOLAN patients and two of 14 standard therapy patients died. In Study 46, eight of 40 standard therapy patients died while no FLOLAN patient died. If data were excluded for patients who died during chronic treatment, the analysis could be biased in favor of the treatment with the highest mortality (i.e. standard therapy group) since the sickest patients who presumably would exercise less, would be excluded due to death. Exclusion of patients who died is particularly problematic in studies with limited patient enrollment due to the loss of power to detect the between-treatment differences. Other alternatives to excluding these data have been proposed, including (1) assigning 0 meters to distance walked for each of these patients, (2) carrying the last observation of exercise forward to Week 8 or 12 for each of these patients and using an analysis of variance, and (3) assigning lowest rank to the change-from-baseline for each patient and using a nonparametric analysis of covariance.

Of these alternatives, the assignment of lowest rank was chosen for the preferred analysis in these studies. This solution assumes that patients who died were the sickest, and their improvement in exercise would have been the least, and therefore assigned lowest rank. Change in exercise capacity for patients who could not walk for other medical reasons was also assigned lowest rank. Exercise capacity, using this analysis, was significantly improved in patients receiving FLOLAN for 8 or 12 weeks compared to patients receiving standard therapy alone. Median exercise capacity was significantly improved ($p = 0.045$) by approximately 100 meters in one trial and by 50 meters ($p = 0.002$) in the other. Combining data from both trials, median exercise capacity was significantly ($p = 0.001$) improved by approximately 60 meters in patients who received FLOLAN.

Mean exercise capacity was improved by 38 meters by the end of the first week of treatment, and remained improved at Weeks 4 and 6. This apparent early onset of consistent improvement in exercise supports the validity of combining data at Weeks 8 and 12.

In a second analysis (parametric analysis of variance), exercise at the end of each study was improved more in patients who received FLOLAN than in those who received standard therapy. Across both trials, mean exercise capacity was improved by approximately 55 meters in FLOLAN patients, but

was decreased by approximately 4 meters in patients randomized to standard therapy.

Furthermore, exercise did not appear to deteriorate in patients followed for up to 30 months in a continuation study (Study 37). Six patients who were followed for 30 months in Study 37, continued to walk over 150 meters more than before having received FLOLAN® (epoprostenol sodium), suggesting a continued long-term benefit from FLOLAN.

No baseline demographic variable or baseline acute hemodynamic response were significant predictors of improved exercise capacity. The chronic use of concomitant medications generally used to treat patients with PPH also was not predictive of improved exercise. However, baseline walk was highly predictive of final walk in an individual patient.

Continuous intravenous administration of FLOLAN has been shown to significantly improve exercise capacity in two well controlled clinical studies. These improvements at Weeks 8 and 12 were also evident as early as the first week of therapy, and appear to be maintained long-term. The substantial and consistent improvement in exercise capacity seen in patients treated with continuous infusions of FLOLAN paralleled the improvement in hemodynamic parameters and quality of life described in Sections 9.7.4 and 9.7.3, respectively.

9.7.3 *Quality of Life*

9.7.3.1 *Nottingham Health Profile*

The NHP, a written self-administered questionnaire, was selected as a general, disease non-specific measure of quality of life for use in PPH trials for the following reasons:

- it has been shown to be reliable and valid across a wide range of health states and
- it is simple to complete and is self-administered.

The NHP measures an individual's perceived health status in several aspects of daily life and is composed of two parts. Part I of the NHP is composed of 38 statements covering six subscales: *sleep, energy, emotional reactions, social isolation, physical mobility and pain* (Appendix A). Respondents were asked to answer "yes" or "no" as to whether the statements apply to them at the time of completing the questionnaire.

To obtain a subscale score for Part I of the NHP, the responses for each item were added; "yes" answers received a score of 1 and indicate poorer quality of life, "no" answers received a score of 0 and indicate improved quality of life. As each subscale item varies in the severity of the experience it describes, a numerical weight was then combined with each affirmative response before calculating each subscale score. The numerical weights that are generally assigned with this instrument were those computed by Hunt et al. (47) obtained from interviews of representative patient and non-patient populations in published articles (47).

The weighted scores for each of the six subscales in Part I of the NHP ranged from 0 (best) to 100 (worst). A decrease in a subscale score in Part I of NHP indicates an improvement in quality of life for that dimension.

Part II of the NHP (Appendix A) was used to assess each patient's functional status in the following areas: *employment, jobs around the home, social life, personal relationships at home, sex life, hobbies and vacations*. As in Part I, a "yes" answer indicated that the patients' present state of health was causing problems with the specified area. Fewer patients giving an affirmative response in a dimension of Part II will result in a lower score for that dimension; this decreased score indicates that the patient's perception of their health has improved (47).

The NHP is recommended for use in populations of patients of 16 years of age and older (47). Thus, patients under 16 years of age enrolled in Study 35/36, Study 37 and Study 46 were excluded from the statistical analyses of Part I and Part II.

The NHP was administered at baseline, at the midpoint and at the conclusion of each controlled trial. For the purpose of this summary, baseline status in each dimension was compared to the patients' status in each dimension at

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Week 8 or Week 12, as appropriate. For the combined study analysis, Baseline data were combined from both controlled trials; also Week 8 data were combined with Week 12 data and analyzed as change from baseline. Data from the NHP administered at the midpoint of each trial were analyzed and presented in each individual study report; these results are not presented in this summary.

The NHP was administered for 48 months at 6 month intervals in Study 37. Results of each assessment in Part I were summarized to evaluate the long-term effects of FLOLAN® (epoprostenol sodium) on quality of life.

NHP subscale scores were not calculated for individual patients if an item in that dimension was not completed for the patient. Patients dying prior to completion of subsequent assessments were not included in the analyses.

NHP Part I

The means and standard errors for each subscale of Part I for all controlled studies at baseline and the end of the study are summarized in Table 43. In the FLOLAN group, each mean subscale score decreased compared to baseline, indicating a trend toward improvement in the patient's perception of their health state as measured by the NHP.

Table 44 shows the median change from baseline (i.e., paired observations) for the NHP subscale scores in all controlled studies separately, and combined across both trials. Between-treatment comparison of the change in NHP subscale scores for *energy, pain, physical mobility* and *social isolation* approached but did not reach statistical significance. Across the two controlled studies (Study 35/36 and Study 46), statistically significant improvements in the *emotional reaction* and *sleep* subscales of the NHP were observed in patients randomized to FLOLAN compared to patients randomized to standard therapy.

Mean scores for the NHP subscales for the uncontrolled Study 37 were also summarized (Table 45). Overall, there was no evidence that improvement in any dimension that was observed during the control trials was significantly diminished during long-term use of FLOLAN, despite disease progression.

NHP Part II

By the end of Study 35/36 no improvement or deterioration was noted in any area of Part II of the NHP for the FLOLAN treated patients and no difference was found between the FLOLAN and standard therapy group (Table 46, Table 47). During Study 46, however, statistically significant improvements were observed in patients treated with FLOLAN in the areas of *jobs around the home* (home life) and *vacations* (Table 48); overall there was no tendency for deterioration in any other dimension in patients receiving FLOLAN.

Discussion

Overall, the NHP indicated that, compared to patients randomized to standard therapy, the FLOLAN patients' perceptions of their health states

improved. This observation is consistent with the improvement in survival, exercise capacity and PPH symptoms observed in the FLOLAN® (epoprostenol sodium)-treated group. In the combined study analysis, *emotional reactions* and *sleep* were improved significantly more in patients randomized to FLOLAN compared to those randomized to standard therapy. Similar between-treatment trends were apparent in patients enrolled in each trial, separately, though these differences did not always reach statistical significance.

The improvements in Part II of the NHP seen in Study 46 in the areas of *jobs around the home* and *vacations* were consistent, given the increased exercise capacity experienced by the FLOLAN treated patients (Section 9.7.2). The smaller number of patients in Studies 35/36 and 37, and the lack of specificity of Part II of the NHP, may explain the lack of any trend in the results for these groups.

Due to the positive effect of FLOLAN on survival in each controlled study, more deaths occurred in the standard therapy group compared to the FLOLAN group. This increase in deaths in the standard therapy group may have resulted in improved mean scores for the quality of life instruments in the standard therapy group as the more severely ill patients died.

Mean scores for Part I of the NHP for heart transplant patients at three months following transplantation and for a normal population of females aged 35-44 have been published by Hunt et al. (47). End-of-trial scores for each dimension in these two patient populations have been compared to scores in patients who received FLOLAN or standard therapy for 8 or 12 weeks, combined (Table 49). The mean scores for *emotional reaction* and *pain* for the FLOLAN treated patients were similar to the mean scores for the normal population of females.

9.7.3.2 *Chronic Heart Failure Questionnaire*

Whereas the NHP assesses the patients' perceptions of their overall health status, disease-specific questionnaires focus on aspects of the patients' health most likely affected by their disease. Thus, disease-specific questionnaires tend to be more sensitive to changes in the patients' functioning that are directly related to their disease.

There was no disease-specific health assessment for patients with PPH. However, disease-specific questionnaires were available for patients with congestive heart failure, a disease with symptoms (dyspnea, fatigue) similar to those experienced by PPH patients. A disease-specific questionnaire developed for use in congestive heart failure, the CHQ (Chronic Heart Failure Questionnaire) was used to assess the impact of FLOLAN therapy in Study 46. No disease-specific questionnaire was used in Study 35/36.

The CHQ (Appendix B) has been validated to ensure that the test evaluates areas and emotional states that are important for patients with congestive

heart failure (41). The questionnaire is divided into four areas or dimensions: *dyspnea, fatigue, emotional function and mastery* (a patient's feeling of control over his/her disease).

The subscales of the CHQ, the range of possible scores, and the minimum changes perceived as clinically meaningful improvement (48) are described below:

Dimension	Number of Questions per Dimension	Minimum Score (Worst function)	Maximum Score (Best function)	Minimum Change for Clinically Significant Difference
Dyspnea	5	5	35	3
Fatigue	4	4	28	2
Emotional Function	7	7	49	4
Mastery	4	4	28	2

Each question in a dimension is rated on a seven point scale; 1 being the worst function and 7 being the best function. The score for each dimension is obtained by simply adding the scores for each question.

Scores for the *fatigue, emotional function or mastery* dimensions of the CHQ were not calculated if answers to questions were missing. As the questionnaire was interviewer-administered, it was rare that an item in one of these dimensions was not completed.

In contrast to scores for these dimensions, the dyspnea score was based on accomplishing specific physical activities over the preceding two weeks. In some instances an activity may not have been attempted over the observation period due to circumstances independent of the disease state of the patients. If one activity listed in the dyspnea dimension was not attempted during the previous two weeks, the dyspnea score was calculated using a formula described in the appendix to the medical report. If more than one activity was not attempted within the two weeks prior to the assessment, the dyspnea score was not calculated.

A designated individual was educated in the administration of the CHQ and was unaware of the patient's treatment assignment. Details of procedures used in educating the interviewers were outlined in Appendix C.

Patients completed the CHQ at Baseline, Week 6 and Week 12 of the study; results from these assessments were analyzed. Patients completed the questionnaire prior to any medical evaluation which could provide information as to the status of their medical condition. Patients under 18 years of age were not included in the statistical analyses of the CHQ, since the questionnaire has not been validated for patients under 18 years of age (41).

Means and standard errors for the CHQ for each evaluation are summarized in Table 50. Mean scores for each dimension of the CHQ for the

FLOLAN® (epoprostenol sodium)-treated group increased compared to baseline, indicating the patients' status in each dimension was improved.

Improvements from baseline were statistically significant in all subscales of the CHQ for the FLOLAN-treated group compared to the standard therapy group at Week 6 and Week 12 of the study (Table 50).

All of the CHQ subscales showed a clinically significant improvement within the FLOLAN-treated group (Table 51). Patients receiving standard therapy showed no clinically significant improvement in any of the subscales and in some subscales patients' quality of life may have deteriorated.

Discussion

The CHQ, a disease-specific instrument, indicated that patients with Class III/IV PPH treated with FLOLAN had an improvement in quality of life in all of the areas measured; the improvements as measured by the CHQ also were clinically significant. These changes confirmed the improvements in the quality of life as measured by the NHP.

Although these instruments did not directly address the difficulty in managing and maintaining the drug delivery system and preparation of FLOLAN, these factors did not outweigh the improvement in quality of life associated with FLOLAN therapy. In addition, quality of life assessed across all studies indicated that the patients' perceptions of their health state did not deteriorate over time with this chronic disease.

9.7.4 *Hemodynamic Profile*

The effects of FLOLAN® (epoprostenol sodium) on each parameter are summarized separately in the tables at the end of this section. For the purposes of discussion, a subset of these parameters (CI, PAP_m, PVR, SAP_m, SV and TPR) has been selected to characterize/summarize the effects of acute and chronic administration of FLOLAN on the hemodynamic profile of patients with PPH.

9.7.4.1 *Acute Administration of FLOLAN*

The acute hemodynamic effects of FLOLAN were evaluated in 389 of the 391 unique patients with PPH who entered the acute dose-ranging segments of all trials. Other than in Study 46, hemodynamics were measured at baseline and at each dose during the dose-ranging segments. In Study 46, hemodynamic parameters, other than CO and PCWP_m, were evaluated at each dose; CO and PCWP_m were evaluated only at baseline and at the highest tolerated dose.

Although 12 ng/kg/min was the maximum dose recommended by the protocol for many dose-ranging segments, higher doses were allowed based on the investigator's clinical judgment. However, because relatively few patients tolerated doses higher than 12 ng/kg/min, hemodynamic measurements from doses greater than 12 ng/kg/min were combined into a single category (" > 12 ") for the analyses. This >12 ng/kg/min category summarizes the hemodynamic data only at the maximum dose for those patients' who tolerated doses greater than 12 ng/kg/min of FLOLAN. Several patients received intermediate doses not specified in the protocol (e.g., 3, 5, 7 ng/kg/min). Hemodynamic results at each of these doses are summarized in tables at the end of this section; however, discussions focus on hemodynamic responses only at the doses specified by protocol.

Two different analyses were performed to demonstrate the acute effects of FLOLAN on hemodynamics:

- Acute Dose-Response Analysis: In this analysis, the response of each hemodynamic parameter to each dose of FLOLAN was evaluated.
- Maximum Dose Analysis: During dose ranging, patients tolerated different doses of FLOLAN; some patients received 12 ng/kg/min without reporting dose-limiting adverse events while others were unable to tolerate 4 or 6 ng/kg/min. Because of the variability in the individual patients' ability to tolerate FLOLAN, the change in hemodynamics from baseline to each individual's maximum tolerated dose was to be analyzed. However, the maximum-tolerated dose was not prospectively evaluated in acute dose ranging trials. Thus, hemodynamics at the maximum dose administered (12.1 ± 0.7 mg/kg/min; Section 9.6) in these trials were combined with the hemodynamics at the maximum tolerated (8.6 ± 0.3 ng/kg/min, Section 9.6) determined during dose-ranging in controlled trials.

For each of these two analyses, hemodynamic responses are first described within the individual trials and then combined across all trials. Since patients could enter acute dose-ranging studies on multiple occasions, and since some patients who entered the controlled studies had previously been included in acute trials, only the first dose-ranging procedure for each patient is included in this summary.

Acute Dose-Response Analysis

A. Analysis of Individual Studies

As shown in Table 52, baseline values were similar across individual trials. Baseline CI, SV, PVR and TPR are summarized below.

Table 52 summarizes the effects of FLOLAN® (epoprostenol sodium) on each hemodynamic parameter by study and by dose. The dose-response relationships for CI, SV, PVR and TPR are summarized below. In general, within each study, mean CI, SV and HR increased and mean PVR, TPR and SAPm decreased with increasing FLOLAN doses. The response of PAPm, though variable, tended to be reduced with increasing doses of FLOLAN. Changes in hemodynamics were not only dose related within each study, but the changes were also similar across all studies.

Dose (ng/kg/min)	CI (L/min/m ²)				
	Study 05/10 n=10 ^a (mean ± SE)	Study 20 n=38 (mean ± SE)	Study 21 n=256 (mean ± SE)	Study 35/36 n=19 (mean ± SE)	Study 46 n=67 (mean ± SE)
(Baseline)	2.2 ± 0.3	1.8 ± 0.1	2.6 ± 0.1	1.8 ± 0.2	2.0 ± 0.1
2	2.5 ± 0.3	1.8 ± 0.1	2.8 ± 0.1	1.8 ± 0.2	NA
4	2.8 ± 0.2	2.2 ± 0.2	2.8 ± 0.1	2.0 ± 0.2	1.8 ± 0.4
8	3.0 ± 0.4	2.5 ± 0.2	3.4 ± 0.2	2.5 ± 0.3	2.7 ± 0.3
12	3.9 ± 0.3	3.2 ± 0.3	3.7 ± 0.3	2.6 ± 0.6	not done

^a Number of patients enrolled for baseline hemodynamic measurements.

Dose (ng/kg/min)	SV (mL/beat)				
	Study 05/10 (mean ± SE)	Study 20 (mean ± SE)	Study 21 (mean ± SE)	Study 35/36 (mean ± SE)	Study 46 (mean ± SE)
Baseline	51 ± 8	39 ± 3	43 ± 1	40 ± 4	43 ± 2
2	52 ± 8	37 ± 4	45 ± 2	41 ± 4	NA
4	56 ± 10	45 ± 5	47 ± 2	43 ± 4	39 ± 8
8	45 ± 11	46 ± 4	53 ± 3	48 ± 5	56 ± 10
12	72 ± 3	59 ± 7	51 ± 4	55 ± 12	not done

Dose (ng/kg/min)	PVR (Wood U)				
	Study 05/10 (mean ± SE)	Study 20 (mean ± SE)	Study 21 (mean ± SE)	Study 35/36 (mean ± SE)	Study 46 (mean ± SE)
Baseline	15 ± 3	18 ± 2	17 ± 1	19 ± 2	16 ± 1
2	9 ± 3	12 ± 2	16 ± 1	18 ± 4	NA
4	12 ± 1	10 ± 2	15 ± 1	15 ± 4	24
8	8	9 ± 1	12 ± 1	11 ± 3	12 ± 3
12	7 ± 2	6 ± 2	12 ± 1	10	not done

Dose (ng/kg/min)	TPR (Wood U)				
	Study 05/10 (mean ± SE)	Study 20 (mean ± SE)	Study 21 (mean ± SE)	Study 35/36 (mean ± SE)	Study 46 (mean ± SE)
Baseline	17 ± 3	21 ± 2	19 ± 1	22 ± 3	20 ± 1
2	15 ± 3	20 ± 3	18 ± 1	22 ± 3	NA
4	16 ± 3	17 ± 2	17 ± 1	19 ± 2	20 ± 5
8	12 ± 2	16 ± 2	14 ± 1	16 ± 2	14 ± 2
12	9 ± 1	10 ± 2	15 ± 2	14 ± 3	not done

B. Combined Across-Study Analysis

Cardiac Index, Stroke Volume and Heart Rate: In the combined analysis (Table 53 and below), mean CI and SV increased with increasing doses of FLOLAN® (epoprostenol sodium). Mean CI increased in a dose-related manner with a maximum increase of 38% over baseline at a dose of 12 ng/kg/min. This increase in mean CI appears to be independent of heart rate which was only modestly increased (maximum mean increase of 12% from baseline at 12 ng/kg/min). SV increased in a dose-related manner with a maximum increase of 26% from baseline at 8 and 10 ng/kg/min. At doses greater than 12 ng/kg/min, increases in CI were maintained, however, heart rate also increased and SV slightly decreased.

Mean Pulmonary Arterial Pressure and Mean Systemic Arterial Pressure: Increasing doses of FLOLAN were associated with dose-related decreases in systemic mean arterial pressure (Table 53). SAPm displayed a maximal decrease (15%) at 10 ng/kg/min with no further decrease in SAPm with increasing doses of FLOLAN. Although the changes in PAPm were more variable, PAPm tended to be reduced as the dose of FLOLAN was increased, with a maximum decrease of 9% at >12 ng/kg/min.

Pulmonary Vascular Resistance, Total Pulmonary Resistance and Systemic Vascular Resistance: Increasing doses of FLOLAN were associated with decreases in mean SVR, with a peak decrease of approximately 41% (at 10 ng/kg/min) compared to baseline (Table 53). Mean PVR appeared to be reduced with increasing doses of FLOLAN, with a maximal reduction of 30% of baseline at 10 and >12 ng/kg/min. Mean TPR also appeared to be reduced with a maximal decrease of 31% from baseline at 10 and 12 ng/kg/min. Interestingly, SVR, PVR and TPR appeared to have reached near maximal responses at approximately 8 ng/kg/min since

increases above 8 ng/kg/min produced minimal change in each parameter.

In summary, increased doses of FLOLAN® (epoprostenol sodium) administered acutely were associated with potentially clinically important increases in CI and SV and reductions in PVR, TPR and SAPm (below). These changes were not accompanied by increases in PAPm.

All Studies Combined

Dose (ng/kg/min)	Parameter (mean ± SE)					
	CI (L/min/m ²)	PAPm (mm Hg)	PVR (Wood U)	SAPm (mm Hg)	SV (mL/beat)	TPR (Wood U)
Baseline	2.4 ± 0.1	58 ± 1	17 ± 1	92 ± 1	43 ± 1	20 ± 1
2	2.6 ± 0.1	57 ± 1	16 ± 1	91 ± 1	44 ± 1	19 ± 1
4	2.6 ± 0.1	56 ± 1	14 ± 1	88 ± 1	47 ± 1	17 ± 1
8	3.1 ± 0.1	54 ± 1	11 ± 1	81 ± 1	52 ± 2	15 ± 1
12	3.5 ± 0.2	53 ± 2	11 ± 1	77 ± 1	53 ± 4	14 ± 2

Maximum Dose Analysis

A. Analysis of Individual Studies

The hemodynamic response (change from baseline) at the maximum dose of FLOLAN was similar between the individual studies (Table 54 and below). Mean CI and SV were increased and PVR, TPR, SVR and SAPm were decreased from baseline in each study at the maximum dose of FLOLAN. Though essentially unchanged in Study 35/36, PAPm was decreased in each other study.

Blood gases were inconsistently affected across the individual studies (Table 54). PaCO₂ was decreased in three trials, increased in one and was not changed in another. Variable results also were evident for PaO₂. Arterial saturation was marginally improved.

In addition to the consistent trends observed in hemodynamics, the magnitude of the change from baseline also was similar between the individual studies. As shown below, at the maximum dose of FLOLAN, PVR and TPR were decreased in each individual study by approximately 3–6 and 5–7 Wood units, respectively. CI increased approximately 0.6–1.0 L/min/m² and SV was increased by 8–13 mL/beat.

