

FLOLAN). More FLOLAN patients than conventional therapy patients were able to stop calcium channel blockers that they had been taking prior to study (5% of conventional, 23% of FLOLAN). About 20% of patients in both groups started vasodilators during study.

Even though all patients were, in accordance with the protocol, to be anticoagulated for the duration of the trial (because of the indwelling venous catheter in the FLOLAN patients), significantly fewer patients in the conventional group were on warfarin than in the FLOLAN group (used warfarin at least 75% of the time on study: 86% of FLOLAN group, 67% of conventional therapy group; took at least 1 dose of warfarin: 95% of FLOLAN group, 75% of conventional therapy group). Heparin was used only by 1 FLOLAN patient during the study. Information on prothrombin times (PT) of patients during the study was not provided.

**D. Efficacy Assessment:** The following table summarizes results of the sponsor's primary efficacy analyses of the 6-Minute Walk Exercise Test:

**Study VA1A4001: Results of 6-Minute Walk Exercise Test**

	Treatment				p-value <sup>c</sup>
	Conventional		FLOLAN		
	N		N		
Baseline					
median <sup>a</sup>					
Week 1	55	240	55	270	
Week 6	53	240	53	270	
Week 12	53	240	55	270	
actual median	55	240.0	56	271.5	
mean <sup>b</sup>					
Week 1	54	271.2	50	271.0	
Week 6	52	271.9	51	265.6	
Week 12	53	270.1	53	268.8	
actual mean	55	269.9	56	270.0	
range	55		56		
Week 1					
median <sup>a</sup>	55	238	55	265	0.4178
actual median	54	242.5	50	283.0	
mean <sup>b</sup>	54	265.8	50	294.7	0.0252
actual mean	54	265.8	50	294.7	
range	54		50		
Week 6					
median <sup>a</sup>	53	235	53	290	0.0028
actual median	51	237.0	48	318.0	
mean <sup>b</sup>	52	257.9	51	299.3	0.0025
actual mean	51	255.6	48	308.9	
range	51		48		
Week 12					
median <sup>a</sup>	53	192	55	316	<0.0001
actual median	44	228.5	50	328.1	
mean <sup>b</sup>	53	220.9	53	308.0	0.0001
actual mean	44	233.6	50	317.5	
range	44		50		

<sup>a</sup> Adjusting for baseline walk and vasodilator use at baseline.

<sup>b</sup> Adjusting for vasodilator use at baseline (analysis of covariance, carrying forward results for missing values or results after transplant or death)

<sup>c</sup> FLOLAN versus conventional treatment

The results showed a highly statistically significant benefit of FLOLAN over conventional treatment in improvement in the 6 Minute Walk Test and Week 6 and Week 12. Examination of the results for patients enrolled before and after Amendment 3 showed similar results for both time periods (personal communication, M. Fan, FDA Biometrics).

A number of patients had missing efficacy data at one or more timepoints. Some baseline characteristics and efficacy results for these patients are summarized in the following table:

Study VA1A4001: Summary of Available Data for Patients Who Had Some Missing 6 Minute Walk Test Data

Patient #	NYHA Class at Entry	Vasodilator (yes/no)	Baseline Walk Stratum (1 or 2) <sup>a</sup>	Distance Walked (meters)			Patient completed?	
				Screening/Baseline	Week 1	Week 6		Week 12
Conventional:								
02305	3	yes	1	231 / 198	168	nd (technical problem)	nd (too ill)	Yes
03305	4	yes	1	130 / 140	192	120	nd	No - died
03307	3	yes	2	220 / 220	196	234	nd	No - lost to F/U
03308	3	no	2	134 / 200	80	12.3	nd	No - died
03301	3	no	2	284.5 / 306	301.5	nd (too ill to travel)	nd	No - consent withdrawn
03310	3	no	2	200 / 200	nd (too ill)	nd (too ill)	36.5	Yes
03304	3	yes	2	260 / 240	275	100	nd	No - died
14302	3	yes	2	323.4 / 399	375	nd (too ill)	137	Yes
10304	3	yes	2	400 / 456	436	320	nd	No - died
15309	3	yes	2	357 / 361	357	278	nd (too ill)	Yes
17301	3	no	2	221 / 218	212	107	nd	No - died
17305	4	no	2	181 / 241	182	179	nd (too ill)	Yes
21305	3	no	1	179 / 197	183	148	nd (too ill)	Yes
FLOLAN								
05304	3	no	2	286 / 289	241.5	nd	nd	No - died
05307	3	no	1	178 / 120	nd (too ill)	144.5	236.5	Yes
07305	3	yes	2	393 / 310	nd (gout attack)	390	405	Yes
07307	3	yes	2	438 / 432	436	nd	nd	No - consent withdrawn*
09303	4	yes	2	200 / 200	nd (too ill)	nd	nd	No - died**
09302	3	yes	2	246 / 240	nd (too ill)	nd	nd	No - died**
09304	3	yes	1	203 / 171	nd (too ill)	nd (could not travel to center)	195	Yes
13301	4	no	1	91.5 / 128.1	194	147	nd	No - died*
15303	3	no	1	119 / 99	59	nd (too ill)	nd (too ill)	Yes
21302	3	yes	2	291 / 529.2	nd (too ill)	nd (toe pain)	175	Yes
21304	3	no	2	137.3 / 207	136	nd (too ill)	160	Yes

<sup>a</sup> Stratum 1 = 50 to <200meters ; Stratum 2 = >200meters  
nd = not done  
\*\* drug stopped prematurely due to adverse experience

Reviewer's original table, based on information in sponsor's tables, NDA Vol. 30.6, pp. 6 through 8, 24 through 26

Thirteen conventional therapy patients and eleven FLOLAN patients missed at least one of the 6 Minute Walk Tests. The most common reason for missing a walk test was patient being too ill to walk (7 conventional treatment patients: 5 FLOLAN patients). Five conventional treatment patients and 4 FLOLAN patients were missing data because they died prior to the scheduled assessment. All 5 of the conventional treatment patients who died had completed through Week 6 of

the study. Two of the 4 FLOLAN patients who died during study died after Week 1 but before Week 6 and did not have the Week 1 walk test done because of being too ill at the time.

Two patients in the FLOLAN group and 1 patient in the conventional treatment group had been exposed to FLOLAN at some time prior to study. Results of the walk tests for these patients are summarized below:

Subject	Treatment	Week	Distance Walked (m)	Change from baseline (m)
07303	FLOLAN	Screening	236	
		Baseline	203	
		Week 1	195	-8.0
		Week 6	296	93.0
		Week 12	418	215.0
16301	FLOLAN	Screening	292.7	
		Baseline	298	
		Week 1	311	13.0
		Week 6	337	39.0
		Week 12	314	16.0
13306	Conventional	Screening	308	
		Baseline	224	
		Week 1	311	87.0
		Week 6	321	97.0
		Week 12	201	-23.0

from sponsor's table. NDA Vol. 30.6, pp..

Summary of baseline, Week 1, Week 6, and Week 12 hemodynamic and blood gas measurements and between group comparisons of the measurements and changes in the measurements are shown in sponsor's tables attached to this review as APPENDIX F. The sponsor found statistically significant improvement in a number of the parameters from baseline. Measures showing a greater than 10% improvement over baseline with FLOLAN included diastolic systemic arterial pressure, diastolic pulmonary arterial pressure, mean pulmonary arterial pressure, cardiac index, cardiac output and peripheral vascular resistance. There was no significant effect on pulmonary capillary wedge pressure or mean arterial oxygen saturation. Conventional treatment patients did not show a greater than 10% improvement in any hemodynamic measure.

The following tables display numbers of patients in each treatment groups getting better or worse during the study with respect to NYHA Class during the study.

VA1A4001: Shift Tables for Change in NYHA Class During Study

Week 1	NYHA Class On Treatment (Conventional/FLOLAN) (N= 55 / 55)		
	II	III	IV
NYHA Class at Baseline (Conventional/ FLOLAN)	II 3 / 1	III 1 / 0	IV 0 / 0
	III 0 / 0	41 / 39	4 / 2
	IV 0 / 0	1 / 5	5 / 8

Week 6		NYHA Class On Treatment (Conventional/FLOLAN) (N = 54 / 52)		
		II	III	IV
NYHA Class at Baseline (Conventional/ FLOLAN)	II	2 / 1	2 / 0	0 / 0
	III	0 / 6	35 / 31	9 / 2
	IV	0 / 2	0 / 6	6 / 4

Week 12		NYHA Class On Treatment (Conventional/FLOLAN) (N = 48 / 51)		
		II	III	IV
NYHA Class at Baseline (Conventional/ FLOLAN)	II	2 / 1	1 / 0	1 / 0
	III	0 / 15	28 / 22	11 / 2
	IV	0 / 3	0 / 3	5 / 5

reviewer's tables, based on data in sponsor's table, NDA Vol. 30.3, p. 132

Over the course of the study more patients in the FLOLAN group showed improvement in NYHA Class than did patients in the conventional treatment group. This improvement was seen both in patients with Class III disease at entry and those with Class IV disease at entry. At the 6 Week visit 25% of patients randomized to FLOLAN showed improvement in NYHA Class as compared to 0% of the conventional treatment patients; at the 12 Week visit 38% of FLOLAN patients as compared to 0% of conventional treatment patients has shown improvement. Also, fewer patients in the FLOLAN group had worsening of NYHA Class as compared to the conventional treatment group. At Week 6 about 20% of conventional therapy patients had worsened as compared to 3.5% of FLOLAN patients; at Week 12 the numbers were 23.6% in the conventional group as compared to 3.5% in the FLOLAN group.

Shifts in other secondary measures of efficacy during the study are tabulated below:

VA1A4001: Direction of Change in Symptom Scores During Study as Compared to Baseline

	Number of Patients							
	Conventional				FLOLAN			
	N	Better	Same	Worse	N	Better	Same	Worse
<b>Dyspnea-Fatigue Rating:</b>								
Week 1	55	4	34	17	55	12	33	10
Week 6	54	7	20	27	52	30	15	7
Week 12	47	5	10	32	51	32	11	8
<b>Borg Dyspnea Score:</b>								
Week 1	54	15	19	20	50	29	6	15
Week 6	51	17	8	26	48	30	11	7
Week 12	42	12	6	24	49	35	6	8
<b>Raynaud's Severity Score:</b>								
Week 1	34	4	17	13	35	18	11	6
Week 6	34	12	9	13	30	14	11	5
Week 12	29	10	4	15	24	15	7	2

reviewer's original table, based on sponsor's SAS datasets, personal communication, M. Fan, FDA Statistical Reviewer.

The sponsor performed non-parametric between group comparisons of change from baseline for NYHA Class, Dyspnea-Fatigue Rating, Borg Dyspnea Score and Raynaud's Severity Score. Results of these comparisons are summarized in the following table.

