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Medical Review(s)

CLINICAL REVIEW

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Established Name iloprost
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Therapeutic Class prostacyclin analog
Applicant CoTherix, Inc

Priority Designation P

Formulation inhalation
Indication pulmonary arterial hypertension

Table of Contents

1. Executive summary	
	Recommendations
	Summary of Clinical Findings
2. Introduction and Background	
3. Significant Findings from Other Reviews	
4. Data Sources and Integrity	
	Financial disclosures
5. Clinical Pharmacology Summary	
6. Review of Efficacy	
7. Integrated Review of Safety	
	Serious safety
	Common adverse events
	Special populations
	Laboratory parameters
	Vital signs and cardiac hemodynamics
	ECG intervals
	Concomitant medications
	Withdrawal phenomena
	Overdose experience
	Adequacy of patient exposure and demographics
	Post marketing experience
	Safety update
Marked up product label	
Appendices	
	ME97218
	ME98008

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval for the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms.

Recommendation on Post-Marketing Actions: satisfactory completion of study C200-002

1.2 Summary of Clinical Findings

Brief Overview of Clinical Program

Iloprost has been studied in over 160 clinical trials spanning two decades and involving more than 12,000 subjects in whom the drug was administered via the intravenous, oral, or inhaled routes. The product was first approved in 1990 in Europe as Ilomedin® for intravenous administration for the treatment of peripheral vascular disease. The European Medicines Agency granted marketing authorization in September, 2003, for Ventavis® (iloprost) inhalation solution for the treatment of patients with primary pulmonary hypertension (PPH). CoTherix, Inc. has signed an exclusive licensing agreement for the commercialization of iloprost in the United States (US), using the proposed trade name of Ventavis®.

The clinical development program for iloprost delivered by inhalation for patients with pulmonary arterial hypertension was begun in 1988. Four non U.S. clinical studies were conducted: a phase 1 study (ME98051) in 13 patients assessed the pharmacokinetics and hemodynamics of inhaled iloprost using three different nebulizers in a crossover design, an exploratory phase 2 study (ME98008) in 63 patients with a 3-month randomized phase comparing inhaled iloprost to conventional therapy, followed by long-term uncontrolled treatment (for up to 2 years), and a phase 3 double blind, efficacy study (ME97218) with 203 patients randomized to placebo or iloprost for 12 weeks. This was followed by a long-term open-label study (303045) in 71 patients who had completed 12 weeks of randomized therapy.

A large number of clinical studies have also been completed with both the intravenous and oral formulations of iloprost. The sponsor chose certain studies with these formulations that they considered relevant for pooling to assess the safety of inhaled iloprost. These studies were clinical trials that were randomized, placebo-controlled, and involved dosing periods of at least 14 days in duration. This pooling used 12 intravenous iloprost trials involving 1473 patients (of whom 764 received iloprost at doses up to 2 ng/kg/min over 6 hours per day for 2 to 4 weeks) and 12 studies with the oral formulation of at least 14 days treatment duration that enrolled 3161 subjects (of whom 2033 received oral iloprost clathrate at doses ranging from 50 ug to 200 ug twice daily for 4 weeks to 1 year). Most of these studies included a follow-up period during which safety information continued to be gathered.

For those studies not presented in the integrated summary of safety (approximately 106 intravenous studies enrolling 7489 subjects, and approximately 22 oral studies enrolling 281 subjects), a summary of deaths, other serious adverse events and discontinuations because of adverse events were provided in the NDA safety update.

Lastly, a phase I study (C200-004) with normal volunteers evaluating the effect of inhaled iloprost on ECGhemody intervals was conducted in the U.S.

Efficacy

One study (ME97218) convincingly showed that patients randomized to iloprost (n=101) were more likely to improve their walk test by at least 10% over baseline, improve their NYHA classification by at least one stage, not experience a deterioration in their disease status, and not die compared to patients randomized to placebo (n=102) during 12 weeks of treatment.

Safety

Deaths

Placebo (and control studies): percents

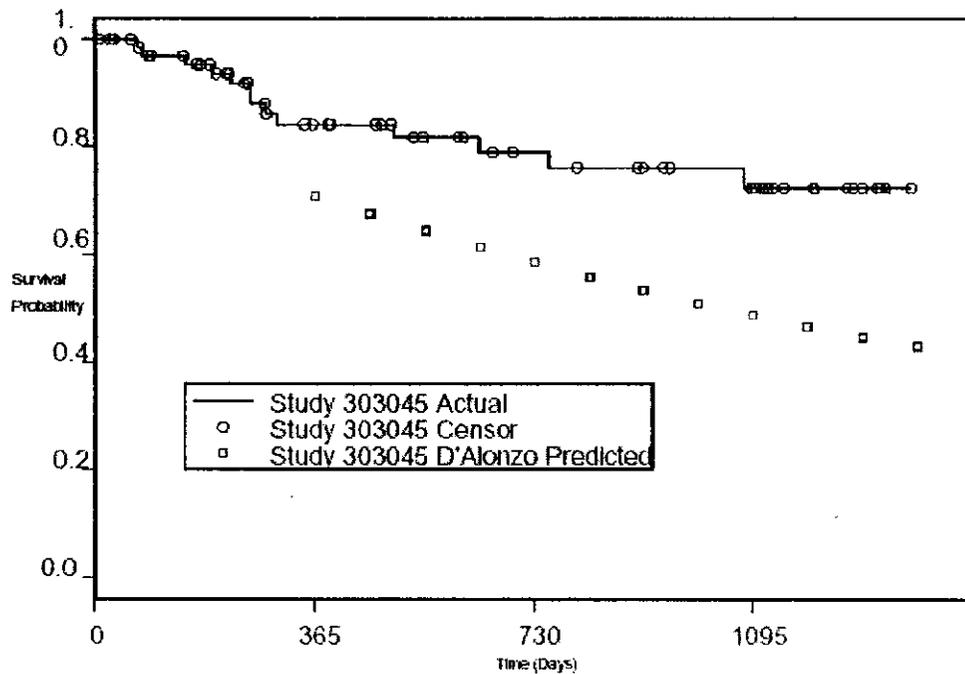
inhaled studies placebo-control		Oral studies Placebo controlled	
Placebo N=133	Iloprost N=129	Placebo N=1128	Iloprost N=2033
3.6%	2.3%	2.3%	1.8%

In both the small data base from the inhaled studies and the much larger data base from the oral studies, mortality rates tended to be smaller in the iloprost group.

In long term study 303045 patients received inhaled iloprost for at least 24 months. Of the 71 patients there were 13 deaths. There were 13 deaths: 8 during the trial and 5 who discontinued study drug prior to death.

Mortality estimate

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Kaplan Meier plot of the time to death for patients treated with iloprost long-term. Actual time to death for these patients was compared with predicted time to death using the baseline hemodynamic data from these same patients inserted into the predicted survival model from a national prospective registry (D'Alonzo GE et al. Survival in patients with primary pulmonary hypertension. *Ann Intern Med* 1991;115:343-9). There is no evidence of an adverse effect on survival.

Other serious events

The table below shows the serious adverse events reported during the randomization phase for the 2 controlled trials (limited to those individual events reported by at least 2 iloprost patients and with an incidence rate greater for the iloprost group than for the placebo group).

No. and (percent) of patients

Adverse event	Placebo-control subtracted+ %
Any event	-0.1
Cardiovascular-any	0.4
Syncope	4.7
Respiratory-any	1.6
Dyspnea	0.1
pneumonia	1.6
Body as a whole-any	1.0
Lab test abnormal	1.6
Digestive-any	-2.9
Metabolic, nutritional-any	-2.2
Skin, appendages-any	0.8

+N=129 for iloprost and N=133 for placebo control

Most common serious events reported during the long term phase of the inhaled studies (n=215) include congestive heart failure (7.9%), aggravation reaction (5.1%), and syncope (4.2%). The oral studies were noncontributory.

Drop outs because of adverse event

There were 6 iloprost patients (4.7%) who withdrew from one of the two randomized inhalation studies because of an adverse event (aggravation reaction (3), congestive heart failure, hypotension, syncope, vasodilatation, edema, headache, cough increased: 1 report each). The control group had 10 patients (7.5%) who withdrew because of an adverse event.

In the oral data base, there were nearly twice the incidence rate of drop outs because of an event in the iloprost group (25.9%) compared to placebo (13%). The events with the largest placebo subtracted rate include headache (8.6%), vasodilatation (3.7%), and nausea (3.1%).

Commonly reported events

In the inhaled data base, the cardiovascular system had the highest reporting incidence rate for body systems with iloprost patients reporting more events than the controls (56.6% vs. 40.6%). Vasodilatation was reported most often by iloprost patients (15.8%+) followed by hypotension (3.3%) and syncope (3.3%). Palpitations also were reported somewhat more frequently in the iloprost group (2.4%).

Events in the respiratory system were reported more often in the iloprost group with cough increased reported rather frequently (12.4 %).

Events in the nervous system reported more often in the iloprost group included trismus (8.6%), headache (7.5%), insomnia (3.2%), and sleep disorder (2.4%).

Other events with a placebo-control subtracted incidence rate $\geq 4\%$ include nausea (5.7%) and rash (4%).

In the oral data base, adverse events reported most frequently by iloprost patients were generally similar to those reported by patients who received inhaled iloprost and included vasodilatation (19.9%), headache 30.0%, nausea (8.6%), vomiting (3.6%), and trismus (3.6%).

Laboratory parameters

Except for the rare increase in liver function tests in both oral and inhaled formulations, there is no strong evidence of an effect of iloprost on laboratory parameters. There was no evidence of liver failure, kidney failure, or bone marrow failure associated with the use of iloprost.