Parameter	Changes from Baseline at the Maximum Dose				
	Study 05/10 (mean ± SE)	Study 20 (mean ± SE)	Study 21 (mean ± SE)	Study 35/36 (mean ± SE)	Study 46 (mean ± SE)
CI (L/min/m ²)	1.0 ± 0.3	0.9 ± 0.1	0.8 ± 0.1	0.6 ± 0.1	0.7 ± 0.1
PAPm (mm Hg)	-3 ± 2	-3 ± 2	-4 ± 1	0 ± 2	-2 ± 1
PVR (Wood U)	-4 ± 2	-6 ± 1	-4 ± 0	-3 ± 1	-5 ± 1
SAPm (mm Hg)	-18 ± 6	-14 ± 2	-15 ± 1	-11 ± 2	-13 ± 1
SV (mL/beat)	13 ± 5	12 ± 2	9 ± 1	8 ± 1	11 ± 2
TPR (Wood U)	-7 ± 2	-7 ± 1	-5 ± 0	-6 ± 1	-5 ± 1

B. Combined Across-Study Analysis

When delivered acutely at a maximum dose, FLOLAN® (epoprostenol sodium) has potent pulmonary and systemic vasodilator effects. As shown below and in Table 53 and Table 54, mean CI and SV were significantly increased (35% and 24%, respectively) above the values obtained at baseline. Moreover, pulmonary and systemic vascular resistance were decreased significantly by 29% and 39%, respectively. These changes were accompanied by a significant reduction in SAPm (15%) and a significant reduction in PAPm (6%). In addition, HR was increased significantly (10%) relative to baseline at the maximum dose of FLOLAN. Although the effects of FLOLAN on blood gases were variable, the combined decrease in PaCO₂ was statistically significant.

All Studies Combined

Parameter	Treatment at the Maximum Dose			
	Baseline	Max. Dose	Change ± SE	Percent Change
CI (L/min/m ²)	2.3	3.1	0.8 ± 0.1 ^a	35
PAPm (mm Hg)	58	54	-3 ± 0 ^a	-6
PVR (Wood U)	17	12	-5 ± 0 ^a	-29
SAPm (mm Hg)	92	78	-14 ± 1 ^a	-15
SV (mL/beat)	43	53	10 ± 1 ^a	24
TPR (Wood U)	20	14	-6 ± 0 ^a	-29

^a Statistical significance implied by confidence interval that does not contain 0.

Summary of Acute Administration of FLOLAN

In summary, the results from the acute dose-ranging segments across all studies demonstrated that FLOLAN had pronounced, potentially beneficial, hemodynamic effects in patients with PPH. In these patients, CI and SV were increased whereas pulmonary and systemic intravascular pressures and resistances were decreased; these hemodynamic effects were dose-related. At patients' maximum doses, mean CI and SV were significantly increased (35% and 24%, respectively) while PVR and SAPm were significantly decreased (29% and 16%, respectively). PAPm was variably affected during dose ranging but was decreased consistently and significantly at patients' maximum doses. Blood gases appeared essentially unchanged following the acute administration of FLOLAN.

§.7.4.2 *Chronic Long-Term Administration of FLOLAN*

The hemodynamic effects of FLOLAN administration for 8 and 12 weeks were evaluated in the controlled studies, Study 35/36 and Study 46, respectively. In addition, hemodynamics were evaluated every 6 months in patients who completed Study 35/36 and were enrolled in the uncontrolled study, Study 37.

Controlled Studies

A. Analysis of Individual Studies

Hemodynamics and blood gases were evaluated at baseline [before FLOLAN® (epoprostenol sodium) administration] and at the end of each trial in each treatment group. The following section summarizes baseline imbalances in the treatment groups, within treatment changes from baseline for each treatment group and between treatment comparisons.

Study 35/36

As shown below and in Table 55, baseline hemodynamic and blood gas values were similar between the two treatment groups, although small differences were noted for several parameters. Baseline PaO₂ was significantly higher in the standard therapy group (120 vs. 65 mm Hg); this difference appears to have been due to one standard therapy patient receiving supplemental oxygen.

Parameter	Baseline (mean ± SE)	
	Standard Therapy	FLOLAN Therapy
CI (L/min/m ²)	1.7 ± 0.2	1.9 ± 0.2
PAPm (mm Hg)	64 ± 4	57 ± 4
PVR (Wood U)	20 ± 3	19 ± 3
SAPm (mm Hg)	99 ± 4	87 ± 4
SV (mL/beat)	36 ± 5	39 ± 5
TPR (Wood U)	25 ± 3	21 ± 3

The hemodynamic profile was improved compared to baseline in patients randomized to FLOLAN therapy for 8 weeks (Table 55 and Table 56, and below). In addition, arterial saturation and mixed venous oxygen saturation were modestly increased in the FLOLAN therapy group. Patients receiving standard therapy showed little change from their baseline hemodynamic values, except SAPm. The decrease in SAPm in the standard therapy group may be due to changes in patients' concomitant medications during the course of the trial. Blood gases deteriorated slightly from baseline in patients receiving standard therapy.

Parameter	Change from Baseline (mean ± SE)	
	Standard Therapy	FLOLAN Therapy
CI (L/min/m ²)	0.2 ± 0.2	0.3 ± 0.1
PAPm (mm Hg)	0 ± 4	-8 ± 4
PVR (Wood U)	0 ± 2	-6 ± 2
SAPm (mm Hg)	-9 ± 3	-2 ± 2
SV (mL/beat)	5 ± 6	4 ± 3
TPR (Wood U)	0 ± 3	-6 ± 3

Although statistically significant differences were not seen between treatments in blood gas values, improvement appeared greater in patients receiving FLOLAN over the 8 weeks compared to patients receiving standard therapy alone.

Study 46

As in Study 35/36, overall baseline hemodynamic parameters were similar between the patients treated with FLOLAN® (epoprostenol sodium) therapy and those treated with standard therapy alone (below and Table 55).

Parameter	Baseline (mean ± SE)	
	Standard Therapy	FLOLAN® Therapy
CI (L/min/m ²)	2.1 ± 0.2	2.0 ± 0.1
PAPm (mm Hg)	59 ± 2	61 ± 2
PVR (Wood U)	16 ± 1	16 ± 1
SAPm (mm Hg)	89 ± 2	90 ± 2
SV (mL/beat)	45 ± 4	46 ± 3
TPR (Wood U)	19 ± 1	20 ± 1

During the course of study, hemodynamic measurements improved in those patients receiving FLOLAN therapy for 12 weeks compared to the baseline values as shown below and in Table 55 and Table 56. As in Study 35/36, several blood gas parameters were improved in FLOLAN patients including arterial saturation, mixed venous oxygen saturation and PaO₂. Patients receiving standard therapy (only) tended to show clinical deterioration in hemodynamics and blood gases over the 12 week trial.

Parameter	Change from Baseline (mean ± SE)	
	Standard Therapy	FLOLAN Therapy
CI (L/min/m ²)	-0.2 ± 0.2	0.3 ± 0.1
PAPm (mm Hg)	2 ± 2	-5 ± 1
PVR (Wood U)	2 ± 1	-3 ± 1
SAPm (mm Hg)	-1 ± 2	-5 ± 2
SV (mL/beat)	-3 ± 3	7 ± 2
TPR (Wood U)	2 ± 1	-4 ± 1

B. Combined Study Analysis

Hemodynamic data at 8 and 12 weeks were combined for this analysis. As noted in the individual studies, overall baseline hemodynamic parameters were similar between those patients receiving FLOLAN therapy and those receiving standard therapy alone as shown below and in Table 55.

Parameter	Baseline (mean ± SE)	
	Standard Therapy	FLOLAN Therapy
CI (L/min/m ²)	2.0 ± 0.1	2.0 ± 0.1
PAPm (mm Hg)	60 ± 2	60 ± 2
PVR (Wood U)	17 ± 1	16 ± 1
SAPm (mm Hg)	91 ± 2	89 ± 1
SV (mL/beat)	43 ± 3	44 ± 3
TPR (Wood U)	21 ± 1	20 ± 1



three patients who were followed for 42 months continued to show these improvements in hemodynamics compared to baseline. Thus, although higher doses of FLOLAN® (epoprostenol sodium) were administered, hemodynamic improvements from baseline were observed throughout the duration of this trial with no apparent deterioration in the effectiveness of FLOLAN therapy.

Parameter	Study Interval ^a					
	Baseline Study 35/36	Month 6	Month 12	Month 18	Month 24	Month 30
Number of patients followed	18	16	12	11	5	5
CI (L/min/m ²)	1.8 ± 0.1	2.2 ± 0.2	2.4 ± 0.2	2.4 ± 0.2	3.3 ± 0.3	2.9 ± 0.4
PAP _m (mm Hg)	61 ± 3	54 ± 3	54 ± 5	52 ± 4	54 ± 10	50 ± 8
PVR (Wood U)	19 ± 2	12 ± 2	12 ± 2	11 ± 3	10 ± 4	10 ± 4
SAP _m (mm Hg)	93 ± 3	90 ± 4	87 ± 2	86 ± 4	90 ± 4	79 ± 6
SV (mL/beat)	41 ± 4	53 ± 5	51 ± 7	53 ± 8	66 ± 5	65 ± 11
TPR (Wood U)	21 ± 2	15 ± 2	14 ± 2	14 ± 2	11 ± 3	11 ± 3

^a Parameter values are expressed as the mean ± SE.

9.7.4.3 Overall Summary of Burroughs Wellcome Co. Sponsored Studies

The results from these Burroughs Wellcome Co.-sponsored clinical trials demonstrated that acute administration of FLOLAN to patients with NYHA Class III/IV PPH resulted in beneficial dose-related hemodynamic effects. Global cardiac function improved as shown by an increased CI and SV and there was evidence of pulmonary vasodilation, as shown by a decrease in PVR and PAP_m. In addition to the acute effects of FLOLAN, the hemodynamic profile was improved in patients treated with a continuous infusion of FLOLAN for 8 or 12 weeks. In general, the hemodynamic changes noted following long-term FLOLAN administration were similar to those observed following acute FLOLAN exposure. After chronic infusions of FLOLAN, however, the effects on SVR and SAP_m appeared to be somewhat reduced compared to acute changes in these patients. The reduction in systemic effects was not associated with reduced pulmonary effects when FLOLAN was given chronically. These observations may suggest a relatively selective, long-term effect of FLOLAN on the pulmonary vasculature.

Arterial saturation and PaO₂ improved more in patients receiving FLOLAN than in patients receiving standard therapy. These enhancements in oxygenation apparently developed over time, since the magnitude of these effects was not evident during acute dose ranging. While Studies 35/36 and 46 demonstrated improved hemodynamic and blood gas effects for 8 and 12 weeks, respectively, evidence from Study 37 suggested that the hemodynamic improvements from baseline were maintained for at least 42 months.

The hemodynamic improvements for patients receiving FLOLAN® (epoprostenol sodium) discussed in this section may be particularly important in explaining other clinical endpoints, including improved exercise capacity

and improved survival. The increase in CI produced by FLOLAN® (epoprostenol sodium) administration may be related to improved exercise capacity and general well being, perhaps by enhancing tissue perfusion. Moreover, the effects of FLOLAN on reducing pulmonary vascular resistance may have slowed the progress of right ventricular failure and subsequent death. Although the hemodynamic data were consistent with these hypotheses, the exact pharmacological mechanism(s) of long-term benefits of FLOLAN therapy are unclear.

9.7.4.4 *Independent Investigator-Sponsored Studies*

In addition to the trials sponsored by Burroughs Wellcome Co., studies have been described by independent investigators. In general, published data substantiates the acute hemodynamic effects observed in studies sponsored by Burroughs Wellcome Co.

Dinh-Xuan et al. (49) reported that PPH patients (n=20, class not described) treated acutely with incrementally increasing doses of epoprostenol (starting dose, 1-2 ng/kg/min) showed a significant decrease in PAPm (6%), PVR (26%) and SVR (27%), with a corresponding increase in CI (27%). Kreiner et al. (50) serially evaluated the acute hemodynamic effects of epoprostenol with six other drugs (nifedipine, amrinone, isoproterenol, captopril, hydralazine and nitroglycerin) commonly used to treat patients with PPH. Although large intra- and inter-individual variability was observed, epoprostenol infusions were associated with the greatest decrease in PVR ($38 \pm 23\%$).

These results are representative of the acute hemodynamic responses to epoprostenol that were reported by Scott et al. (51), 1990; Jones et al. (52); Philippoteau et al. (53); Rozkovec et al. (54); Bush et al. (55); Jones et al. (56); Simmoneau et al. (57); Watkins et al. (58). Although dosing regimen for epoprostenol and hemodynamic endpoints varied among the studies, PVR and SVR consistently were reduced and CO (CI) consistently was increased. Though the effects of epoprostenol on PAPm were variable, there was no evidence that PAPm consistently increased with epoprostenol administration (50-54).

Though no information was available describing the hemodynamic effects of chronic FLOLAN/epoprostenol therapy, Jones et al. (56) reported that epoprostenol administration for up to 25 months provided long-term benefit to patients with PPH who were unresponsive to oral vasodilators. These investigators noted that continuous infusions of epoprostenol were associated with improvements in quality of life and exercise capacity. These results confirmed earlier observations of this group (59) in which a 27 year old woman with severe PPH was effectively treated for 13 months with continuous epoprostenol infusion, enabling her to live independently at home.

In summary, continuous infusions of epoprostenol as reported in the literature produced acute, potentially beneficial hemodynamic effects in patients with

PPH. Most notably, mean CI was increased and mean PVR was decreased. Importantly, these hemodynamic benefits were often associated with reduced PAPm and with improvements in symptoms of PPH and exercise capacity (49, 56, 59).

9.8 Integrated Summary Of Safety

The summarization of safety information on the use of FLOLAN® (epoprostenol sodium) in treating patients with PPH includes data from the following sources:

1. Studies sponsored by Burroughs Wellcome Co.
2. Reports of FLOLAN's use in treating patients with PPH from the published literature.
3. Reports from physicians who requested FLOLAN to treat patients with PPH in Canada under Emergency Drug Regulations (EDR).

The following safety data from PPH trials sponsored by Burroughs Wellcome Co. have been summarized:

1. Adverse experiences reported during acute dose ranging procedures, during the chronic use of FLOLAN and during and shortly following FLOLAN withdrawal.
2. Laboratory evaluations following FLOLAN's chronic and acute use.
3. Electrocardiograms following FLOLAN's chronic use.
4. Physical examinations following FLOLAN's chronic use.

Adverse events reported in PPH patients from published articles and from physician reports in Canada under the EDR have also been summarized.

Adverse events have also been summarized in patients who received FLOLAN to treat other diseases. FLOLAN has been administered to over 8,000 patients with a variety of clinical conditions other than PPH. As discussed in Section 1, adverse events reported in patients with diseases other than PPH have been summarized by clinical indication in Section 9.8.6. Sources for these reports are as follows:

1. Studies sponsored by Burroughs Wellcome Co.
2. Studies sponsored by
3. Reports of FLOLAN use from published articles.
4. Reports from physicians who requested FLOLAN under the EDR in Canada.
5. The Clinical Safety Surveillance Service of Wellcome Research Laboratories (UK).

9.8.1 *Adverse Experiences in Patients with PPH*

9.8.1.1 *Introduction to Integrated Summary of Adverse Experiences*

Adverse experiences have been summarized for Burroughs Wellcome Co. sponsored trials in PPH as follows. 1) adverse experiences occurring during

acute dose ranging in both controlled and uncontrolled studies; 2) adverse experiences occurring during chronic, continuous infusions of FLOLAN® (epoprostenol sodium) in controlled clinical trials; 3) adverse experiences occurring during chronic, uncontrolled studies.

Adverse experiences related to the drug delivery system (eg, adverse experiences occurring secondary to a malfunction of the infusion pump, catheter placement, infection, etc.) are summarized separately. In addition, adverse experiences resulting in permanent discontinuation of FLOLAN and potential drug-demographic interactions and drug-drug interactions are summarized in this section. Adverse experiences resulting from withdrawal of FLOLAN are summarized in Section 9.8.5.

Summary tables included in the text contain data abstracted from detailed tables included in this submission.

Adverse events were collected by 1) verbal probes administered at clinic visits or by telephone, 2) spontaneous reports by patients or 3) direct observation by clinical investigators.

In each analysis for this report, the number of patients with an adverse experience in each study was summarized. If an adverse experience occurred on multiple occasions in one patient, the experience was included only once; the most serious rating was reported for analysis.

Adverse experiences were summarized using a standard dictionary of modified COSTART (Coded Symbols for Thesaurus of Adverse Reaction Terms) term. COSTART preferred terms were assigned and grouped by body system for acute treatment (Appendix D) and chronic treatment (Appendix E for controlled studies and Appendix F for uncontrolled studies). Assignment of COSTART terms reflects adverse experiences of special interest. For example, all catheter-related skin site problems, regardless of the raw term, were assigned the COSTART terms "Inflammation Injection Site" or "Injection Site Reaction" depending on the investigator's description. In contrast, the COSTART term "Infection" was used to encompass presumed viral infections such as those events described by investigators as "cold," "flu," etc. Bacteremia and sepsis were coded as "sepsis." Non-specific musculo-skeletal pain of the extremities was assigned the preferred term "Pain," whereas other types of pain were coded specifically, for example jaw pain, which has proven to be characteristic of chronic FLOLAN infusions. A new COSTART term was developed to capture the most characteristic pharmacologic effect of FLOLAN, vasodilation. The COSTART term "Flushing" was used to capture events related to cutaneous vasodilatation (e.g. erythema, hot flashes, facial flush, flushed appearance, pink face, reddening of body).

In addition, different COSTART terms describing similar or related adverse experiences (e.g., nausea and vomiting) are grouped in all summaries, e.g., "nausea/vomiting," in tables describing overall frequency. These events are listed separately in tables summarizing seriousness.

9.6.1.1 Adverse Experiences During Acute Dose Ranging

Each patient who entered any of the Burroughs Wellcome Co. PPH trials underwent acute dose ranging with FLOLAN® (epoprostenol sodium). Adverse experiences occurring during dose-ranging procedures in controlled and uncontrolled trials were analyzed together. One patient (36012) in Study 35/36 received FLOLAN briefly during the dose-ranging procedure but was withdrawn and not randomized to chronic therapy due to the occurrence of pulmonary edema. This patient is excluded from the *Summary of Patient Accountability and Demographics* but is included in summaries of adverse experiences occurring during acute dose ranging. This discrepancy explains the one patient difference from the number of patients reported in *Summary of Patient Accountability and Demographics* and the number of patients reported in this Summary (391 vs. 390 patients). Though patients may have entered dose-ranging procedures on numerous occasions, only adverse experiences occurring during the first dose ranging for each patient were summarized in analyses of overall adverse experiences. However, serious and life-threatening adverse experiences that occurred during any acute dose-ranging procedures were also summarized.

Though the objective of the dose-ranging procedure differed somewhat between the acute studies and the chronic studies, doses were to be increased to some degree of intolerance in each procedure. In the acute studies, the FLOLAN dose was increased to produce the maximal effect on pulmonary artery pressure, cardiac output, pulmonary vascular resistance, or total pulmonary resistance to determine pulmonary vasoreactivity in each patient. To obtain a full range of responses, doses were to be increased until acute intolerance was reached. In contrast, the aim of dose ranging in chronic studies was to determine the dose of FLOLAN to be administered chronically by increasing the dose to a maximum tolerated dose, usually an increment below the dose eliciting an intolerable adverse experience (see Section 9.6, FLOLAN Administration).

In the uncontrolled, acute studies, all adverse experiences which occurred during dose ranging were rated by the investigator for severity and causality but not for seriousness. In Study 35/36 all adverse experiences during dose-ranging were rated for severity, seriousness and causality. In Study 46, a list of "expected pharmacological effects" of FLOLAN was provided which investigators used to identify adverse experiences that occurred during dose ranging. These expected adverse experiences were recorded by a code and not rated for severity, seriousness, or causality. Only *unexpected* events in Study 46 were rated for severity, seriousness, and causality. All adverse events reported during dose ranging are summarized. In addition, the most frequent adverse experiences observed during acute dose ranging with FLOLAN are summarized. In Studies 21, 35/36, 37 and 46, dose limiting adverse experiences were identified and are summarized. Investigators did not identify dose-limiting events in Studies 05/10 and 20.

Overall Summary of Adverse Experiences During Acute Dose Ranging

The number of patients with adverse experiences is summarized in Table 58 in decreasing order of frequency for all 391 unique patients undergoing acute

dose-ranging with FLOLAN® (epoprostenol sodium). Adverse experiences reported in 20 (5%) or more patients were: flushing (58%), headache (49%), nausea/vomiting (32%), hypotension (16%), chest pain (11%), anxiety/nervousness/agitation (11%), dizziness (8%), bradycardia (5%), and abdominal pain (5%). Of these, flushing, headache, nausea/vomiting, hypotension and dizziness were likely related to the main pharmacologic effect of FLOLAN, arterial vasodilatation. Bradycardia was often associated with a reduction in blood pressure, suggesting that vagal tone may have increased.

Sixty four (16%) of the 391 patients were younger than 16. Though the most common adverse experiences were similar (Table 59), the frequency distribution appears somewhat different than in patients older than 16 years (Table 60); headache and flushing were less frequent and nausea/vomiting was the most frequent adverse event in children.

The Relationship of Adverse Experiences to Dose During Acute Dose-Ranging

The frequency of first onset of each adverse experience by dose is summarized in Table 61. In Table 61, the dose range "(2,4)" does not include 2 but includes 4 ng/kg/min. In general, flushing was the first adverse experience observed and was followed by headache. Adverse experiences were infrequent at FLOLAN infusion rates 2 ng/kg/min and below; only flushing was reported in more than 5% of patients. Flushing was initially observed at 8 ng/kg/min or less in 201 patients (90% of patients with flushing). Flushing was first observed at doses between 2 and 6 ng/kg/min in 135 (61%) patients reporting this adverse experience. Headache was first reported between 4 and 8 ng/kg/min in 53% of patients reporting headache. Nausea/vomiting, hypotension, and anxiety/nervousness/agitation were first reported in most patients at doses higher than 4 ng/kg/min. The dose at onset of chest pain and dizziness appeared to be distributed across doses.

Dose-Limiting Adverse Experiences During Acute Dose-Ranging

The frequencies of dose-limiting adverse experiences is summarized in Table 62. Nausea/vomiting (19%), headache (18%), hypotension (15%) and flushing (14%) were reported most commonly as the adverse experiences that limited dosing. These are similar to the most frequent adverse experiences in acute treatment overall (Table 58)

In children younger than 16 undergoing acute dose-ranging, nausea/vomiting (34%) was the most common dose-limiting adverse experience (Table 63). Anxiety/nervousness/agitation (16%) and hypotension (13%) were the only other dose-limiting events reported in greater than 5% of patients under 16 years old

Serious, Life-Threatening and Fatal Adverse Experiences During Dose-Ranging Procedures

Seriousness of adverse events was not rated in acute dose-ranging studies that did not have a chronic treatment phase (05/10, 20, 21). However, a total of 106 patients underwent at least one dose-ranging procedure in a chronic study. Seriousness was rated in these trials. For purposes of this summary, if an adverse experience occurred more than once in a patient, the most serious occurrence was reported. In contrast to the overall summaries of adverse experiences (which included each patient only in their first dose-ranging if they entered more than one dose-ranging procedure), this section summarizes serious, life-threatening and fatal adverse experiences occurring during all dose-ranging segments of a chronic study.

A. Fatal Adverse Experiences:

No fatal events occurred dose-ranging procedures. However, one patient in Study 46 suffered a pneumothorax as a complication of the cardiac catheterization procedure prior to beginning dose ranging. FLOLAN® (epoprostenol sodium) was not administered and the patient was not randomized. The patient died several days later (see Section 1, Table 4). The CRF for this patient is found in Section 12, Volume 1.71.