Study VA1A4001: Summary of Secondary Efficacy Analyses

	Conventional		Week 1			Conventional		Week 6			Conventional		Week 12		
	n	change	FLOLAN		95% C I	n	change	FLOLAN		95% C I	n	change	FLOLAN		95% C I
			n	change				n	change				n	change	
Change in NYHA Class	55		55		0.0, 0.0	54		52		0.0, 1.0	48		51		0.0, 1.0
mean		0.07		-0.05			0.20		-0.27			0.29		-0.43	
median		0.00		0.00			0.00		0.00			0.00		0.00	
range															
Change in Dyspnea-Fatigue Rating:	55		55		-1.0, 0.0	54		52		-2.0, -1.0*	47		51		-3.0, -2.0*
mean		-0.47		0.22			-0.70		1.13			-1.34		1.25	
median		0.00		0.00			-0.50		1.00			-1.00		1.00	
range															
Change in Borg Dyspnea Score:	54		50		0.5, 2.0*	51		48		1.0, 2.5*	42		49		1.5, 3.5*
mean		0.24		-0.97			0.25		-1.28			0.62		-1.79	
median		0.00		-1.00			0.50		-1.00			1.00		-2.00	
range															
Raynaud's Severity Score:	nd		nd		nd	47		48		0.0, 2.0	40		45		0.0, 3.0
mean							-0.34		-0.79			-0.50		-1.69	
median							0.00		0.00			0.00		-1.00	
range															

nd = not done

reviewer's table, based on sponsor's tables, NDA Vol 30 3, pp. 133, 135, 137, and 139

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No clear effect of FLOLAN relative to conventional therapy on these secondary efficacy parameters could be discerned. Numerically, there appeared to be greater improvement in NYHA Class with FLOLAN but this difference was not statistically significant. There appeared to be a benefit of FLOLAN on Borg Dyspnea Score; however, the Dyspnea-Fatigue Rating appeared to worsen in the FLOLAN group.

[Reviewer's comment: It should be noted that the procedure described for obtaining the Borg Dyspnea Score (see Appendix C) was somewhat complex and lacked crispness. The description implies sort of an amalgam of a visual analog scale with a categorical scale. Different patients and different testing personnel may have actually performed this part of the evaluation differently].

There appeared to be a trend toward greater improvement of Raynaud's in the FLOLAN group. However, these analyses are essentially evaluable analyses not including all patients randomized or all patients treated.

- E. **Safety:** All patients treated in this study experienced one or more adverse events. Adverse events occurring in two or more patients in either treatment group are summarized by body system in the following table:

Study VA1A4001: Adverse Events Occurring in 2 or More Patients

Event	Conventional (N = 55)	FLOLAN (n = 56)
Body as a Whole		
Any event	55 (100%)	56 (100%)
asthenia	54 (98%)	56 (100%)
collagen disease	46 (84%)	46 (82%)
chest pain	25 (45%)	29 (52%)
jaw pain	0	42 (75%)
ascites	18 (33%)	13 (23%)
headache	3 ( 5%)	26 (46%)
pain	1 ( 2%)	18 (32%)
infection	5 ( 9%)	10 (18%)
abdominal pain	4 ( 7%)	8 (14%)
back pain	3 ( 5%)	7 (13%)
injection site reaction	0	8 (14%)
fever	4 ( 7%)	3 ( 5%)
chills	2 ( 4%)	4 ( 7%)
injection site pain	0	5 ( 9%)
neck pain	1 ( 2%)	4 ( 7%)
sepsis	1 ( 2%)	3 ( 5%)
injection site hemorrhage	0	3 ( 5%)
unevaluable reaction	1 ( 2%)	2 ( 4%)
abdominal enlargement	0	2 ( 4%)
cellulitis	0	2 ( 4%)
flu syndrome	2 ( 4%)	0

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<b>Respiratory System</b>		
Any event	55(100%)	56(100%)
dyspnea	55(100%)	56(100%)
increased cough	45 (82%)	46 (82%)
hypoxia	36 (65%)	31 (55%)
epistaxis	4 ( 7%)	5 ( 9%)
rhinitis	4 ( 7%)	3 ( 5%)
respiratory disorder	2 ( 4%)	4 ( 7%)
pleural effusion	0	4 ( 7%)
pharyngitis	1 ( 2%)	3 ( 5%)
sinusitis	2 ( 4%)	2 ( 4%)
lung edema	1 ( 2%)	2 ( 4%)
pneumonia	0	3 ( 5%)
bronchitis	1 ( 2%)	1 ( 2%)
pneumothorax	0	2 ( 4%)
<b>Cardiovascular System</b>		
Any event	55(100%)	55 (98%)
peripheral vascular disorder	55(100%)	54 (96%)
vascular disorder	49 (89%)	53 (95%)
palpitations	39 (71%)	35 (63%)
pallor	29 (53%)	18 (32%)
tachycardia	23 (42%)	24 (43%)
syncope	11 (20%)	4 ( 7%)
flushing	0	13 (23%)
right heart failure	7 (13%)	6 (11%)
hypotension	0	7 (13%)
shock	3 ( 5%)	3 ( 5%)
arrhythmia	1 ( 2%)	1 ( 2%)
bradycardia	1 ( 2%)	1 ( 2%)
hemorrhage	0	2 ( 4%)
myocardial infarction	0	2 ( 4%)
migraine	1 ( 2%)	1 ( 2%)
thrombocytopenia	0	2 ( 4%)
<b>Metabolic and Nutritional Disorder</b>		
Any event	52 (95%)	53 (95%)
edema	48 (87%)	44 (79%)
weight decreased	31 (56%)	25 (45%)
hypercalcemia	28 (51%)	27 (48%)
hyperkalemia	0	2 ( 4%)
thirst	2 ( 4%)	0
<b>Digestive System</b>		
Any event	44 (80%)	51 (91%)
gastrointestinal disorder	40 (73%)	34 (61%)
anorexia	26 (47%)	37 (66%)
nausea	9 (16%)	23 (41%)
diarrhea	3 ( 5%)	28 (50%)
vomiting	0	7 (13%)
flatulence	2 ( 4%)	3 ( 5%)
rectal hemorrhage	1 ( 2%)	3 ( 5%)
constipation	1 ( 2%)	2 ( 4%)
<b>Musculoskeletal System</b>		
Any event	42 (76%)	49 (88%)
arthralgia	36 (65%)	43 (77%)
arthritis	25 (45%)	29 (52%)
leg cramps	4 ( 7%)	3 ( 5%)
<b>Nervous System</b>		
Any event	43 (78%)	36 (64%)
dizziness	42 (76%)	33 (59%)
depression	2 ( 4%)	7 (13%)
anxiety	2 ( 4%)	3 ( 5%)
insomnia	0	5 ( 9%)
somnolence	1 ( 2%)	2 ( 4%)
nervousness	0	2 ( 4%)
paresthesia	0	2 ( 4%)

<b>Hemic and Lymphatic System</b>		
Any event	44 (80%)	31 (55%)
cyanosis	44 (80%)	30 (54%)
<b>Skin and Appendages</b>		
Any event	31 (56%)	42 (75%)
sweat	20 (36%)	23 (41%)
skin ulcer	13 (24%)	22 (39%)
rash	2 ( 4%)	14 (25%)
pruritus	1 ( 2%)	2 ( 4%)
<b>Urogenital System</b>		
Any event	1 ( 2%)	8 (14%)
urinary tract system	0	4 ( 7%)
hematuria	0	3 ( 5%)
<b>Special Senses</b>		
Any event	3 ( 5%)	2 ( 4%)

from sponsor's table, NDA Vol. 30.3, pp. 151 through 155

A number of adverse events occurred in both conventional and FLOLAN groups with a high frequency. These included asthenia, collagen disease, dyspnea, increased cough, peripheral vascular disorder, vascular disorder and edema, all of which occurred in over 80% of patients in each group. Other frequent events included chest pain, hypoxia, palpitations, pallor, tachycardia, decreased weight, hypercalcemia, anorexia, arthralgia, arthritis, dizziness and cyanosis. Many of these events were likely related to patients' underlying disease. Events occurring at a 10% or higher greater frequency in the FLOLAN group as compared to the conventional treatment group are shown in the following table:

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Study VA1A4001: Adverse Events Occurring with  $\geq 5\%$  Difference Between FLOLAN and Conventional Therapy Groups

Adverse Event	Conventional Treatment (% of patients) (N = 55)	FLOLAN (% of patients) (N = 56)
<b>Occurrence More Common with FLOLAN</b>		
Body As a Whole		
chest pain	45%	52%
jaw pain	0	75
headache	5	46
pain	2	32
infection	9	18
abdominal pain	7	14
back pain	5	13
injection site reaction	0	14
injection site pain	0	9
neck pain	2	7
injection site hemorrhage	0	5
Respiratory System:		
pleural effusion	0	7
pneumonia	0	5
Cardiovascular System		
vascular disorder	89	95
flushing	0	23
hypotension	0	13
Digestive System		
anorexia	47	66
nausea	16	41
diarrhea	5	50
vomiting	0	13
Musculoskeletal System		
arthralgia	65	77
arthritis	45	52
Nervous System		
depression	4	13
insomnia	0	9
Skin and Appendages		
sweat	36	41
skin ulcer	24	39
rash	4	25
Urogenital		
urinary tract infection	0	7
hematuria	0	5
<b>Occurrence More Common with Conventional Treatment</b>		
Body as a Whole		
ascites	33	23
Respiratory		
hypoxia	65	55
Cardiovascular		
palpitations	71	63
pallor	53	32
syncope	20	7
Metabolic and Nutritional		
edema	87	79
decreased weight	56	45
Digestive System		
gastrointestinal disorder	73	61
Nervous System		
dizziness	76	59
Hemic and Lymphatic System		
cyanosis	80	54

from sponsor's table, NDA Vol. 30.3, pp. 151 through 155

A number of adverse events were more common in the FLOLAN group than the conventional treatment group. These events in general reflect the current labeling for FLOLAN. Also, seen in this study were a number of events related to the injection site, which obviously did not occur in the conventional treatment patients who did not have an indwelling venous catheter in this open-label study. A few events that appeared at similar frequency in the primary pulmonary hypertension studied are notable in this study for occurring more frequently in the FLOLAN group as compared to the conventional group (e.g., hypotension, anorexia, and rash).

Sixty-five percent of conventional group patients and 63% of FLOLAN patients had at least one serious adverse event. Serious adverse events occurring in 2 or more patients are summarized in the following table:

Study VA1A4001: Serious Adverse Events Occurring in 2 or More Patients

Adverse Event	Conventional (N = 55)	FLOLAN (N = 56)
<b>Body as a Whole</b>		
Any event	28 (51%)	23 (41%)
asthenia	26 (47%)	16 (29%)
collagen disorder	2 ( 4%)	8 (14%)
ascites	3 ( 5%)	2 ( 4%)
chest pain	3 ( 5%)	2 ( 4%)
sepsis	1 ( 2%)	2 ( 4%)
fever	2 ( 4%)	0
<b>Respiratory System</b>		
Any event	30 (55%)	24 (43%)
dyspnea	26 (47%)	17 (30%)
hypoxia	12 (22%)	10 (18%)
respiratory disorder	2 ( 4%)	4 ( 7%)
increased cough	4 ( 7%)	1 ( 2%)
pneumonia	0	3 ( 5%)
lung edema	1 ( 2%)	1 ( 2%)
pneumothorax	0	2 ( 4%)
<b>Cardiovascular System</b>		
Any event	16 (29%)	19 (34%)
peripheral vascular disorder	7 (13%)	9 (16%)
right heart failure	5 ( 9%)	5 ( 9%)
tachycardia	1 ( 2%)	7 (13%)
vascular disorder	2 ( 4%)	5 ( 9%)
palpitations	2 ( 4%)	4 ( 7%)
syncope	3 ( 5%)	2 ( 4%)
pallor	2 ( 4%)	1 ( 2%)
shock	1 ( 2%)	2 ( 4%)
myocardial infarction	0	2 ( 4%)
<b>Metabolic and Nutritional Disorder</b>		
Any event	10 (18%)	12 (21%)
edema	5 ( 9%)	7 (13%)
hypercalcemia	4 ( 7%)	3 ( 5%)
weight decreased	2 ( 4%)	2 ( 4%)
hyperkalemia	0	2 ( 4%)
<b>Hemic and Lymphatic System</b>		
Any event	7 (13%)	6 (11%)
cyanosis	7 (13%)	5 ( 9%)
<b>Digestive System</b>		
Any event	6 (11%)	4 ( 7%)
anorexia	4 ( 7%)	1 ( 2%)
gastrointestinal disorder	3 ( 5%)	2 ( 4%)
<b>Nervous System</b>		
Any event	6 (11%)	3 ( 5%)
dizziness	6 (11%)	3 ( 5%)

<b>Musculoskeletal System</b>		
Any event	3 ( 5%)	2 ( 4%)
arthralgia	3 ( 5%)	1 ( 2%)
arthritis	1 ( 2%)	2 ( 4%)
<b>Skin and Appendages</b>		
Any event	3 ( 5%)	1 ( 2%)
skin ulcer	3 ( 5%)	1 ( 2%)

from sponsor's table, NDA Vol. 30.3, pp. 156 through 158

Serious events showing a 5% or greater difference in frequency between treatment groups included: a greater frequency in the FLOLAN group of pneumonia (5% vs. 0%), collagen disorder (14% vs. 4%), tachycardia (13% vs. 2%), and vascular disorder (9% vs. 4%); and a greater frequency in the conventional treatment group of dyspnea (47% vs. 30%), increased cough (7% vs. 2%), asthenia (47% vs. 29%), anorexia (7% vs. 2%) and dizziness (11% vs 5%).