Vital signs

There was evidence of a small blood pressure decrease when examining the blood pressure results from the inhalation studies (mean changes in blood pressure[@] from baseline at week 12 were -2.4/-2.8 mmHg for iloprost and -1.4/+1.0 mmHg in the placebo-control). Judging from the adverse events reports, a (short lived) vascular effect of iloprost is likely. The majority of these events, however, rarely resulted in drop out or a serious event. However, very ill patients are usually susceptible to decreases in blood pressure. Heart rate increased[^] (mean change from baseline 5-7 bpm) in subjects taking compared to placebo (3

+ all percents are placebo-control subtracted unless otherwise noted

@measured pre and post inhalation

^ see results of ECG study C200-004

bpm) and the reporting of palpitations in the inhalation studies was slightly higher in iloprost group (2.4% placebo-control subtracted).

ECG intervals

Iloprost increased heart rate (5-7 bpm) compared to placebo (3bpm). There is no evidence that iloprost prolongs or shortens PR, QRS, or QT intervals.

Dosing Regimen and Administration

The efficacy study (ME97218) used the following dosing scheme: patients start with an initial dose of 2.5 µg (as delivered at the mouthpiece of the nebulizer for approximately 4.5 min). If this dose is well tolerated, the dose was to be increased to 5 µg per inhalation (over 9 min). The recommended dosing regimen (2.5ug or 5 ug) is 6-9 times per day (total daily dose 15 ug to 45 ug) according to individual need and tolerability. Study AX 15 measured serum concentration of inhaled iloprost with 3 different nebulizers. Mean serum concentrations, regardless of nebulizer, were close to zero by 30 minutes.

Mean total daily dose used at the end of the study was 35 ug with the range being 12.5 ug to 45 ug. Mean number of inhalation was 7.3 with the range being 6 to 9. Most patients did not use the inhaler at night.

Study C220-004 evaluated in normal volunteers increasing doses of inhaled iloprost solution every 2 hours beginning with 5 µg followed by 7.5 ug, 10 ug, 12.5 ug, 15 ug, and 20 µg for a total of 6 dose inhalations (total cumulative dose of 70 µg) or up to a maximally tolerated dose to maximize exposure. There were 13 subjects (31.7%) who failed to go to the highest scheduled dose (20 ug). Five reached their maximum tolerated dose because of (mild to moderate) transient chest pain/discomfort/tightness, not thought to be cardiac in nature. Often these events were accompanied by headache, nausea, and dizziness. The remaining 8 subjects discontinued for other reasons. Most could tolerate at least 10 ug. There is a possibility that patients, unlike normal volunteers, can tolerate (and possibly have increased efficacy from) a higher dose.

Drug-Drug Interactions

Iloprost is extensively metabolized by beta-oxidation. *In vitro* metabolism studies with iloprost in human liver microsomes and cDNA-expressed human cytochrome P450 isoenzymes revealed minor inhibitory effects of iloprost on the metabolism of model P450 substrates. The extent of inhibition observed *in vitro* did not indicate any potential for drug-drug interactions when iloprost is co-administered with commonly prescribed drugs known to be metabolized by CYP2C19 and CYP2C8. The effects of possible genetic polymorphism were not studied.

Iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. Iloprost, because it can inhibit platelet function, also has the potential to increase the risk of bleeding when used with anticoagulants.

Special Populations

Hepatic: as a result of the decreased clearance of iloprost, plasma concentrations achieved with i.v. infusion of 1 ng/kg/min in patients with hepatic impairment were twice the steady-state concentrations observed in healthy volunteers. The half-life remained unchanged.

In a study (AM75) with administration of a single 100 ug dose of the oral formulation, subjects with Childs-Pugh stage A (n=5) had a 5 fold increase and those with stage B (n=3) had a 15 fold increase in AUC_{0-8h}, compared to normal subjects (n=4). No deaths or serious adverse events were reported. The table below displays the reported adverse events by degree of hepatic impairment.

TT 4: Adverse events, all reported cases

Adverse event (HARTS)	Stage A (N=5)	Stage B (N=6)	Healthy (N=4)	Total
Vasodilation	5	7 (1 severe)	2	14
Headache	2 (1 severe)	6 (3 severe)	1	9
Nausea	1	6 (2 severe)	0	7
Vomiting	0	7 (1 severe)	0	7
Diarrhea	1	2	0	3
Drowsiness ¹	1	2	0	3
Pain in extremity	2	0	0	2
Abdominal pain	1	0	0	1
Back pain	0	1	0	1
Hypotension	0	1	0	1
Anorexia	0	1	0	1
Abnormal stools	1	0	0	1
Hot flashes	1	0	0	1
Sweating increased	0	1	0	1
Group totals	15	34	3	52

There were more reported events with the Stage B patients and the events tended to be more "severe" in nature.

Renal: patients with mild or moderate renal insufficiency had the same PK profile as normal volunteers, but patients with renal failure severe enough to require dialysis had up to a 3-fold reduction in the clearance of iloprost (higher plasma concentrations and AUC values, with lower total clearance, similar half life).

There is little evidence to support an effect of age, race, or gender on the safety of iloprost. The effect of these variables on efficacy was not addressed.

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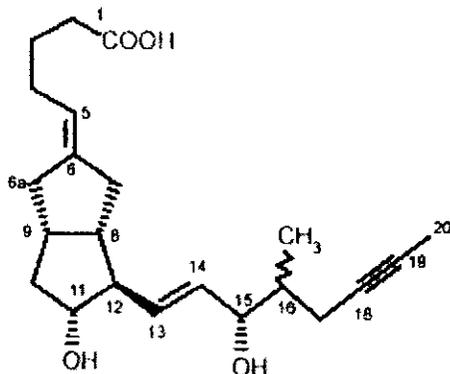
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Iloprost is an optically active diastereoisomeric mixture which also exhibits geometric (Z – E) isomerism.

The molecular formula for iloprost is C₂₂H₃₂O₄. The chemical structure is shown below.

Chemical Structure of Iloprost



Clinical trials in support of iloprost inhalation solution for PAH were performed with Ilomedin 20, diluted at the time of nebulization with isotonic saline (1:1). Ilomedin 20 is an approved parenteral formulation of iloprost in Europe. Table 3 shows that the proposed commercial formulation (Ventavis®) is comparable to that used in the inhaled clinical studies.

Table 3 Iloprost Inhalation Solution Formulation

Ingredient	Ilomedin 20 ^a (mg/mL)	Ilomedin 20 Diluted 1:1 with Saline (mg/mL) ^b	Ventavis [®] (mg/mL)
Iloprost	0.020	0.010	0.010
Ethanol 96%			0.810
Fructose			0.121
Hydrochloric acid			0.510
Sodium chloride			9.000
Water for injection (mL)			992.849
Total weight (µg)	1002.400	1003.550	1003.300

^a Approved European parenteral formulation of iloprost
^b Used in Studies ME97218, ME98098, ME98051, and 303045

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2.2 Currently Available Treatment for Indications

There are three products approved by the FDA for the treatment of pulmonary arterial hypertension. **Flolan® (epoprostenol sodium)** (Glaxo Smith-Kline) is a prostacyclin solution that is administered continuously via a permanently indwelling central venous catheter using

an ambulatory infusion pump.

Tracleer® (bosentan) (Actelion Ltd) is a dual endothelin receptor antagonist that is administered orally.

Remodulin® (treprostinil sodium) (United Therapeutics) is a prostacyclin analogue administered by continuous subcutaneous infusion via a self-inserted catheter, using an infusion pump.

2.3 Availability of Proposed Active Ingredient in the United States

Final drug product will be imported from Germany.

2.4 Important Issues With Pharmacologically Related Products

Flolan® is administered as a continuous chronic infusion through a central venous catheter.

A large study evaluating the effect of FLOLAN on survival in NYHA Class III and IV patients with congestive heart failure due to severe left ventricular systolic dysfunction was terminated after an interim analysis of 471 patients revealed a higher mortality in patients receiving FLOLAN plus conventional therapy than in those receiving conventional therapy alone. The chronic use of FLOLAN in patients with congestive heart failure due to severe left ventricular systolic dysfunction is therefore contraindicated.

Some patients with pulmonary hypertension have developed pulmonary edema during dose initiation, which may be associated with pulmonary veno-occlusive disease. FLOLAN should not be used chronically in patients who develop pulmonary edema during dose initiation.

2.5 Pre-submission Regulatory Activity

Schering AG has studied iloprost for more than 20 years. The product was first approved in 1990 in Europe as Ilomedin® for intravenous administration for the treatment of peripheral vascular disease. In September 2003 the European Medicines Agency granted marketing authorization for Ventavis® (iloprost) inhalation solution for the treatment of patients with pulmonary arterial hypertension. CoTherix, Inc. has signed an exclusive licensing agreement for the commercialization of iloprost in the United States (US), using the proposed trade name of Ventavis®.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

The active ingredient, iloprost, is a synthetic analog of the natural, highly unstable prostacyclin PGI₂. Iloprost drug substance consists of a fixed mixture (approximately 47:53, 4S:4R) of two diastereoisomers as controlled by the manufacturing process. The diastereoisomers do not interconvert during storage. Iloprost is an oily substance, which is only slightly soluble in water, but has good solubility in methanol, ethanol, ethyl acetate, and acetone. The aqueous solubility of iloprost is improved by forming a salt with alkalis and tromethamine. Due to its instability at room temperature and refrigerated conditions, the drug substance should be stored frozen (—) and protected from light.

The drug product, Iloprost Inhalation Solution, is a clear, colorless, sterile, aqueous solution containing 10 µg/mL of iloprost formulated for inhalation via a nebulizer. It is supplied as a 2-mL solution in glass

ampules containing 20 µg of iloprost and the inactive ingredients sodium chloride, tromethamine (trometamol), ethanol (96%), water for injection, and hydrochloric acid (for pH adjustment to a target of 8.1). The formulation of iloprost as a tromethamine salt provides increased stability to both temperature and light. Thus, the drug product solution can be stored at room temperature without the need for light protection.