B. Serious and/or Life Threatening Adverse Experiences:

In Study 35/36 one life-threatening adverse experience, pulmonary edema, occurred during acute dose ranging. This patient was subsequently thought to have pulmonary veno-occlusive disease. Pulmonary veno-occlusive disease may predispose patients to developing pulmonary edema during treatment with vasodilators (60). The event resolved with discontinuation of FLOLAN and administration of furosemide and supplemental oxygen. The patient was withdrawn from the study before randomization to chronic therapy (see Section 1, Table 4). The CRF for this patient is found in Section 12, Volume 1.76. There were no life-threatening adverse experiences during acute dose-ranging procedures in Study 37. In Study 46 non-dose-limiting, "expected" adverse experiences were not rated for seriousness, but no life-threatening unexpected adverse experiences were reported.

Several patients experienced more than one serious adverse experience during a dose-ranging procedure. Thus, the number of adverse experiences in the following table is greater than the number of patients with serious events.

The number of patients with each serious or life-threatening adverse experience is summarized below, using data abstracted from individual study reports.

**Serious or Life-Threatening Adverse Experiences
During Dose-Ranging Procedures in Chronic Studies**

Adverse Experience	No. of Patients With at Least One Occurrence of Each Experience (N = 106 Patients)	
	Serious	Life-Threatening
dizziness	4	
nausea	3	
headache	2	
supraventricular tachycardia	2	
pulmonary edema		1
vomiting	1	
agitation	1	
pneumothorax	1	
asthenia	1	
chest pain	1	
tachycardia	1	
thinking abnormality	1	
subclavian artery dissection	1	

In summary during dose-ranging with FLOLAN® (epoprostenol sodium), the most common adverse experiences and the adverse experiences that limited further increases in dose were generally related to the major pharmacologic effect of FLOLAN, arterial vasodilatation. Adverse events abated rapidly after reduction or discontinuation of the infusions.

9.8.1.3 Adverse Experiences During Chronic Infusion: Controlled Studies

Adverse experiences that occurred during the chronic treatment segments of Studies 35/36 and 46 are summarized in this section. Adverse experiences were assessed and reported differently in the two chronic, controlled studies.

Seriousness, intensity and causality were recorded for all adverse events reported in Study 35/36. In Study 46, seriousness, intensity and causality were recorded for each *unexpected* adverse experience. Unexpected events in Study 46 were defined as adverse experiences that were unanticipated in terms of nature and/or severity, but were attributed to PPH, to FLOLAN or to other medications used to treat PPH. Unexpected adverse events in Study 46 also included any event attributed to an intercurrent illness, to procedures and/or to medications used to treat other diseases. Because of prior experience with FLOLAN in the treatment of PPH, in Study 46 *expected* adverse experiences related to the pharmacologic effects of FLOLAN, to PPH or its treatment were collected only in a checklist format to indicate if they occurred at least once during the study. The frequency of episodes of each

adverse experience was not collected, nor were attributes of intensity, seriousness or causality.

If an event occurred on numerous occasions in a patient, only the most serious occurrence was included in analyses. Fatal adverse experiences in Study 46 were recorded on a separate CRF page for deaths, and not summarized with adverse experiences (Table 64). For purposes of this summary, fatal events are hand tabulated.

Overall Summary of Adverse Experiences in Chronic Controlled Studies

For purposes of combining adverse experience data from both chronic, controlled studies, Table 64 summarizes unexpected and expected adverse experiences. The frequency of expected events in Study 46 is shown in the "complications" column. All adverse experiences in Study 35/36 as well as unexpected adverse experiences in Study 46 are summarized by maximum seriousness in Table 64. If an *expected* adverse experience was judged by the investigator as unusual in nature, severity or frequency, it was also recorded as an unexpected adverse experience. In Table 64 such adverse experiences are included in the appropriate "Serious" or "Life-Threatening" column and not in the "Complications" column, to prevent double reporting. Therefore, the "Any" column summarizes the number of patients with each adverse experience, regardless of expectedness. Absence of data for an adverse event indicates that no events were reported for that term. As above, fatal adverse experiences in Study 46 are summarized separately.

Some adverse experience terms are combined to summarize similar or related events, for example nausea/vomiting. Adverse experiences from Studies 35/36 and 46 are presented in descending frequency according to frequency in the FLOLAN® (epoprostenol sodium) group in Table 65. A higher incidence of a particular adverse experience in the FLOLAN patients is presumed to represent adverse experiences related to FLOLAN therapy, whereas a higher frequency in the standard therapy group should be related to the underlying illness, a co-morbid event or another drug.

Table 65 presents a profile of the signs and symptoms that occurred in this population of patients with severe PPH. Compared to standard therapy, the adverse experiences that appear to be associated with chronic FLOLAN infusions in this population included: nausea and vomiting, tachycardia, jaw pain, myalgias, flushing, diarrhea, arthralgias, and catheter related infections.

It is difficult to define a clinically meaningful difference between treatment groups for any particular adverse experience. For purposes of this discussion, a difference in the frequency of 10% or more in absolute terms between the FLOLAN and standard therapy groups is considered clinically meaningful. These are summarized below (data abstracted from Table 64 and Table 65):

**Adverse Experiences that Occurred with a ≥ 10 Percent Difference
between Treatment Groups (All Adverse Experiences
Regardless of Seriousness)**

Adverse Experience	% of Patients	
	FLOLAN [®]	Standard Therapy
Headache	83%	33%
Dizziness	83%	70%
Nausea/vomiting	67%	48%
Jaw pain	54%	0%
Myalgia	44%	31%
Flushing	42%	2%
Diarrhea	37%	6%
Pain	35%	15%
Tachycardia	35%	24%
Heart failure/Right heart failure	31%	52%
Hypoxia	25%	37%
Anxiety/Nervous/Tremor	21%	9%
Chills/Fever/Sepsis/Flu syndrome	25%	11%
Injection site reaction/inflammation	21%	0%
Injection site pain	13%	0%
Syncope	13%	24%
Shock	0%	13%

It appears that events reported more frequently in the FLOLAN[®] (epoprostenol sodium) patients are those related either to 1) vasodilatation which is the major pharmacologic effect of FLOLAN, 2) previously well described events related to FLOLAN such as jaw pain and myalgias, or 3) to the chronic, indwelling catheter required for the continuous infusion of FLOLAN. In contrast, the more frequent adverse experiences in the standard therapy group appear to be related to the consequences of PPH. Interestingly, hypotension, an expected FLOLAN effect, was reported with equal frequency in both groups. This similarity between treatment groups may be due to the frequent use of oral vasodilators in the standard therapy group.

Sepsis did not occur $\geq 10\%$ more frequently in the FLOLAN group. However, because of the importance of this event in patients with chronic, indwelling catheters, sepsis was analyzed separately and discussed in Section 9.8.1.6.

The incidence of heart failure/right heart failure was greater in standard therapy patients and most likely represents progression of the underlying disease process. Nausea/vomiting, which occurred more frequently in FLOLAN-treated patients, may have been a consequence of vasodilatation, since there is no evidence of a direct emetic effect of FLOLAN. Diarrhea appeared to be relatively common in FLOLAN treated patients, as has been reported during treatment with other prostaglandins (e.g., misoprostil, PGE₁) (61, 62).

Serious, Life-Threatening and Fatal Adverse Experiences During Chronic Infusion: Controlled Studies

To summarize the seriousness of adverse experiences in chronic studies, it was necessary to hand tabulate data abstracted from individual study reports. This was required because fatal adverse experiences in Study 46 were recorded on a separate CRF page for deaths and not summarized with adverse experiences in Table 64.

A. Fatal Adverse Experiences

- Table 66 lists patients who died in all studies. Treatment assignment (FLOLAN® (epoprostenol sodium) or standard therapy), demographic information, study segment at time of death, and cause of death are presented. CRFs for these patients are found in Section 12, Volumes 1.69–1.71.

During the 8-week chronic treatment of study 35/36 one of eleven FLOLAN and 3 of 14 standard therapy patients died. During the 12 week chronic treatment phase of Study 46, 8 of 40 standard therapy and none of the 41 FLOLAN patients died. The majority of the deaths were ascribed to progressive right heart failure as a consequence of severe pulmonary hypertension. The single death reported in the patients receiving FLOLAN was judged not to be related to FLOLAN but to sudden death associated with PPH.

Table 67 compares baseline characteristics of patients who died to those who survived in the two controlled studies, both within and between treatment groups. In the standard therapy group, hemodynamic, NYHA class, and exercise data suggest that the eleven patients who died had more severe disease at baseline than those who survived. Baseline characteristics between treatment groups were similar.

B. Serious and Life-Threatening Adverse Experiences:

The number of patients with serious and life-threatening adverse experiences combined is summarized below for Studies 35/36 and 46 (abstracted from Table 64). However, because seriousness was not assessed for *expected* adverse experiences in Study 46, serious and life-threatening events may be underestimated for both treatments. Hypertension and supraventricular tachycardia appeared to occur more frequently in FLOLAN® (epoprostenol sodium)-treated patients, but the number of patients studied is too small in each treatment group to make a meaningful comparison. Two cerebrovascular accidents were reported in patients receiving FLOLAN. One was thought to be an embolic event related to the central venous catheter in a patient with a patent foramen ovale. The second patient did not have a patent foramen, but had a history consistent with transient ischemic attacks. Intracranial hemorrhage was ruled out.

**Serious and Life-Threatening Adverse Experiences
During Chronic Treatment: Controlled Studies**

Adverse Experience	FLOLAN® (No. of Patients)	Standard Therapy (No. of Patients)
sepsis	5	1
dyspnea	4	4
supraventricular tachycardia	3	0
procedural complications	2	0
chest pain	2	1
tachycardia	2	0
cerebrovascular accident	2	0
flushing	2	0
nausea	2	1
convulsions	2	0
asthenia	1	4
cellulitis	1	0
fever	1	0
flu syndrome	1	0
injection site inflammation	1	0
pain	1	0
headache	1	0
bradycardia	1	0
extrasystoles bigeminy	1	0
hypotension	1	0
pallor	1	0
syncope	1	2
thrombosis	1	0
peripheral vascular disorder	1	0
diarrhea	1	0
cyanosis	1	0
dizziness	1	1
cough increased	1	0
hypoxia	1	1
pneumonia	1	0
sweating	1	0
ascites	0	1
abdominal pain	0	1
digitalis intoxication	0	1
atrial fibrillation	0	1
right heart failure	0	2
palpitation	0	1
vomiting	0	2
hypokalemia	0	1
edema	0	1
peripheral edema	0	3
depression	0	2
urinary tract infection	0	1

Adverse Experiences Resulting in Adjustment or Discontinuation of FLOLAN® (epoprostenol sodium) in Chronic, Controlled Studies

The FLOLAN dose was decreased, increased, or temporarily or permanently discontinued in response to clinical events. Adverse experiences that resulted in a FLOLAN dose adjustment or discontinuation are summarized by maximum seriousness in Table 68. In some patients the dose adjustment was related to a constellation of adverse experiences that were sometimes recorded as separate events.; thus data in Table 68 tends to overestimate the number of dose changes or discontinuations due to an adverse experience.

Only one patient in the controlled studies (in Study 46) had a permanent discontinuation of FLOLAN as a result of adverse experiences (see Section 1, Table 4). These events were chills, feeling sick, pallor and musculoskeletal pain.

During the chronic treatment phase of Study 35/36 the FLOLAN dose was reduced five times due to adverse events in a total of four of the 11 patients receiving FLOLAN. These events included flushing, tachycardia, dizziness and nausea. The FLOLAN dose was increased in one patient due to an adverse experience or worsening PPH symptoms.

Table 69 summarizes the frequency of, and reasons for, dose changes in Study 46. The chronic infusion case report form for Study 46, requested a coded reason for each FLOLAN dose change. The FLOLAN dose was increased when the investigator judged events were due to an increase in PPH symptoms (at least once in 61% of patients) or to symptoms of insufficient FLOLAN (12%). The FLOLAN dose was reduced because of expected adverse events related to FLOLAN in 39%, unexpected adverse experiences in 7%, or a decrease in PPH symptoms in 2%.

Adverse Experiences in Chronic, Controlled Studies by Age (Table 70)

Since there were only four patients 65 years of age or older in Studies 35/36 and 46, no formal analysis of safety by age in older patients was undertaken; adverse event profiles in these four patients were reviewed individually. The only serious events were cerebrovascular accident (non-hemorrhagic) and pneumonia in one patient each. The frequency of adverse experiences in the five patients younger than 16 and in those 16 or older are summarized in Table 70. In this limited sample size, there was no evidence that the adverse event profile differed in younger or older patients who received FLOLAN.

Adverse Experiences in Chronic, Controlled Studies by Gender (Table 71)

In general, the profile of the most frequent adverse experiences was similar between males and females. Females reported dyspnea, asthenia, dizziness, nausea and vomiting, chest pain, hypotension and anorexia somewhat more frequently than males. Only cyanosis and sweating appeared to be more frequently reported in males receiving FLOLAN.

In the standard therapy group, asthenia and angina appeared to be more frequent in males. Only palpitation appeared to be more common in females.

Adverse Experiences in Chronic Controlled Studies by Race (Table 72)

There were only nine black patients and eight patients whose race was designated as "other" in studies 35/36 and 46 (less than 10% of patients, respectively), thus it was not possible to assess racial differences in the safety of FLOLAN® (epoprostenol sodium). There does not, however, appear to be a difference in the adverse event profiles of black and white patients.

Adverse Experiences in Chronic Controlled Studies: Possible Drug Interactions

Data on three classes of drugs used in the treatment of PPH were examined for a possible interaction with FLOLAN resulting in a difference in the incidence of adverse experiences. The type of drug and possible mechanism for interaction are: 1) other vasodilators: FLOLAN could accentuate the frequency or severity of hypotension, headache and tachycardia; 2) diuretics: FLOLAN could accentuate the frequency or severity of signs and symptoms related to volume depletion such as dizziness, hypotension or renal dysfunction; 3) digoxin: FLOLAN could alter digoxin plasma concentrations by increasing bioavailability via an increase in splanchnic blood flow; and/or by increasing elimination by increasing renal blood flow and glomerular filtration rate.

A. Vasodilators

For purposes of this discussion the following drugs are considered vasodilators: captopril, diltiazem, hydralazine, isosorbide dinitrate, nifedipine, nitroglycerin, and verapamil. Table 73 lists adverse experiences in descending order of frequency, by treatment group, and within treatment group whether or not patients received one or more vasodilators for at least 75% of the time in the study. The small number of patients in each subgroup does not allow formal analysis of trends.

Of the more commonly reported adverse events in the FLOLAN patients, the following tended to be more frequent in patients receiving vasodilators than those not receiving vasodilators: chest pain, palpitation, arrhythmia, tachycardia, jaw pain, myalgia, cough, arthralgia, hypotension, and heart failure.

Thus it appeared that the concomitant use of oral vasodilators may have accentuated some of the more common adverse experiences associated with chronic FLOLAN infusions. It is not possible to determine whether a FLOLAN-oral vasodilator interaction was the cause of the increased incidence of an adverse event, whether the vasodilator was prescribed in part due to the adverse event, or whether there was no relation. Complicating the analysis was the use of multiple medications by

patients, and the occurrence of adverse experiences known to be related to concomitant medications such as cough with captopril, edema with nifedipine, headache with nitrates, cardiac conduction disturbances with diltiazem and verapamil, tachycardia with hydralazine and worsening heart failure with verapamil.

B. Digoxin

Use of digoxin at baseline and during Studies 35/36 and 46 was similar between treatment groups. Digoxin use was likely related to the frequency and severity of heart failure and/or supraventricular tachycardia. Of the patients on digoxin, fewer patients in the FLOLAN® (epoprostenol sodium) group had heart failure reported compared to patients in the standard therapy group (35% vs. 78%).

Inspection of Table 74 reveals a trend toward a greater incidence of palpitation and unspecified arrhythmia with digoxin use in both treatment groups.

It does not appear that the concomitant use of FLOLAN and digoxin poses any additional risk. The only patient reported to have digitalis toxicity was in the standard therapy group.

C. Diuretics

The frequency of adverse experiences stratified by diuretic use is summarized in Table 75. Hypotension tended to be somewhat more frequent with diuretic use in both FLOLAN and standard therapy patients, but there is no indication that hypotension occurred more frequently with the use of FLOLAN and diuretics and combined medications than use of diuretics alone. Adverse experiences that may be related to hypotension, such as dizziness and syncope, were not increased with the concomitant use of FLOLAN and diuretics.

9.8.1.4 *Adverse Experiences During Chronic Infusion: Uncontrolled PPH Trials: Study 37 and Extended Infusions in Studies 05/10 and 21*

Study 37, the uncontrolled, continuation study for patients who completed Study 35/36, provided safety information from 18 patients receiving FLOLAN for longer than three months. Adverse experiences during acute dose-ranging for these patients were discussed in Section 9.8.1.2. Two patients in the continuation study had received FLOLAN for greater than 36 months (42 and 48 months, respectively) at the data cut-off point for this report. In Studies 05/10 and 21, patients could receive an extended infusion of FLOLAN for up to 96 hours after completion of the dose-ranging procedure.

Adverse experiences reported during chronic infusion of FLOLAN® (epoprostenol sodium) in Study 37 are summarized by maximum seriousness in Table 76. The following summarizes the most common (≥ 50%) adverse experiences, regardless of seriousness or attributability to FLOLAN:

Adverse Experiences Occurring in ≥ 10 Patients in Study 37

Adverse Experience	Number of Patients (%) (N = 18 Patients)
asthenia	16 (89)
diarrhea	16 (89)
dyspnea	16 (89)
infection site reaction/inflammation	15 (83)
nausea	14 (78)
dizziness	12 (67)
infection	11 (61)
chest pain	11 (61)
pallor	11 (61)
headache	11 (61)
jaw pain	11 (61)
peripheral edema	10 (56)
flushing	10 (56)
procedural complications	10 (56)

In Study 05/10, seven patients received an extended FLOLAN infusion. Headache and nausea were reported in 4 patients, and flushing and vomiting in 3 patients (data from Study Report). The extended FLOLAN infusion was discontinued in 3 patients in Study 05/10 due to adverse experiences (see Section 1, Table 4). Diplopia and photosensitivity resulted in discontinuation of FLOLAN in one patient after one hour of infusion. These resolved within 30 minutes. In a second patient, headache and nausea resulted in discontinuation after 3.5 hours. The third patient had nausea and vomiting resulting in discontinuation of the FLOLAN infusion after 3.5 hours.

In Study 21, thirteen patients received an extended infusion of FLOLAN. Events reported in two or more patients were hypotension (5), bradycardia (4), headache (2), cardiac arrest (2), hypoxia (2), and flushing (2).

Serious, Life-Threatening and Fatal Adverse Experiences During Uncontrolled Chronic Studies

A. Fatal Adverse Experiences:

None of seven patients receiving an extended infusion in Study 05/10 died. There were 6 deaths among the 13 patients in Study 21 who received an extended infusion (Table 66). CRFs for these patients are found in Section 12, Volumes 1.72-1.75. All were severely ill upon entry into the study and each improved to some degree during the FLOLAN infusion (See Study 21 Study Report). Three of the deaths occurred as the FLOLAN infusion was being withdrawn or shortly thereafter.

Though the deaths were judged not attributable to FLOLAN® (epoprostenol sodium), a possible contribution of withdrawal of FLOLAN cannot be excluded. These deaths are discussed in Section 9.8.5, Withdrawal of FLOLAN. The fourth patient, a 1-year-old male, continued to have pulmonary edema and died despite improved cardiac output. A six-year-old female died of severe pulmonary hypertension following cardiac transplantation. She received transient hemodynamic benefit from FLOLAN, insufficient to prevent progressive right heart failure. The sixth patient, after initial improvement, suddenly worsened and died of progressive heart failure after receiving an extended FLOLAN infusion for 2 weeks.

As of the data cutoff date, four of the 18 patients who received chronic FLOLAN infusions in Study 37 after completing Study 35/36 had died (Table 66). The causes of death of two of the patients were related to progressive complications of PPH after receiving FLOLAN for 32 and 28 months, respectively. One death was attributed to the drug delivery system, and one to unknown causes after 18 and 13 months on FLOLAN, respectively.

B. Serious and Life-threatening Adverse Experiences in Study 37:

Serious and life-threatening adverse experiences occurring in Study 37 are summarized together by maximum seriousness (Table 76). Seriousness was not assessed in Studies 05/10 and 21. Listings and descriptions of individual events are found in the Interim Study Report. The following was abstracted from Table 76:

Serious and/or Life-threatening Adverse Experiences Occurring in ≥ 5 Patients in Study 37

Adverse experience	No. Patients (N = 18 Patients)
dyspnea	14
asthenia	12
dizziness	9
injection site inflammation/ reaction	7
chest pain	7
pallor	7
syncope	7
diarrhea	6
infection	5
procedural complications	5
sepsis	5
hypotension	5
nausea	5
cyanosis	5
peripheral edema	5
depression	5

In summary, the adverse experience profile in patients receiving FLOLAN® (epoprostenol sodium) infusions for up to 48 months was similar to the profile in the chronic, controlled studies described in Section 9.8.1.3.

9.8.1.5 Adverse Experiences Resulting in the Permanent Discontinuation of FLOLAN

As discussed above, FLOLAN was withdrawn permanently in 4 patients. One patient discontinued FLOLAN during Study 46 due to chills, pallor, malaise and myalgias. FLOLAN was withdrawn in 3 patients in the extended infusion segment of Study 05/10 due to diplopia and photosensitivity in one patient; headache and nausea in another; and nausea and vomiting in a third patient. CRFs for these patients are found in Section 12, Volume 1.76.

9.8.1.6 Adverse Experiences Associated with the Drug Delivery System: Controlled and Uncontrolled Chronic Studies

Although the relationship of all adverse experiences to the drug delivery system was not assessed prospectively in Studies 35/36 or 37, investigators noted many of the adverse experiences reported by patients that were associated with the delivery system. Adverse experiences associated with the drug delivery system in those studies were assessed by review of investigator comments. In Study 37, six embolic events and 49 episodes of infection (including sepsis and irritation at the catheter site) were reported. Adverse events clearly attributable to excess FLOLAN (including chest pain, headache, hypotension, nausea, muscle aches and seizure) that were associated with pump malfunctions, flushing catheter and changing intravenous tubing were reported on 57 different occasions. PPH symptoms clearly attributable to insufficient FLOLAN (including chest pain, shortness of breath, lightheadedness, pallor) that were associated with pump malfunctions and flushing catheters were reported on 62 occasions.

In Study 46 events related to the delivery of FLOLAN were prospectively identified. Malfunctions of the drug delivery system did not necessarily result in an adverse experience. Adverse experiences caused by a delivery system problem resulting in an excessive dose of FLOLAN, such as an inadvertent bolus during priming of the extension tubing, or an error in pump setting or drug reconstitution, were usually consistent with the pharmacologic effects of FLOLAN (e.g., hypotension, headache, nausea and vomiting). Adverse experiences related to inadequate FLOLAN dose tended to be exacerbation of PPH signs and symptoms (eg. dizziness, dyspnea, pallor, syncope). These subtherapeutic doses were sometimes due to delivery system problems such as catheter thrombi, pump malfunction, or reconstitution errors. Adverse experiences attributable to the drug delivery system in Study 46 are summarized in Table 77.

Though summarized with other adverse experiences, infections related to the drug delivery system are discussed separately in the following section.