Nineteen patients had FLOLAN decreased and/or temporarily stopped due to adverse events. Events leading to interruption of FLOLAN treatment included nausea and/or vomiting (5 patients), sepsis (3 patients), hypotension (3 patients), respiratory disorder (2 patients), abdominal pain (2 patients), headache (2 patients), and one patient each had diarrhea, metabolic acidosis, pulmonary edema, hyperkalemia, pneumonia, myocardial infarction, and arrhythmia. Disease-related events that led to interruption of FLOLAN treatment included one case each of: syncope, dyspnea on exertion, cardiovascular collapse, tachycardia, hypoxia, palpitations and edema. There was no clear relationship between interruption of FLOLAN and distance walked on any of the 6 Minute Walk Exercise tests.

There were 4 deaths in the FLOLAN group and 5 in the conventional treatment group. The patients who died are described briefly in the table below:

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## Study VA1A4001: Summary of Patient Deaths

Patient #	Sex (M/F)	Age (yr)	NYHA Class.	Vasodilator (yes/no)	Baseline Walk Category*	Disease	Description
Conventional							
03306	F	65	4	yes	1	overlap syndrome	Pt with hx chronic hypotension. Meds potassium, Lasix, cisapride, tamazepam, docusate Ca, Senokot, omeprazole, oxygen. Pt did not take coumadin because worried about falling. Hosp for pancreatitis suffered respiratory arrest during an episode of emesis. Died with respiratory failure, renal failure, and pancreatitis at about day 70 on study.
03308	F	71	3	no	2	limited scleroderma	Pt with Hx GI bleed, pneumonia, elevated WBC. Meds famotidine, oxygen, glaucoma drops, Xanax Lasix, digoxin and others. Pt admitted to hosp with chest pressure. Was not on coumadin. Suffered a respiratory arrest and died (about 60 days on study)
08304	M	66	3	yes	2	limited scleroderma	Pt with hypertension, peptic ulcer disease, chronic sinusitis. Pt was admitted for dehydration, suffered worsening CHF and died (at outlying hospital). Pt died at about 60 days on study of progressive right heart failure
15304	F	52	3	yes	2	features of SSD	No medical problems other than SSD listed. Meds include Procardia XL prior to and during the study. The patient presented to primary MD (not study site) with increased cough and shortness of breath. She was hospitalized but symptoms worsened. Possibility of MI was considered. CXR c/w pulmonary edema. Pt died of acute pulmonary edema after 2 days later (day 71 on study treatment).
17301	F	46	3	no	2	overlap syndrome	No medical problems listed other than SSD. Pt was on multiple meds prior to and during study including prednisone, Lanoxin, Relafan, Zantac, Resteril, Albuterol, Alupent, coumadin. Pt was hospitalized (not at study site) for a syncopal episode. She was placed on telemetry and over the next few days showed "arrhythmias" and had another syncopal episode. Pt died on day 68 of study treatment. Cause of death: severe pulmonary hypertension leading to fatal arrhythmia vs right ventricular MI vs PE
FLOLAN							
06304	F	53	3	no	2	limited scleroderma	Pt with CREST and pulmonary hypertension, hx of syncope. Suffered a syncopal episode while on FLOLAN; felt to have worsening right hear failure, FLOLAN increased (to about 7ng/kg/min). Pt worsened became unresponsive. Declared DNR. Died about day 48 of FLOLAN
08303	M	67	4	yes	2	limited scleroderma	Pt with ischemic heart disease, hypertension, gout, gastric reflux as well as SSD. Med included Cardizem, Prinivil, Pepcid, Reglan, Flovent, Trilisate aspirin. Pt walked 200m on baseline day. following day was started on FLOLAN 2ng/kg/min and dose gradually increased to 6 (or 8?) ng/kg/min over next two weeks. Dose decreased to 4 because of irritability, flushing and headache. About 7 hrs after FLOLAN started pt developed increased difficulty breathing, CXR c/w pulmonary edema; pt intubated. Blood cultures grew gram neg. Pt treated with antibiotics, stabilized, extubated. Suffered an acute massive anterior MI a week later and died (about day 19) on FLOLAN. AEs on FLOLAN included paresthesias, rash, bleeding from CVP line, inc. urinary frequency, reddened heel, skin tear.
09302	F	39	3	yes	2	systemic sclerosis	No medical problems other than SSD listed in CRF but hosp records indicate cardiomegaly, CHF, and hypertension. Meds included Lasix, digoxin, Trontal, nifedipine, Synthroid, prazocin, dicloxacillin. After about a week on FLOLAN pt developed low grade fever, a week later - weakness. FLOLAN was stopped (about day 14). She developed nausea, abdominal pain, LUQ pain, vomiting and flushing. She developed pneumonia and was treated with antibiotics. She developed pulmonary edema. and worsening pericardial effusion, underwent pericardiocentesis and was discharged. One day later she was admitted to a different hospital with coffee ground emesis, hypoxia and sepsis. Pt continued to deteriorate and died of respiratory failure due to pulmonary hypertension, and scleroderma with a number of complicating factors including pneumonia, hepatic

13301	M	71	4	no	1	limited scleroderma	congestion, coagulopathy, upper GI bleed, renal failure and peripheral vascular disease. Pt on Lasix, allopurinol, indocin, coumadin, digoxin. Pt was started on FLOLAN 6mg/kg/min. This was increased to 8mg/kg/min. Pt experienced headache, jaw pain, diarrhea, nausea, nosebleeds, and URI while on FLOLAN. Over subsequent weeks FLOLAN was increased further stepwise to 16mg/kg/min because of dyspnea on exertion and edema. Pt collapsed at home on about day 70 of FLOLAN. Paramedics found him in ventricular fibrillation. Cardioversion was unsuccessful. Efforts at resuscitation on arrival in ER also were unsuccessful.
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\* baseline walk category: 1 = 50 to <200m; 2 =  $\geq$ 200m

reviewer's original table

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There is very little specific information given regarding the patients who died. Most of the deaths appear to have occurred at hospitals that were non-study hospitals and the little information that is recorded in the case report forms is second hand in most cases. The case report form for this study was poorly designed for collecting medical history not related to scleroderma spectrum of diseases. A checklist was provided listing medical problems that were exclusion criteria. At the end of the list were blank spaces for "Other" (See sample sheet in Appendix G). There were no striking differences in characteristics of the patients who died as compared to those who survived. Only one of the 5 conventional treatment deaths was a male as compared to 2 of the 4 FLOLAN deaths. The FLOLAN survivors tended to be younger than the FLOLAN deaths (52.6yrs as compared to 57.5yrs). However, numbers of deaths were too small to make any reliable assessments of possible risk factors for death with either conventional or FLOLAN therapy.

- J. **Reviewer's comments:** This study has a number of limitations. First, the study was essentially open-label even though efforts were made to mask presence of an indwelling catheter during the 6 Minute Walk Exercise Test. Second, there was some data missing for up to 20% of patients for the primary efficacy assessment .

Walk distance did not particularly appear to predict risk of death over the study time.

The magnitude of improvement in the 6 Minute Walk Exercise Test seen in this study was somewhat less than that seen in the original NDA application. The analyses of the secondary efficacy parameters are not inconsistent with a beneficial effect of FLOLAN on pulmonary hypertension in these patients. However, these analyses are essentially evaluable analyses not including all patients treated, and cannot be regarded as providing substantial support for efficacy of the drug.

**Supporting Safety Study:**

**Title:** A Multicenter, Open-Label Protocol to Provide Chronic FLOLAN (epoprostenol sodium) Infusions Plus Conventional Therapy to Patients with Pulmonary Hypertension Secondary to the Scleroderma Spectrum of Diseases: A Continuation Study Following Study VA1A4001 (NDA Vols. 4.008 through 4.010; study protocol in Vol. 4.010, pp. 3 through 33).

- A. **Summary of study:** This is an ongoing long-term safety study designed to provide long-term infusion of FLOLAN to patients with moderate to severe secondary pulmonary hypertension who have completed Study VA1A4001 and to provide additional long-term safety and survival data on use of the drug in these patients. Patients who had completed Study VA1A4001 through week 12 were eligible to enter this open label study. Patients who had been on FLOLAN in VA1A4001 were continued on the same FLOLAN dose to start with Patients who had been on conventional therapy were started on FLOLAN at 2ng/kg/min which was increased at a rate of 1-2ng/kg/min every 15 minutes or longer until dose-limiting side effects

occurred. Further changes in the infusion rate were made over time based on persistence, worsening, or recurrence of symptoms of pulmonary hypertension or occurrence of intolerable adverse events. Investigators were cautioned against abrupt discontinuation of FLOLAN because of the rebound increase in pulmonary arterial pressure that has been seen with discontinuation of FLOLAN infusion. Information collected during the study included demographic data, dosing information, and adverse events. Adverse events felt to be due to drug delivery system malfunction and those felt to be due to the disease were documented separately from the other adverse events. Any patients discontinuing FLOLAN were to be noted. Patient deaths were to be recorded. Conditions for patient withdrawal from the study included: the study is terminated; the patient's FLOLAN infusion was discontinued for more than 30 days; patient receives lung or heart-lung transplant; patient withdraws consent; patient begins receiving commercially available FLOLAN; patient is lost to follow-up; or patient dies.

- B. **Results:** [Note: This study is ongoing. The sponsor indicates that this is an interim report and data have not been verified against source documents, validated or quality assured]. Enrollment started on January 15, 1997. As of March 31, 1998, a total of 97 patients had been enrolled. Disposition of patients is summarized in the following table:

Study VA1A4002: Disposition of Patients

	Number of Patients		
	Total	from conventional group	from FLOLAN group
Eligible patients	99	48	51
Patients not entered	2	2 <sup>a</sup>	0
Patients enrolled	97	46	51
Discontinued due to:			
Adverse event	2	2 <sup>b</sup>	0
Death	19 <sup>c</sup>	6	13
Withdrew consent	2	1	1 <sup>e</sup>
Receipt of commercially available FLOLAN	3	0	3 <sup>d</sup>

<sup>a</sup> reasons for non enrollment: (both patients from the conventional group; 1 pt judged unreliable because of compliance problems; 1 pt, reason unknown);

<sup>b</sup> one patient (#02307) suffered respiratory distress on the first day of FLOLAN administration and the drug was permanently discontinued; however, she died 5 days later;

<sup>c</sup> does not include patient #02307 described in "b";

<sup>d</sup> Two of these patients (#03309 and #22302) subsequently died of unspecified causes.