3.2 Animal Pharmacology/Toxicology

The pharmacodynamic profile of iloprost showed it to be a

- potent vasodilator and anti-platelet/antithrombotic agent.

- potential mechanisms of action that contribute to iloprost's therapeutic effect include platelet anti-aggregatory and antithrombotic effects, favorable effects on microvascular perfusion and microvascular integrity, and inhibition of leukocyte-vessel wall interactions.

- data from in vitro studies and from in vivo studies with systemic administration of iloprost demonstrated that iloprost inhibited pulmonary vasoconstriction and reduced PVR, thereby normalizing pulmonary pressure.

- iloprost had platelet anti-aggregatory and antithrombotic effects, had beneficial effects on vascular remodeling and in situations with endothelial dysfunction, and inhibited some aspects of inflammation.

- side effects are likely to result from exaggerated pharmacological effects of the compound (e.g., systemic hypotension). Investigation of the effects of iloprost on other organ systems indicated that iloprost was not likely to induce serious adverse effects in the therapeutic dose range.

- no major unexpected interactions were found when iloprost was tested in combination with other cardiovascular drugs.

- possible additive or potentiating effects of co-administration of iloprost with other vasodilators and anti-platelet/anticoagulant drugs should be taken into consideration when initiating therapy with iloprost.

There were no indications from animal studies of sex-specific differences in the effects of iloprost.

Tachyphylaxis to the antiplatelet effects can be avoided by discontinuing treatment.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Iloprost has been studied in over 160 clinical trials spanning two decades and involving more than 12,000 subjects in whom the drug was administered via the intravenous, oral, or inhaled routes. Data for the clinical efficacy and safety reviews came exclusively from clinical trials, all were conducted outside the United States. Only the approval for the inhaled formulation is being sought in this NDA.

Safety data used for the safety review were obtained from studies using the oral, intravenous, and inhaled formulation. All data were made available from studies using the inhaled formulation. Selected safety data from the oral and intravenous formulations were submitted. An attempt was made, however, to submit all serious safety (deaths, serious adverse events, withdrawals because of an adverse event).

4.2 Tables of Clinical Studies

Efficacy (studies with inhalation formulation only)

The 3 clinical studies using the inhaled formulation are shown below.

Table 2.5.1 Comparison of Study Designs for the Iloprost Studies

	ME97218 (Phase 3)	ME98008 (Phase 2)	ME98051 (Phase 1)
Randomization	Yes	Yes	Yes
Blinding	Yes	No	No
Control	Placebo	Common background therapy (excluding prostanoids)	Crossover study
Design	Double-blind parallel	Open-label parallel	Single dose crossover
Study Duration	12 weeks randomized and long-term open label (ongoing Study 303045)	12 weeks randomized and 2 years open label	1 day
Patient Population	PPH or SPH NYHA Class III or IV	PPH or SPH NYHA Class II, III, or IV	PPH or SPH
Sample size	101 iloprost 102 placebo	30 iloprost 33 control	13 iloprost
Primary efficacy endpoint	Composite response ^a	None	None
Secondary efficacy endpoints	6-minute walking distance NYHA Class changes Deterioration of PAH Mortality Mahler Dyspnea Index Hemodynamic parameters and gas exchange Quality of Life Need for transplantation	Composite response ^b 6-minute walking distance NYHA Class changes Deterioration of PAH Mortality Mahler Dyspnea Index Hemodynamic parameters and gas exchange Quality of Life Need for transplantation	Hemodynamic parameters and gas exchange

^a The composite response endpoint was defined as (1) improvement in the 6-minute walk test at 12 weeks by at least 10% vs. baseline, (2) improvement by at least one NYHA class at 12 weeks vs. baseline, and (3) no death or deterioration of PAH before 12 weeks

^b Composite response endpoint was retrospectively defined for the phase 2 study as (1) improvement in the 6-minute walk test by at least 10% vs. baseline, (2) improvement by at least one NYHA class vs. baseline, and (3) no death

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–Phase 3 double-blind, placebo-controlled study ME97218 (Report A02997) with 203 patients, comprising 12 weeks of randomized treatment followed by open-label therapy in a subset of 71 patients (ongoing Study 303045).

–Phase 2 randomized, controlled, exploratory study ME98008 (Report A02337) with 63 patients, comprising 12 weeks of randomized treatment and 2 years of open-label treatment.

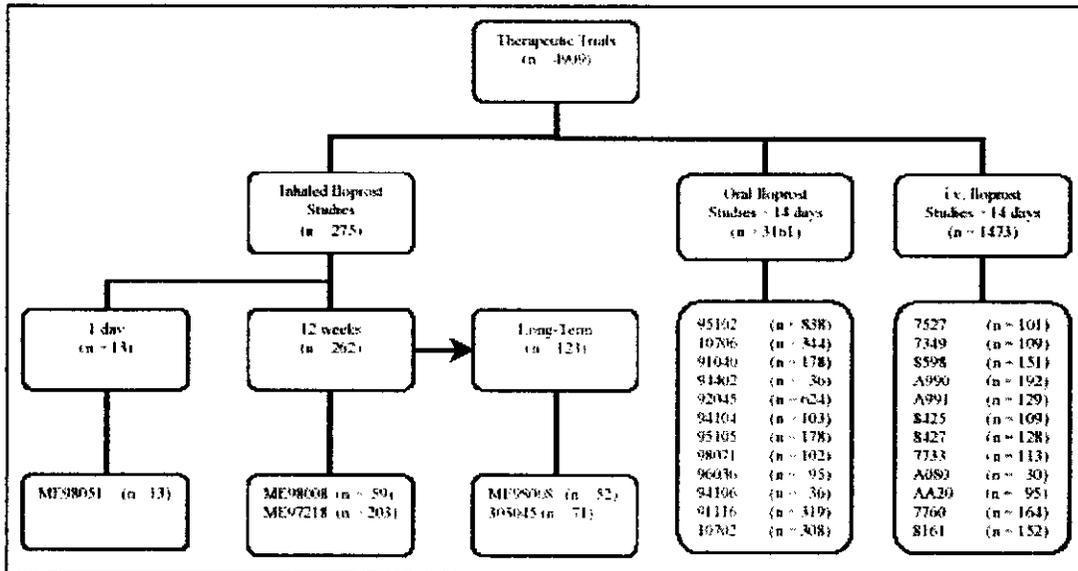
–Phase 1 cross-over PK/PD study ME98051 (Report AX15) in 13 patients

Safety

While many uncontrolled and short-term studies were conducted with intravenous and oral iloprost as part of PK and PD assessments, the studies that were considered by the sponsor to be relevant for pooling (and reasonable to the reviewer) to assess the safety of inhaled iloprost were clinical trials that were randomized, placebo-controlled, and involved dosing periods of at least 14 days in duration. This comprised 12 intravenous iloprost trials involving 1473 patients, of whom 764 received iloprost at doses up to 2 ng/kg/min over 6 hours per day for 2 to 4 weeks. For oral dosing of iloprost, there were 12 studies

of at least 14 days treatment duration that enrolled 3161 subjects, of whom 2033 received oral iloprost clathrate at doses ranging from 50 ug to 200 ug BID for 4 weeks to 1 year. Most of these studies included a follow-up period.

Figure 2.5.2 Summary of Clinical Studies included in Safety Analyses



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The Safety Update included

- update from the ongoing long-term Study 303045 (inhaled formulation)
- study report from Study C200-004, an ECG trial examining the effect of inhaled iloprost on QT interval and other parameters.
- serious safety from clinical trials not provided in the NDA[^] (intravenous, intra-arterial, and oral formulations only);
- update on postmarketing reports received since the filing of the NDA.
- amendment October, 15, 2004, updating the safety of the ongoing blinded study C200-002.

4.3 Review Strategy

Efficacy of inhaled iloprost in patients with pulmonary hypertension is based on one clinical trial (ME97218). There was one other "efficacy trial" (ME98008) was exploratory, open-label, and comparative and the study report underwent revisions after unblinding occurred (correction of walking distance, missing data for patient disposition, and drug dosing).

[^] The 118 oral and i.v. and/or i.a. studies summarized in the Safety Update took place approximately from the mid-1980s to the mid-1990s and were performed under the auspices of Schering, AG

4.4 Compliance with Good Clinical Practices

ME97218 was conducted in Europe under cGCP and the Declaration of Helsinki.

4.5 Financial Disclosures

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

(from summary of clinical pharmacology studies)

Iloprost is a mixture of 4R- and 4S-methyldiastereoisomers. In humans, iloprost is entirely metabolized, with no unchanged drug found in the urine. The major metabolites of iloprost were the tetranor derivatives (inactive with respect to pharmacodynamic actions) and glucuronides. These metabolites were also detected in plasma, along with dinoriloprost after i.v. infusion (2 ng/kg/min). No selective metabolism of the two isomers was observed in humans after oral dosing. The metabolic pattern was the same in female and male subjects.

Iloprost was 60% bound to human plasma proteins, and this binding was independent of concentration. Approximately 75% of the binding was to albumin, with the remaining 25% binding to other proteins.

Following inhalation of iloprost from three different nebulizer devices, there was a rapid appearance of iloprost in serum: peak concentrations were achieved in all PAH patients either at the end of the 9-12 minute inhalation or within 5 minutes afterwards. The serum half-life of iloprost ranged from 6.5 to 9.4 minutes for the three nebulizer devices. These values, calculated from mean serum concentration time curve from the end of inhalation up to 30 minutes after the end of inhalation, reflect both phases (alpha phase and beta phase) of elimination.

The estimated bioavailability of inhaled iloprost was approximately 80%.