Sepsis and Catheter Related Infections: Chronic Studies

The risk of infection related to the presence of a chronic indwelling catheter is an important consideration in choosing chronic, continuous FLOLAN infusion as a therapeutic option for patients with severe PPH.

Catheter related infections in the chronic studies (35/36, 37 and 46) may be summarized in several ways: 1) the number of patients who experience an infection (incidence), 2) the number of infections per patient, and 3) the number of infections per patient over time (expressed as infections per patient per year).

Local infections involving the skin and subcutaneous tissues proximate to the site of entry of the central venous catheter, were relatively frequent but rarely serious. They were usually managed by antibiotic therapy, and occasionally replacement of the catheter. For purposes of this report, all investigator descriptions suggesting a local infection were grouped; bacteriologic confirmation was not required.

Thus, the terms injection site reaction and injection site inflammation were considered to indicate local infections. Approximately 21% of the FLOLAN[®] (epoprostenol sodium) patients reported local infections (Table 65, Section 9.8.1.3). A majority of patients in Study 37 reported local infections during the long term use of FLOLAN (Table 76).

The term sepsis was used to encompass all presumed or proven systemic infections whether or not related to a central venous catheter. All patients using central venous catheters in the chronic studies were receiving FLOLAN. The following summarizes the incidence of sepsis in the chronic studies using data abstracted from the individual study reports:

Study	FLOLAN Pts with Sepsis/Total	Number of Episodes	Patient-Months of Exposure	Infections/Patient/Year	Standard Pts with Sepsis/Total
35/36	0/11	0	22	0	1/14
37	5/18	12	503	0.29	0/0
46	5/41	5	123	0.49	1/40
Total	10/74	17	648	0.32	2/54

None of the episodes of sepsis in patients receiving FLOLAN were fatal. In the literature, infection rates in non-oncology indications (hyperalimentation, antibiotics) generally range from about 0.13 to 0.17 per patient per year (63-65). In oncology indications, rates of sepsis appear to be higher, about 0.58 to 0.78 per patient per year (66-70). Thus rates of sepsis associated with chronic FLOLAN infusions in PPH patients appear to be somewhat higher than reported in some, but not all, other clinical conditions requiring long-term infusions.

9.8.1.7 Adverse Experiences in Patients with Severe PPH Receiving FLOLAN in Burroughs Wellcome Sponsored Studies. Summary and Conclusions

1. Acute dose-ranging with FLOLAN for the purpose of assessing pulmonary vasoreactivity or determining an initial chronic infusion dose of FLOLAN can be safely performed in most patients.
2. The most frequent adverse experiences during dose-ranging are related to the main pharmacologic effects of FLOLAN, pulmonary and systemic vasodilatation.

3. Adverse experiences, including those reported as severe, are short-lived upon reduction or discontinuation of the FLOLAN® (epoprostenol sodium) infusion.
4. FLOLAN doses that result in adverse experiences during acute administration are well-tolerated during chronic therapy.
5. During chronic studies, adverse experiences likely associated with the underlying disease were common in patients treated with standard therapy alone and in patients receiving FLOLAN plus standard therapy.
6. During chronic treatment, jaw pain, headache, tachycardia, flushing, diarrhea, nausea, dizziness and myalgias were probably related to FLOLAN therapy.
7. During chronic treatment worsening heart failure, syncope, hypoxia and shock were more common in the standard therapy group and were probably related to worsening of PPH. In some cases, these events were associated with inadvertent, abrupt interruptions of FLOLAN delivery.
8. In patients receiving FLOLAN, investigators increased the dose of FLOLAN in response to adverse events suggestive of worsening PPH.
9. Adverse experiences related to the drug delivery system (fever, injection site problems) occurred in patients receiving FLOLAN.
10. There was a risk of sepsis in patients receiving FLOLAN via permanent central venous catheter. No factor predicted an increased risk of sepsis in individual patients.
11. Patients younger than 16 received higher doses of FLOLAN acutely.
12. There were no apparent FLOLAN-demographic interactions.
13. The concomitant use of other vasodilators may have accentuated the incidence of some common FLOLAN-related adverse experiences. However, vasodilators as well as digoxin and diuretics appear to be well tolerated when used in combination with FLOLAN.
14. Based on data from a small number of patients, continuous FLOLAN infusions are safe in patients with severe PPH for greater than three years.

9.8.1.8 *Canadian Emergency Drug Release Program in Patients with PPH*

FLOLAN is available in Canada for compassionate use and is used primarily acutely to evaluate pulmonary vasoreactivity in patients with PPH and SPH (Secondary Pulmonary Hypertension). Less frequently, FLOLAN has been requested for acute use in patients with renal failure, multi-organ failure and TTP (thrombotic thrombocytopenic purpura). FLOLAN is provided by Burroughs Wellcome Inc. (Canada) for named-patient use only after each

emergency drug request is approved by the HPB (Health Protection Branch) of the Canadian Government. This provision, called the EDR (Emergency Drug Regulation), is an approved exemption to the Canadian drug laws.

Between 18 November 1985 and 05 April 1993, Burroughs Wellcome Inc. provided FLOLAN® (epoprostenol sodium) under the EDR for 142 patients. Physicians were requested to provide a brief report on the use of FLOLAN to the HPB and to Burroughs Wellcome Inc., but sometimes the physicians did not respond. Of the 142 patients, Burroughs Wellcome Inc. has received letters or follow-up forms on 86 patients. Available safety information was extracted from these reports and was summarized for this NDA.

Of the 86 patients with reports, 63 patients received FLOLAN and 23 did not. Of the 63 patients who received FLOLAN, 26 had PPH, 36 had SPH and 1 had TTP. Safety information, i.e., the adverse experiences and deaths occurring in these 63 patients, is summarized in Table 78. Adverse events are summarized in Section 9.8.6 for SPH and TTP. Reasons for not administering FLOLAN included: cardiac catheterization data indicating that administration of FLOLAN would be contraindicated or that pulmonary hypertension was not present upon catheterization; deterioration in the patient's clinical condition such that no further therapy was being administered; or the patient was too unstable to undergo the dose-ranging procedure with a potent vasodilator.

Two deaths were reported in patients with PPH. A 30-year-old female with advanced PPH, who underwent dose-ranging with FLOLAN, had no adverse experiences. She subsequently died while awaiting heart-lung transplant. A 31-year-old male with advanced PPH, tolerated dose-ranging with FLOLAN with no adverse experiences. Several hours after the completion of the FLOLAN infusion, and after initiation of oral vasodilators, he developed cardiogenic shock, had a cardiac arrest and died. The investigator stated that the death was not related to FLOLAN. Overall, the adverse event profile reported through the Canadian EDR program was similar to that reported in Burroughs Wellcome Co. sponsored PPH trials.

9.8.1.9 *Adverse Events Reported in Patients with PPH: Published Literature*

Physician-investigators at the Papworth Hospital in the United Kingdom have used FLOLAN in the short-term and chronic treatment of patients with PPH in studies not sponsored by Burroughs Wellcome Co. or The Wellcome Foundation Ltd. (UK). Copies of their publications are included in Section 4.4. Summaries of these investigations include information on an unknown number of PPH patients, since some publications reported FLOLAN use in a mixed patient population.

Of the 25 publications that report FLOLAN use in 83 patients with PPH, 8 articles report adverse experiences (50-52, 56, 71-74). Over-reporting is likely since several papers originate from the same investigators and may include patients more than once. The following summarizes adverse experiences reported during acute and chronic FLOLAN infusions and a best estimate of the number of cases.

Published Literature

Adverse Experience	No. of Events (N = 88 Patients)
Acute Infusion	
hypotension	3 ^a
nausea	3
syncope	1
bradycardia	1
flushing	*
gastrointestinal cramping	*
headache	3
abdominal pain	1
Chronic Infusion	
ascites	4
bacteremia/septicemia	4
worsening PPH symptoms (due to FLOLAN® interruption)	5
death	7

* The number of events not specifically reported in all publications

In summary, the adverse event profile reported in the literature in patients with PPH treated with FLOLAN® (epoprostenol sodium) is similar to that reported in patients with PPH who were enrolled in Burroughs Wellcome Co. trials.

9.8.2 Clinical Laboratory Evaluations

Clinical laboratory assessments, including hematology, coagulation times, and blood chemistries, were collected at baseline and following chronic FLOLAN treatment in Studies 35/36 and Study 37, as well as following acute exposure in Studies 05/10, 20, and 21. Clinical laboratory evaluations were not required for Study 46.

For purposes of discussion, expanded normal ranges were defined for each laboratory parameter (Table 79). The highest and lowest values of the expanded normal range for each parameter are the highest and lowest values, respectively, across all centers for that parameter.

Summaries of clinical laboratory evaluations and analyses of changes from baseline during studies are presented. However, in patients who received FLOLAN during Study 35/36 and entered Study 37, changes during Study 37 were calculated using baseline values from Study 35/36. Statistical significance of changes from baseline values was assessed using non-parametric 95% confidence intervals.

In all studies, adverse events associated with changes in clinical laboratory parameters are summarized in Section 9.8.1.

9.8.2.1 *Hematology*

Study 35/36

In the controlled Study 35/36, median and mean values of both treatment groups for all hematologic parameters were within the expanded normal range at Baseline and at Week 8 (Table 80). However, during the study, platelet count increased in patients treated with FLOLAN® (epoprostenol sodium) and decreased in patients treated with standard therapy (Table 81). This difference between treatment groups in the change of platelet counts was statistically significant. The median increase in platelet count among FLOLAN-treated patients was 56,000/mm³ (mean = 46,800/mm³) which was statistically significant (Table 82). The platelet count of the standard-therapy group decreased a median of -3,500/mm³ and a mean of -8,700/mm³. No other changes in hematologic parameters were statistically significant either between treatment groups or within treatment groups and no changes in either treatment group were clinically significant.

Study 37

Hematology values were monitored every 6 months in continuation Study 37. The mean values for all hematology tests were within the expanded range through 30 months (Table 83). Changes in hematologic parameters during Study 37 were examined for within-treatment significance (Table 84). The changes from baseline in Study 35/36 in the following parameters were significant:

Study 37

Parameter	Mean Change from Baseline of Study 35/36	Time
Platelets	26,000 ± 10,800/mm ³	Baseline for Study 37
	36,300 ± 13,500/mm ³	Month 6
Neutrophils	5.7 ± 2.3%	Month 6

Studies 5/10, 20 and 21

The hematology values before and after short-term exposure to FLOLAN are summarized in Table 85. Seven parameters had significant changes as follows:

Studies 05/10, 20, and 21

Parameter	Mean Pretreatment	Mean Posttreatment	Mean Change
RBC (x 10 ⁶ /mm ³)	4.98	4.61	-0.38 ± 0.08

Studies 05/10, 20, and 21

Hematocrit(%)	43.6	41.0	-2.6 ± 0.3
WBC(x 10 ³ /mm ³)	8.5	9.6	1.1 ± 0.3
Neutrophils(%)	57.2	61.3	4.1 ± 1.2
Bands(%)	2.2	3.4	1.2 ± 0.4
Lymphocytes(%)	34.0	28.4	-5.6 ± 1.2
Platelets(x 10 ³ /mm ³)	239	201	-37.2 ± 3.9

Summary

Patients receiving chronic FLOLAN® (epoprostenol sodium) treatment also received anticoagulant therapy. Results from the chronic studies did not reveal significant reductions of hemoglobin or hematocrit. The clinical relevance of increased platelet count and neutrophil count observed during chronic FLOLAN therapy is unclear. The interpretation of the decreases in RBC, hematocrit, and platelets in the acute studies is complicated by the lack of a control group but the changes were not clinically significant. Patients underwent invasive cardiovascular procedures during which some blood loss and some dilutional effects were expected.

9.8.2.2 *Coagulation Time*

Study 35/36

During Study 35/36 coagulation times were assessed at screen and at the end of the study (Table 86). No statistically significant changes occurred from the beginning to the end of the study and there was no difference between treatment groups. The median values for PT and aPTT were within the expanded normal range at the beginning and end of the study for both treatment groups. The mean values for aPTT were above the expanded normal range at screen for patients randomized to FLOLAN and at the end of the study for patients randomized to standard therapy alone. The mean values for PT at the end of the study were above the expanded normal range for both treatment groups.

Study 37

During Study 37, the mean values for aPTT were within the expanded normal range at all timepoints through 30 months (Table 87). Mean values for PT were slightly above the normal range at all assessments; changes were consistent with the use of anticoagulant therapy since all patients were receiving anticoagulant therapy at doses to maintain PT between 1.3 and 1.5 times control during the study to prevent clotting of the central venous catheter.

Summary

In summary, administration of FLOLAN did not appear to affect coagulation times significantly during continuous infusion of FLOLAN for up to

30 months. PTs were slightly above normal during Study 37 reflecting the fact that patients were receiving anticoagulant therapy during the studies.

9.8.2.3 *Blood Chemistry*

Study 35/36

In controlled Study 35/36, median and mean values for all clinical chemistry parameters of FLOLAN® (epoprostenol sodium)-treated patients were within the expanded normal range at the end of the 8-week study (Table 88). At Baseline, the mean direct bilirubin and LDH of patients randomized to FLOLAN were slightly above the expanded normal range, but these values were within the expanded normal range after 8 weeks. Approximately half of the patients in both treatment groups had LDH values above the normal range at baseline and at the end of the study.

Uric acid values increased significantly in patients receiving standard therapy (mean and median = +0.6 mg/dL), whereas the values of patients receiving FLOLAN tended to decrease (Table 89). Although the between-treatment group comparison was statistically significant ($p < 0.05$), the difference is not likely to be clinically meaningful. No other changes in clinical chemistry parameters were statistically significant between treatment groups. Though no between treatment difference was apparent in any other parameter, SGOT was significantly decreased below baseline in patients who received FLOLAN (Table 90). This decrease was not clinically significant.

Study 37

Patients in Study 37 had a mean LDH value above the normal range at baseline as well as at each assessment during Study 37 (Table 91). Mean bicarbonate was slightly below the normal range at 18 months. The means for total bilirubin and direct bilirubin were slightly above the baseline (Study 35/36) normal range.

Changes from baseline during Study 37 are presented in Table 92. Although changes from baseline in the following parameters were statistically significant, the changes did not appear to be clinically significant:

Study 37

Parameter	Mean Change from Baseline (Study 35/36)	Time
Calcium	-0.5 ± 0.2 mg/dl	Month 24
Cholesterol	-30 ± 8 mg/dL	Month 12
Uric acid	-1.1 ± 0.4 mg/dL	Month 6
	-1.6 ± 0.2 mg/dL	Month 30
Total bilirubin	-0.4 ± 0.1 mg/dL	Month 6
AP	-46 ± 18 U/L	Month 6
	-54 ± 24 U/L	Month 12
SGOT	-5.9 ± 3.0 U/L	Baseline (Study 37)
	-12.3 ± 3.9 U/L	Month 18
	-10.0 ± 3.2 U/L	Month 24
	-14.5 ± 3.5 U/L	Month 30
Creatinine	0.1 ± 0.0 mg/dL	Month 24
	0.2 ± 0.0 mg/dL	Month 30

Studies 05/10, 20 and 21

In Studies 05/10, 20, and 21 following the short-term use of FLOLAN® (epoprostenol sodium), seven of the patients had immediate posttreatment assessments. Paired pretreatment and posttreatment values have been summarized for those patients who had both assessments (Table 93). Though the following changes were statistically significant, none were judged clinically relevant:

Studies 05/10, 20, and 21

Parameter	Mean Pretreatment	Mean Posttreatment	Mean Change
Sodium (mEq/L)	140	138	-1.2 ± 0.3
Calcium (mEq/L)	9.6	9.2	-0.4 ± 0.05
Glucose (non-fasting) (mg/dL)	97	103	6 ± 2
Cholesterol (mg/dL)	167	153	-14 ± 3
BUN (mg/dL)	17	15	-1.8 ± 0.4
Total protein (g/dL)	6.8	6.2	-0.6 ± 0.1
Albumin (g/dL)	4.3	3.9	-0.4 ± 0.04
Total bilirubin (mg/dL)	0.9	1.1	0.2 ± 0.1
AP (U/L)	191	178	-13 ± 3
LDH (U/L)	293	328	35 ± 12

Patients with severe PPH typically have elevated liver enzymes, apparently due to poor circulation and elevated central venous pressure. The values measured in this study were consistent with the underlying disease. The changes which occurred following short-term use of FLOLAN did not appear to be clinically significant.

9.8.2.4 Summary

During chronic FLOLAN® (epoprostenol sodium) therapy platelet count increased from baseline values at Week 8 and Month 6. Neutrophil count was also above baseline values at Month 6. The clinical relevance of these changes is unclear. Patients receiving chronic FLOLAN therapy also received anticoagulant medication to prevent clotting of the central venous catheter. Although PTs were slightly above normal, the changes in hemoglobin and hematocrit were not suggestive of blood loss. The changes in clinical chemistry values did not appear to constitute a clinical pattern.

The decreases in RBC and hematocrit observed following short-term exposure to FLOLAN were expected in patients who also underwent invasive cardiovascular procedures during which some blood loss occurred and fluids were injected for cardiac output determinations. The changes in blood chemistry values were small following acute FLOLAN infusions and did not appear to be clinically relevant.

9.8.3 Electrocardiograms

A 12-lead ECG was performed on each patient in Study 35/36 at Baseline and at the end of the 8-Week Treatment Phase. 12-lead ECGs were not recorded in Studies 20 and 21, given the short duration of infusions. ECGs also were not recorded in Study 46. The results from controlled Study 35/36 and continuation Study 37 and are summarized below. Adverse events associated with changes in ECG are summarized for all studies in Section 9.8.1.

Study 35/36

During Study 35/36, four FLOLAN-treated patients and two standard therapy-treated patients had treatment emergent abnormalities on 12-lead ECG at the end of the study. For one standard-therapy patient, the investigator commented that the abnormality was due to the medical management of the patient. Investigators did not comment on the other findings. The treatment emergent abnormalities in Study 35/36 are presented below.

Abnormality	FLOLAN		Standard Therapy	
	No.	%	No.	%
Junctional Tachycardia	1	10%	0	0%
Right Atrial Enlargement	1	10%	0	0%
First degree AV block	1	10%	0	0%
Nonspecific ST-T wave changes	2	20%	1	8%
Other	1	10%	0	0%

Study 37

Quantitative ECG data recorded at screen and at the end of Study 35/36 are summarized in Table 94. No clinically significant changes in ECG intervals were apparent.

During Study 37, treatment-emergent changes were based on changes from baseline in Study 35/36. There were no statistically significant changes in quantitative ECG parameters (Table 95). In general, there were no clinically significant treatment-emergent normal variants or abnormalities. Treatment-emergent abnormalities in Study 37 and frequency of occurrence are summarized below.

Abnormality	No. of Patients	%
Nonspecific ST-T wave changes	8	44%
Right atrial enlargement	7	39%
Sinus tachycardia	3	17%
First degree AV block	3	17%
Incomplete right bundle branch block	3	17%
Right bundle branch block	2	12%
Right ventricular hypertrophy	2	12%
Premature ectopic atrial beats	1	6%
Junctional tachycardia	1	6%
Left posterior hemiblock	1	6%
Nonspecific intraventricular conduction delay	1	6%
ST depression	1	6%
ST elevation	1	6%
Accessory pathway (WPW)	1	6%

Summary

Although ECG abnormalities occurred more frequently in patients treated with FLOLAN® (epoprostenol sodium), the observed effects were sporadic and not clearly associated with any known effect of FLOLAN. Serious bigeminy, tachycardia, and supraventricular tachycardia were reported as adverse experiences in FLOLAN-treated patients during Study 35/36. No consistent posttreatment ECG abnormalities were apparent in patients who received FLOLAN in the acute dose-ranging studies. The changes observed during the uncontrolled trial were consistent with the cardiac effects of PPH.

9.8.4 Physical Examinations

Patients in Study 35/36 underwent a physical examination at screen and at the end of the 8-week study. Patients in uncontrolled Study 37 were examined every 6 months. Clinically significant changes detected by physical examination of patients in Study 46 were recorded and analyzed as adverse experiences or complications (Section 9.8.1).

Two FLOLAN-treated patients and four standard therapy-treated patients had abnormalities recorded by the investigator at the end of 35/36 that were not present at screen. One FLOLAN-treated patient had developed slight crackles in both lung bases and dry, itchy skin; all findings were rated "mild" by the investigator. Tense ascites also was reported in this patient. Another FLOLAN-treated patient had a change in mental status recorded as

“moderate” increased stress due to family problems at the end of the study. Among standard therapy patients, “moderate” depression due to PPH, “moderate” parasternal lift, a mildly enlarged liver, and ascites were each noted in one patient at the end of the study.

The physical examination administered at entry into Study 37 was used for comparison during long term follow-up in Study 37. Two patients had no follow-up examinations. Four patients had no treatment-emergent abnormalities. Twelve patients had at least one treatment-emergent abnormality. Treatment-emergent abnormalities are summarized below.

Body Region	Abnormality	No. of Patients
Extremities	Edema	7
Skin	Cyanosis	4
	Plethora	1
	Wounds and subclavian puncture	1
	Acne	1
	Hyperpigmentation	1
	Facial flushing	1
Head & Neck	Neck veins distended	1
	Ascites	2
Abdomen	Enlarged liver	1
	Tender submandibular	1
Lymph nodes	Cachexia	1
Overall Cardiovascular	Increased S2	2
	Tricuspid regurgitation murmur	4
	Systolic murmur	4
	S3 gallop	2
	S4 gallop	2
	Jugular venous distension	3
	Right ventricular lift	4
	Decreased peripheral pulses	2

No FLOLAN® (epoprostenol sodium)-related abnormalities were apparent in the controlled trial (Study 35/36). The incidence of ascites is summarized in Section 9.8.1. Generally, the treatment-emergent abnormalities in the uncontrolled trial (Study 37) were difficult to distinguish from abnormalities that would be expected in patients with PPH.

9.8.5 *Withdrawal from FLOLAN*

This section summarizes the adverse events that occurred during and immediately following the withdrawal of FLOLAN when administered short-term or chronically. Since the type and severity of adverse events and the degree of rebound pulmonary hypertension may vary during withdrawal of FLOLAN following short-term or chronic use, adverse events and hemodynamics were summarized separately in these situations. In either case, by protocol FLOLAN was to be withdrawn slowly.

FLOLAN® (epoprostenol sodium) was withdrawn after short-term use following dose-ranging of each patient in Studies 05/10, 20 and 21 and following dose-ranging of each standard therapy patient in Studies 35/36 and 46. In Studies 05/10, 20 and 21, FLOLAN was to be withdrawn by reducing the infusion rate by 50% in repeated decrements. The time interval separating these decrements was not specified but was to be based on investigator's judgement. The infusion rate was to be discontinued when the rate reached 1 ng/kg/min or less. In Studies 35/36, 37 and 46 the infusion rate was to be reduced in 2 ng/kg/min decrements; a minimum of 15 minutes was to separate each change in rate. Post-treatment hemodynamics and adverse events were monitored by protocol for one hour following dose-ranging procedures in 188 patients of the 339 patients enrolled in acute dose-ranging trials (Studies 05/10, 20, and 21). Only post-treatment adverse events were monitored after dose-ranging procedures in standard therapy patients in Studies 35/36 and 46.