<sup>e</sup> This patient (#06303) withdrew consent because jaw pain and diarrhea were too uncomfortable for her to tolerate and she did not feel her symptoms were improved sufficiently to warrant continuation on FLOLAN.

reviewer's table, based on information in NDA Vol. and Vol. 30.10, pp. 163 and 164, and 30.6 pp. 6 and 7

Generally demographic features, disease and duration disease of the Study VA14002 population were similar to those of the overall Study VA1A4001 population. Mean age was 54.8 yrs, 90% of patients were female, 79% of patients were NYHA Class III, and 71% of patients had limited scleroderma.

FLOLAN doses in this study ranged from 0 to 51ng/kg/min for former conventional therapy patients and from 2 to 76ng/kg/min for former FLOLAN patients. At

enrollment into this study median FLOLAN infusion rate was 10ng/kg/min for former FLOLAN patients and 2ng/min/kg for former conventional patients.

As of 3/31/98 a total of 22 patients treated with FLOLAN in this study had died. Most of these patients (15 of 22) had been on FLOLAN in Study VA1A4001. The demographic and baseline characteristics of the patients who died were similar to those of the patients who survived with the exception that the patients who died tended to have had a longer history of pulmonary hypertension and a longer history of scleroderma than the survivors as summarized in the following table:

Study VA1A4002: Summary of Baseline Disease History Characteristics for Patients Who Died\*

	FLOLAN deaths* (n = 20)	FLOLAN survivors (n = 77)
<b>Pulmonary hypertension</b>		
mean	17.20	15.26
median	7.00	8.00
range	—	—
<b>Scleroderma</b>		
mean	95.85	85.87
median	73.50	48.00
range	—	—

\* patients #03309, and #22302, who the sponsor considers to have died 'off study' are counted as survivors.

from sponsor's table, NDA Vol. 30.8, p. 56

Causes of death and time on treatment at death are summarized in the following table:

Study VA1A4002: Summary of Deaths

	Number of Patient Deaths
<b>Time in study before death†:</b>	
< 1 week	2
1 week to < 4 weeks	3
4 weeks to < 12 weeks	8
12 weeks to < 24 weeks	3
24 weeks to < 48 weeks	4
<b>Causes of death:</b>	
progressive right heart failure/right heart failure	9
hypotension	2
respiratory arrest	2
sepsis	2
pulmonary hemorrhage	1
hyperkalemia	1
worsening interstitial fibrosis	1
cardiopulmonary arrest	1
vasculitis	1

\* The protocol specified that "Each patient's survival time will be calculated as the time from initiation of study drug until the patient dies or is discontinued from the study or the study is terminated. The date of initiation of study drug will correspond to the date the patient *first* received FLOLAN therapy, either as a participant in Protocol VA1A4001 or in this study." (NDA Vol. 30.10, p. 26). However, in the sponsor's tables here the time appears to be only time enrolled in Study VA1A4002.

reviewer's table, based on information in sponsor's tables NDA Vol.

[Note: According to the sponsor's Safety Update submitted 4/20/99 and covering the period 4/1/98 through 12/31/98 an additional 12 patients in this

study have died. These deaths have occurred between 31 and 99 week on study. Most frequent causes of death were: right heart failure (7 patients), hypotension (4 patients), renal failure (2 patients), pulmonary hemorrhage (1 patient), cardiac failure (1 patient). Most patients suffered other events as well).

About 99% of patients in this study have experienced one or more adverse events. The most frequent events reported included: jaw pain (64%), diarrhea (49%), nausea (40%), headache (38%), pain (30%), and flushing (21%).

Serious adverse events were experienced by about 34% of patients in this study. These events included: right heart failure (11%), sepsis (5%), hypotension (4%), pericardial effusion (3%), and pneumonia (3%).

[Note: Occurrence of serious non-fatal adverse events was reported in an additional 6 patients in the sponsor's Safety Update mentioned above].

Two patients had FLOLAN permanently discontinued because of adverse events. One patient (#02307, a 67 year old woman) experienced respiratory distress upon initiation of FLOLAN. The drug was stopped but she died 5 days later. Another patient (#06310, a 60 year old man) became hypotensive when FLOLAN was started; the dose was decreased but hypotension persisted, so the FLOLAN was discontinued. A number of patients (18% of patients) had adverse events which lead to dose decrease and/or temporary discontinuation of FLOLAN. These events included: hypotension (4%), nausea (3%); reaction unevaluable (orthostasis, pinched nerve in back, tearing of eyes, and bacteremia), and dehydration (2%).

Adverse events attributable to the drug delivery system were experienced by about 22% of patients. These included: injection site pain, injection site reaction, sepsis, injection site hemorrhage, and cellulitis. One patient reported anxiety due to drug delivery system.

Adverse events attributed to FLOLAN were experienced by 89% of patients. The most frequent of these events were: jaw pain (64%), diarrhea (45%), headache (33%), nausea (33%), pain (22%), and flushing (18%).

- C. **Reviewer's comments:** The events observed in this ongoing open-label extension of Study VA1A4001 are similar to the events reported for FLOLAN in the controlled clinical study. During the 14 month period covered by the application a total of 97 patients have been enrolled and 22 of these have died. While the majority of these cases were due mainly to progression right heart failure, in several cases sepsis (clearly associated with the central line) and/or hypotension (due to the FLOLAN) were major cause of death or contributed to the death. This study highlights the morbidity and mortality associated with intravenous administration of FLOLAN as well as the morbidity and poor prognosis associated with the underlying disease.

**Discussion:**

In this application the sponsor has requested approval of FLOLAN for treatment of "pulmonary hypertension"

**Efficacy:** To support the requested expansion of the indication for FLOLAN the sponsor has submitted report of a single controlled clinical trial (Study VA1A4001) for demonstration of efficacy in secondary pulmonary hypertension. The May 1998 Guidance for Industry: **Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products** identifies the following as characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim:

- large multicenter study - No single study site should contribute an unusually large fraction of the patients and no single investigator or site should be disproportionately responsible for the favorable effect seen.
- demonstration of consistency across study subsets – Analysis of the results of the trial for consistency across key patient subsets should address concerns about generalizability of findings to various populations.
- multiple studies in a single study – Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug.
- multiple endpoints involving different events – Statistically persuasive evidence of an effect on two or more prospectively identified, distinct, but logically related, endpoints.
- statistically very persuasive finding – In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect.

The study submitted for the requested indication is deficient with regard to all five of the above criteria. Study VA1A4001 was a fairly small (111 randomized, treated patients) multicenter trial. Because of the small number of patients it was difficult to assess consistency of results across subsets. For instance numbers of males and numbers of older patients were particularly small (15 men [10 conventional, 5 FLOLAN]; 32 patients  $\geq 65$  years [19 conventional, 13 FLOLAN]). The small size of the study also precluded meaningful analysis of the results by other methods of grouping the patients, such as by center or by geographic area. FDA Biometrics has concluded that the result for the primary efficacy analysis was not consistent across sites. (See FDA Statistical review, by M. Fan dated 5/24/99).

Multiple efficacy endpoints were examined in the study. These included 6 Minute Walk Test (primary), Borg Dyspnea Score, Dyspnea Fatigue Index, Raynauds Score and mortality. Hemodynamic measures of the pharmacologic effect of FLOLAN also were assessed. No benefit was seen on mortality. A modest improvement in the 6 Minute Walk Test was seen. There was no improvement in the Dyspnea Fatigue Index. By the sponsor's analysis, there was some improvement in the Borg Dyspnea Score; however, the instructions for collecting that data were somewhat confusing and the analysis done by the sponsor used a different structuring of categories than was specified in the study protocol. Some of the hemodynamic parameters showed significant improvement. FDA Biometrics has determined that the study is not internally consistent with regard to results across the various endpoints. Finally, FDA Biometrics has determined that the sponsor's finding on the primary



occurred in over 20% of patients. The known and expected adverse events for FLOLAN (such as jaw pain, diarrhea and headache) were reported in up to 75% of patients on FLOLAN in the 12-week trial and in a majority of the patients in the long-term extension study.

There were no evidence of improved survival with FLOLAN in the controlled trial (VA1A4001). This is in contrast to the result observed in a 12-week clinical trial (Study 46) in primary pulmonary hypertension which is reported in the FLOLAN labeling where 8 of 40 patients on conventional therapy alone died as compared to 0 of 41 patients on FLOLAN plus conventional therapy. Possibly risk factors for primary pulmonary hypertension and secondary pulmonary hypertension are a bit different. Also, in the primary pulmonary hypertension study there was an issue that the patients randomized to conventional therapy alone were somewhat sicker than those randomized to FLOLAN. (See Medical Officer's Review of NDA 20-444 by E. Triantas dated 2/8/95).

The information in this application and the safety update indicate a significant morbidity associated with use of intravenous FLOLAN with no apparent benefit of FLOLAN on mortality.

**Conclusions and Recommendations:**

The sponsor has provided one trial which gives some support for efficacy of FLOLAN in treating patients with secondary pulmonary hypertension due to scleroderma spectrum of diseases. However, the evidence provided by that trial is not sufficiently convincing to support approval of FLOLAN for the requested indication:

[

Therefore, I recommend that this application not be approved.

Major deficiencies include failure of Study VA1A4001 to meet the criteria for adequacy as a single trial supporting efficacy of FLOLAN in treatment of secondary pulmonary hypertension. Specifically:

1. The trial was too small to establish consistency across centers due to small numbers of patients enrolled at each center,
2. Consistency across subsets of patients (such as by gender, or by age) was not established.
3. There was inconsistency of results across endpoints.
4. The efficacy result was not statistically persuasive as a single study.

Additionally, the population studied does not adequately reflect the population for which the sponsor wishes to label the drug.

[

Also, for the resubmission, in accordance with the December 2, 1998 Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients (Federal Register, 63:66632) the sponsor should submit plans for pediatric studies and/or information to support any planned request for waiver or deferral of pediatric studies.

These comments and recommendations should be conveyed to the sponsor.

*/S/*  
Kathy M. Robie-Suh, M.D., Ph.D. *5/26/99*

cc:  
NDA 20-444  
HFD-180  
HFD-180/LTalarico  
HFD-180/KRobie-Suh  
HFD-181/BStrongin  
HFD-180/JChoudary  
HFD-180/EDuffy  
HFD-720/MFan  
f.t 5/26/99 jgw

*/S/* *5-26-99*

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## APPENDIX A

### FLOLAN® (epoprostenol sodium) for Injection Reconstitution Insert

554128



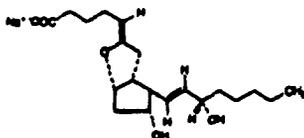
### FLOLAN® (epoprostenol sodium) for Injection

**DESCRIPTION:** FLOLAN (epoprostenol sodium) for Injection is a sterile sodium salt formulated for intravenous administration. Each mL of FLOLAN contains epoprostenol sodium equivalent to either 0.5 mg (248,000 ng) or 1.5 mg (744,000 ng) epoprostenol, 3.76 mg glycine, 3.76 mg sodium chloride, and 50 mg sodium hydroxide (added to adjust pH).