Metabolism

Iloprost is only marginally metabolized by cytochrome P450 enzymes (CYP2C9, CYP2C19 and CYP3A4). (Report A09478)

Platelet function

Iloprost administered intravenously and orally inhibited platelet aggregation. Platelet aggregation was inhibited in a dose dependent manner at the end of the i.v. infusion (1 and 3 ng/kg/min). The inhibitory effect on platelets ceased 45 minutes after the end of the i.v. infusion, and ceased 2 hours after oral

administration. This effect on platelets was longer than the half-life of iloprost. Iloprost also increased cyclic AMP content of platelets and did not alter the in vitro sensitivity of platelets. (Report 6496)

Hepatic impairment (Reports AM75 and 8432)

As a result of the decreased clearance of iloprost, plasma concentrations achieved with i.v. infusion of 1 ng/kg/min in patients with hepatic impairment were twice the steady-state concentrations observed in healthy volunteers. The half-life remained unchanged.

Renal

Patients with mild or moderate renal insufficiency had the same PK profile as normal volunteers, but patients with renal failure severe enough to require dialysis had up to a 3-fold reduction in the clearance of iloprost (higher plasma concentrations and AUC values, with lower total clearance, similar half life). (Report 8148)

Drug Interactions

- digoxin PK was not altered by i.v. iloprost infusion (Report A646).
- oral preparations of nifedipine, mepindolol and pentoxifylline and i.v. infusion of iloprost with did not reveal interactions of clinical relevance regarding hemodynamic parameters (blood pressure, heart rate, orthostatic reactions and peripheral perfusion) (Report 8412).
- Captopril, nifedipine and diltiazem did and iv iloprost did not significantly affect pharmacodynamics in normal volunteers/patients (Reports 8168, B598 and B599
- Acetylsalicylic acid, within the 10-300 mg/day dose range, did not have an effect on the clearance of iloprost. (Report AD19)

Effect of food

Food (hospital breakfast) increased the oral bioavailability of iloprost by 20%. Dosing of iloprost during the efficacy trial was independent of food intake.

5.2 Pharmacodynamics

See section 7 (Vital signs and cardiac hemodynamics)

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Ventavis® is indicated for the treatment of pulmonary arterial hypertension in patients with NYHA class III or IV \square symptoms.

Methods

The clinical efficacy of iloprost was demonstrated in one randomized, placebo controlled, 12 week, double blind study (Protocol ME97218).

General Discussion of Endpoints

The primary efficacy endpoint was a combined responder endpoint defined as:

- a) improved exercise capacity \geq 10% versus baseline,

b) improvement by at least one NYHA class at 12 weeks, and
c) no deterioration of PHT or death before 12 weeks.
These are clinically acceptable endpoints.

For the primary variable, each patient was classified as responder or non-responder. The primary population for the evaluation of efficacy was the intent-to-treat (ITT) population.

For the primary efficacy variable the method for treatment comparison was the two-sided Mantel-Haenszel test stratified for PHT (primary/secondary) and NYHA (III/IV) at the 0.05 significance level.

Patients who prematurely discontinue the study medication because of the defined criteria of deterioration or because of treatment with not allowed concomitant prostanoid medication during the study period were counted as non-responders.

Patients with missing information for the primary endpoint were counted as non-responders.

Patients assigned a value of 0 meters for their baseline exercise capacity assessment who showed any improvement at 12 weeks will satisfy the first part of the combined responder criterion (improvement by 10%).

Patients who receive a lung or heart and lung transplantation during the study period were considered not assessable for efficacy if this was only the result of transplant availability.

Study Design

This study was a prospective, double-blind, 2-arm, parallel-group, placebo-controlled, multicenter investigation in patients with primary or secondary pulmonary hypertension (PHT). The patients were randomly assigned to inhalation of placebo aerosol or iloprost aerosol for 12 weeks in addition to their background therapy.

The individually tolerated dose at the mouthpiece (determined within the first 7 days of randomization) was 15 ug, 22.5 ug, 30 ug, or 45 ug.

The initial total daily dose of iloprost was 30 ug divided into 6 equal-dose inhalations of 5 ug; if this dose was well tolerated, the total daily dose was increased to 45 ug divided into 9 equal-dose inhalations of 5 ug. The minimum interval between inhalations was 2 hours.

In case of poor tolerability, the dose was reduced to 2.5 ug with a total daily dose of 15 ug divided into 6 equal-dose inhalations. If this dose was well tolerated, the total daily dose was increased to 22.5 ug divided into 9 equal-dose inhalations of 2.5 ug.

Dose adaptations during the following 11-week period were allowed for poor tolerability determined by the investigator. Temporary interruptions of therapy of up to two weeks were allowed as medically required

Randomization

The patients were assigned to treatment groups by central telephone randomization and prospectively stratified for pulmonary hypertension (primary or secondary) and for the New York Heart Association (NYHA) class (III or IV).

Patients were to be assessed on day 8 (\pm 2 days), at week 4, at week 8 and at week 12 (\pm 5 days, respectively) for the end of treatment visit, or in the event of discontinuation of treatment at the time point

of withdrawal. An additional follow-up visit was scheduled four weeks after the end of the treatment period for assessment of safety.

Inclusion criteria

- male or female patients, aged 18-70,
- with primary or secondary pulmonary hypertension presenting under consolidated background therapy,
- NYHA functional class III or IV at study entry,
- entry mean pulmonary artery pressure > 30 mmHg at rest.

Patients with secondary pulmonary hypertension could be included if the underlying cause was one of the following: chronic thromboembolic pulmonary hypertension, connective tissue disease with isolated PHH or interstitial pulmonary disease, or drug-associated PHT (e.g. fenfluramine).

Efficacy Findings

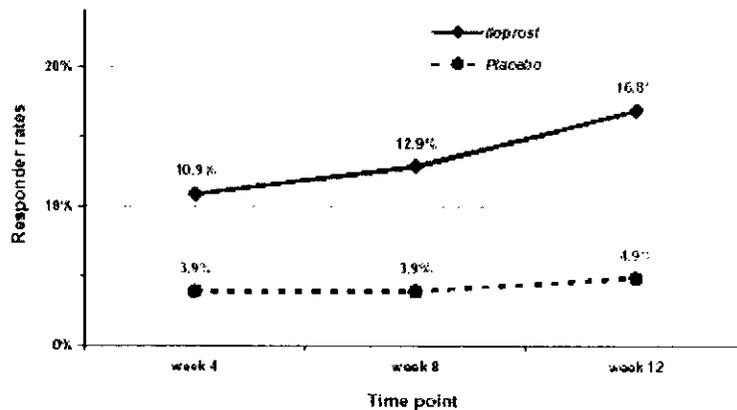
There were 235 patients screened with 201 randomized (101 to iloprost and 102 to placebo). The numbers of subjects completing the study through week 12 were 97 (96.0%) randomized to iloprost and 88 (86.3%) randomized to placebo. Of the 7 iloprost patients who prematurely discontinued study medication before week 12, 3 remained in the study. Of the 18 placebo patients who discontinued study medication, 4 remained in the study.

The overall responder rates for the combined analysis were iloprost 16.8% (17/101) and placebo 4.9% (5/102) with two-side p=0.007.

Table 28: Summary of the primary endpoint and components, statistical analysis – ITT population

Endpoint	Primary analysis	Result	Secondary analyses	Result
combined responder endpoint	stratified Mantel-Haenszel test	treatment: p = 0.007 odds ratio 3.970 [1.466;10.750]	logistic regression model	treatment: p = 0.011 other prognostic factors: n.s.
Walking distance (≥10% improvement)	stratified Mantel-Haenszel test	treatment: p = 0.059		
NYHA class (≥1 class improvement)	stratified Mantel-Haenszel test	treatment: p = 0.032		
Mortality (until week 12)	Fisher's exact test (pooled data)	treatment: p = 0.369		
Deterioration	Fisher's exact test (pooled data)	treatment: p = 0.407		

The figure below shows the percent of responders, by treatment group, at weeks 4, 8 and 12.



The difference in response rate between study groups was evident by the first 4 weeks of treatment (10.9% iloprost vs. 3.9% placebo). This difference continued to increase at the 8 week (12.9% vs. 3.9%) and 12 week (16.8% vs. 4.9%) visits.

The results by strata are shown below.

TT 33: Combined responder criterion by predefined strata – ITT population

Stratum	Iloprost (n = 101)		Placebo (n = 102)	
	Responders	Responders	Responders	Responders
PPH/III	5/34	14.7%	2/36	5.6%
PPH/IV	6/19	31.6%	1/19	5.3%
SPH/III	5/26	19.2%	2/24	8.3%
SPH/IV	1/22	4.5%	0/23	0.0%
All	17/101	16.8%	5/102	4.9%

The iloprost group responded better to treatment compared to the placebo group regardless of stratum.

See individual study report for evaluation of the 6 minute walk test, changes in NYHA classification, changes in dyspnea index, cardiac hemodynamic parameters, and changes in quality of life scales.

Conclusions

The study convincingly showed that patients randomized to iloprost were more likely to improve their walk test by at least 10% over baseline, improve their NYHA classification by at least one stage, not experience a deterioration in their disease status, and remain alive compared to patients randomized to placebo during 12 weeks of treatment.

Study ME98008

Note: the study report was revised by the sponsor because of correction of walking distance, missing data for patient disposition, and drug dosing. Because of the various changes to the report after the results were known, the open-label nature of the study, and the different nebulizer used calling into question the amount of dosing, this was considered to be a safety study. However, the efficacy results are included in this section for completeness. There is no reason to believe that this study contradicts the findings of study ME97218.

Introduction

This was an open-label, multicenter, randomized, parallel-group comparative safety study. A total of 60 clinically stable patients were randomized and treated for 3 months either with iloprost or with any conventional treatment that was deemed to be appropriate for each respective patient (prostanoids and beta-blockers were excluded). All patients were to receive their usual common background therapy. At the end of the 12 week randomization phase, patients were allowed to receive iloprost for up to 2 years.

Patient population

The study population comprised patients with primary or secondary pulmonary hypertension depending upon etiology:

Group A: Primary pulmonary hypertension, comprising the sporadic, familial and post-partum form as well as drug associated (e.g., appetite suppressant drugs), provided there was no clinical manifestation other than pulmonary hypertension.