FLOLAN was withdrawn following long-term, chronic use in two patients randomized to FLOLAN in Study 35/36, in 5 patients following extended infusions in Studies 05/10, 20 and 21, in two patients in Study 46 who experienced intolerable adverse events and in nine patients in Studies 37 and 46 during the perioperative period surrounding transplantation. FLOLAN was to be withdrawn slowly in these situations, as described above. Only adverse events were monitored during slow withdrawal of chronic therapy.

In contrast to the slow, planned withdrawal of FLOLAN administered short-term or chronically, FLOLAN was abruptly discontinued when unanticipated problems with the delivery system occurred during chronic treatment. An effort was made to identify and summarize adverse events that were reported under these circumstances. FLOLAN infusions were temporarily stopped in 31 patients due to the occurrence of unanticipated problems, including catheter occlusion, drug reconstitution difficulties, and pump malfunctions.

9.8.5. *Withdrawal Following Short-Term Exposure to FLOLAN*

An increase in PAPm or PVR of 20% or more above baseline, within 1 hour of discontinuation of FLOLAN, was considered evidence of rebound pulmonary hypertension. As shown in Table 96, PAPm or PVR increased by 20% or greater in 35 of the 188 patients (19%) monitored following withdrawal of FLOLAN during acute dose-ranging studies. Mean maximum changes from baseline in PAPm and PVR were 12.5 mm Hg and 4.7 Wood units, respectively. The maximum change in PAPm was 53 mm Hg; the maximum change in PVR was 27 Wood units.

No adverse events were reported following the withdrawal of FLOLAN in acute dose-ranging Studies 05/10 and 20 or following the initial dose-ranging procedures in Studies 35/36 and 46. However, nine patients in Study 21 reported post-treatment adverse experiences. In two patients, nausea or sweating were reported during dose ranging and continued during

post-treatment follow-up. These events were judged not related to FLOLAN® (epoprostenol sodium) withdrawal. Mild thrombocytopenia was reported in another patient following withdrawal of FLOLAN; attribution of the thrombocytopenia was judged as unknown; the patient did not experience any untoward sequelae from this event. Three other patients reported headache; however, onset times in two patients were not reported, and it was assumed that headache was associated with administration of the drug rather than with its withdrawal. In the third patient, onset of headache was subsequent to withdrawal of FLOLAN and was judged severe, but not serious. Rebound pulmonary hypertension was reported as an adverse event in one patient following discontinuation of FLOLAN. PAPm increased from 85 mm Hg at baseline to a post-treatment maximum of 93 mm Hg. However, PVR did not increase above baseline and CO was not reduced below baseline. No symptoms relating to rebound pulmonary hypertension were reported. Onset of nausea or dizziness were reported in two patients following withdrawal of FLOLAN. In each case, the nausea and dizziness were short in duration (5-16 minutes) and were mild to moderate in intensity.

9.8.5.2 *Withdrawal Following Long-Term Exposure to FLOLAN*

- **Planned Withdrawal**

In Study 35/36 withdrawal of FLOLAN was to be attempted and hemodynamics monitored, by protocol, in all FLOLAN-treated patients at the end of the chronic therapy phase. However, in the first 2 patients undergoing withdrawal of FLOLAN, symptoms of PPH returned during, or shortly after, withdrawal. In one patient, PAPm and RAP increased with a decrease in mixed venous saturation. Clinical signs of withdrawal included dyspnea and chest tightness. Another patient experienced pallor, which was not considered serious but was of moderate intensity. In both patients symptoms disappeared and pulmonary hemodynamics improved when FLOLAN therapy was reinstated. Due to the seriousness of these symptoms, the protocol was amended and all subsequent patients were immediately placed on maintenance FLOLAN therapy following the 8-week treatment if they chose to enter a continuation protocol.

Because of the observations in Study 35/36, FLOLAN was not withdrawn, by protocol, in any patient in Study 46 following the 12-week treatment phase. Thus, only limited data are available on withdrawal of FLOLAN following chronic treatment for 8 or 12 weeks. However, during the 12-week treatment phase of Study 46, FLOLAN was withdrawn permanently due to adverse events in 1 patient (Section 9.8.1.3) and withdrawn briefly due to adverse events in a second patient. No adverse experiences were reported during or following withdrawal of FLOLAN in these 2 patients. FLOLAN was discontinued temporarily in two other patients (Study 46) in order to administer other

medications through the central venous catheter. In another patient in Study 46, FLOLAN® (epoprostenol sodium) was permanently discontinued due to the patient's inability to master the procedures required to administer FLOLAN. No adverse experiences were reported following withdrawal of FLOLAN in these three patients.

Nine patients underwent transplantation in Studies 37 and 46; FLOLAN was discontinued pre-operatively in five patients and post-operatively in three patients. The time of FLOLAN discontinuation was not specified for one patient. No untoward sequelae were reported as resulting from the discontinuation of FLOLAN in any of these patients.

In addition to the withdrawal of FLOLAN following chronic administration in Studies 35/36, 37 and 46, FLOLAN was withdrawn in two patients in Study 21 who received chronic infusions for 15 and 58 days. No adverse events were reported associated with withdrawal from FLOLAN in these two patients.

Three other patients died either during or within hours following the protocol-specified discontinuation of an extended infusion of FLOLAN in Study 21. One patient, a 28-year-old black female with severe PPH and right heart failure, entered the study with PAP of 99/45 mm Hg and SAP of 66/47 mm Hg. Prior to dose-ranging the patient developed sudden respiratory decompensation requiring intubation and mechanical ventilation, and vasopressor support. During dose ranging, PAP decreased and CO increased. During the first several hours of extended infusion of FLOLAN (10 ng/kg/min), the patient experienced two episodes of severe bradycardia and hypotension which required cardiopulmonary resuscitation and vasopressor therapy. Additionally, the patient developed aspiration pneumonia secondary to endotracheal intubation. After approximately 14 hours of FLOLAN therapy, the infusion rate was reduced to 8 ng/kg/min in an effort to increase arterial oxygen saturation. Over the next two days the patient's condition improved, PAP was reduced and an infusion of dopamine was weaned. During withdrawal of the extended infusion of FLOLAN the patient's condition deteriorated. Approximately 22 hours after discontinuation of FLOLAN the patient had a fatal cardiac arrest; the event was judged, by the investigator, to be secondary to severe PPH and unrelated to FLOLAN.

The second patient was a 42-year-old white female with a history of dyspnea on exertion, pneumonia, and a possible pulmonary contusion as the result of a recent motor vehicle accident. On entry into Study 21, the patient was experiencing arterial oxygen desaturation in spite of mechanical ventilation and supplemental oxygen. During dose ranging, arterial oxygen saturation increased, and the patient was placed on an extended infusion of FLOLAN. The patient experienced a cardiac arrest as the FLOLAN infusion was being reduced and diltiazem therapy initiated, with the family's agreement resuscitation was not attempted.

The death was judged by the investigator as possibly related to either reduction of the dose of FLOLAN® (epoprostenol sodium), pneumonia, or the pulmonary contusion.

The third patient who died following withdrawal of an extended infusion of FLOLAN, was a 33-year-old black female with a history of pulmonary hypertension, lupus erythematosus, hilar adenopathy, aortic stenosis, and chronic thrombocytopenia. The patient entered Study 21 several hours after a cesarean section, and while receiving ventilator support and dopamine therapy. CO increased during dose-ranging, and the patient was placed on an extended infusion of FLOLAN. After approximately 48 hours of FLOLAN therapy, the patient experienced three episodes of decreased HR and SAP, accompanied by tonic movements. The FLOLAN infusion was stopped one hour later. Approximately one hour and 4.5 hours following discontinuation of FLOLAN, the patient experienced two additional seizure-like episodes with decreases in HR and SAP. The patient died of a cardiac arrest approximately 5 hours after the infusion of FLOLAN was discontinued.

- **Abrupt Discontinuation**

Adverse events and a single death have been associated with the inadvertent abrupt withdrawal of FLOLAN. In Study 37, one patient died due to interruption of FLOLAN. This 69-year-old male with NYHA Class III PPH, had been receiving FLOLAN continuously for 13 months. Two months after FLOLAN had been initiated, the patient began experiencing pallor and shortness of breath whenever FLOLAN was temporarily interrupted during catheter care. Typically, symptoms resolved within 30–60 minutes after restarting the infusion. For several days prior to the terminal event, the symptoms of PPH became increasingly severe and prolonged following flushing of the central venous catheter with heparin. The terminal event occurred when the patient became extremely symptomatic after flushing the central catheter. The death was attributed to the interruption of FLOLAN during flushing of the drug-delivery system.

In Studies 35/36 and 37, FLOLAN was temporarily and abruptly withdrawn in three other patients due to complications with the central venous catheter. One patient experienced serious cough, dyspnea, and chest pain; another patient experienced dyspnea; and the third patient experienced exacerbation of PPH symptoms including dyspnea, asthenia and pallor following FLOLAN withdrawal. These adverse events were relieved when FLOLAN was restarted.

The dose of FLOLAN was inadvertently reduced abruptly, during Study 35/36 in another patient; syncope and dyspnea, both judged as serious, were reported. Both events resolved when the original infusion rate of FLOLAN was restored.

FLOLAN infusion was abruptly interrupted temporarily during the 12-week chronic treatment on 40 other occasions, in 23 patients, due to

problems with administering FLOLAN® (epoprostenol sodium). No deaths were reported and in each case FLOLAN was reinitiated without difficulty. Adverse experiences associated with these unanticipated interruptions in FLOLAN administration are summarized below.

Study 46

Adverse Experience	N ^a	% ^b
Dyspnea	10	25%
Dizziness	4	10%
Asthenia	4	10%
Chest Pain	3	8%
Palor	2	5%
Headache	2	5%
Hypotension	1	3%
Anxiety	1	3%
Malaise	1	3%
Syncope	1	3%
Cyanosis	1	3%
Flushing	1	3%
Restlessness	1	3%
Nausea	1	3%
Bleeding	1	3%
Thrombosis	1	3%
Pain	2	5%

^a number of times an event occurred

^b no. of experiences / no. of unanticipated interruptions (40)

The predominate adverse experiences reported with the temporary, abrupt discontinuation of FLOLAN during 12 weeks of chronic therapy in Study 46 were symptoms associated with PPH (dyspnea, dizziness, asthenia, and chest pain). Although occurring frequently, these events were not described as serious.

9.8.5.3 Summary

FLOLAN was always to be withdrawn slowly and under the supervision of a physician with experience in using potent vasodilators. FLOLAN was withdrawn from patients after short-term administration and after long-term exposure. FLOLAN was withdrawn by protocol design, withdrawn due to intolerable adverse experiences in two patients, withdrawn due to transplantation, and withdrawn inadvertently due to malfunctions in the drug-delivery system.

Rebound pulmonary hypertension was observed in 19% of the patients monitored for up to one hour following withdrawal of FLOLAN after acute dose-ranging procedures. Four patients reported headache, dizziness, nausea, or mild thrombocytopenia following withdrawal of FLOLAN after acute dose ranging. In each case, the event was short in duration and judged by the investigator as not serious.

Experience is limited with withdrawing FLOLAN during chronic infusions. Significant clinical deterioration occurred in two patients when FLOLAN was withdrawn slowly after eight weeks of treatment. A single death occurred

when FLOLAN® (epoprostenol sodium) was inadvertently and abruptly withdrawn during chronic FLOLAN treatment. The adverse events which were most frequently observed when FLOLAN was abruptly withdrawn during chronic treatment were exacerbation of PPH signs and symptoms (dyspnea, dizziness, asthenia).

Increases in PAPm and PVR, with reduction of CO and the re-emergence of PPH symptoms following withdrawal of acute and chronic infusions of FLOLAN, suggest that consideration be given to invasive hemodynamic monitoring during discontinuation of FLOLAN. In clinical trials, Burroughs Wellcome Co. recommended that withdrawal of FLOLAN therapy in critically ill patients be done slowly, in 2 ng/kg/min decrements over several hours to days, and under the supervision of a physician with experience using this potent vasodilator.

9.8.6 *Adverse Experience Reports in Indications Other than PPH*

9.8.6.1 *Introduction*

FLOLAN has been in world-wide clinical development since 1978. Safety data have been generated over many years and have been compiled from diverse sources. To further evaluate the overall safety profile of FLOLAN, reports of adverse experiences associated with FLOLAN administration in indications other than PPH have been reviewed and summarized in this section. Attempts have been made to identify the number of patients treated with FLOLAN, the number of patients in the control group (when available), the number of deaths, and the adverse experience profiles reported for each indication.

FLOLAN has been used in 29 indications, other than PPH, that have been classified within 11 therapeutic areas/procedures categories (Table 97). Deaths and adverse experiences from four sources (1. Burroughs Wellcome Co. - U.S.; 2. Burroughs Wellcome Inc. - Canada; 3. and 4. published literature) have been summarized for each of these 29 indications.

In addition to the presentation of adverse experience profiles by indication for clinical studies conducted by Burroughs Wellcome Co., Burroughs Wellcome Inc., and and investigator-sponsored studies reported in the literature, an overall summary of postmarketing adverse experiences has been compiled from information provided by the fifth source, the Clinical Safety Surveillance Service, Wellcome Research Laboratories, Beckenham, U.K. These postmarketing adverse experiences are reported separately in Section 9.8.6.13.

Summaries of adverse experiences in this section tend to be more qualitative than quantitative in nature. Some sources summarized adverse experiences, including severity, causality and frequency, while other sources reported adverse experiences without providing complete details. The variability in

reporting practices make clinical interpretations difficult. Details describing the sources of data, and guidelines used to summarize adverse experiences from the five sources, are discussed below.

Studies Sponsored by Burroughs Wellcome Co. (U.S.A.)

In addition to the PPH indication, Burroughs Wellcome Co. sponsored clinical trials in the following indications: persistent pulmonary hypertension of the newborn, congestive heart failure, hemodialysis, thrombotic thrombocytopenic purpura, acute respiratory failure, acute renal failure, renal transplantation and chronic obstructive pulmonary disease. The first clinical studies were initiated in 1980.

Clinical data from Burroughs Wellcome Co.-sponsored studies were obtained from individual case report forms on file at Burroughs Wellcome Co., from final study reports for secondary pulmonary hypertension (Studies 04 and 18), acute respiratory failure (Study 13) and acute renal failure (Study 28/32) and from the previous NDA (19-607) for hemodialysis studies.

Data from clinical studies sponsored by Burroughs Wellcome Co. represent the most complete source of data summarized in this section. The clinical data are comprehensive through 31 March 1993, which is the date of the most recent annual IND report. In addition, mortality data on the studies in congestive heart failure are included through termination of the clinical studies on 17 June 1993.

Emergency Drug Regulation Sponsored by Burroughs Wellcome Inc. (Canada)

FLOLAN® (epoprostenol sodium) has been available for acute use in Canada under provisions of the EDR (Emergency Drug Regulation). In addition to use in patients with PPH, FLOLAN has also been used in with SPH (secondary pulmonary hypertension) and TTP (thrombotic thrombocytopenic purpura). Physicians reported in letters or follow-up forms submitted to Burroughs Wellcome Inc. adverse experiences associated with use of FLOLAN. Adverse experiences have been extracted from the letters and forms, and summarized (Table 78). Adverse experiences occurring in the Canadian EDR through 05 April 1993 for patients with PPH are summarized in Section 9.8.1; adverse experiences for patients with SPH and TTP are summarized in this section (Section 9.8.6).

Studies Sponsored by

The number of episodes of adverse experiences, not the number of patients experiencing an adverse event, has been summarized for trials sponsored by provided technical reports, manuscripts and other supporting documents to Burroughs Wellcome Co., describing their clinical experiences in treating patients with acute stroke, unstable angina/ischemic heart disease, myocardial infarction and peripheral

vascular disease and in patients undergoing cardiopulmonary bypass. Severe adverse experiences were identified in these documents and have been summarized for each of these five indications.

also provided documentation containing adverse experiences without severity ratings in three other indications: persistent pulmonary hypertension of the newborn, hemolytic-uremic syndrome and placental perfusion. Adverse experiences, regardless of severity were summarized for these indications.

conducted trials in three other indications: accelerated hypertension, kidney transplantation and hemodialysis. No safety data were provided for these indications.

Studies Reported in the Published Literature

Adverse experiences occurring in diseases other than PPH, and reported in the literature, were compiled using PRODBIB, a database developed and maintained by Burroughs Wellcome Co. The publications in PRODBIB are obtained by reviewing articles in significant journals and searching the commercial medical databases (i.e., Medline, Biological Abstracts, Chemical Abstracts, Science Citation Index, and Excerpta Medica) on a regular basis. For each article an indication(s) was identified; the number of FLOLAN® (epoprostenol sodium)-treated patients and number and type of adverse experiences were entered into the PRODBIB database. To ensure inclusion of all reported adverse experiences, abstracts of meetings, surveys and review articles were retrieved as well as original publications and published letters.

The PRODBIB database for FLOLAN included the first publication on epoprostenol (prostacyclin) in 1976 and the first report of clinical use of FLOLAN in 1978. A search of the published literature was conducted for all papers identified through 12 January 1993 that described the administration of FLOLAN to humans. Parameters used for the search included (1) use in humans and (2) FLOLAN, prostacyclin, epoprostenol or PG_{I2}, and excluded publications with PPH as the sole disease and Burroughs Wellcome Co.-sponsored studies. It was not possible to exclude -sponsored studies from this search due to the database structure of PRODBIB; thus, adverse experiences reported in documentation provided by and in publications have been included multiple times.

The PRODBIB database identified 944 unique publications which report 7229 FLOLAN-treated patients (Section 7; Bibliographic Listings). Data from individual studies may have been reported multiple times; PRODBIB identifies all publications, and thus includes any multiple reporting of results, e.g., an abstract from a scientific meeting followed by a complete article would include the number of patients and their adverse experiences data twice. Adverse experiences from review articles and surveys have been summarized and included in the PRODBIB database; however, the number of patients receiving FLOLAN and reported in review articles and surveys were

not included in the total number of treated patients. Thus, the number 7229 is an overestimate of the number of treated patients.

When multiple diseases were reported in a single publication, adverse experiences and number of patients receiving FLOLAN® (epoprostenol sodium) were identified and classified for each disease. For example, the article by C. Y. Hsu et al. (75), reported the use of FLOLAN in 43 patients. The article was classified into PRODBIB under two diseases, acute nonhemorrhagic stroke and ischemic stroke. When compiling the information by PRODBIB, the article was included under each disease, and the publication and numbers of patients and adverse experiences were counted twice. For this reason, the numbers of patients, adverse experiences and publications presented in the tables and discussion are considered to be inflated. In spite of this limitation, the PRODBIB database does provide an overview of the clinical experience with FLOLAN in terms of indications in which it has been used, numbers of treated patients, reported adverse experiences, and numbers of publications.

The PRODBIB database identified 212 diseases and procedures for which FLOLAN has been used; adverse experiences were reported in 90 of these (Table 98). As noted, one indication is termed "No Indication Indexed." Safety data were summarized under this category if a particular disease was not identified in a given publication. To simplify presentation of the data, these 90 diseases and procedures were subsequently classified under 29 indications and organized according to the 11 major therapeutic areas, as previously described and as outlined in Table 97. Adverse experience profiles for these 29 indications are presented in Table 99 through Table 109. When the occurrence of adverse experiences was reported in publications without the number of patients specified, e.g., "some patients experienced . . ." or ". . . has been associated with FLOLAN," the experience was reported in Table 99 through Table 109 as UNK (unknown) under "Number of Adverse Experiences."

Clinical Safety Surveillance Service (Wellcome, U.K.)

Safety data compiled by the CSSS (Clinical Safety Surveillance Service), Wellcome Research Laboratories, Beckenham, U.K., contain adverse experiences which were reported spontaneously, either directly to the CSSS, or to the local Regulatory Authorities in each country. These reports describe the international clinical experience with FLOLAN since it was first marketed; the reports are summarized in Section 9.8.6.13. The status of foreign applications is presented in Section 8.

9.8.6.2 *Format for Presentation of Adverse Experiences and Deaths*

Text Format:

For each indication, overall exposure to FLOLAN and control therapy (as available) is summarized from each source (Burroughs Wellcome Co.,

and published literature). Deaths are summarized separately by source. Adverse experiences are summarized by source as follows. Serious or overall adverse experiences are summarized for trials conducted by Burroughs Wellcome Co. Only severe adverse experiences are summarized for trials conducted by . . . overall adverse experiences are summarized from the literature.

Table Format:

Table formats vary depending upon the source of adverse experience data as follows:

1. Adverse Experiences reported in the literature (Table 99–Table 109)

Each table contains a summary of the number of patients who received FLOLAN® (epoprostenol sodium) and an adverse experience profile for each indication within a therapeutic area. Overall exposure to FLOLAN across all indications within the therapeutic area is summarized as the final entry in each table.

2. Adverse Experiences reported by

The number of patients who received FLOLAN and the overall frequency of severe experiences are summarized for each of the five major indications.

3. Adverse Experiences reported by Burroughs Wellcome Co. (Table 115 and Table 116)

The number of patients who received FLOLAN and the overall adverse event profile are summarized for the hemodialysis indication. Serious Adverse Experiences are summarized for patients enrolled in the CHF trials.

9.8.6.3 *Adverse Experiences in Cardiovascular Studies*

Use of FLOLAN in patients with cardiovascular disorders has been categorized into 6 indications, (1) Congestive Heart Failure, (2) Ischemic Heart Disease, (3) Myocardial Infarction, (4) Heart Surgery, (5) Hypertension, and (6) Other Cardiovascular Disorders.

There is overlap in reporting of adverse events in studies sponsored by . . . for ischemic heart disease and myocardial infarction. Adverse events reported in three pilot trials (1024, 1091 and 1096) have been summarized under the indication, ischemic heart disease, where as adverse events reported in a single, large, multinational, placebo-controlled trial in patients with acute myocardial infarction have been summarized under the indication, myocardial infarction.

In addition to the clinical trials in patients with myocardial infarction, also sponsored trials in patients with angina and ischemic heart disease. Deaths and severe adverse experiences reported in these trials are summarized under the indication, Ischemic Heart Disease.

Burroughs Wellcome Co.-sponsored three clinical trials in patients with CHF: (1) a pilot, controlled trial in 33 patients, (2) a multinational, controlled survival trial in 471 patients and (3) an uncontrolled, continuation treatment trial in 17 patients. Deaths and Serious Adverse Experiences are summarized in this section under the indication, Congestive Heart Failure.

Congestive Heart Failure (CHF)

The numbers of patients receiving FLOLAN® (epoprostenol sodium) or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.		
Pilot, continuation studies ^a	23	17
Randomized survival study	237	234
	0	0
Literature	162	unknown

^a Pilot trial: 16 FLOLAN patients, 17 standard therapy patients
 Continuation trial: 7 standard therapy patients elected FLOLAN for a total of 23 FLOLAN patients

Burroughs Wellcome Co. conducted three clinical trials in patients with severe CHF (NYHA Class III/IV). Thirty-three patients entered the first trial, a pilot, multicenter, open, parallel, controlled study, and were randomized to receive either FLOLAN plus standard therapy or standard therapy alone for 12 weeks. Standard therapy consisted of diuretics, digoxin, angiotensin converting enzyme (ACE) inhibitors, and other vasodilators as appropriate. Survival, hemodynamics and exercise capacity were monitored throughout the treatment phase. All patients who successfully completed the 12-week treatment phase were given the option of receiving FLOLAN for up to three years in an open, uncontrolled continuation study.