Epoprostenol (PGI<sub>2</sub>, PGG<sub>2</sub> prostanoid, a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation.

Epoprostenol is (2Z,5a,11a,13E,15S)-6,8-epoxy-11,15-dihydroprosta-6,13-dien-1-ol acid.

Epoprostenol sodium has a molecular weight of 374.48 and a molecular formula of C<sub>20</sub>H<sub>34</sub>NaO<sub>5</sub>. The structural formula is



FLOLAN is a white to off-white powder that 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), and Water for Injection, USP.

The reconstituted solution of FLOLAN has a pH of 7.0 to 8.0 and is thermally unstable at a lower pH.

#### CLINICAL PHARMACOLOGY:

**General:** Epoprostenol has two major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. The effect of epoprostenol on heart size in animals varies with dose. At low doses, there is rapidly induced bradycardia, but at higher doses, epoprostenol causes reflex tachycardia in response to direct vasodilation and hypotension. No major effects on cardiac conduction have been observed. Additional pharmacologic effects of epoprostenol in animals include bronchodilation, inhibition of gastric acid secretion, and decreased gastric emptying.

**Pharmacokinetics:** Epoprostenol is rapidly hydrolyzed at neutral pH in blood and is also subject to enzyme-catalyzed degradation. Animal studies using <sup>14</sup>C-labeled epoprostenol have indicated a high clearance (80 mL/min/kg), small volume of distribution (257 mL/kg), and a short half-life (2.7 minutes). During reconstituted in animals, steady-state plasma concentrations of <sup>14</sup>C-labeled epoprostenol were reached within 15 minutes and were proportional to infusion rates.

In acute chemical assays it is highly sensitive and specific to assess PGE in the human pharmacokinetics of epoprostenol. The in vitro half-life of epoprostenol in human blood at 37°C and pH 7.4 is approximately 2 minutes. The in vivo half-life of epoprostenol in man is therefore expected to be no greater than 2 minutes. The in vivo pharmacologic half-life of epoprostenol in human patients, based on inhibition of platelet aggregation, was similar for males ( $n = 10$ ) and females ( $n = 10$ ).

**Labelled epoprostenol** has been administered to humans in order to identify the metabolic products of epoprostenol. Epoprostenol is converted to two major metabolites: 6-keto-PGF<sub>1α</sub>, formed by epoxidation of epoprostenol and 6,15-dihydro-15,14-dihydro-PGF<sub>1α</sub> (metabolically inactive), both of which have pharmacological activity similar to epoprostenol and that epoprostenol in animal test systems. The recovery of radioactivity in urine and feces over a one-week period was 62% and 4% of the administered dose, respectively. Further additional major metabolites have been isolated from urine, indicating that epoprostenol is extensively metabolized in man.

#### Clinical Trials in Primary Pulmonary Hypertension (PPH):

**Antehypertensive Effects:** Acute intravenous infusions of FLOLAN for up to 16 minutes in patients with secondary and primary pulmonary hypertension produce dose-related increases in cardiac index (CI) and stroke volume (SV), and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), and mean systemic arterial pressure (MSAP). The effects of FLOLAN on mean pulmonary artery pressure (MPAP) in patients with PPH were variable and minor.

Chronic continuous infusions of FLOLAN in patients with PPH were studied in two prospective, open, randomized trials of 8 and 12 weeks duration comparing FLOLAN plus standard therapy to standard therapy alone. Changes of FLOLAN were documented on clinical in DOSE AND ADMINISTRATION and overall 82 compliance of study and. Standard therapy varied among patients and included some or all of the following antihypertensives in essentially of patients and vasodilators, diuretics, and digoxin in one-half to two-thirds of patients, and supplemental oxygen in about half the patients. Except for two New York Heart Association (NYHA) functional Class II patients, all patients were either functional Class III or Class IV. No results were similar in the two studies, the pooled results are described. Clinical hemodynamic effects were generally similar in both studies. CI, SV, and stroke volume (SV) were increased, and PVR, TPR, and MSAP (MSAP), TPR, and stroke volume (SV) were decreased in patients and reduced FLOLAN intravenously compared to those who did not. Table 1 illustrates the treatment-related hemodynamic changes in these patients after 8 or 12 weeks of treatment.

Table 1  
Hemodynamics During Chronic Administration of FLOLAN

Hemodynamic Parameter	Baseline		Mean change from baseline at end of treatment period*	
	FLOLAN (n = 32)	Standard Therapy (n = 34)	FLOLAN (n = 48)	Standard Therapy (n = 41)
CI (L/min/m <sup>2</sup> )	2.9	2.8	0.3 <sup>†</sup>	-0.1
MPAP (mm Hg)	60	60	-6 <sup>†</sup>	-1
PVR (Wood U)	16	17	-4 <sup>†</sup>	1
MSAP (mm Hg)	60	61	-4	-3
SV (ml/min/m <sup>2</sup> )	44	43	6 <sup>†</sup>	-1
TPR (Wood U)	20	21	-5 <sup>†</sup>	1

\*All 8 weeks: FLOLAN n = 10; Standard Therapy n = 11

†At 12 weeks: FLOLAN n = 32; Standard Therapy n = 30

†Denotes statistically significant change between FLOLAN and Standard Therapy group

CI = cardiac index; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance.

These hematologic improvements appeared in parallel with FLOLAN use administered for at least 35 months in an open, non-randomized study.

**Clinical Effects:** Overall efficacy, as measured by the 6-month walk test, improved significantly in patients receiving continuous intravenous FLOLAN plus standard therapy for 6 to 12 weeks compared to those receiving standard therapy alone. Improvements were observed as early as the first week of therapy. Improvements in exercise capacity were accompanied by significant improvements in dyspnea and fatigue, as measured by the Composite Heart Failure Questionnaire and the Oxygen Pulses Index.

Survival was improved in NYHA Functional Class II and Class III/IV patients treated with FLOLAN for 12 weeks in a multicenter, open, randomized, parallel study. At the end of the treatment period, 8 of 49 patients receiving standard therapy alone died, whereas none of the 41 patients receiving FLOLAN died (P = 0.005).

**INDICATIONS AND USAGE:** FLOLAN is indicated for the long-term intravenous treatment of chronic pulmonary hypertension in NYHA Class II and Class III/IV patients (see CLINICAL PHARMACOLOGY: Clinical Use).

**CONTRAINDICATIONS:** A large study evaluating the effect of FLOLAN on survival in NYHA Class II and IV patients with CHF due to chronic left ventricular systolic dysfunction was terminated due to adverse effects in 471 patients receiving a higher frequency of intravenous FLOLAN plus standard therapy than in those receiving standard therapy alone. The divergent use of FLOLAN in patients with CHF due to chronic left ventricular systolic dysfunction is therefore contraindicated.

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

**Warnings:** FLOLAN must be administered only on a strict daily regimen. FLOLAN should not be reconstituted or diluted with any other parenteral solutions or solutions other than during administration.

**Adverse Reactions:** Adverse reactions (including interactions in drug delivery) or sudden large reductions in dosage of FLOLAN may result in symptoms characteristic of left ventricular pulmonary hypertension, including systemic, diastolic, and aortic, in aortic valve, and Class II/III patients. Death was judged attributable to the reconstitution of FLOLAN. Adverse reactions should be treated.

**Postmarketing Studies:** Some patients with pulmonary hypertension have developed pulmonary edema during dose ranging, which may be associated with pulmonary vasoconstriction. FLOLAN should not be used intravenously in patients who develop pulmonary edema during dose ranging.

**Specific:** See ADVERSE REACTIONS, Adverse Events Attributable to the Drug Delivery System.

**PRECAUTIONS:**

**General:** FLOLAN should be used only by clinicians experienced in the diagnosis and treatment of PHH. The diagnosis of PHH should be carefully established by standard clinical tests to exclude secondary causes of pulmonary hypertension.

FLOLAN is a potent pulmonary and systemic vasodilator. Dose ranging with FLOLAN must be performed in a setting with adequate personnel and equipment for physician monitoring and emergency care. Although dose ranging is critical, this was performed during right heart catheterization employing a pulmonary artery catheter. In order to reduce the risk of hypotension, systemic hypotension should be equal to the reconstitution and administration of FLOLAN as well as to the infusion of saline. Systemic hypotension is reconstituted rapidly, even with vasopressors in the delivery of FLOLAN may result in symptoms associated with severe pulmonary hypertension including systemic, diastolic, and aortic. The decision to initiate therapy with FLOLAN will be based upon the understanding that there is a high likelihood that intravenous therapy with FLOLAN will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully evaluated.

**Based on clinical trials, the acute hemodynamic response to FLOLAN did not correlate with improvements in exercise tolerance or survival during chronic use of FLOLAN. Dosage of FLOLAN during chronic use should be adjusted to the best sign of response or severity of symptoms. Alterations to PHH in the treatment of severe forms associated with FLOLAN (see DOSAGE AND ADMINISTRATION). Following chronic administration, starting and acute dose ranging and least side should be monitored closely for several hours.**

**Information for Patients:** Patients receiving FLOLAN should receive the following information. FLOLAN must be reconstituted only with STERILE SALINE for FLOLAN. FLOLAN is infused continuously through a permanent intravenous catheter using a pump. Thus, therapy with FLOLAN requires commitment by the patient to drug administration, drug administration, and care of the permanent catheter and infusion pump. Some patients may be advised to stop the drug and in the case of the catheter, and their instructions in the delivery of FLOLAN may result in symptoms characteristic of severe pulmonary hypertension. The decision to receive FLOLAN for PHH should be based upon the understanding that there is a high likelihood that therapy with FLOLAN will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully evaluated.

**Drug Interactions:** Additional reductions in blood pressure may occur when FLOLAN is administered with diuretics, anti-hypertensive agents, or other vasodilators. When other antihypertensive agents or vasodilators are used concurrently, there is the potential for FLOLAN to increase the risk of bleeding. However, patients receiving FLOLAN should be closely monitored for orthostatic hypotension, dizziness, and vasodilation, and supplemental oxygen.

**Cardiopulmonary, Hemodynamic, Improvement of Function:** Long-term studies in animals have not been performed to evaluate cardiopulmonary effects. A comprehensive test in dogs revealed no effects of pulmonary hypertension. The Ames test and DNA adduct tests were also negative, although the possibility of spontaneous mutagenesis of these tests remains. Fertility was not impaired in rats given FLOLAN by subcutaneous injection at doses up to 100 mg/kg/day (100 mg/kg/day; 2.5 times the recommended human dose (4.5 mg/kg/day or 245.1 mg/kg/day) based on body surface area).

**Reproductive:** Pregnancy Category B. Reproductive studies have been performed in pregnant rats and rabbits at doses up to 100 mg/kg/day (100 mg/kg/day) in rats, 2.5 times the recommended human dose, and 11.6 mg/kg/day in rabbits, 4.5 times the recommended human dose based on body surface area and have revealed no evidence of maternal toxicity or harm to the fetus due to FLOLAN. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human outcomes, the drug should be used during pregnancy only if clearly needed.

**Labor and Delivery:** The use of FLOLAN during labor, vaginal delivery, or cesarean section has not been adequately studied in humans.

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

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use:** Clinical studies of FLOLAN did not include sufficient numbers of patients aged 65 and over to determine whether they responded differently from younger patients. In general, data available for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

**ADVERSE REACTIONS:** During clinical trials, adverse events were classified as follows: (1) adverse events during acute dose ranging; (2) adverse events during chronic dosing; and (3) adverse events associated with the drug delivery system.