Group B: Isolated pulmonary hypertension, comprising patients with collagenosis but without involvement of internal organs or clinical manifestation other than pulmonary hypertension.

Group C: Secondary pulmonary hypertension, comprising patients with thromboembolic disease, and pulmonary hypertension secondary to diseases of heart, lung, liver, or other organs. These patients were eligible for study entry only if best available therapy for the underlying disease had been used and pulmonary hypertension was the main limiting factor for exercise tolerance and/or prognosis.

The groups B and C were later pooled into the category secondary pulmonary hypertension (SPH)

Inclusion criteria

Male or female patients, aged 18-70 years, with primary or secondary pulmonary hypertension and a mean pulmonary artery pressure ≥ 30 mmHg (groups A and B) or ≥ 40 mmHg (group C) while resting during appropriate conventional treatment.

NYHA class

The table below shows the number and percent of patients who improved their classification status by at least 1, by treatment group.

TT 12 NYHA class: Improvements during the randomized phase

Based on re-assessed NYHA classes. Figures denote number / percentage of patients who, during the randomized phase, improved by at least one class compared with baseline.

Time point	Iloprost N = 30	Control N = 33
Week 4	8 (26.7%)	3 (9.1%)
Week 8	9 (30.0%)	2 (6.1%)
EOR	6 (20.0%)	2 (6.1%)

EOR=Last examination or data recorded at end of randomized phase, not necessarily equal to actual week 12 but used synonymously in certain listings (other synonyms for EOR include "month 3" and "final" examination of the randomized phase) .

The incidence rate for improvement at EOR (end of randomization phase) was more than 3 times higher in the iloprost group (20.0%) compared to the control group (6.1%). This difference in improvement between the treatment groups was seen by week 4.

Mahler dyspnea index

TT 14 Mahler Dyspnea Index: Focal score and sum of transition scores during randomized phase, descriptive statistics

		Focal score			Sum of transition score Changes to baseline		
		Iloprost	Control	Overall	Iloprost	Control	Overall
Baseline	N	30	33	63	<i>not applicable</i>		
	Mean	4.767	4.758	4.762			
	SD	2.128	1.601	1.855			
	Median	5.500	5.000	5.000			
Month 1	N	26	30	56	26	30	56
	Mean	5.077	5.267	5.179	2.115	-0.200	0.875
	SD	2.448	1.893	2.150	2.369	2.107	2.509
	Median	6.000	5.500	6.000	3.000	0.000	0.000
Month 2	N	23	27	50	23	27	50
	Mean	5.217	5.296	5.260	1.478	-0.667	0.320
	SD	2.173	2.072	2.098	3.058	2.236	2.832
	Median	6.000	6.000	6.000	0.000	0.000	0.000
EOR	N	24	30	54	24	30	54
	Mean	5.000	4.867	4.926	1.125	-1.100	-0.111
	SD	2.228	2.315	2.256	2.437	2.657	2.772
	Median	6.000	5.000	6.000	0.000	0.000	0.000

Focal score ranges from 0 (worst condition) to 12 (best condition).
 Transition score ranges from -9 (least favorable change) to 0 (no change) to 9 (most favorable change).
 Source: Biometrical tables D1.3 (focal score), D1.6 (transition score)

There was a small improvement in the mean focal score for the iloprost group (4.7 at baseline to 5.0 at end of randomization phase). There was little change for the control group.

There was some improvement in the transition score in the iloprost group compared to placebo.

These results were classified according to improved, unchanged, and deteriorated. The incidence rates are shown below, by treatment group.

TT 15 Mahler Dyspnea Index: Focal score and transition score (classified results at EOR)
 Results refer to changes from baseline to EOR. Figures denote number / percentage of patients.

		Iloprost n = 24		Control n = 30		Overall n = 54	
Focal score, classified changes	Improved	10	41.7%	5	16.7%	15	27.8%
	Unchanged	8	33.3%	18	60.0%	26	48.1%
	Deteriorated	6	25.0%	7	23.3%	13	24.1%
Sum of transition score, classified values	Positive	8	33.3%	3	10.0%	11	20.4%
	Zero	14	58.3%	17	56.7%	31	57.4%
	Negative	2	8.3%	10	33.3%	12	22.2%

The results favor iloprost.

6 minute walk

Absolute changes in the mean walk distance at trough at the end of the randomization (EOR) phase are shown below, by treatment group. (T28 shows the same information only with patients who died (n=4, 2 per treatment group) being assigned a walk distance of 0 m). N.B. post-inhalation examination (peak) was

not conducted at baseline, the corresponding pre-inhalation (trough) examination was taken as baseline value for all change-from-baseline analyses of post-inhalation examinations.

T25 Walking distance: absolute changes, descriptive statistics (strict LOCF)

ITT-population

time point	stratum	iloprost				control				overall			
		n	mean	median	sd	n	mean	median	sd	n	mean	median	sd
EOR (before)	PPH	20	23.6	6.5	69.3	20	67.9	53.0	109.9	40	45.7	37.0	93.4
	SPH	10	73.3	31.3	169.1	13	-16.4	0.0	99.8	23	22.6	15.5	138.6
	all strata	30	40.1	27.3	112.2	33	34.7	30.0	112.5	63	37.3	27.5	111.5

T28 Walking distance: absolute changes, descriptive statistics (LOCF with death = 0 m)

ITT-population

time point	stratum	iloprost				control				overall			
		n	mean	median	sd	n	mean	median	sd	n	mean	median	sd
EOR (before)	PPH	20	4.1	6.5	115.6	20	67.9	53.0	109.9	40	36.0	37.0	115.9
	SPH	10	64.9	27.3	173.3	13	-35.6	-10.0	125.5	23	8.1	10.0	153.2
	all strata	30	24.3	20.0	137.6	33	27.1	30.0	125.4	63	25.8	27.0	130.3

In both cases, the mean absolute change was much better for the PPH group receiving control compared to iloprost (67.9 m vs. 4.1 m). On the other hand, the SPH group performed better if they were randomized to iloprost (mean increase 64.9 m) compared to placebo (mean decrease 35.6m). The clinical relevance of these results is unknown.

Mortality

There were 4 deaths, 2 per group.

Responders

A retrospectively defined composite response criterion was applied in order to explore the benefit for the patient: response was defined as:

- an improvement in physical capacity measured by an improvement of the NYHA class,
- by an improvement of the walking distance by at least 10% compared to baseline], and
- the patient still had to be alive at the respective time point.

Patients fulfilling this composite criterion were called "responders".

TT 17 Composite response criterion: Response rates during randomized phase

Figures denote number / percentage of patients with response.

Visit	Time point of measurement relative to inhalation	Iloprost n = 30		Control n = 33		Overall n = 63	
Month 1	after	4	13.3%	0	0.0%	4	6.3%
Month 2	before	7	23.3%	2	6.1%	9	14.3%
EOR	before	4	13.3%	0	0.0%	4	6.3%
	after	4	13.3%	1*	3.0%	5	7.9%

* Assessment after iloprost inhalation.

The trend favors iloprost.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In addition to the studies with the inhaled formulation, review of safety also included studies with the oral and, to a lesser extent, intravenous formulations.

SERIOUS SAFETY

Deaths

Inhaled formulation

Randomization phase

There were 3 deaths (3/129, 2.3%) reported in patients randomized to iloprost and 5 deaths (5/133, 3.6%) in patients randomized to placebo-control during the blinded phase of the 2 clinical trials.

Iloprost deaths

Patient no. 98008-253, a 63-year-old female with secondary pulmonary hypertension (NYHA class IV), was hospitalized because of cardiac decompensation after 2 months of treatment with study drug. The day before the patient died, she was placed on Flolan i.v. infusion in addition to iloprost inhalation. Post-mortem attributed death to right-heart failure with suspected bronchopneumonia.

Patient no. 98008-249, a 62 year-old male with primary pulmonary hypertension (NYHA class III), was randomized to iloprost but "he never received any study medication". He developed purulent bronchitis about 1 week after randomization and died about 1 week later from what was described as right heart failure.

Patient no. 97218-28, a 27-year-old male with secondary pulmonary hypertension (NYHA class IV), was withdrawn from treatment 1 day after start of study drug because of deterioration of his condition. Open-label iloprost (nominal dose of 100 ug/day) was started along with furosemide 60 mg/day. The patient died 2 days later. Cause of death: Acute decompensated cor pulmonale.

In conclusion, only the death of patient #28 could be reasonably linked to iloprost, mostly because of a temporal relationship and a possible hypotensive effect.

Long term phase

Death During the Weeks 13-16 Follow-up Period in ME97218

Five patients died during the open label iloprost follow up treatment (all patients who remained in the study either stayed on iloprost or were switched to iloprost). Two patients (97218-79 and 97218-245) had been randomized to iloprost inhalation and 3 patients (97218-31, 97218-239, and 97218-387) had been randomized to placebo. For 3 of the 5 patients, the code was broken and off-label Ilomedin inhalation was started.

Patient no. 97218-79, a 60-year-old male with thromboembolic PAH (NYHA class III), was randomized to received iloprost. After 94 days of study drug, the patient began to deteriorate clinically. He was

hospitalized and treatment with Lasix and Flolan was begun. The patient died the next day. Post-mortem attributed death to cor pulmonale.

Patient no. 97218-245, a 58-year-old male with secondary pulmonary hypertension (NYHA class IV) resulting from pulmonary fibrosis and rheumatoid arthritis, was randomized to receive iloprost inhalation. After having received 85 days of study drug, the patient was hospitalized with a recurrent chest infection, and was treated with vancomycin and an increased dosage of prednisolone. The patient died from a cardiac arrest after having received off-label Ilomedin for approximately 6 weeks. The death was attributed to bronchopneumonia and pulmonary fibrosis.