Based on results of the pilot study, a randomized, multinational, open, parallel, controlled, randomized survival study in CHF was initiated in January 1992. Four hundred seventy-one patients with Class III/IV CHF were randomized to receive either FLOLAN plus standard therapy or standard therapy alone until the study ended. Patients were eligible if they were NYHA Class III/IV despite an optimal triple regimen of digitalis glycoside, loop diuretic and an ACE inhibitor. CI must have been 2.5 L/min/m² or less (unless the patients were receiving intravenous vasoactive medications), and PCWP_m must have been greater than or equal to 15 mm Hg. Survival was the primary efficacy endpoint; quality of life, exercise capacity, and improvement in symptoms of CHF were secondary endpoints.

Results:

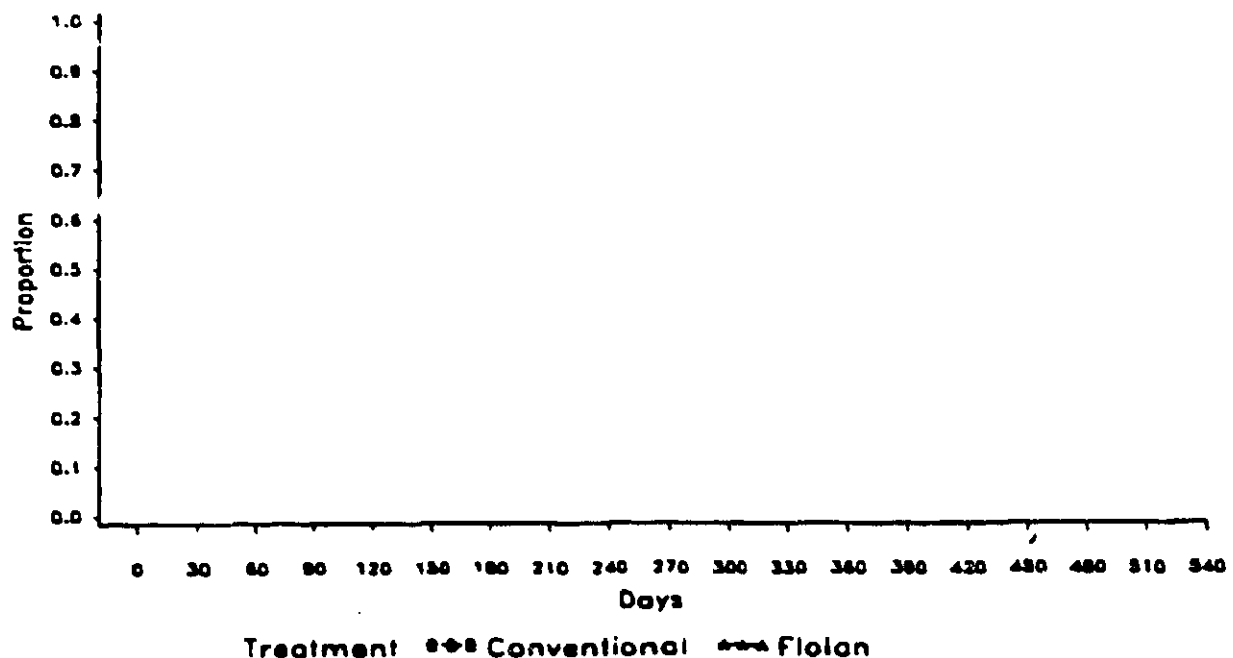
- **Deaths**

In the pilot study, 2 of 16 patients in the FLOLAN® (epoprostenol sodium)-treated group died, and 8 of 17 patients in the standard therapy group (control) died during the 12-week treatment period.

Hemodynamics and exercise capacity appeared to be improved during the 12 weeks (76). Seventeen patients (10 randomized to FLOLAN and 7 randomized to standard therapy, in the pilot study) entered the open continuation study during the months of May to September 1991 and received FLOLAN. Seven of the 17 patients in the open continuation study died.

Of the 471 patients enrolled in the randomized survival study, 237 patients were randomized to FLOLAN plus standard therapy and 234 patients were randomized to standard therapy alone. As of 17 June 1993, 95 deaths were reported in patients treated with FLOLAN, and 78 deaths were reported in the standard therapy group. Median survival in the FLOLAN-treated group was 0.53 year; median survival in the standard therapy group was 0.98 year. The survival curve for the two treatment groups is shown below.

FIRST Survival Curve - Primary End Point
All-Cause Mortality As of 17JUN93
All Patients Worldwide



12000004 11 11/001 11 20

Based on the reduction in survival in patients treated with FLOLAN, the pivotal and continuation studies were discontinued on 17 June 1993. All but three patients in the pivotal and continuation studies were successfully withdrawn from FLOLAN therapy. These three patients

remained on FLOLAN® (epoprostenol sodium) in a compassionate-use study, as it was judged by the investigator that withdrawal of FLOLAN would have been severely detrimental to these patients' clinical conditions. Two of the patients continue to receive FLOLAN; the third patient died of progressive heart failure.

- **Adverse Events**

A summary of Serious Adverse Experiences reported through 31 March 1993 in the three clinical studies in CHF conducted by Burroughs Wellcome Co. is provided in Table 115. As of this date, adverse event data were available on 175 FLOLAN patients and 171 standard therapy patients in the large randomized survival trial. Serious Adverse Experiences were those adverse experiences rated as serious, life-threatening or fatal, AND attributable to FLOLAN, the drug delivery system or study-related procedures. These events have been reported to FDA in IND Safety Reports. The information in Table 115 was hand-tabulated from a non-quality-assured database. The most frequently reported Serious Adverse Experiences were sepsis (n = 18), pulmonary edema (n = 11) and hypotension (n = 10). Included in this tabulation were the 198 FLOLAN patients enrolled in the three studies as of 31 March 1993.

The adverse experience reported most frequently in FLOLAN-treated patients in the literature was flushing (n = 10; Table 99A).

Based on the survival results in the pivotal study sponsored by Burroughs Wellcome Co., FLOLAN should not be used in the chronic treatment of severe left ventricular heart failure.

Ischemic Heart Disease

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co	0	0
Literature	949	unknown

* Data are available on 304 of the 361 patients enrolled in the Upjohn-sponsored studies.

- **Deaths**

In the studies sponsored by Burroughs Wellcome Co., 5 patients in the FLOLAN-treated group and 3 in the control group died. No deaths were reported in the literature.

- **Adverse Experiences**

Table 110 summarizes the number of episodes of severe adverse experiences reported by patients in the studies sponsored by Burroughs Wellcome Co. Hypotension was the most frequently reported severe adverse experience.

reported as a severe adverse experience occurring more frequently in FLOLAN® (epoprostenol sodium)-treated patients than in patients in the control group (26 vs 3). In addition, other severe adverse experiences, angina (4 vs 0), cardiac arrest (5 vs 1) and myocardial infarction (10 vs 5), may have occurred more frequently in FLOLAN-treated patients. Overall, severe adverse experiences were reported more frequently in FLOLAN-treated patients (120 events in 187 FLOLAN patients, vs 46 events in 117 control patients).

Adverse experiences reported most frequently in the literature in 949 patients with ischemic heart disease were flushing (n = 203), nausea (n = 102), headache (n = 77), chest pain (n = 46) and vomiting (n = 44) (Table 99B). Other important adverse experiences included heart infarction (n = 2), heart muscle ischemia (n = 10), and heart ventricle fibrillation (n = 2), which were expected to occur in patients with ischemic heart disease. Diabetes mellitus and hyperglycemia also were mentioned, but no frequency/incidence was reported.

Myocardial Infarction

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	509	unknown

- **Deaths**

In the study sponsored by [redacted]; 9 patients in the FLOLAN-treated group and 4 in the control group died. One of these deaths among FLOLAN-treated patients was reported in the literature (77).

- **Adverse Experiences**

Table 111 summarizes the severe adverse experiences reported by [redacted]. Hypotension was reported as a severe adverse experience occurring more frequently in FLOLAN-treated patients than in patients in the control group (8 vs 1). In addition, the frequencies of chest pain (6 vs 2) and right bundle branch block (3 vs 0) appeared to have been increased in the FLOLAN-treated group. The overall occurrence of severe adverse experiences in the two treatment groups was approximately equal (47 events in 91 FLOLAN patients, vs 28 events in 53 control patients).

Adverse experiences reported in the literature in patients who received FLOLAN for treatment of myocardial infarction were adverse experiences generally associated with use of a potent vasodilator (Table 99C). Other

important adverse experiences included heart failure (n = 11), heart infarction (n = 3), pericarditis (n = 5) and tachycardia (n = 6), which were expected in patients with myocardial infarction. Hematemesis and hematuria also were reported, but no frequency/incidence was presented.

Heart Surgery

One study each of percutaneous transluminal coronary angioplasty and restenosis are included in this category.

The number of patients receiving FLOLAN® (epoprostenol sodium) is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	453	unknown

- Deaths

Death occurred in a patient(s) receiving FLOLAN during PTCA (78; Table 99D); however no details were provided regarding number of deaths or treatment group(s) in which the death(s) occurred.

- Adverse Experiences

Adverse experiences reported in the literature (Table 99D) included heart infarction (n = unk), T wave change (n = 10), and tachyarrhythmia (n = unk); these events are expected in this patient population.

Hypertension

In the literature, some publications describing the use of FLOLAN in females with pregnancy-induced hypertension were categorized with the indication hypertension; deaths and adverse experiences reported in these publications are summarized below. Adverse experiences and deaths reported in the other publications describing the use of FLOLAN in pregnancy-induced hypertension are presented in Section 9.8.6.10 (Obstetric and Gynecologic Disorders).

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	165	unknown

* Two patients were enrolled in a pilot trial in accelerated hypertension, however no safety data are available.

- Deaths

Two deaths were reported in the literature (79). One preterm newborn, whose mother received FLOLAN to treat pregnancy-induced

hypertension, died following treatment of the mother (Table 99E). A fetal death at 26 weeks' gestation also was reported. This death does not appear in Table 99E. These two deaths were not judged associated with maternal infusion of FLOLAN® (epoprostenol sodium).

- Adverse Experiences

Adverse experiences which occurred most frequently in hypertensive patients treated with FLOLAN included flushing (n = 18), nausea (n = 10), bradycardia (n = 9) and sweating (n = 9) (Table 99E). Fetal bradycardia was reported in one case while the mother was receiving FLOLAN to treat severe pregnancy-induced hypertension. During the fourth day of FLOLAN infusion in the mother, three prolonged episodes of fetal bradycardia prompted the delivery of the infant by Cesarean section at 27 weeks' gestational age. The infant and mother were doing well at 3 weeks post delivery (80).

Other Cardiovascular Disorders

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	29	unknown

- Deaths

One death was reported in the literature; the death occurred in an infant who received FLOLAN in addition to other drugs for cardiovascular support during a complicated postoperative course. Use of FLOLAN in this case was an incidental fact in the published letter reporting an overdose of vecuronium. The infant died from sepsis (81; Table 99F).

- Adverse Experiences

In addition to those adverse experiences expected with use of a potent vasodilator, one case of sepsis was reported in the literature (Table 99F).

9.8.6.4 Adverse Experiences in Pulmonary Studies - Other Than PPH

Use of FLOLAN in pulmonary disorders other than PPH has been categorized into 3 indications, (1) Asthma, (2) Secondary Pulmonary Hypertension, and (3) Other Pulmonary Disorders.

Asthma

The number of patients receiving FLOLAN® (epoprostenol sodium) is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	141	unknown

- Deaths/Adverse Experiences

No deaths were reported in the literature. The adverse experience reported most frequently, following aerosol administration of FLOLAN, was pharyngotracheal irritation (n = 9; Table 100A).

Secondary Pulmonary Hypertension

Burroughs Wellcome Co. and _____ conducted pilot studies in PPHN (persistent pulmonary hypertension of the newborn); results of the studies have been included in this indication.

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	5	0
Burroughs Wellcome Inc. (EDR)	36	0
Literature	353	unknown

- Deaths

Four of the 5 infants died in the studies sponsored by Burroughs Wellcome Co. The 4 deaths were judged unrelated to FLOLAN and were attributed to the patients' critically ill condition.

All 5 infants died in the study sponsored by _____ One death was from underlying disease, one death had unknown relationship to FLOLAN, and two deaths were related to FLOLAN; no information about causal relationship was available for one patient's death. In one infant whose death was related to FLOLAN, her condition initially improved with FLOLAN. Due to technical problems, the FLOLAN infusion was inadvertently and abruptly terminated and was restarted 40 minutes later. The infant developed severe bradycardia and hypotension, and subsequently died. A septal infarct was discovered at autopsy. The second infant whose death was related to FLOLAN experienced severe hypotension, hypoxemia and bradycardia, and died during the first hour of FLOLAN infusion.

Three of the 36 patients, who received FLOLAN® (epoprostenol sodium) under provisions of the EDR in Canada, died. Two deaths were judged unrelated to FLOLAN; no information about causal relationship to FLOLAN was provided for the third death.

Two deaths were reported in the literature; one death occurred in the study sponsored by _____ discussed above (82). The second death occurred in a patient who had pulmonary hypertension and was critically ill following the birth of her third child. She died 72 hours after FLOLAN was discontinued (74).

- Adverse Experiences

Adverse experiences occurring in infants with PPHN in the studies sponsored by Burroughs Wellcome Co. and _____ are summarized below.

<u>Adverse Experience</u>	<u>Burroughs Wellcome Co.</u> n = 5
bradycardia	1 ^a
cyanosis	0
flushing	1
hypotension	5
tachycardia	2

^a Number of patients with at least one report of the adverse experience.

The most-frequently reported adverse experiences in patients in the Canadian EDR were flushing (n = 9), headache (n = 7), hypotension (n = 5) and nausea (n = 5; Table 78).

Adverse experiences in patients with SPH were reported in the literature, however none were reported with significant frequency (Table 100B). Hyperglycemia was mentioned in the literature, with no frequency given. Heart arrest (n = 1) was reported; this occurred in the infant (above) whose FLOLAN infusion was inadvertently terminated in a study sponsored by _____

Other Pulmonary Disorders

The numbers of patients receiving FLOLAN or control treatment are summarized below:

<u>Source</u>	<u>FLOLAN</u>	<u>Control</u>
Burroughs Wellcome Co. ^a	12	10
Literature	60	unknown

^a One patient was enrolled in an uncontrolled pilot trial in acute respiratory failure, and 21 patients were enrolled in pilot trials in COPD (chronic obstructive pulmonary disease).

- Deaths

No deaths occurred in the studies sponsored by Burroughs Wellcome Co. Fourteen deaths were reported in the literature (Table 100C); 13 deaths were reported out of 27 critically ill patients with acute respiratory failure who had received FLOLAN® (epoprostenol sodium) (83). A 50% mortality rate is not unusual in this critically ill patient population. The other death reported by Howell and Armstrong (84) was in a patient with chronic granulomatous disease, who had an episode of pneumonia and received a 2-day infusion of FLOLAN; he died 6 weeks later.

- Adverse Experiences

Serious adverse experiences reported in the trials of other pulmonary disorders sponsored by Burroughs Wellcome Co. were thrombocytopenia (n = 1), anemia (n = 1), decreased oxygen saturation (n = 1), and ventricular tachycardia (n = 1) in patients treated with FLOLAN, and increased flatulence and stool (n = 1), and decreased hemoglobin (n = 1) in control patients. Rebound hypertension was reported in the FLOLAN-treated patient with acute respiratory failure, but no adverse experiences were reported for this patient.

Flushing (n = 27) and erythema (n = 9) were the most commonly reported adverse experiences in the literature in patients with other pulmonary disorders being treated with FLOLAN (Table 100C).

9.8.6.5 Adverse Experiences in Extracorporeal Circulation Studies

Use of FLOLAN in extracorporeal circulation procedures has been categorized into 2 indications, (1) Extracorporeal Circulation and (2) Hemodialysis.

Cardiopulmonary Bypass

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	997	unknown

* Data are available on 533 of the 641 patients enrolled in the studies sponsored by

- Deaths

In the cardiopulmonary bypass studies sponsored by Burroughs Wellcome Co., 8 patients died in the FLOLAN-treated group and 7 died in the control group.

No deaths were reported by PRODBIB (Table 101A). However, it was discovered that one patient, who subsequently died, was inadvertently

not included in the PRODBIB database. This patient died three days after receiving FLOLAN® (epoprostenol sodium) during cardiopulmonary bypass (85). Table 101A includes the publication but not the death of this patient.

- Adverse Experiences

In the studies sponsored by [redacted] hypotension was reported as a severe adverse experience occurring more frequently in FLOLAN-treated patients than control patients (31 vs 5; Table 114). Other severe adverse experiences were reported with approximately the same frequency in the two treatment groups. Overall, severe adverse experiences were reported somewhat more frequently in the FLOLAN-treated group (63 events in 284 FLOLAN patients) than in the control group (45 events in 249 control patients).

Adverse experiences for FLOLAN when used during cardiopulmonary bypass were reported in the literature (Table 101A), however none were reported with any significant frequency. In addition to those adverse experiences that were expected based on the potent vasodilatory actions of FLOLAN, other adverse experiences were reported infrequently. Diabetes mellitus and hyperglycemia also were mentioned, but no frequency/incidence was reported.

Hemodialysis

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	144	94
High Sodium Dialysate	138	90
Low Sodium Dialysate	5	4
Literature	515	unknown

* Six patients were enrolled in a pilot trial conducted by [redacted] however no safety information is available.

- Deaths

Data from the clinical trials sponsored by Burroughs Wellcome Co. were extracted from the previous NDA [redacted] and from subsequent annual reports. Seventeen patients who received FLOLAN-facilitated dialyses and 4 patients who received heparin-facilitated dialyses (control) died. Deaths occurred between several hours to several months after the study dialysis. All deaths were considered to be related to the patients' grave underlying medical conditions, and not related to FLOLAN or to participation in the study.

No deaths were reported in the literature (Table 101B). However, a published letter reported successful treatment of 3 patients with FLOLAN® (epoprostenol sodium)-facilitated dialyses (86). One of these 3 patients died; death was due to myocardial infarction and cardiogenic shock.

- Adverse Experiences

Table 116 summarizes the overall adverse experiences that occurred in the clinical trials sponsored by Burroughs Wellcome Co. Adverse experiences reported more frequently in FLOLAN-dialyzed patients (using bicarbonate or acetate dialysate with high sodium concentrations [sodium greater than 139 mEq/L]) than in heparin-dialyzed patients were those adverse experiences expected with use of a potent vasodilator. In addition to the adverse experiences expected with use of FLOLAN, dizziness also was reported (9 vs 0). Overall, adverse experiences were reported more frequently in FLOLAN-dialyzed patients than in heparin-dialyzed patients (284 events in 138 FLOLAN patients vs 89 events in 90 control patients; Table 116).

Hypotension was the adverse experience most frequently reported in the literature (n = 24; Table 101B). Other adverse experiences reported less frequently were those expected with administration of a potent vasodilator.

As described in the previous NDA, the use of [redacted] with [redacted] concentrations [redacted] mEq/L) was associated with sudden and unexpected severe hypotension in 2 of 5 patients who received FLOLAN-facilitated dialyses. The use of FLOLAN in dialyses with acetate dialysate with low sodium concentrations is contraindicated.

9.8.6.6 Adverse Experiences in Renal Studies

Use of FLOLAN in renal disorders has been categorized into 2 indications/procedures, (1) Kidney Transplantation, and (2) Other Nephrologic Disorders.

Kidney Transplantation

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co. ^a	31	16
Literature	89	unknown

^a Forty-seven patients received kidney transplants in studies sponsored by Burroughs Wellcome Co. A total of 28 cadaveric donors provided 56 kidneys; there were 31 recipients of FLOLAN-treated kidneys and 16 recipients of phentolamine-treated kidneys (control); 9 kidneys were not suitable for transplantation due to anatomical problems. Treatment assignment of the 28 donors is not available.

^b A clinical trial in kidney transplantation was sponsored by [redacted] but no safety information was available.

- Deaths

In the studies sponsored by Burroughs Wellcome Co., one recipient of a phentolamine-treated kidney died 21 days after surgery. Death was due to bronchopneumonia and pleuritis and was not related to study treatment. No deaths were reported in the literature.

- Adverse Experiences

In the studies sponsored by Burroughs Wellcome Co., adverse experiences occurring in the cadaveric donors that received FLOLAN® (epoprostenol sodium) were hypotension (n = 2) and tachycardia (n = 1). One adverse experience, hypotension, occurred in one phentolamine-treated donor. Adverse experiences were not collected for the recipients. Adverse experiences reported in the literature were those expected with use of a potent vasodilator (Table 102A).

Other Nephrologic Disorders

Burroughs Wellcome Co. sponsored two uncontrolled pilot trials in patients with acute renal failure.

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	4	0
Literature	6	unknown

- Deaths

Two patients died in the studies sponsored by Burroughs Wellcome Co. Both deaths were due to sepsis, and occurred 8 and 24 days after FLOLAN was discontinued. They were judged not related to FLOLAN. No deaths were reported in the literature.

- Adverse Experiences

Adverse experiences reported in the studies sponsored by Burroughs Wellcome Co. were hypotension (n = 2), nausea (n = 2), chest pain (n = 1), unstable mean arterial pressure (n = 1), hypertension while receiving FLOLAN (n = 1) and hypertension after discontinuation of FLOLAN (n = 1). Two adverse experiences were reported in the literature; hypotension and uterine contraction each were reported one time (Table 102B).

9.8.6.7 Adverse Experiences in Hematologic Studies

Use of FLOLAN in hematologic disorders has been categorized into 3 indications, (1) Platelet Function and Thrombosis, (2) Hemolytic Uremia Syndrome, and (3) Thrombotic Thrombocytopenic Purpura.

Platelet Function and Thrombosis

The number of patients receiving FLOLAN® (epoprostenol sodium) is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	180	unknown

- **Deaths / Adverse Experiences**

No deaths were reported in the literature. Most of the adverse experiences were expected based on potent vasodilatory actions of FLOLAN (Table 103A).

Hemolytic Uremia Syndrome

The numbers of patients receiving FLOLAN are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	14	unknown

Results:

- **Deaths**

One critically ill infant in the study sponsored by [redacted] died 36 hours after termination of a 24-hour infusion of FLOLAN. No deaths were reported in the literature.

- **Adverse Experiences**

In the study sponsored by [redacted] hypotension was reported in one patient and diabetes (requiring insulin) was reported in two patients. One of these cases of diabetes resolved 3 weeks after terminating FLOLAN infusion. The other case continued; information regarding long-term followup was unavailable. Diabetes may have been related to the effects of the hemolytic uremia syndrome on the pancreas.

In general, adverse experiences reported in the literature, in patients with hemolytic uremic syndrome, were expected with administration of a potent vasodilator (Table 103B).

Thrombotic Thrombocytopenic Purpura

The numbers of patients receiving FLOLAN are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	3	0
Burroughs Wellcome Inc. (EDR)	1	0
Literature	34	unknown

- Deaths

Two of the 3 patients died in the study sponsored by Burroughs Wellcome Co. One patient developed a gastrointestinal hemorrhage while receiving FLOLAN® (epoprostenol sodium) and the infusion was stopped. Two days later she developed a midbrain hemorrhage, and died 2 days later. The other patient died due to an intracerebral hemorrhage while receiving FLOLAN.