**Adverse Events During Acute Dose Ranging:** During acute dose ranging, FLOLAN was administered in 2 mg/kg/day treatment until the patients developed symptomatic pulmonary hypertension. The most common adverse events were and the adverse events that occurred before treatment in those were generally related to the major pharmacologic effect of FLOLAN, vasodilation. The most common dose-ranging adverse events (occurring in 2% of patients) were: flushing, headache, hypotension, and dizziness, but also include chest pain, dizziness, dyspnea, nausea, abdominal pain, musculoskeletal pain, and tachycardia.

Less than the adverse events reported during acute dose ranging in decreasing order of frequency:

FLOLAN (eposonamide sodium) by Injection

Table 1  
Adverse Events During Acute Dose Ranging

Adverse Events Occurring in ≥1% of Patients	FLOLAN (% of patients) (n = 281)
Flushing	30
Headache	29
Nausea/vomiting	22
Hypotension	16
Abdominal discomfort, epigastric	11
Chest pain	11
Dizziness	9
Dyspnea	5
Stomatitis	5
Abdominal pain	5
Musculoskeletal pain	3
Dysrhythmia	2
Back pain	2
Diarrhea	1
Dyspepsia	1
Headache/Postdrome	1
Tachycardia	1

Adverse Events During Chronic Administration: Interpretation of adverse events is complicated by the direct nature of PHH, which are similar to some of the pharmacologic effects of FLOLAN (e.g., dizziness, hypotension). Adverse events primarily related to the underlying disease include dyspnea, fatigue, chest pain, right ventricular failure, and pulmonary hypertension. Adverse events not primarily related to the underlying disease include hypotension, dizziness, and tachycardia. In order to estimate the adverse effects of the drug from the adverse effects of the underlying disease, less than 2% of adverse events that occurred at a rate of less than 1% in the two groups in clinical trials.

Table 2  
Adverse Events Regardless of Attribution Occurring with ≥10% Difference Between FLOLAN and Standard Therapy Alone

Adverse Event	FLOLAN (% of patients) (n = 57)	Standard Therapy (% of patients) (n = 54)
<b>Cardiopulmonary System (Common with FLOLAN)</b>		
<b>GENERAL</b>		
Chest discomfort/Pain-like symptoms	25	11
<b>CARDIOVASCULAR</b>		
Tachycardia	36	24
Flushing	42	2
<b>GASTROINTESTINAL</b>		
Dyspepsia	37	6
Nausea/vomiting	67	48
<b>MUSCULOSKELETAL</b>		
Joint Pain	54	0
Myalgia	44	31
Non-specific musculoskeletal pain	38	15
<b>NEUROLOGICAL</b>		
Headache/Postdrome/Headache	21	8
Dizziness	63	79
Headache	83	33
Hypotension, Hypertension, Palpitations	12	2
<b>Other Systemic System (Common with Standard Therapy)</b>		
<b>CARDIOVASCULAR</b>		
Heart failure	31	52
Syncope	13	24
Shock	0	13
<b>RESPIRATORY</b>		
Hypoxia	25	37

Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving FLOLAN. Table 4 lists additional adverse events reported in PHH 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 Alone

Adverse Event	FLOLAN (% of patients) (n = 57)	Standard Therapy (% of patients) (n = 54)
<b>GENERAL</b>		
<b>Adverse</b>		
<b>CARDIOVASCULAR</b>		
Anginal pectoris	18	20
Arrhythmia	27	20
Bradycardia	15	8
Supraventricular tachycardia	8	0
Pulsi	21	32
Cyanosis	2	26
Puffiness	63	61
Cardiovascular accident	4	0
Hemorrhage	19	11
Hypertension	27	31
Hypotensive episode	2	6
<b>GASTROINTESTINAL</b>		
Abdominal pain	27	31
Anorexia	28	30
Anxiety	12	17
Constipation	6	2
<b>METABOLIC</b>		
Edema	95	62
Hypokalemia	2	4
Weight reduction	27	24
Weight gain	5	2
<b>MUSCULOSKELETAL</b>		
Arthralgia	8	0
Bone pain	2	0
Chest pain	19	66
<b>NEUROLOGICAL</b>		
Confusion	6	11
Convulsion	4	0
Depression	37	44
Parosmia	4	4

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FLQLAN (epinephrine) for Injection

Table 4  
Adverse Events Reported of Attribution Occurring with <10% Difference  
Between FLQLAN and Standard Therapy Arms (per%)

Adverse Event	FLQLAN (% of patients (n = 88))	Standard Therapy (% of patients (n = 88))
<b>RESPIRATORY</b>		
Cough increase	28	48
Dyspnea	20	25
Exhalms	4	2
Fluorid exhalms	4	2
<b>DERMATOLOGIC</b>		
Pruritus	4	0
Rash	10	13
Swelling	16	20
<b>SPECIAL SENSES</b>		
Anorexia	8	4
Vision abnormality	4	0

Adverse Events Attributable to the Drug Delivery System: Chronic infusions of FLQLAN 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, asepsis 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 FLQLAN. 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 important loss of or a reduction in FLQLAN were associated with symptoms related to excess or treatment FLQLAN, respectively less ADVERSE REACTIONS: Adverse Events During Chronic Administration.

**OVERDOSEAGE:** Signs and symptoms of excessive doses of FLQLAN during clinical trials are the expected dose-limiting pharmacologic effects of FLQLAN, including flushing, headache, hypertension, tachycardia, nausea, vomiting, and diarrhea. Treatment will obviously require dose reduction of FLQLAN.

One patient with secondary pulmonary hypertension accidentally received 50 mL of an unexpelled concentration of FLQLAN. The patient reacted and became unconscious with an initially unrecordable blood pressure. FLQLAN was discontinued and the patient required cardiovascular support. No less events have been reported following overdosage of FLQLAN.

Single intravenous doses of FLQLAN at 10 and 20 mg/kg and 27,027 times the recommended acute single human dose based on body surface area were lethal to mice and rats, respectively. Symptoms of acute toxicity were hypoxia, ataxia, loss of righting reflex, deep slow breathing, and hyperthermia.

**DOSEAGE AND ADMINISTRATION:**

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

**Dosage:**

**Acute Dose Ranging:**

The initial chronic infusion rate of FLQLAN 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 other cases, the infusion rate is initiated at 2 mcg/min and increased in increments of 2 mcg/min every 15 minutes or larger until dose-limiting pharmacologic effects are obtained. The most common dose-limiting pharmacologic effects (occurring in 21% of patients) during dose ranging are nausea, vomiting, headache, hypertension, and flushing, but also include chest pain, anxiety, dizziness, bradycardia, dyspnea, distal pain, muscle weakness, and tachycardia. During acute dose ranging in clinical trials, the mean maximum dose which did not elicit dose-limiting pharmacologic effects was  $2.8 \pm 0.3$  mcg/min.

**Continuous Chronic Infusion:**

Chronic continuous infusion of FLQLAN should be administered through a central venous catheter. Temporary peripheral intravenous infusions may be used until central access is established. Chronic infusions of FLQLAN should be initiated at 4 mcg/min less than the maximum-tolerated infusion rate determined during acute dose ranging. If the maximum-tolerated infusion rate is less than 5 mcg/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 mcg/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 FLQLAN. In general, increases in dose from the initial chronic dose should be avoided. In the controlled 12-week trial, for example, the dose increased from a mean starting dose of 2.3 mcg/min (4 mcg/min less than the maximum-tolerated dose) to 8.2 mcg/min by the end of week 12, just 1.8 mcg/min less than the mean maximum-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 mcg/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 sitting 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 pharmacologic events other than those observed during acute dose ranging may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Dose decreases should be implemented in 2 mcg/min increments every 15 minutes or larger until the dose-limiting effects resolve. After withdrawal of FLQLAN or infusion rate reductions in infusion rates should be avoided. Except in life-threatening situations (e.g., uncontrolled renal colic, etc.), infusion rates of FLQLAN should be adjusted only under the direction of a physician.

In patients receiving lung resections, doses of FLQLAN were tapered after the resection of cardiovascular bypass.

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

The ambulatory infusion pump used to administer FLQLAN should (1) be small and lightweight, (2) be able to adjust infusion rates in 2 mcg/min increments, (3) have an indicator, and (4) infusion, and low battery alarms, (5) be accurate to 5% of the programmed rate, and (6) be positive pressure driven (air-driven or piston) with intervals between piston re-actuating 3 seconds of infusion rates used to deliver FLQLAN. The reservoir should be made of polypropylene, polycarbonate, or glass, infusion pumps used in clinical trials were the CADD-1 HPZ 5 HD (Pharmacia Deltec, Wash-Med 410 C (Medtronic, Inc.), and the Auto Springs ASDF (Crescent Health Care).

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

To facilitate extended use of chronic infusions, a standard temperature (25°C (77°F)), a seal pouch with heat gel packs was used in clinical trials (see DOSAGE AND ADMINISTRATION: Storage and Stability). The seal pouches and gel packs used in clinical trials were obtained from Pabo Labs, Palo Alto, California. Key was used which must be capable of maintaining the temperature of reconstituted FLQLAN between 2° and 8°C for 12 hours.

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

A concentration for the solution of FLQLAN for acute dose ranging or chronic therapy should be selected when a compatible with the infusion pump being used with respect to maximum and minimum flow rates, reservoir capacity, and the infusion pump offers total above FLQLAN when administered chronically, should be prepared in a drug delivery reservoir appropriate to the infusion pump with a total reservoir volume of at least 100 mL. FLQLAN should be prepared using 2 mL of STERILE DILUENT for FLQLAN.

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Table 5

To each 100 mL of solution with the Concentration (mg/mL) of	Dose:
2,000 mg/mL	Divide contents of one 0.5 mg vial with 5 mL of STERILE DILUENT for FLOLAN. Withdraw 5 mL and add to sufficient STERILE DILUENT for FLOLAN to make a total of 100 mL.
5,000 mg/mL	Divide 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 mg/mL	Divide 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.
15,000 mg/mL	Divide 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 topically.  
More than one solution strength may be required to approximate the range of infusions anticipated during acute dosing. Generally, 2,000 mg/mL and 15,000 mg/mL are satisfactory concentrations to deliver between 2 to 16 mcg/min in adults. Infusion rates may be calculated using the following formula:

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

Tables 6 through 9 provide infusion delivery rates for doses up to 16 mcg/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. Higher infusion rates and flow rates, where conventional solutions may be necessary with long-term administration of FLOLAN.