Patient no. 97218-31, a 62-year-old female with secondary pulmonary hypertension (NYHA class III), was randomized to placebo. By study Week 12, the patient's condition had worsened, with edema, dyspnea, hypotension, epigastric pressure, cough, hyponatremia because of diuretic therapy, and hyperkalemia. During scheduled catheterization, the patient became somnolent and hypotensive with low hemodynamic cardiac function and atrial tachycardia... She was admitted to the ICU for decompensated cor pulmonale and beginning cardiogenic shock. The patient received 87 days of study drug. The blind was broken and the patient began off-label Ilomedin and i.v. Ilomedin. She died 2 weeks later. Post-mortem attributed death to chronic right-heart failure.

Patient no. 97218-239, a 68-year-old female with SPH (NYHA class III), was randomized to receive placebo. Study drug was discontinued after 53 days and patient withdrew from the randomized phase early due to worsening of right-heart failure. An atrial septostomy was performed, and the patient started off-label Ilomedin. Hypoxemia due to shunting, possibly causing respiratory alkalosis, was reported. The patient died 37 days after starting off-label Ilomedin at week 13. Case of death was given as cardiac arrest.

Patient no. 97218-387, a 71-year-old male with thromboembolic PAH (NYHA class IV), was randomized to receive placebo. After having received 92 days of study drug, the patient was hospitalized for his 12-week screening, and suddenly developed severe hematemesis. Study drug was stopped. The patient went into hemorrhagic shock and was transferred to the ICU, where he was intubated and ventilated due to right-heart failure. The patient developed a ventilator-associated respiratory infection and died 6 days later.

The long term treatment phase for Study 98998 reported 4 deaths on iloprost (after three months of randomized treatment, up to two years of iloprost long term treatment was allowed).

Patient no. 98008/300341 -65, a 35-year-old male with PPH (HIV-associated) received iloprost aerosol. According to a witness, he suffered sudden cardiac arrest (about 15 months after start of iloprost treatment). Resuscitation was unsuccessful. Postmortem was not performed.

Patient no. 98008/300341-302, a 42-year-old male with PPH received treatment with iloprost aerosol for 3 weeks when he developed progressive right heart failure, with increasing ankle edema and ascites. After 1.5 months of treatment with iloprost aerosol, he again developed signs of recurrent right heart failure. The patient was listed for lung transplant. Study medication with iloprost aerosol was discontinued. About 2 months after end of treatment with iloprost aerosol, he was hospitalized for surgery for repair of ureteral stenosis. The day after surgery he received massive transfusion because of hemorrhaging. Progressive right heart failure occurred and he died 2 days after surgery,

Patient no. 98008/300341-602, a 57-year-old male, SPH patient, was randomized to the control therapy. One month later he was hospitalized for severe right ventricular decompensation and started on iloprost. He was discharged but died later of RV decompensation at another hospital. According to information

from the other hospital, the patient stopped study medication iloprost aerosol after 3 weeks of therapy, because of insufficient effect (progressive deterioration).

Patient no. 98008/300341-602, a 48-year-old female, SPH patient, was randomized to the control therapy. She started long term treatment with study medication iloprost aerosol. She was hospitalized after 11 months of therapy with iloprost for worsening dyspnea, edema, and ascites. The patient died of right heart failure with alcoholic liver cirrhosis.

In conclusion, it does not seem likely that iloprost directly contributed to the death of these patients.

Oral

The table below shows the number and percent of deaths in the selected oral studies, by drug group.

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Table 52 Oral Safety Population - Incidence of Deaths^a

Parameter	Statistic	Iloprost (n=2033)	Placebo (n=1128)
Deaths During the Double-Blind Randomized Period, Including Those Within 2 Days After Discontinuation of Study Drug^b			
Patient Deaths	n (%)	21 (1.0%)	20 (1.8%)
Cause of Death	Adverse events	14 (0.7%)	11 (1.0%)
	Other	7 (0.3%)	9 (0.8%)
Day of Death	n	21	20
	Mean ± SD	102.1 ± 77.62	81.4 ± 65.12
	Median (range)	88.0 (4.0-263.0)	76.5 (4.0-220.0)
Deaths during the Double-Blind Randomized Period, Including Those Within 30 Days After Discontinuation of Study Drug^c			
Patient Deaths	n (%)	49 (2.4%)	44 (3.9%)
Cause of Death	Adverse Events	36 (1.8%)	26 (2.3%)
	Other	13 (0.6%)	18 (1.6%)
Day of Death ^d	n	49	44
	Mean ± SD	91.4 ± 76.50	88.0 ± 69.21
	Median (range)	59.0 (4.0-324.0)	69.0 (4.0-310.0)
Deaths occurring during follow-up period (study 94106 excluded) not including those within 30 days of discontinuation of Study drug			
	n (%)	60 (3.0%)	27 (2.4%)
Deaths during the Open-label Period for Study 94106			
Patient Deaths	n (%)	1 (2.8%)	—
Cause of Death	Other	1 (2.8%)	—
Day of Death		119	—

Sources: ISS Table O6.5 05Jun04; ISS Table O6.5.1 07Jun04

^a Data in this table are derived from the Death CRF.

^b That is, deaths within 2 days after the last medication date on the Medication CRF.

^c That is, deaths within 30 days after the last medication date on the Medication CRF.

^d From Day 0, the last day before start of dosing.

Of the reported deaths that occurred either during the trial or within 2 days after study drug discontinuation, 21 (1.0%) were in patients randomized to oral iloprost and 20 (1.8%) were randomized to placebo. The mean number of days patients were receiving iloprost prior to death was 102 with a range of 4-263 days.

Reported deaths occurring either during the trial or within 30 days after discontinuation of the study drug include 49 (2.4%) iloprost patients and 44 (3.9%) of placebo patients.

The table below briefly discusses the 21 oral iloprost patients who died during the randomized period or within 2 days of stopping drug (plus one subject who died while on drug during the open label phase).

Pt#/age/sex	Comments
Study 92045 indication: PAOD stage III/IV	
92045-174/76/M	Received iloprost 200 ug total daily dose for 5 days. On Day 4, episodes of mild hypotension and with progressive anuric. Death on day 7 of uremia.
92045-294/82/F	received a total average daily dose of 287.2 µg for 46 days. Developed severe diarrhea probably induced by iv antibiotics. Died of diabetic decompensation.
92045-373/64/F	Received total average daily dose of 297.7 µg. Severe chest pain followed by sudden death on Day 262 (suspected acute MI).
92045-628/84/F	Received a total average daily dose of 214.3 µg bid. Died on day 7 from bronchopneumonia.
92045-704/72/M	Received a total average daily dose of 100 µg. Died at home from probable acute MI on day 176.
92045-878/71/M	Received total average daily dose, 284.7 µg. Hospitalized on day 7 and day 108 because of pulmonary edema. Sudden death on Day 175 (suspected congestive heart failure).
92045-1111/56/M	Received a total average daily dose of 100 µg bid. Died suddenly of cardiovascular arrest on day 87.
92045-1114/61/M	Received total average daily dose, 100 µg. Notice of sudden death on day 205: last clinic visit day 115.
92045-1250/69/M	Received total average daily dose 114.3 µg. Severe stroke on day 46 followed by death on day 69.
92045-1281/74/M	Received total average daily dose 297.7 µg. treated for 260 days. Transient ischemic attack on day 232. Hospitalized for moderate dyspnea. Sudden death on day 260, Autopsy revealed acute MI.
92045-1309/67/F	Received total average daily dose 294.1 µg. Cardiac arrest on day 100 with unsuccessful resuscitation. Suspected acute MI.
92045-1340/49/M	Received a total average daily dose of 100 µg treatment, 22 days. Prestudy ECG showed signs of myocardial ischemia. Developed severe central chest pain on day 20. ECG changes and laboratory results indicated acute MI. Died of ventricular fibrillation on day 23.
Study 95102 (Indication: Raynaud's syndrome)	
95102-104.541/58/M	Sudden cardiac death on day 57.
95102-302.734/77/F	Sudden death on day 3
95102-502.482/84/F	Randomized to high-dose iloprost (100-150 µg bid). Developed congestive heart failure on day 88 followed by death 1 day later.
95102-1001.727/89/M	Randomized to high-dose iloprost (100-150 µg bid). Pneumonia on day 62 followed by MI. Death on day 67 from sepsis.
95102-1308.727/77/F	Myocardial infarction followed by death on day 59.
95102-1409.481/62/M	Randomized to high-dose iloprost (100-150 µg bid). Sudden death on day 30. Possible MI

95102-1410.532/79/F	Randomized to high-dose iloprost (100-150 µg bid). Died at home on day 181 from sepsis.
95102-1414.018/65/M	Randomized to low-dose (50 µg bid) iloprost. Sudden death on day 159.
95102-1534004/86/M	Died in a motor vehicle accident month 5.
Study 94106 (Indication: PAOD Stage III/IV)	
27/27/F+	Randomized to iloprost 50 µg bid. Died in motor vehicle accident month 4.

+died >3 months after randomization period.

These deaths, occurring mostly in elderly, very sick patients, do not appear to be related to the use of iloprost. There is no indication that there is decreased survival with the use of inhaled or oral iloprost.

Intravenous

There were 5 deaths (4/764, 0.5% iloprost and 1/709, 0.1% placebo) reported in patients who participated in the intravenous iloprost studies (limited to the double-blind, randomized treatment phase). Adding in the 30-day follow-up period, a total of 8 deaths were reported in the iloprost treatment group (8/764, 1.0%) and 12 deaths were reported (12/709, 1.7%) in the placebo treatment group.

During infusion of the 4 iloprost patients who died during treatment, there were reports of confusion and disorientation with and without accompanying hypotension (8598-178, 7527-103, 8425-218, 8427-75). This suggests that at least with the iv formulation, iloprost may be provoking serious hypotension.

Other Serious Adverse Events

Inhalation

The table below shows the serious adverse events reported during the randomization phase for the 2 controlled trials (limited to those individual events reported by at least 2 iloprost patients and with an incidence rate greater for the iloprost group than for the placebo group).