The one patient, who received FLOLAN under provisions of the EDR in Canada, died from hypotension related to sepsis 9 days after receiving FLOLAN.

It should be noted that these patients were critically ill, and were unresponsive to standard therapies prior to the use of FLOLAN. Hemorrhage is not uncommon in these patients. No deaths were reported in the literature.

- Adverse Experiences

Adverse experiences in the studies sponsored by Burroughs Wellcome Co. included flushing (n = 2), headache (n = 2), nausea (n = 2), vomiting (n = 2), bradycardia (n = 1), hypotension (n = 1), gastrointestinal hemorrhage (n = 1) and petechiae (n = 1).

No adverse experiences were reported in the patient receiving FLOLAN in the Canadian EDR.

Adverse experiences experienced by TTP patients and reported in the literature were expected with administration of a potent vasodilator with antiplatelet properties (Table 103C).

9.8.6.8 Adverse Experiences in Peripheral Vascular Disease Studies

Use of FLOLAN in patients with peripheral vascular disorders has been categorized into 5 indications, (1) Peripheral Vascular Disease, (2) Raynaud's Disease, (3) Takayasu's Disease, (4) Buerger's Disease, and (5) Other Peripheral Vascular Disorders.

Peripheral Vascular Disease

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	1814	unknown

* Data are available on 473 of the 511 patients enrolled in the studies.

- Deaths

In the studies sponsored by Burroughs Wellcome Co. 4 patients in the FLOLAN® (epoprostenol sodium)-treated group and 2 patients in the control group died. No deaths were reported in the literature.

- Adverse Experiences

In the studies sponsored by Burroughs Wellcome Co. hypotension was reported as a severe adverse experience, occurring more frequently in FLOLAN-treated patients than in patients in the control group (13 vs 0; Table 112). In addition, angina pectoris (5 vs 1) appeared to occur more frequently in FLOLAN-treated patients. The occurrence of adverse experiences in the two treatment groups was approximately equal (40 events in 286 FLOLAN patients vs 25 events in 187 control patients).

Adverse experiences reported most frequently in the literature were headache (n = 127) and flushing (n = 83) (Table 104A). Diabetes mellitus and hyperglycemia also were mentioned, but no frequency/incidence was reported.

Raynaud's Disease

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	309	unknown

- Deaths/ Adverse Experiences

No deaths were reported in the literature. Adverse experiences reported most frequently were headache (n = 40), nausea (n = 36), flushing (n = 18), hypotension (n = 18), jaw pain (n = 18) and abdominal pain (n = 17) (Table 104B). Depression (n = 8) also was reported. Hyperglycemia was mentioned, but no frequency/incidence was reported.

Takayasu's Disease

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	151	unknown

- Deaths/ Adverse Experiences

No deaths were reported in the literature. The adverse experience reported most frequently was headache (n = 30; Table 104C).

Hyperglycemia also was mentioned, but no frequency/incidence was reported.

Buerger's Disease

The number of patients receiving FLOLAN® (epoprostenol sodium) is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	333	unknown

- **Deaths/Adverse Experiences**

No deaths were reported in the literature. The adverse experience reported most frequently was headache (n = 63; Table 104D). Hyperglycemia also was mentioned, but no frequency/incidence was reported.

Other Peripheral Vascular Disorders

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	20	unknown

- **Deaths/Adverse Experiences**

No deaths were reported in the literature. A few adverse experiences were reported for these patients, however none appeared unusual in terms of frequency or clinical significance (Table 104E).

9.8.6.9 *Adverse Experiences in Neurologic, Ophthalmologic and Otologic Studies*

Use of FLOLAN in neurologic, ophthalmologic and otologic disorders has been categorized into 4 indications, (1) Stroke, (2) Vascular Headache, (3) Retinal Vein Occlusion, and (4) Sudden Deafness.

Stroke

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	304	unknown

* Data are available on 112 of the 143 patients enrolled in the studies sponsored by

- Deaths

In the studies sponsored by 4 patients in the
 FLOLAN® (epoprostenol sodium)-treated group and 4 patients in the
 control group died.

One patient's death was reported twice in the literature (75; Table 105A).

- Adverse Experiences

Hypotension was reported as a severe adverse experience occurring more frequently in FLOLAN-treated patients than in patients in the control group (3 vs 0) in the studies sponsored by (Table 113). The inability to speak was reported in two FLOLAN-treated patients. Overall, severe adverse experiences were reported more frequently in FLOLAN-treated patients than in patients in the control group (16 events in 74 FLOLAN patients vs 2 events in 38 control patients).

Adverse experiences reported most frequently in the literature were flushing (n = 52) and headache (n = 46) (Table 105A). Other important adverse experiences included micturition disorder/frequency (n = 14), neurological deficit (n = 10), orbit pain (n = 12), paresthesia (n = 12), dizziness (n = 10) and vertigo (n = 10). Hyperglycemia also was mentioned, but no frequency/ incidence was reported.

Vascular Headache

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	38	unknown

- Deaths/ Adverse Experiences

No deaths were reported in the literature. Headache (n = unknown) was the only reported adverse experience (Table 105B).

Retinal Vein Occlusion

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co	0	0
Literature	80	unknown

- Deaths/ Adverse Experiences

No deaths were reported in the literature. Most of the reported adverse experiences were not unexpected with use of FLOLAN, with the

- exception of heart ventricle arrhythmia and hyperglycemia. No frequencies for adverse experiences were reported (Table 105C).

Sudden Deafness

The number of patients receiving FLOLAN® (epoprostenol sodium) is summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	48	unknown

- **Deaths/Adverse Experiences**

No deaths were reported in the literature. Adverse experiences occurring most frequently in FLOLAN-treated patients included flushing (n = 11) and headache (n = 6) (Table 105D).

9.8.6.10 *Adverse Experiences in Obstetric and Gynecologic Studies*

The disorders Dysmenorrhea, Intrauterine Growth Retardation, Postpartum Eclampsia, Preeclampsia, Pregnancy Hypertension and Pregnancy Toxemia were combined for the following discussion.

study examined the effects of FLOLAN on placental perfusion in pregnant women at 29 to 34 weeks' gestation.

Some publications describing use of FLOLAN in women with pregnancy-induced hypertension were summarized in PRODBIB as "hypertension" rather than "pregnancy-induced hypertension;" these publications are reported in the indication, Hypertension, in Section 9.8.6.3.

The numbers of patients receiving FLOLAN or control treatment are summarized below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	113	unknown

- **Deaths**

No deaths (maternal, fetal or neonatal) occurred in the study sponsored by

Given the limitations of the PRODBIB database, a manual review of the publications revealed that 11 pregnant women have received FLOLAN for treatment of pregnancy-induced hypertension and intrauterine

growth retardation. Of the 11 pregnancies, there were 4 fetal and 2 neonatal deaths. (As noted in Table 106, only 3 fetal and 2 neonatal deaths were reported in the PRODBIB database.) The reported cases of pregnancy-induced hypertension and intrauterine growth retardation had severely compromised the mother and/or fetus, and use of FLOLAN® (epoprostenol sodium) was investigated only after failure of conventional medications.

- Adverse Experiences

Adverse experiences occurring in the FLOLAN-treated patients in the study sponsored by _____ were flushing (n = 3) and hypotension (n = 1). The adverse experiences reported most frequently in the literature were those that are associated with use of a potent vasodilator (Table 106). Although some prostaglandins produce uterine contraction, only 1 case was reported with use of FLOLAN.

9.8.6.11 Adverse Experiences in Collagen Vascular Disease Studies

The disorders CRST Syndrome (calcinosis, Raynaud's, sclerodactyly, and telangiectasis), Scleroderma, and Systemic Lupus Erythematosus were combined for the following discussion.

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	37	unknown

- Deaths/ Adverse Experiences

No deaths were reported in the literature. In addition to adverse experiences expected with use of a potent vasodilator, depression (n = 8) also was reported in the literature (Table 107).

9.8.6.12 Adverse Experiences in Gastroenterologic and Endocrinologic Studies

The disorders Diabetic Microangiopathy, Liver Failure and Stomach Ulcer were combined for the following discussion.

The number of patients receiving FLOLAN is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	29	unknown

- Deaths/ Adverse Experiences

No deaths were reported in the literature. Adverse experiences expected with use of a potent vasodilator were reported in the literature (Table 108).

9.8.6.13 Adverse Experiences in Other Disorders

The disorders/conditions Endotoxin Shock, Prostaglandin I₂ Deficiency, and "Indication Not Indexed" were combined for the following discussion.

The number of patients receiving FLOLAN® (epoprostenol sodium) is presented below:

Source	FLOLAN	Control
Burroughs Wellcome Co.	0	0
Literature	314	unknown

- Deaths/Adverse Experiences

No deaths were reported in the literature. The adverse experiences reported most frequently were those expected with use of a potent vasodilator. Others also were reported. Hyperglycemia was reported, but no frequency/incidence was given (Table 109).

Summary

Over seven thousand patients with diseases other than PPH have received FLOLAN. Most adverse experiences reported in the clinical trials sponsored by Burroughs Wellcome Co. and reported in the literature, were expected given the potent vasodilatory actions of FLOLAN.

The increase in mortality with chronic FLOLAN treatment in patients with Class III/IV congestive heart failure indicates that FLOLAN should not be used in this patient population. The use of FLOLAN in dialysis with acetate dialysate with low sodium concentrations is also contraindicated.

9.8.6.14 Summary of Postmarketing Adverse Experiences

The Clinical Safety Surveillance Service, Wellcome Research Laboratories, U.K., has received international reports of postmarketing adverse experiences associated with the use of FLOLAN, since it was first marketed in August 1983 through 13 November 1992. Wellcome has no estimate of the total number of patients treated with FLOLAN, therefore the frequency of these adverse experiences cannot be calculated. The use of FLOLAN in hemodialysis currently is approved in eight countries; in addition, the drug is available internationally on a named-patient basis and in investigator-sponsored studies for other indications (Section 8).

Seventeen patients with postmarketing adverse experiences were spontaneously reported to the Clinical Safety Surveillance Service. Two of the 17 patients had adverse experiences that were rated as fatal, and five of the 17 patients had cases that were classified as serious. The adverse experiences, as reported to Wellcome and using raw terms, are summarized below.

<u>Adverse Experience</u>	<u>Fatal</u>	<u>Serious</u>	<u>Total</u>
Accidental overdose	0	1	1
Coagulation disorder	0	0	2
Confusion	0	0	1
Depression	0	0	2
Desaturation	0	0	1
Diarrhea	0	0	2
Dyspepsia	0	0	1
Gangrene	0	1	1
Headache	0	0	1
Hemoptysis ^a	1	0	1
Hypotension	0	1	2
Hypoxia ^a	1	0	2
Injection site pain	0	0	1
Nausea	0	0	2
Phlebitis	0	0	1
Pulmonary embolism	0	2	2
Pulmonary hemorrhage	0	1	1
Rash	0	0	1
Subarachnoid hemorrhage	1	0	1
Unconscious	0	0	1
Vaginal hemorrhage	0	0	1
Vasodilation	0	0	2
Vomiting	0	1	2

^a One patient experienced hemoptysis and hypoxia that were reported with a fatal outcome.

Available details about the 17 patients and their adverse experiences are presented below.

Fatal Cases:

A 64-year-old male, in the U.K., had a history of polyarteritis nodosa, disseminated intravascular coagulation, vascular infarct and renal impairment #5982[CSSS log number]) He received FLOLAN[®] (epoprostenol sodium) at an infusion rate of 5-10 ng/kg/min for 4 days, for unknown reason. The adverse experiences, hemoptysis and severe hypoxia, developed one day after FLOLAN therapy was discontinued, and persisted until his death 17 days later. The cause of death was listed as cardiorespiratory arrest; preliminary autopsy findings included a small pulmonary embolus, ARDS, renal failure and gastrointestinal bleeding. The reporting physician thought it was unlikely that FLOLAN caused the adverse reactions. The patient was receiving the concomitant medications prednisolone (5 mg q.d. p.o.), flurbiprofen (50 mg t.i.d. p.o.), and cyclophosphamide (100 mg q.d.).

A 75-year-old male, in the U.K., with an unknown medical history, experienced a fatal subarachnoid hemorrhage 12 hours after completing a

12-hour infusion of FLOLAN® (epoprostenol sodium) #19871). The patient died 3 days after the event, in spite of supportive treatment. The patient had no history of bleeding. The patient was receiving the concomitant medications thyroxine (150 µg), furosemide (40 mg), minoxidil (10 mg), ranitidine (150 mg), alginic acid, magnesium trisilicate, aluminum hydroxide, and sodium bicarbonate.

Serious (but not fatal) Cases:

A 59-year-old female, in the U.K., had a history of Raynaud's disease, scleroderma, and hysterectomy #18178). The patient received FLOLAN at an unknown infusion rate for 4 days, for unknown reason. The adverse experience, a clinically diagnosed pulmonary embolism, was treated with heparin and warfarin, and the patient recovered from the pulmonary embolism in 9 days. A lung scan performed 3 days after onset of symptoms was normal. The patient had completed a 17-day course of pivampicillin (500 mg q.d. p.o.) 4 days before the initiation of the FLOLAN infusion. The patient was receiving the concomitant medications stanozolol (5 mg p.o.), nifedipine (10 mg t.i.d. p.o.), and naftidrofuryl oxalat (200 mg b.i.d. p.o.).

A 54-year-old female, in the U.K., had a history of Raynaud's disease, scleroderma, angina, depression, congestive heart failure, and hypotension #18179). The patient received FLOLAN at an unknown infusion rate for 2 days, for unknown reason. The adverse experience, a clinically diagnosed pulmonary embolism, was treated with heparin, and the patient recovered from the pulmonary embolism. A lung scan performed a few days after heparin treatment was normal. The patient was receiving the concomitant medications glyceryl trinitrate (12 mg topically), mianserin (30 mg p.o.), furosemide (40 mg p.o.), and atenolol (50 mg p.o.).

A 45-year-old female, in the U.K., had a history of Raynaud's phenomenon and scleroderma #19075). The first reported adverse experiences were an accidental overdose of FLOLAN accompanied by hypotension, loss of consciousness and vomiting. The patient was receiving FLOLAN, at an unknown infusion rate and for unknown reason, via a central line because her peripheral veins were inaccessible. She routinely received infusions of FLOLAN every 3 months for several years. On this occasion, the nurse accidentally administered an overdose of 50 mL while attempting to remove a bubble from the line. The patient became unconscious with an initially unrecordable blood pressure. The infusion of FLOLAN was stopped and the patient regained consciousness within seconds. After 20 minutes, her mean arterial blood pressure was 80 mm Hg. She was treated with prochloralazine for vomiting. The patient was receiving the concomitant medications penicillamine (375 mg p.o.), nifedipine (20 mg p.o.), and guanethidine (20 mg p.o.).

A 21-year-old female, in the U.K., had a history of excision of spinal astrocytoma and developmental kyphoscoliosis, with new onset of severe pneumothorax #19968). The patient received FLOLAN infusions at a rate of

12 ng/kg/min to treat elevated pulmonary vascular pressure. During the first day of FLOLAN® (epoprostenol sodium) infusions, the patient had a period of arterial desaturation following endotracheal aspiration. The desaturation was a result of the reported adverse experience, a pulmonary hemorrhage. Oxygen saturation and PaO₂ improved after frank blood was removed. Coagulation at the time was normal. The FLOLAN was discontinued and there were no further adverse experiences despite continued endotracheal suction over many days. The physician thought the cause of the hemorrhage was "trauma from endotracheal aspiration but [FLOLAN] probably prevented haemostasis." The patient was receiving intravenously the concomitant medications benzylpenicillin (1.2 g q.4 hr.), cefuroxime (750 mg t.i.d.), erythromycin (500 mg q.i.d.), dobutamine (5 µg/kg/min), and dopamine (3 µg/kg/min).

A 73-year-old female, in the U.K., had a history of severe diabetic-associated vascular disease (#10411). She received FLOLAN at an unknown infusion rate for 2 days, for unknown reason. The adverse experience was reported as gangrene of the entire large bowel including rectum and terminal ileum. The temporal relationship between the FLOLAN infusion and diagnosis of gangrene is not specified. At surgery, the main vessels supplying the large bowel were intact except for the middle colic artery. The bowel was resected. The patient died 11 days after the event from a chest infection. The patient was receiving the concomitant medications insulin (28 U s.c.), spironolactone (50 mg p.o.), furosemide (20 mg p.o.), senna (1 tab p.o.), ibuprofen (200 mg p.o. t.i.d.), and coproxamol (dextropropoxyphen 32.5 mg + paracetamol 325 mg p.o. t.i.d.).

Other Cases

A 64-year-old female, in the U.K., had a history of arteriosclerotic Raynaud's syndrome [sic] with ulceration of her hands (#5365). She received FLOLAN for unknown reason, at an infusion rate of 12 to 16 µg/hr, for 3 days. The adverse experience, profound clinical depression, occurred within 24 hours of initiation of FLOLAN therapy. The patient was treated with amitriptyline and she recovered from the depression. The patient was receiving the concomitant medication flucloxacillin.

A 44-year-old female, in the U.K., had a history of Raynaud's syndrome with ulceration of her hands, and systemic sclerosis (#5366). She received FLOLAN for unknown reason, at an infusion rate of 12 to 16 µg/hr, for 3 days. The adverse experience, profound clinical depression, occurred within 24 hours of initiation of FLOLAN therapy. The patient was treated with amitriptyline and she recovered from the depression. Depression recurred on reintroduction of FLOLAN 3 months later. The patient was receiving the concomitant medication evening primrose.

A female between 50 and 59 years of age, in Denmark, with unknown medical history, experienced a coagulation disorder, vasodilation, and dyspepsia associated with FLOLAN infusion (#4474). The dose and duration of

FLOLAN® (epoprostenol sodium) therapy are unknown. The severity of her symptoms also is unknown, but the patient recovered from the three adverse experiences.

A male between 50 and 59 years of age, in Denmark, with unknown medical history, experienced a coagulation disorder, vasodilation, and hypotension associated with FLOLAN therapy (#4475). The dose and duration of FLOLAN infusion are unknown. The severity of his symptoms also is unknown, but the patient recovered from the three adverse experiences.

A 17-year-old male, in Germany, received FLOLAN for primary pulmonary hypertension (#11192). He experienced nausea, vomiting, diarrhea, and headache while receiving FLOLAN at an infusion rate of 8–32 ng/kg/min for 23 hours. All adverse experiences resolved upon discontinuation of FLOLAN therapy.

A 16-year-old female, in the U.K., had a history of a motor vehicle accident 2 months prior, and no menses for 3 months prior to the adverse experience (#18616). During the course of her hospitalization, she developed ARDS and pulmonary hypertension; her severe pulmonary hypertension was treated successfully with varying doses of FLOLAN infusions for 18 days. After discontinuing FLOLAN therapy, she had the adverse experience, vaginal hemorrhage, from which she recovered. The pulmonary hypertension was subsequently treated with nifedipine (i.v.). The patient developed renal failure requiring hemofiltration, raised INR and platelet dysfunction; however the time course of these complications is not specified. She was receiving intravenously the concomitant medications insulin, alfentanil, dopamine, propofol, and nitroglycerin.

A 72-year-old male, in France, had a history of Raynaud's syndrome and scleroderma (#20599). The patient was hospitalized because of a change in general condition and aggravation of Raynaud's, and he was treated with an infusion of FLOLAN at the rate of 5 ng/kg/min for 24 hours. During the infusion, the patient had the reported adverse experience, confusion. The patient's blood pressure fell at the third hour of infusion from an unknown level to 112/59 mm Hg, and to 97/63 15 minutes later. At 4 hours he became confused and agitated, and then pulled out his infusion line. Diazepam (5 mg p.o.) was administered and the patient became calm over the next 45 minutes. The infusion of FLOLAN was restarted. Neurological examination was unremarkable. At 20 hours the patient exhibited major confusion with temporospatial disorientation and misrecognition of people. The infusion of FLOLAN was discontinued and not restarted, and the patient recovered from the adverse experience, confusion. Serum electrolytes during the symptoms of confusion were normal. A cerebral scan 3 hours after onset of marked confusion but after recovery also was normal. The patient was receiving colchicine (1 mg), ketanserin (dose unknown) and lorazepam (1 mg) concomitantly.

A 57-year-old male, in the U.K., with a history of peripheral vascular disease and dilated cardiomyopathy, received FLOLAN at an unknown infusion rate

for 5 days, for unknown reason #9458). The patient had the adverse experiences nausea, rash, and diarrhea during the infusion. The physician reported that the "symptoms disappeared following the slowing down of the infusion rate." The patient recovered from the adverse experiences. Concomitant medications were captopril, digoxin, furosemide, and warfarin.

An 83-year-old female patient in the UK with unknown history received a 2-day infusion of FLOLAN® (epoprostenol sodium) at 4 ng/kg/min, for unknown reason #19207). She experienced phlebitis and injection site pain during the infusion, and later recovered from these adverse experiences. The patient was receiving the concomitant medications naproxen (1 g p.o.), ranitidine (300 mg p.o.), and buprenorphine (400 µg p.o.).

A patient of unknown sex and age, in the U.K., medical history unknown, received FLOLAN at a dose of 5 ng/kg/min during hemodialysis, and had a 50% fall in arterial oxygen tension with signs of hypoxia. The patient had a similar but less profound reaction on rechallenge the following day at a dose of 2.5 ng/kg/min. No additional information is available.

Some of the postmarketing adverse experiences, such as hypotension, nausea, vasodilation, vomiting and headache are known to occur with administration of a potent vasodilator such as FLOLAN. These and other postmarketing adverse experiences, such as depression, diarrhea and rash, have been reported with FLOLAN in the literature and in controlled and uncontrolled Wellcome studies. Injection site pain and phlebitis also have been reported with FLOLAN, and are expected based on the mode of administration of FLOLAN.

In many cases, the investigator did not rate attribution. Several of the case summaries suggested that the underlying diseases may have contributed to the adverse experiences. FLOLAN can potentially affect clotting by its platelet antiaggregatory activity. However, it is not known what role this activity contributed to these patients' adverse experiences.

9.8.7 *Drug Abuse And Overdosage*

9.8.7.1 *Drug Abuse Information*

Although FLOLAN appeared to have no abuse potential, patients received chronic infusions of FLOLAN through a permanent central venous catheter. The central venous access may pose a risk for patients with a potential for drug abuse.

9.8.7.2 *Overdosage Information*

Acute intravenous studies have been performed in mice and rats to determine dosing limits. In mice, the median lethal dose was not determined since animals recovered from bolus injections of up to 60 mg/kg. Inactivity, bradyapnea, hypothermia, ataxia, and skin flush (increased redness) were observed in mice administered 1 to 10 mg/kg. In rats, the median lethal dose

was estimated at 66.3 mg/kg. Death was preceded by collapse and respiratory failure within 1-10 minutes of injection.

Excessive doses of FLOLAN® (epoprostenol sodium) in human patients can also be expected to produce effects related to major pharmacological effects of FLOLAN: potent pulmonary and systemic arterial vasodilation. The clinical manifestations of those effects are summarized below.