Table 6

Patient Weight (kg)	Infusion Rates for FLOLAN at a Concentration of 2,000 mg/mL							
	Dose or Drug Delivery Rate (mcg/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 mg/mL							
	Dose or Drug Delivery Rate (mcg/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	1.8	2.4	2.8	3.4	3.8
30	—	1.4	2.2	2.8	3.6	4.3	5.0	5.6
40	1.0	1.8	2.8	3.6	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	2.8	4.2	5.6	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	5.6	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	17.2
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 mg/mL							
	Dose or Drug Delivery Rate (mcg/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	3.2
40	1.0	1.4	1.8	2.4	2.8	3.4	3.8	4.3
50	1.2	1.6	2.0	2.6	3.0	3.6	4.2	4.8
60	1.4	2.2	2.8	3.6	4.3	5.0	5.8	6.7
70	1.7	2.5	3.4	4.2	5.0	5.8	6.7	7.7
80	1.9	2.8	3.8	4.8	5.8	6.8	7.8	8.8
90	2.2	3.2	4.3	5.4	6.5	7.6	8.7	9.8
100	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8

Table 9

Patient Weight (kg)	Infusion Rates for FLOLAN at a Concentration of 15,000 mg/mL							
	Dose or Drug Delivery Rate (mcg/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	—	1.0	1.3	1.6	1.9	2.2	2.6	3.0
40	—	1.2	1.6	2.0	2.4	2.8	3.4	3.8
50	1.0	1.4	1.8	2.4	2.8	3.4	3.9	4.5
60	1.1	1.7	2.2	2.8	3.4	4.0	4.6	5.1
70	1.3	1.9	2.5	3.2	3.8	4.5	5.2	5.9
80	1.4	2.2	2.9	3.6	4.3	5.0	5.8	6.5
90	1.6	2.4	3.2	4.0	4.8	5.6	6.4	7.2

**FLOLAN (oprelvekin) for Injection**

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 (32° 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 pack and administered up to 24 hours with the use of two (two 6-oz) gel packs in a cold pack. When closed or in use, reconstituted FLOLAN must be handled from temperatures greater than 25°C (77°F) and less than 9°C (48°F), and must not be exposed to direct sunlight.

Use of 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 (32° to 46°F) for no longer than 48 hours. When administered at room temperature, reconstituted solutions may be used for no longer than 8 hours. This solution period allows the patient to reconstitute a 3-day supply (240 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 (32° to 46°F) until they are used.

Use with a Cold Pack: Prior to infusion with the use of a cold pack, solutions may be stored refrigerated at 2° to 8°C (32° to 46°F) for up to 24 hours. When a cold pack 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 (32° to 46°F), either in refrigerated storage or in a cold pack 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 other colors, FLOLAN should not be administered.

HOW SUPPLIED: FLOLAN for Injection is supplied as a sterile freeze-dried powder in 17 mL, 50 mL glass vials with gray butyl rubber closures, individually packaged in a carton.

17 mL vial containing oprelvekin sodium equivalent to 0.5 mg (500,000 ng), carton of 1. (NDC 6081-0489-01)

17 mL vial containing oprelvekin sodium equivalent to 1.5 mg (1,500,000 ng), carton of 1. (NDC 6081-0494-01)

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 80 mL, 500 mL glass vials with butyl rubber stoppers and caps for closure.

30 mL vial of STERILE DILUENT for FLOLAN, lot of 4 (NDC 6081-0489-01)

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. 4,257,728; 4,258,222; and 4,258,212 (See Patent)

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## Overall Table of Clinical Studies

Study Identifier Report Location (R) CRF Location (C)	Design	Study Start Investigator(s) Publication	Age Range in Years	Treatment Group, Dose Regimen	Treatment Duration	Number of Study Participants	Batch Number
<b>Clinical Studies in Secondary Pulmonary Hypertension (SPII)</b>							
<i>Controlled Clinical Study</i>							
VA1A4001 (R) Vol. 4.003, pt (C) Vol. 4.017- 4.018	Standard therapy controlled, chronic, open-label, randomized, parallel, multicenter	24OCT96 Barst, et al. None	23-78	Chronic FLOLAN* 1-25ng/kg/min plus Conventional Therapy	12 weeks	M=5 F=51	5Z3503 6M3505 6O3509 7C3507 5X5030 5X5032
				Conventional Therapy:	12 weeks	M=10 F=45	
<i>Ongoing Uncontrolled Clinical Study</i>							
VA1A4002 (R) Vol. 4.008, pt (C) Vol. 4.019- 4.024	open-label, extension of Study VA1A4001	5JAN97 Barst et al. None	23-78	Chronic FLOLAN* 1-25 ng/kg/min plus Conventional Therapy	Interim results up to 64 weeks	M=10 F=87	5Z3503 6M3505 6O3509 7C3520 7D3513 6P3514 7H3530
<b>Clinical Studies in Primary Pulmonary Hypertension (PPH)</b>							
<i>Controlled Studies</i>							
BW35/36 Please See Original NDA 20-444 for the study report (Vol. 1.25-1.29) and CRFs (Vol. 1.69-1.76)	Study 35: Class I & II Study 36: Class III & IV Standard therapy controlled, chronic, open, randomized, multicenter	10APR87 Rubin et al. Ann Int Med (1990) 112:485- 91	12-66	Acute FLOLAN* 2 to 22 ng/kg/min	Approx. 10-20 min at each dose	M=7 F=18	4F2742 6J2757 6K2783 7T2744 7X2797 7T2783 7T2740
				Chronic FLOLAN* 2 to 12 ng/kg/min	8 weeks	M=4 F=7	
				Conventional Therapy	8 weeks	M=3 F=11	
BW46 Please See Original NDA 20-444 for the study report (Vol 1.30-1.33) and CRFs (Vol. 1.70- 1.76)	Standard therapy controlled, chronic, open, randomized, parallel, multicenter	12SEP91 Barst et al. NE J Med (1996) 334:296-302	6-70	Acute FLOLAN* 2 to 30 ng/kg/min	Approx. 10-20 min at each dose	M=22 F=59	9P2776 9W2761 0M2719 0M2721 0M2722 1M2703 1M2704
				Chronic FLOLAN* 1 to 30 ng/kg/min	12 weeks	M=10 F=31	
				Conventional Therapy	12 weeks	M=12 F=28	

### Table of Clinical Studies (cont'd)

Study Identifier Report Location (R) CRF Location (C)	Design	Study Start Investigator(s) Publication	Age Range in Years	Treatment Group, Dose Regimen	Treatment Duration	Number of Study Participants	Batch Number
<b>(Other Information in Secondary Pulmonary Hypertension (SPH))</b>							
Menon (R) Vol. 4.011, p250 (C) not available	Uncontrolled study of acute effects of prostacyclin in SPH/SSc	Reported MAR98 Menon N. Arthritis and Rheumatism (1998) 41:466-9.	39-64	FLOLAN* Peripheral vein infusion, initial dose: 2 ng/kg/min increased 2 ng/kg min every 10 minutes; maximum 12 ng/kg/min	acute 1 hour	F = 7	Not reported
Olschewski (R) Vol. 4.011, p299 (C) not available	Open-label, uncontrolled, sequential acute treatment study of O <sub>2</sub> , NO intravenous epoprostenol, aerosolized epoprostenol, and aerosolized iloprost for PH and SPH	Reported 1996 Olschewski H. Ann Int Med (1996) 124:820-4.	30-56	FLOLAN* 5-7.5 ng/kg/min, O <sub>2</sub> 2-8L/min, NO 10-25 ppm, aerosolized prostacyclin 52-112µg, aerosolized iloprost 9-21µg.	20 min	M = 1 F = 5	Not reported
Mark (R) Vol. 4.011, p236 (C) not available	Case report of treatment of PH associated with use of fenfluramine and phenteramine	Reported AUG97 Mark E. NE J Med (1997) 337: 602-6.	29	FLOLAN* 2-5 µg/kg/min IV	Not reported	F = 1	Not reported
Turanlahti (R) Vol. 4.011, p403 (C) not available	Factorial, dose response study of vasodilators in children with PH	Reported 1998 Turanlahti M. Heart (1998) 79:169-74.	0.3 - 16	FLOLAN* 10-20 ng/kg/min  NO nifedipine	10 min	M = 7 F = 13	Not reported
<b>Clinical Studies in Primary Pulmonary Hypertension (PPH)</b>							
Humbert (R) Vol. 4.011, p155 (C) not available	Case reports of pulmonary edema in pulmonary capillary hemangiomatosis	Reported 1997 Humbert M. Eur Respiratory J (1997) 10:468s	25 - 34	FLOLAN* 8-12 ng/kg/min	Not reported	F = 2	Not reported
Jolliet (R) Vol. 4.011, p165 (C) not available	Controlled trial of sequential doses of NO, prostacyclin, and nifedipine to test vasoreactivity in PPH	Reported MAR96 Jolliet P. Thorax (1997) 52:369-372.	Not reported	FLOLAN* 1ng/kg/min initial dose increased 1 ng/kg/min 10 ng/kg/min maximum  Nitric oxide Nifedipine	Not reported  Not reported	n = 10  n = 10 n = 10	Not reported

### Table of Clinical Studies (cont'd)

Study Identifier Report Location (R) CRF Location (C)	Design	Study Start Investigator(s) Publication	Age Range in Years	Treatment Group, Dose Regimen	Treatment Duration	Number of Study Participants	Batch Number
Lawhorn (R) Vol. 4 011, p232 (C) not available	Case report of ondansetron for nausea and vomiting associated with prostacyclin	Reported APR97 Lawhorn S. J Heart and Lung Transplantation. (1997) 16:472-3.	38	FLOLAN* 1-22ng/kg/min	Chronic	F = 1	Not reported
McLaughlin (R) Vol. 4 011, p245 (C) not available	Open study of epoprostenol in patients with PPH	01JAN94 McLaughlin V. Ftal. NEJM (1998) 338:273-7	40 (mean)	FLOLAN* 2ng/kg/min with increases to a mean dose of 40ng/kg/min.	12-24 months	M=8 F=19	Not reported
Morales (R) Vol. 4 011, p260 (C) not available	Case report of patients with PPH treated with epoprostenol prior to lung transplant.	Reported 1997 Morales P. et al. Arch Bronconeumol (1997) 33:148-50	19, 49	FLOLAN* 4-6 ng/kg/min	26 days, 6 months	M=1 F=1	Not reported
Nguyen (R) Vol. 4 011, p266 (C) not available	Case report of acquired hemophilia in PPH	Reported 1997 Nguyen L. et al. Eur Resp J (1997) 25:414s.	60	FLOLAN* Dose not reported	6 months	M = 1	Not reported
Raffy (R) Vol. 4 011, p332 (C) not available	Case report of paradoxical acute brain thromboembolism in patient with PPH and patent foramen ovale	Reported OCT93 Raffy O. Eur Heart J (1996) 17, 153-154	34	FLOLAN* 5-10 ng/kg/min	Not reported	F = 1	Not reported
Tokarczyk (R) Vol. 4 011, p401 (C) not available	Controlled, open-label study of thrombocytopenia during chronic prostacyclin infusions in PPH	Reported 1997 Tokarczyk T. et al. Circulation (1997) 96:1-134.	41  38	FLOLAN* 26±23 ng/kg/min (mean dose)  Conventional therapy	3-52 months	M = 5 F = 25  n=15	Not reported
<b>Congenital Heart Disease</b>							
Schulze-Nieck (R) Vol. 4 011, p370 (C) not available	Open-label, sequential treatment study of O <sub>2</sub> plus prostacyclin and NO for preoperative evaluation in congenital heart disease	Reported 1994 Schulze-Niecke I. European Heart Journal (1994) 15: 524	Not reported	FLOLAN* 5-20 ng/kg/min	Acute	n=21	Not reported

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**Table of Clinical Studies (cont'd)**