No. and (percent) of patients

Adverse event	Iloprost N=129	Placebo-control N=133	Placebo-control subtracted %
Any event	29 (22.5)	30 (22.6)	-0.1
Cardiovascular-any	16 (12.4)	16 (12.0)	0.4
Syncope	6 (4.7)	0	4.7
Respiratory-any	7 (5.4)	5 (3.8)	1.6
Dyspnea	2 (1.6)	2 (1.5)	0.1
pneumonia	2 (1.6)	0	1.6
Body as a whole-any	10 (7.8)	9 (6.8)	1.0
Lab test abnormal	2 (1.6)	0	1.6
Digestive-any	2 (1.6)	6 (4.5)	-2.9
Metabolic, nutritional-any	1 (0.8)	4 (3.0)	-2.2
Skin, appendages-any	1 (0.8)	0	0.8

14.12

Syncope was not reported as a serious event by the placebo-control group compared to 4.7% reporting rate by the iloprost group. No other event is particularly noteworthy.

Of the 215 patients who were exposed to inhaled iloprost (total inhaled iloprost population), 66 (30.7) reported a serious adverse event. The table below shows the number and percent of patients reporting these events (limited to events reported by at least 2 patients).

Adverse event	Iloprost N=215
Any event	66 (30.7)
Cardiovascular-any	34 (15.8)
Congestive heart failure	17 (7.9)
Syncope	9 (4.2)
Chest pain	2 (0.9)
Supraventric tach	2 (0.9)
Tachycardia	2 (0.9)
Respiratory-any	13 (6.0)
Dyspnea	4 (1.9)
pneumonia	3 (1.4)
sinusitis	2 (0.9)
Body as a whole-any	36 (16.7)
Aggravation reaction	11 (5.1)
Death	7 (3.3)
Surgery	7 (3.3)
No drug rxn	5 (2.3)
Asthenia	3 (1.4)
Infection	3 (1.4)
Accidental injury	2 (0.9)
Back pain	2 (0.9)
Lab test abnormal	2 (0.9)
Digestive-any	5 (2.3)
Nervous-any	3 (1.4)
Metabolic, nutritional-any	9 (4.2)
Peripheral edema	4 (1.9)
Edema	3 (1.4)
Urogenital-any	2 (0.9)
Kidney failure	2 (0.9)
Skin, appendages-any	1 (0.5)

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I4.17

Commonly reported serious events include congestive heart failure (7.9%), aggravation reaction (5.1%), and syncope (4.2%).

Oral

The table below shows the reported serious events in the double blind, randomized trials, limited to those events reported by $\geq 1\%$ of the iloprost patients and reported by a greater percent of iloprost patients compared to placebo patients.

	Iloprost	Placebo
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Adverse event	N=2033	N=1128
Any event	367 (18.1)	218 (19.3)
Cardiovascular-any	126 (6.2)	64 (5.7)
Peripheral gangrene	28 (1.4)	10 (0.9)
Angina pectoris	22 (1.1)	5 (0.4)
Respiratory-any	32 (1.6)	25 (2.2)
Body as a whole-any	208 (10.2)	116 (10.3)
Aggravation reaction	62 (3.0)	32 (2.8)
Infection	37 (1.8)	15 (1.3)
Digestive-any	34 (1.7)	19 (1.7)
Nervous-any	33 (1.6)	10 (0.9)
Metabolic, nutritional-any	28 (1.4)	15 (1.3)
Skin, appendages-any	31 (1.5)	30 (2.7)
Urogenital-any	17 (0.8)	15 (1.3)
Musculoskeletal-any	11 (0.5)	12 (1.1)
Heme and lymph-any	6 (0.3)	7 (0.6)
Special senses-any	6 (0.3)	0
Endocrine-any	3 (0.1)	1 (0.1)

O6.1

None of the events listed in the table seems worrisome.

Intravenous

There were few serious events reported for either the iloprost group or the placebo group and no event was reported by more than 1 patient per treatment group.

Dropouts and Other Significant Adverse Events

Inhalation

There were 6 iloprost patients (4.7%) who withdrew from one of the two randomized studies because of an adverse event (aggravation reaction (3), congestive heart failure, hypotension, syncope, vasodilatation, edema, headache, cough increased: 1 report each). In contrast, the control group had 10 patients (7.5%) who withdrew because of an adverse event (aggravation reaction (3), congestive heart failure (2), sepsis, shock, chest pain, pulmonary embolus, supraventricular tachycardia, tachycardia, hematemesis, nausea, hypoxia, respiratory disorder (1 each)). I4.10

Oral

Selected adverse events ($\geq 0.5\%$ in either treatment group) resulting in drug withdrawal from the oral trials are shown below.

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Table 55 Oral Safety Population - Adverse Events Leading to Withdrawal of Study Drug: Events Reported in $\geq 0.5\%$ of Patients in Either Treatment Cohort

HARTS Body System & Term	Iloprost (n=2033)	Placebo (n=1128)
Overall	526 (25.9%)	147 (13.0%)
Body as a Whole	231 (11.4%)	77 (6.8%)
Pain in extremity	93 (4.6%)	39 (3.5%)
Aggravation reaction	50 (2.5%)	22 (2.0%)
Pain	34 (1.7%)	0
Infection	17 (0.8%)	9 (0.8%)
Asthenia	16 (0.8%)	5 (0.4%)
Abdominal pain	12 (0.6%)	3 (0.3%)
Surgery	9 (0.4%)	2 (0.2%)
Nervous System	219 (10.8%)	23 (2.0%)
Headache	194 (9.5%)	10 (0.9%)
Dizziness	22 (1.1%)	5 (0.4%)
Cardiovascular System	157 (7.7%)	34 (3.0%)
Vasodilatation	75 (3.7%)	0
Peripheral gangrene	19 (0.9%)	8 (0.7%)
Angina pectoris	11 (0.5%)	1 (0.1%)
Myocardial infarct	7 (0.3%)	6 (0.5%)
Digestive System	146 (7.2%)	20 (1.8%)
Nausea	82 (4.0%)	10 (0.9%)
Diarrhea	45 (2.2%)	5 (0.4%)
Vomiting	44 (2.2%)	5 (0.4%)
Musculoskeletal System	74 (3.7%)	7 (0.6%)
Myalgia	13 (0.6%)	0
Skin and Appendages	30 (1.5%)	16 (1.4%)
Skin ulcer	18 (0.9%)	11 (1.0%)
Metabolic & Nutritional Disorders	20 (1.0%)	7 (0.6%)
Respiratory System	13 (0.6%)	9 (0.8%)

Source: ISS Table 15.8 (02Jun04)

Nearly twice the incidence rate of drop outs because of an event occurred in the iloprost group (25.9%) compared to placebo (13%). The events with the largest placebo subtracted rate include headache (8.6%), vasodilatation (3.7%), and nausea (3.1%).

Selected adverse events

hypotension, syncope: inhalation

The number and percent of patients who received inhaled iloprost and reported an event suggestive of low blood pressure[†] are shown below.

Adverse event	Iloprost N=129	Placebo-Control N=133	control subtracted %
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[†] postural hypotension is excluded: more control-placebo patients reported this event compared to iloprost patients

Hypotension	10 (7.8)	6 (4.5)	3.3
Syncope	10 (7.8)	6 (4.5)	3.3

Both of these events were reported 1.7 times as often by iloprost patients compared to the placebo-controls.

Syncope was reported as a serious event by 6 (4.7%) patients who were randomized to inhaled iloprost (n=129) compared to no patients randomized to placebo-control (n=133). None of the other events suggestive of low blood pressure was reported as a serious event. The 6 iloprost patients are discussed below.

Patient no./age/sex	Comments
97218-48/63/F	Ten days after the start of study drug the patient developed syncope thought to be the result of intermittent second degree AV block. Catecholamines were administered and the patient was transferred to a local ICU, where she recovered within 2 days. The patient completed both the 12-week randomized phase and the 4-week follow-up phase of the study, and received a total of 119 days of therapy. She was started on off-label iloprost. After one further occurrence of syncope due to AV block, a cardiac pacemaker was implanted, after which there were no more reports of syncope.
97218-104/66/F	The patient reported two episodes of syncope during the randomized phase and further episodes of syncope during long-term treatment with iloprost inhalation. The first event occurred 6 days after start of drug while experiencing an episode of diarrhea. She was hospitalized and resuscitated. The ECG revealed bradycardia that resolved with 1 mg of atropine i.v. Approximately 7 weeks after the start of study drug, the patient had a vasovagal syncope after standing up abruptly without any exercise. She had taken her last dose of study drug more than 6 hours before the syncopal event. The patient's dose of furosemide was reduced to 25 mg/day as a result of this event. She recovered and received a total of 91 days of study drug during the randomized phase of the study. The patient stayed on drug. She had one further syncopal episode while climbing stairs (a while after last inhalation). The event occurred a long time after the last inhalation. She improved from NYHA class IV to class II and experienced no further episodes of syncope.
97218-258/66/F	Twenty-nine days after starting study drug, the patient developed bloody diarrhea and was hospitalized. A diagnosis of diverticulitis was made. Six days after being discharged from the hospital and while still experiencing bloody diarrhea, the patient collapsed after walking 50 meters during a scheduled exercise tolerance test. The last dose of study medication was 3 hours prior to performing the exercise tolerance test. She was hospitalized overnight. The patient performed the exercise tolerance test the next day without incident 15 minutes after inhaling study drug and was then discharged from the hospital. She completed the study without any further reports of syncope.
97218-260/20/F	Approximately 3 months after the start of study drug, the patient experienced several episodes of syncope while climbing stairs. She was hospitalized for observation and ECG exam; no abnormal findings

	were reported The patient completed the study.
97218-351/22/F	Approximately 5 weeks after the start of study drug, the patient was hospitalized for syncope and hypotension after starting diuretic treatment for right-heart failure. Study drug was discontinued 45 days after the start of the study. The patient started off-label iloprost. She again had right-heart decompensation with new syncopal episodes. The patient was hospitalized, listed for lung transplantation and atrial septostomy, but died before the transplant could be performed.
98008-301/29/F	The patient was hospitalized twice for syncope. Approximately 5.5 weeks after the start of study drug, she experienced an episode of syncope after hyperventilating. The patient had taken a dose of study drug 2 hours before the event. The event occurred after psychological stress, and started with nausea and tinnitus, and then syncope, which lasted for 2-3 minutes. Approximately 1 week later, the patient was hospitalized because of syncope. The diagnosis of hyperventilation as a cause of the syncope was confirmed by a provocation test. No further events were reported. She remained on drug.