Expected Adverse Experiences Attributable to Excess FLOLAN		
Abdominal pain	Diarrhea	Shortness of breath
Anorexia	Fatigue	Syncope
Back pain	Flushing	Tachycardia
Bradycardia	Headache	Weakness
Cardiovascular collapse	Hypotension	Seizure
Chest pain	Nausea/vomiting	

The adverse experience profile of FLOLAN is similar to that of other potent vasodilators. However, the short half-life of FLOLAN allows potentially life threatening adverse experiences to be resolved quickly by decreasing or discontinuing the infusion of FLOLAN.

In many of the clinical trials, patients were dosed by protocol to intolerance. Therefore, during the course of their dose titration, either during dose ranging or during chronic infusions, patients intentionally received overdoses of FLOLAN. Overdoses were quickly identified by symptoms, adjustments made to the FLOLAN dose, and the incident resolved before a serious episode ensued. While several serious adverse experiences of excess FLOLAN occurred during dose titration, these typically were resolved by decreasing or discontinuing the FLOLAN dose. No fatal events occurred during dose-titration procedures.

These situations in which patients were dosed to intolerance in a clinical setting are clearly different from situations where a patient unintentionally received a substantial overdosage of FLOLAN. Pump malfunctions, drug reconstitution error, inadvertent bolus, human errors, etc. occurred, though infrequently. These patients presented with symptoms/adverse experiences of excess FLOLAN. Again, these effects typically were resolved by decreasing or discontinuing the dose of FLOLAN. On several occasions, patients also received additional supportive assistance (e.g., supplemental oxygen, agents for nausea/vomiting, fluids, etc.) One patient in the U.K., who was being treated with FLOLAN for scleroderma, accidentally received 50 mL of an unspecified concentration of FLOLAN (#19-075). The patient vomited and became unconscious with an initially unrecordable blood pressure. FLOLAN was discontinued and the patient regained consciousness within seconds. Prochloralazine was administered to relieve vomiting. No fatal events were reported following overdosage of FLOLAN.

Although overdosages of FLOLAN are a critical concern, the ability to titrate doses and the short half-life of FLOLAN allow the clinical events of overdosage to be controlled and resolved quickly.

9.8.8 *Integrated Summary Of Benefits And Risks Of FLOLAN® (epoprostenol sodium)*

PPH is a rare disease that is defined clinically as an increased mean pulmonary artery pressure in the absence of recognized causes. Primary pulmonary hypertension is most commonly associated with plexogenic pulmonary arteriopathy, but these pathologic changes are nonspecific and may be seen in a wide variety of conditions associated with increased pulmonary arterial pressure. The characteristic histologic features of plexogenic pulmonary arteriopathy are thought to be due to intense, prolonged vasoconstriction. Current research suggests that abnormalities in pulmonary endothelial cell function may be the proximate cause of this vasoconstriction (13, 87).

Although the pathogenesis of PPH is still speculative, the clinical features of this disease are well understood. PPH usually affects young adults, women more commonly than men. Patients present with dyspnea and also complain of fatigue, dizzy spells and chest pain. Physical examination, electrocardiogram and chest roentgenographic findings suggest pulmonary hypertension. Recognized causes of pulmonary hypertension must be excluded. Pulmonary function tests and arterial blood gases are required to rule out intrinsic pulmonary disease or abnormalities in respiratory control. Perfusion lung scanning is a useful modality for detecting pulmonary emboli. An echocardiogram is an important method for excluding mitral valve and left ventricular disease. The diagnosis of PPH is established at cardiac catheterization by confirming an elevated mean pulmonary artery pressure without other obvious cause. Unfortunately, recognition of the disease may be delayed because of its rarity (4). As the disease progresses, pulmonary vascular resistance usually continues to increase and eventually PPH patients develop right ventricular failure (88). Death most commonly occurs through progressive right ventricular failure, but sudden deaths are also frequent (4, 37). Survival in more advanced stages of the disease is poor. The NIH Registry (NHLBI Registry of Primary Pulmonary Hypertension), the most complete available description of the natural history of PPH, reveals a median survival for PPH patients with a NYHA functional class of III to be 31.5 months and for functional class IV PPH patients to be only six months (3).

PPH is described as a progressive and often fatal illness. It is incurable and there are few effective treatment options (12, 87). Patients with evidence of right ventricular failure are usually given cardiac glycosides and diuretics for symptomatic relief of edema (12, 87). Supplemental oxygen does not relieve pulmonary vasoconstriction, but is supplied to those PPH patients with either resting hypoxemia or exercise induced arterial oxygen desaturation (12, 87). Anticoagulant therapy, as prophylaxis for thromboembolic disease and *in situ* pulmonary thrombosis, has been associated with improved survival in PPH (37), but the benefit is small (30). Calcium-channel blockers have been reported to increase survival in a non-randomized trial, but this benefit is restricted to only the small percentage of PPH patients who had a substantial fall in both pulmonary artery pressure and pulmonary vascular resistance

following acute administration of these agents (30). Although the ability of these agents to improve survival and/or exercise capacity has not clearly been established for all patients with PPH, most patients entering the Burroughs Wellcome Co. sponsored studies were already receiving multiple drug regimens.

Heart-lung and single lung transplantation have been successfully performed in small numbers of patients with severe PPH (10, 89). However, transplantation is not a reasonable option for the vast majority of PPH patients. Because of the scarcity of donor organs, more PPH patients currently die on the transplant waiting list than can possibly be transplanted (10, 90, personal communication United Network for Organ Sharing, Richmond, VA). Recent work suggests that chronic FLOLAN® (epoprostenol sodium) infusion may allow patients with severe PPH to survive long enough to obtain a lung transplant (44). This intriguing option, unfortunately, does not ensure that organ availability will improve.

Chronic, continuous FLOLAN infusion is an effective treatment for PPH. It significantly improves survival in PPH patients in NYHA functional classes III and IV. During the 12-week treatment period of Burroughs Wellcome Co.-sponsored Study 46, there were 8 deaths in the standard therapy group and no deaths in the group treated with FLOLAN ($p = 0.003$). Survival also appeared to be improved in patients who received FLOLAN in Burroughs Wellcome Co.-sponsored Studies 35/36, 37, 46 and 47. Survival benefit of FLOLAN was confirmed by a comparison against historical PPH controls described in the NIH Registry. In addition to prolonging life expectancy, FLOLAN also significantly improved exercise capacity and quality of life in NYHA Class III and IV PPH patients. FLOLAN treated patients had a median increase in their 6-minute walk of 40 meters in the combined results of Studies 35/36 and 46, while the standard therapy group's walking distance decreased 24 meters ($p=0.001$). There were significantly greater improvements in the Chronic Heart Failure Questionnaire, a useful tool for assessing symptoms of dyspnea and fatigue, in the FLOLAN group compared to the standard therapy patients over the course of Study 46. Unlike previous work with calcium-channel blockers, the FLOLAN survival benefit was not limited to only those PPH patients with a favorable hemodynamic response during the initial acute dose-ranging procedure. There was no evidence that acute hemodynamic response to FLOLAN infusion was predictive of improved survival.

The survival and symptomatic benefits of FLOLAN treatment may have been due to its effects on pulmonary hemodynamics. By the end of Burroughs Wellcome Co. sponsored controlled studies, FLOLAN treated patients had a significant decrease in pulmonary vascular resistance and improvement in cardiac output. These effects were sustained, as documented by serial cardiac catheterization at 6-month intervals, for up to 42 months of continuous FLOLAN treatment through Study 37. The reduction in pulmonary vascular resistance decreases the risk for right ventricular failure, the most common cause of death in PPH. Concomitant therapy with anticoagulants,

vasodilators, cardiac glycosides and/or diuretics did not influence the survival benefits of FLOLAN® (epoprostenol sodium).

Numerous authorities have cautioned about the risks inherent with trial administration of vasodilators to PPH patients (91, 92). Presently available vasodilators affect both the pulmonary and systemic circulation. There is the potential, therefore, in patients with severe PPH and a relatively fixed pulmonary vascular resistance for a vasodilator to cause a predominant systemic effect and little or no pulmonary vasodilation. In such circumstances an already stressed right ventricle may not be prepared to accommodate an increased cardiac output. There have been reports of severe systemic hypotension, worsened pulmonary hypertension, acute right ventricular failure and even death complicating acute administration of vasodilators in PPH (17, 18, 91). These catastrophic adverse events have occurred primarily following the use of long-acting oral vasodilators.

Acute administration of FLOLAN in Burroughs Wellcome Co. sponsored dose-ranging studies in PPH patients was performed exclusively during right heart catheterization. Small numbers of severe complications due to this procedure have occurred, but cardiac catheterization is required in this patient population for diagnostic purposes. Initiation of FLOLAN during catheterization was relatively safe. The dose-ranging procedures were usually limited by symptoms. However, the symptoms, restlessness, flushing, headache, nausea and vomiting and dizziness, though sometimes severe were quickly reversible with dose reduction. Of the 390 unique individual dose-ranging procedures with FLOLAN, only 5 were stopped for adverse hemodynamic effects in the absence of symptoms. Increased pulmonary artery pressure, reversible with dose reduction, was the limiting factor in these 5 cases. No fatalities occurred in Burroughs Wellcome Co. sponsored dose-ranging studies with FLOLAN. This remarkable safety record, in an extremely ill and fragile patient population, is probably due to two reasons. First, FLOLAN has a balanced effect on the pulmonary and systemic circulation, causing peak reductions in pulmonary vascular resistance and systemic vascular resistance of 29% and 39% respectively. More importantly, FLOLAN has the advantage of an extremely fast onset of action and short duration of effect. This allows rapid recognition of harmful cardiovascular side effects and equally rapid resolution by reduction or cessation of the FLOLAN infusion. The only life threatening event described in Burroughs Wellcome Co. -sponsored studies following acute administration of FLOLAN was an episode of pulmonary edema in a patient ultimately proven at autopsy to have pulmonary veno-occlusive disease. Some investigators are concerned that patients with pulmonary veno-occlusive disease may be predisposed to developing pulmonary edema following use of vasodilators (60). Based on this observation, FLOLAN should be used with extreme caution in patients clinically suspected of having this variant of PPH.

Chronic continuous FLOLAN treatment requires insertion of an indwelling central venous catheter and may require support services for home parenteral infusion therapy. Adverse events related to the indwelling catheter and home

infusion in the Burroughs Wellcome sponsored studies were not uncommon. Chills, fever, sepsis and flu-like syndromes were recorded together and occurred in 25% of FLOLAN® (epoprostenol sodium) treated patients. Inflammation or other reactions at the intravenous injection site were noted in 21% of these patients and 13% of the FLOLAN group complained of pain at this site. Although systemic infections did occur more frequently in the FLOLAN group, serious and life threatening adverse events in the FLOLAN treated patients were no more common than in the standard therapy group. Procedural complications (3.8%) were infrequent. Once initiated, FLOLAN treatment should be given on a chronic and continuous basis. Even brief interruptions in FLOLAN administration have been associated with severe and even fatal adverse events. Despite the complexities of this type of care, patients judged the benefits of chronic FLOLAN use to outweigh the disadvantages of its administration. Patients rated the tasks required for dealing with the infusion pump and catheter, reconstituting the FLOLAN and performing routine activities as generally "easy" by the end of the 12-week, controlled, Study 46. Patient compliance with the infusion protocol remained extremely high throughout the Burroughs Wellcome Co.-sponsored controlled and extended, uncontrolled studies. Patients' subjective evaluation of their quality of life significantly improved while on FLOLAN. This improvement was sustained over the several months of Studies 35/36 and 46.

Symptoms were common during chronic FLOLAN infusion. These symptoms, in most situations, could be clustered into those consistent with the underlying disease of PPH or those secondary to treatment. After patients were discharged home on the maximal effective FLOLAN dose determined at the initial dose-ranging trial, dose titration upward was required in 73% of patients to manage breakthrough symptoms of PPH, i.e., dyspnea, chest pain and right ventricular failure. Chronic infusion doses of FLOLAN did not substantially change during the 8- and 12-week controlled studies. However, there was a marked increase in chronic infusion doses in the extended, uncontrolled Study 37. FLOLAN infusion rates were 6.9 ± 0.7 ng/kg/min at the beginning of this study and were 17.6 ± 3.0 ng/kg/min and 36.7 ± 6.4 ng/kg/min after 1 and 2 years of this study respectively. With increases in doses, adverse events attributable to FLOLAN, i.e., jaw pain, headache, nausea and vomiting, flushing, diarrhea and arthralgias, were frequent. Fortunately, these symptoms tended to be mild and transient. Often they resolved without dose adjustment, but temporary reduction of FLOLAN dosage was occasionally necessary to manage these symptoms. The mechanisms responsible for the apparent functional effect and symptom tolerance to FLOLAN are not understood.

In summary, chronic continuous FLOLAN infusion is an effective treatment for PPH patients in NYHA functional classes III and IV. This effectiveness has been demonstrated by a significant increase in survival as well as improvements in exercise capacity and quality of life by PPH patients treated with FLOLAN chronically. FLOLAN treatment is also relatively safe. Acute dose ranging is symptom limited, but the symptoms are generally not life threatening and resolve quickly with dose reduction. Only rarely have

asymptomatic increases in pulmonary artery pressures limited acute dose escalation. Adverse events are common in patients receiving chronic FLOLAN® (epoprostenol sodium) infusions. These most commonly reflect the underlying disease of PPH, but adverse events attributable to FLOLAN are also frequent. Investigators are generally able to distinguish symptoms due to PPH from complaints related to FLOLAN, and effectively titrate FLOLAN dose levels. The complexities involved with maintaining the infusion pump and catheter, and reconstituting FLOLAN do not negate the symptomatic benefits of chronic FLOLAN treatment.

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Meeting Minutes

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Meeting Minutes

IND

**Flolan (epoprostenol) Injection
Burroughs Wellcome Co.
February 14, 1991**

Attendees:

Burroughs Wellcome:

Donald Knight
Judy Littlejohn, M.D.
Walker Long, M.D.
James Crow, Ph.D.
Hugh Tilson, M.D.
Tony Segretti, Ph.D.
Mike Thorn
Mary Lou Schenck
Robyn Barst, M.D.
Lewis Rubin, M.D.

FDA:

Stephen B. Fredd, M.D.
Eugenie Triantas, M.D.
Mohammad Hogue, Ph. D.
Ferrin Harrison, Ph.D.
Thomas Hassall
Katurah Hartley

Meeting Document: Dated February 6, 1991

Background:

Burroughs Wellcome is currently investigating the use of Flolan (epoprostenol) injection for the treatment of Primary Pulmonary Hypertension (PPH). For this meeting, Burroughs Wellcome wished to present survival data they believe supports the establishment of a Treatment Protocol for patients with PPH. These survival data were analyzed from clinical trials 35, 36, and 37, the US National Registry of Patients with PPH, and a clinical trial conducted in the UK.

Meeting:

I. Flolan versus Standard Therapy (Studies 35, 36, and 37)

Dr. Fredd said he did not think that these studies Flolan versus standard therapy were adequate to support the establishment of a treatment IND nor serve as a basis for NDA approval because of the small number of patients who have received long-term Flolan therapy. Of the 14 patients in Class II-IV on standard therapy at the start, 8 were crossed over to Flolan. Thus, 14 is the number of patients on short term rather than long term therapy. What is needed is a comparison of long term patients who have been randomized to either standard therapy or Flolan. This may be possible to do with a historical control. He said these data were adequate for generating hypotheses and he agreed that the information gained was important. However there appear to be too few patients in the comparison on which to reach a conclusion. Furthermore, the crossover design makes it hard to compare the baseline characteristics of the groups.

Dr. Huque asked if a Cox regression was used to analyze the covariates of right atrial pressure, pulmonary artery pressure, mixed venous oxygenation, and cardiac output in the firm's assessment of probability of survival of patients. Burroughs Wellcome replied that they analyzed one parameter at a time and the effects of Flolan prevailed in each analysis. They added that the patients who were crossed over, were excluded from the analysis. Dr. Fredd noted that this resulted in exclusion of eight patients who have survived on drug but who, on a per protocol basis, are assigned to the standard therapy group for the intent to treat analysis. This distorts the intent to treat finding.

Dr. Fredd suggested that BW continue to collect data on 10-15 more patients and re-analyze the survival data. He added that the division believes a historically controlled comparison is the most reasonable way to demonstrate efficacy in this condition.

II. Historical Control Data

Dr. Fredd said that if confidence intervals were calculated on the basis of these data they would probably overlap due to the small numbers of patients. He asked if the firm had calculated confidence intervals for the patients followed for 2 years. Burroughs Wellcome said they could calculate this confidence intervals. They added that the patients in the National Registry were generally fairly healthy patients as compared to the Flolan patients. They noted, in addition, that while confidence interval analysis may be informative it would not be expected to replace the analyses they have already performed and reported.

Dr.s Barst and Rubin compared the characteristics of the patients in the National Registry to those entered in the Flolan study as follows:

- 1) Many of the PPH patients included in registry are probably not considered PPH patients by today's standards. Instead, many have interstitial lung disease and where the survival of secondary PPH is better.
- 2) The registry lists patients regardless of treatment status, whereas in the Flolan study those patients who had failed other therapies were entered.
- 3) Patients in the registry were entered within a window of their diagnosis. The Flolan patients were diagnosed and then survived a period of time before being entered in the study.

Dr. Fredd asked if using the New York Heart Association (NYHA)

classifications helps make patients more comparable. Burroughs Wellcome said they have some reservations about using this classification because the interpretation of the classes is subjective and differs from clinician to clinician. They added that criteria for defining Class I and late Class IV are clear. The criteria for classes in between are more equivocal. Dr. Fredd asked whether they had considered combining patients in Class III & IV and repeat the analysis of Flolan versus the historical control, so as to make the patients more comparable. The firm responded that in their study, Class III and IV Flolan patients were "failures" to standard therapy while the Class III and IV patients in the national registry would include patients who improved. This may decrease the chance of showing a drug effect.

Dr. Fredd asked if Flolan is being considered as a bridge to transplant or an alternative therapy for PPH. He said the Division has no objection to a claim for treatment. Burroughs Wellcome replied that they have had Flolan patients in which a transplant is no longer needed. However, for others it is a bridge to transplant. They added that with some Class IV patients, Flolan can help optimize ventricular function such that only a single lung transplant may be necessary versus a more risky heart and lung transplant.

III. Pump Delivery System

Dr. Fredd said Burroughs Wellcome needed to submit information on the pump delivery system they intend to market. Burroughs Wellcome said they had no plans to market the pump, however they will recommend a non-pulsatile pump in their labeling. They added that no patients have died due to pump failure. They said most of the risks of administration lie in potential infections in the central lines. Patient education is important in preventing these problems.

Dr. Fredd asked if there were any known interactions between the pump components, i.e. tubing, and Flolan. Burroughs Wellcome replied that they have checked for these interactions, but none have been found. Burroughs Wellcome added that they will provide the stability data of the drug in the syringe.

Dr. Fredd added it would be useful to have some comparability between the types of pumps that may be used in order that the pump that is recommended is known not to adversely affect safety and efficacy.

IV. Adequacy of Proposed Trials

Dr. Fredd said these trials do not meet the criteria for adequate and well-controlled trials. However, Flolan is being reviewed

under the Sub-part E regulations for serious and life threatening illness. Other factors related to the importance of the drug with respect to therapeutic need may be considered. He added it is important that more patients be studied in order to avoid being misled by the data from so few patients.

Burroughs Wellcome said they have been impressed with the consistent results seen from Flolan. In the first 18-24 months of treatment, Flolan is never worse. Dr. Fredd questioned the consistency of outcomes for Class IV patients. He said it must be kept in mind that the FD&C Act requires two adequate and well controlled studies for drug approval. For an important drug in a condition that afflicts only a small population it may be possible to find adequate evidence of replication within the database in other, non-mortality studies. On the basis of this discussion, he noted that it is not possible to predict the outcome of a thorough review of the data. He added that at this point, Burroughs Wellcome can submit an NDA or elect to gather additional information.

Burroughs Wellcome said they understood Dr. Fredd's regulatory position, but they needed some guidance as to the best way to provide additional evidence that Flolan is safe and effective. They said they feel they have taken the historical control analysis as far as it can go, considering the differences in the patients. They said they have concerns about additional studies because the registry is becoming out of date, the advent of single lung transplant is changing the nature of the disease, and oral vasodilator therapy is becoming more common and will increase the survival of those patients on standard therapy. In essence, a new historical control study may not be comparable. They said the problem with doing randomized, prospective comparisons is that the disease is rare and therefore, recruitment is difficult. In addition, single lung transplant will require an increase in the sample size and will improve survival on standard therapy patients. Those patients on standard therapy who are sickest would go to transplant sooner and would be censored.

Dr. Fredd suggested that they study patients starting with a homogeneous baseline where patients requiring single lung transplants would be considered a failure. Burroughs Wellcome replied there are no standards as to when a lung transplant is warranted. Initially, patients waited 18-24 months for a heart and lung transplant and now, some surgeons suggest a single lung transplant sooner, which effects survival.

Dr. Fredd said he is not convinced that the historical control data are completely out-of-date. However, he added that it may be possible to approve the drug possibly on exercise studies alone. In this event mortality claims could not be made in the labeling. It would be necessary, however, to demonstrate that

there is an identifiable benefit to the drug that is clinically relevant.

He also suggested that they consider quality of life trials. Burroughs Wellcome said that quality of life trials are too subjective and require too many patients. They said their exercise study was however, impressive in that the pulmonary data correlated well. Burroughs Wellcome said they could do a randomized trial looking for pulmonary effects during a 3-4 month period. They said the trial could not be blinded. Dr. Fredd agreed that the unblinded trial design would be acceptable.

Burroughs Wellcome said that they believe they need a mortality claim because the drug will be expensive and the third parties will have to pay. Dr. Fredd said that cost and reimbursement factors can not be a factor in considering labeling.

Dr. Fredd said that the original exercise study, a new randomized exercise study, and the mortality study may be sufficient to support labeling claims. Until the NDA is submitted, patients should still be continued in the trials, but not under a treatment IND. He added that once the NDA is submitted a treatment IND can be considered to obtain additional information on the drug and to continue to make the drug available to patients for whom it is considered a reasonable option.

Burroughs Wellcome said they would be interested in a treatment IND once the NDA was submitted. However, until that time, they will begin plans for a new exercise tolerance study in which they will study the effects of Flolan on pulmonary hemodynamics and function.

Dr. Triantas asked what other medications were used in the mortality trial. Burroughs Wellcome said the patients could be on standard therapy including oral vasodialators and coumadin. Dr. Triantas added that in their new study they should have the same standard therapy between groups so that the only difference is Flolan.

Summary:

1. BW should continue to collect data on 10-15 more patients and re-analyze the survival data.
2. For an NDA it would be useful to have some information comparing the types of pumps that may be used to demonstrate that the recommended pump(s) are known not to adversely affect safety and efficacy.
3. Two adequate and well controlled studies are required for approval. However, adequate evidence of replication within the database in other, non-mortality studies may be applied.

4. If a repeat mortality study is done, the historical control might be defined so that patients requiring surgery (including single lung transplants) would be considered treatment failures.
5. It may be possible to approve the drug on exercise studies without a claim of effect on mortality. An identifiable benefit to the drug that is clinically relevant would have to be demonstrated.
6. The original exercise study, a new randomized exercise study, and the mortality study results may be sufficient to support approval. Labeling claims would depend on the strength of the data submitted.

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