Study Identifier Report Location (R) CRI Location (C)	Design	Study Start Investigator(s) Publication	Age Range in Years	Treatment Group, Dose Regimen	Treatment Duration	Number of Study Participants	Batch Number
<b>Hemodialysis</b>							
Novacek (R) Vol. 4.011, p281 (C) not available	Controlled, open-label trial in hemodialysis, comparing unfractionated heparin, low molecular weight heparin, and prostacyclin	Reported SEP97 Novacek G. Thrombosis Res (1997) 88:283-90	23-65	FLOLAN* 5ng/kg/min	1 week	M = 3 F = 2	Not reported
				Cross-over to control groups	1 week		
<b>Hepatic Failure</b>							
Reinelt (R) Vol. 4.011, p339 (C) not available	Case report of hepatic failure after septic shock	Reported 1995 Reinelt H. Clin Intensive Care (1995) 6:290-2	76	FLOLAN* 5 ng/kg/min	6 days	M = 1	Not reported
<b>Pulmonary Veno-occlusive Disease</b>							
Palmer (R) Vol. 4.011, p308 (C) not available	Case report of prostacyclin infusion in pulmonary venous obstructive disease	Reported SEP96 Palmer S. et al. Chest (1998) 113:237-240.	42	FLOLAN* 2 ng/kg/min	15 min	F = 1	Not reported
<b>Persistent Pulmonary Hypertension of the Newborn</b>							
Parker (R) Vol. 4.011, p312 (C) not available	Case report of neonatal alveolar-capillary dysplasia treated with inhaled nitric oxide and PGI <sub>2</sub>	Reported FEB97 Parker T. Am J Respiratory and Critical Care Med (1997) 155:743-6	17 days	FLOLAN* 8-230 ng/kg/min  Inhaled NO	Day 17-Day 58  Days 2-44, 51-53, 55-60	M = 1	Not reported

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**Table of Clinical Studies (cont'd)**

Study Identifier Report Location (R) CRF Location (C)	Design	Study Start Investigator(s) Publication	Age Range in Years	Treatment Group, Dose Regimen	Treatment Duration	Number of Study Participants	Batch Number
<b>Raynaud's Phenomenon</b>							
Kingma (R) Vol. 4.011, p203 (C) not available	Randomized, controlled, crossover study of prostacyclin effect on hemodynamics in Raynaud's	Reported AUG94 Kingma K. J Cardiovascular Pharmacology (1995) 26:388-93.	24-60	FLOLAN® 2-8 ng/kg/min for 5h followed by 1 wk washout.	Repeated for 3 weeks	M = 3 F = 9	Not reported
<b>Refractory Heart Failure</b>							
Pacher (R) Vol. 4.011, p307 (C) not available	Randomized, open-label, controlled, prospective comparison of prostaglandin, prostacyclin, and dobutamine	Reported 1998 Pacher R. et al. J Heart and Lung Transplantation (1998) 17:43.	53 (mean)	PGE <sub>1</sub> 10 ± 5 ng/kg/min  FLOLAN® 4 ± 2 ng/kg/min  Dobutamine 4 ± 2 mcg/kg/min	Not reported  Not reported  Not reported	n = 30  n = 8  n = 30	Not reported
<b>Sepsis</b>							
Radermacher (R) Vol. 4.011, p324 (C) not available	Open-label study of prostacyclin effects on gastric intra-mucosal pH in septic shock	Reported 1995 Radermacher P. et al Intensive Care Med (1995) 21:414-21.	43-81	FLOLAN® Acute dose of 10 ng/kg/min followed by 3-10 ng/kg/min for 3-32 days	3-32 days	M = 14 F = 2	Not reported

## APPENDIX C

### BORG DYSPNEA SCORE

Following the walk, the person administering the test will 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 4½."

- 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

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## APPENDIX D

### Appendix D: Dyspnea-Fatigue Rating

The following clinical index of dyspnea and fatigue has been applied in previous studies to rate the condition of patients with CHF and PPH. The index has 3 components, each rated on a scale of 0 to 4, for the magnitude of the task that evokes dyspnea or fatigue, the magnitude of the pace (or effort) with which the task is performed and the associated functional impairment in general activities. The ratings for each component are added to form an aggregate score, which can range from 0, for the worst condition, to 12, for the best. Since dyspnea and fatigue are prime symptoms and sources of clinical distress, the index should also aid in assessing the severity of pulmonary hypertension. In double-blind CHF trials, changes in the index showed good correlations with patients' self-selected ratings of improvement. (Feinstein AR, Fisher MB, Pigeon JG. *Am J Cardiol* 1989; 64:50-5)

The ratings for the 3 components of the dyspnea/fatigue index

Magnitude of Task (at normal pace):

- 4 = *extraordinary*. Becomes short of breath or fatigued (hereafter called "symptomatic") only with extraordinary activity such as carrying very heavy loads on level ground, lighter loads uphill or running. No symptoms with ordinary tasks.
- 3 = *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.
- 2 = *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.
- 1 = *light*. Becomes symptomatic with light activities, such as walking on the level, washing or standing.
- 0 = *none*. Symptomatic at rest, while sitting or lying down.

Magnitude of Pace:

- 4 = *extraordinary*. Essentially all conceivable physical tasks are performed at normal pace.
- 3 = *major*. Major tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Less strenuous tasks can be done at normal pace.
- 2 = *moderate*. Moderate tasks, as defined earlier, are performed at a reduced pace, taking longer to complete. Light tasks can be done at normal - pace.
- 1 = *light*. Light tasks are done at a reduced pace.
- 0 = *None*. Symptomatic at rest.

**Functional Impairment:**

- 4 = *none*. Can carry out usual activities and occupation (if employed before onset of pulmonary hypertension) without symptoms.
- 3 = *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.
- 2 = *moderate*. Patient has changed jobs or has abandoned at least 1 usual activity.
- 1 = *severe*. Patient is unable to work or has given up most or all usual activities.
- 0 = *very severe*. Unable to work and has given up most or all usual activities.

In categories 2, 1 and 0 for any of these component ratings, the impairment should be caused by shortness of breath or fatigue or both. If caused by other factors, the impairment should not be rated with this index. Also, *usual activities* refer to requirements of daily living, maintenance or upkeep of residence, yard work, gardening, washing, shopping, cooking, etc.

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## APPENDIX E

### Appendix E: Functional Classifications of Patients With Diseases of the Heart

- CLASS I Patients with cardiac disease but without resulting limitations in physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
- CLASS II Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
- CLASS III Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
- CLASS IV Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Excerpted from *Diseases of the Heart and Blood Vessels - Nomenclature and Criteria for Diagnosis*, 6th Edition, Boston, Little Brown and Company, copyright 1964 by the New York Heart Association, Inc. 7th edition, revised, 1973.

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Protocol: VAIN4001  
Population: All Patients, Intent-to-Treat

Table 26  
Summary of Hemodynamic and Blood Gas Measurements at Baseline and Week 12

Variable	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	25th-Tile	75th-Tile	Max.
Heart Rate (bpm)	Conv.	55	Baseline	55	84.46	13.50	85.33				
			Week 12	48	82.90	13.18	84.00				
	Flolan	56	Baseline	56	83.70	10.85	83.50				
			Week 12	50	86.91	11.49	85.83				
SAPs (mm Hg)	Conv.	55	Baseline	55	122.93	14.18	119.33				
			Week 12	48	119.96	15.06	119.83				
	Flolan	56	Baseline	56	126.70	18.73	124.00				
			Week 12	49	118.08	21.38	112.67				
SAPd (mm Hg)	Conv.	55	Baseline	55	72.13	11.18	73.00				
			Week 12	48	72.92	9.78	72.50				
	Flolan	56	Baseline	56	75.85	11.33	75.67				
			Week 12	49	68.43	9.64	67.67				
SAPm (mm Hg)	Conv.	55	Baseline	55	89.07	10.78	88.56				
			Week 12	48	88.60	9.94	87.83				
	Flolan	56	Baseline	56	92.80	12.37	91.56				
			Week 12	49	84.98	12.33	85.56				
RAPm (mm Hg)	Conv.	55	Baseline	55	11.13	5.49	10.67				
			Week 12	47	12.24	6.25	12.33				
	Flolan	56	Baseline	56	13.14	5.02	13.83				
			Week 12	50	11.71	6.60	12.17				
PAPs (mm Hg)	Conv.	55	Baseline	55	82.87	17.07	81.67				
			Week 12	48	82.52	19.76	78.17				
	Flolan	56	Baseline	56	83.07	16.75	80.67				
			Week 12	50	74.49	17.35	76.00				
PAPd (mm Hg)	Conv.	55	Baseline	55	32.25	7.75	30.33				
			Week 12	48	32.40	9.01	31.00				
	Flolan	56	Baseline	56	34.78	8.71	34.33				
			Week 12	50	30.21	8.22	30.00				
PAPm (mm Hg)	Conv.	55	Baseline	55	49.12	10.19	48.22				
			Week 12	48	49.10	11.78	47.83				
	Flolan	56	Baseline	56	50.88	10.58	50.33				
			Week 12	50	44.97	10.54	46.33				

APPENDIX F

Protocol: VA1A4001  
Population: All Patients, Intent-to-Treat

Table 26

Summary of Hemodynamic and Blood Gas Measurements at Baseline and Week 12

Variable	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	25 <sup>th</sup> -Tile	75 <sup>th</sup> -Tile	Max.
Cardiac Output (L/min)	Conv.	55	Baseline	55	4.05	1.26	3.93				
			Week 12	48	3.94	1.49	3.62				
	Flolan	56	Baseline	56	3.40	1.18	3.27				
			Week 12	50	4.29	1.39	4.05				
Cardiac Index (L/min/m <sup>2</sup> )	Conv.	55	Baseline	55	2.23	0.65	2.11				
			Week 12	48	2.15	0.70	2.08				
	Flolan	56	Baseline	56	1.93	0.59	1.86				
			Week 12	50	2.44	0.66	2.34				
PCWP (mm Hg)	Conv.	55	Baseline	53	9.03	3.22	10.00				
			Week 12	46	9.63	5.79	8.83				
	Flolan	56	Baseline	55	9.27	3.07	9.00				
			Week 12	48	9.77	5.69	8.67				
SvO <sub>2</sub> (%)	Conv.	55	Baseline	54	58.76	9.89	60.67				
			Week 12	45	59.09	8.66	60.00				
	Flolan	56	Baseline	54	57.41	10.76	58.17				
			Week 12	47	61.38	12.26	63.33				
SaO <sub>2</sub> (%)	Conv.	55	Baseline	55	92.52	6.59	94.00				
			Week 12	48	93.06	4.89	93.00				
	Flolan	56	Baseline	56	92.65	6.76	94.00				
			Week 12	49	92.82	8.52	94.33				
PVR (U)	Conv.	55	Baseline	53	11.17	5.31	9.33				
			Week 12	46	11.66	6.61	10.84				
	Flolan	56	Baseline	55	14.20	7.06	13.48				
			Week 12	48	9.17	4.42	8.48				

## APPENDIX G

CONFIDENTIAL



### MEDICAL HISTORY SCREEN

GOLD protocol number: **VA1A4001**

Investigator number:	Subject's initials:	Subject's number:	Session number: 1
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Does this patient have a history of:	Yes		No ✓	Unknown ✓
	Past history ✓	Present at Screen ✓		
Anorexic agents				
Liver disease <sup>2</sup>				
Diabetes <sup>2</sup>				
DVT <sup>2</sup>				
IV drug abuse <sup>1</sup>				
Left heart failure <sup>1</sup>				
Other family members with PH, Specify type of PH:				
Exposure to Flolan <sup>1</sup>				
Pulmonary embolism <sup>1</sup>				
Renal dysfunction <sup>2</sup>				
Residence at high altitude				
Smoking				
Valvular heart disease <sup>1</sup>				
Other, Specify:				

<sup>1</sup> Patient may not be entered in study if present at Screen.  
<sup>2</sup> If present at Screen, comment in the INVESTIGATOR COMMENT LOG on clinical significance in regards to study entry eligibility.

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