There were 6 reports of serious syncopal episode during long term treatment with inhaled iloprost. All patients were into their 3rd month (or more) of iloprost treatment. The majority of these patients remained on iloprost. Most (or all) of the syncopal events occurred a few hours after last drug intake.

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oral

No. and (percent) of patients

Adverse event	Iloprost N=2033	Placebo N=1128	Placebo subtracted %
Dizziness	171 (8.4)	67 (5.9)	2.5
Hypotension	40 (2.0)	9 (0.8)	1.2

O5.1

Events suggestive of low blood pressure were reported somewhat more by iloprost patients

Bleeding tendencies

Inhalation

As with other prostaglandins, there is a hypothetical risk of bleeding with iloprost because of the inhibitory effect on platelet aggregation. There is a theoretical increased risk with the concomitant use of heparin or coumarin-type.

Table 28 Inhaled Safety Population - Intensity of Bleeding Events of Special Interest by Treatment

Severity	All Adverse Events		Serious Adverse Events	
	Iloprost (n=129)	Placebo/Control (n=133)	Iloprost (n=129)	Placebo/Control (n=133)
Overall	18 (14%)	15 (11%)	1 (1%)	2 (2%)

There was a small difference between the incidence rates of reporting bleeding events+ for the 2 treatment groups. Serious bleeding events were rarely reported.

During long-term treatment, 10/123 (8%) of iloprost-treated patients had serious bleeding events: hemoptysis (2 patients), anemia (2), subarachnoid hemorrhage (2), shock followed by death (2), hemorrhage (1) and hematemesis (1). Concomitant administration of anticoagulants was either interrupted or stopped for the following adverse events: hematemesis, hemoptysis, and subarachnoid hemorrhage.

There was no indication of increased bleeding tendencies in the oral studies (Table 63).

Common Adverse Events

Inhalation

The table below shows the adverse events by body system and by individual events during the randomized phase of the 2 clinical trials (limited to those events reported by at least 4 iloprost patients and the incidence rate being greater than 2% in the iloprost group compared to the control group).

No. and (percent) of patients

Adverse event	Iloprost	Placebo-Control	Placebo-Control
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+ includes anemia, epistaxis, hematuria, decreased hemoglobin, ecchymosis, hemorrhage, rectal bleeding, subcutaneous hematoma, eye hemorrhage, hematemesis, hemoptysis, petechia, hypochromic anemia, gum hemorrhage, hypermenorrhea, iron deficiency anemia, and shock.

	N=129	N=133	subtracted %
Any event	114 (88.4)	112 (84.2)	4.2
Cardiovascular-any	73 (56.6)	54 (40.6)	16.0
Vasodilatation+	35 (27.1)	15 (11.3)	15.8
Hypotension	10 (7.8)	6 (4.5)	3.3
Syncope	10 (7.8)	6 (4.5)	3.3
Palpitations	8 (6.2)	5 (3.8)	2.4
Respiratory-any	71 (55.0)	58 (43.6)	11.4
Cough increased	46 (35.7)	31 (23.3)	12.4
Hemoptysis	6 (4.7)	2 (1.5)	3.2
Nervous -any	56 (43.4)	46 (34.6)	8.8
Trismus	16 (12.4)	5 (3.8)	8.6
Headache	32 (24.8)	23 (17.3)	7.5
Insomnia	6 (4.7)	2 (1.5)	3.2
Sleep disorder	5 (3.9)	2 (1.5)	2.4
Body as a whole-any	55 (42.6)	44 (33.1)	9.5
Back pain	9 (7.0)	5 (3.8)	3.2
Flu syndrome	8 (6.2)	5 (3.8)	2.4
Fever	4 (3.1)	1 (0.8)	2.3
Digestive-any	47 (36.4)	46 (34.6)	1.8
nausea	17 (13.2)	10 (7.5)	5.7
Vomiting	6 (4.7)	2 (1.5)	3.2
Tongue pain	5 (3.9)	0	3.9
Metabolic, nutritional-any	42 (32.6)	40 (30.1)	2.5
Gamma-GT increased	6 (4.7)	2 (1.5)	3.2
Alk phos increased	6 (4.7)	1 (0.8)	3.9
Skin, appendages-any	26 (20.2)	14 (10.5)	9.7
Rash	11 (8.5)	6 (4.5)	4.0
Musculoskeletal-any	14 (10.9)	11 (8.3)	2.6
Muscle cramps	7 (5.4)	3 (2.3)	3.1
Special senses-any	14 (10.9)	5 (3.8)	7.1
Conjunctivitis	4 (3.1)	1 (0.8)	2.3
Hemic, lymphatic-any	5 (3.9)	4 (3.0)	0.9
Urogenital-any	5 (3.9)	10 (7.5)	-3.6

14.2

Overall, the incidence rate of reporting adverse events was slightly higher for the iloprost patients (88.4%) compared to their control counterparts (84.2%).

The cardiovascular system had the highest reporting incidence rate for body systems with iloprost patients reporting more events than the controls (56.6% vs. 40.6%). Vasodilation was reported most often by iloprost patients (15.8%+) followed by hypotension (3.3%) and syncope (3.3%). Palpitations also was reported somewhat more frequently in the iloprost group (2.4%).

+ includes: erythema facial and palmar, face rush, facial flush, heart puff, heat puff, heatwaves, hot flushes, red coloured face, red spot upper lip, reddened nose and mouth, reddening of throat, redness around the mouth, redness at knees, warm feeling of lower legs, warm swollen legs.

+ all percents are placebo-control subtracted unless otherwise noted

Events in the respiratory system were reported more often in the iloprost group with cough increased reported rather frequently (12.4 %).

Events in the nervous system reported more often in the iloprost group included trismus (8.6%), headache (7.5%), insomnia (3.2%), and sleep disorder (2.4%).

Other events with a placebo-control subtracted incidence rate \geq 4% include nausea (5.7%) and rash (4%).

Oral formulation

Adverse events (limited to those reported by at least 35 (1.7%) iloprost patients and reported more often by iloprost patients compared to placebo patients) collected during the selected clinical trials using the oral formulation are shown below, by drug group.

No. and (percent) of patients (oral formulation)

Adverse event	Iloprost N=2033	Placebo N=1128	Placebo subtracted %
Any event	1674 (82.3)	825 (73.1)	9.2
Cardiovascular-any	795 (39.1)	250 (22.2)	16.9
Vasodilatation	547 (26.9)	79 (7.0)	19.9
Hypotension	40 (2.0)	9 (0.8)	1.2
<i>Dizziness+</i>	<i>171 (8.4)</i>	<i>67 (5.9)</i>	2.5
Respiratory-any	223 (11.0)	145 (12.9)	-1.9
Nervous -any	1133 (55.7)	318 (28.2)	27.5
Headache	946 (46.5)	186 (16.5)	30.0
Trismus	86 (4.2)	7 (0.6)	3.6
Body as a whole-any	843 (41.5)	397 (35.2)	6.3
<i>Pain in extremity</i>	<i>265 (13.0)</i>	<i>108 (9.6)</i>	3.4
<i>Pain</i>	<i>155 (7.6)</i>	<i>37 (3.3)</i>	4.3
Digestive-any	702 (34.5)	271 (24.0)	10.5
Nausea	352 (17.3)	98 (8.7)	8.6
Vomiting	164 (8.1)	51 (4.5)	3.6
<i>Diarrhea</i>	<i>201 (9.9)</i>	<i>66 (5.9)</i>	4.0
Metabolic, nutritional-any	159 (7.8)	95 (8.4)	-0.6
Skin, appendages-any	216 (10.6)	134 (11.9)	-1.3
Rash	62 (3.0)	19 (1.7)	1.3
Musculoskeletal-any	196 (9.6)	85 (7.5)	2.1
Muscle cramps	35 (1.7)	8 (0.7)	1.0
<i>Myalgia</i>	<i>66 (3.2)</i>	<i>14 (1.2)</i>	2.0
Special senses-any	69 (3.4)	29 (2.6)	0.8
Hemic, lymphatic-any	55 (2.7)	45 (4.0)	-1.3
Urogenital-any	114 (5.6)	69 (6.1)	-0.5

O5.1

Adverse events reported most frequently by oral iloprost patients were generally similar to those reported by patients who received inhaled iloprost and included vasodilatation (19.9%), headache 30.0%, nausea (8.6%), vomiting (3.6%), and trismus (3.6%).

+ adverse events shown in italics are those that were either absent or infrequently reported in the inhaled study database.

IV formulation

The sponsor presented adverse events with the iv formulation from only 1 of 12 studies because of "the lack of a fully manipulable electronic database." Study A990, a US trial in patients with atherosclerotic peripheral vascular disease, was the largest study in the i.v. safety summary (12.2% of the entire pooled summary). The results are shown below (limited to those adverse events reported by at least 4% of patients in either treatment group during the double-blind treatment period of study A990).

Adverse Event	Number (%) of Patients	
	Ilprost (n=93)	Placebo (n=99)
One or more adverse events ^a	85 (91)	53 (54)
Headache	71 (76)	15 (13)
Vasodilatation	55 (59)	9 (9)
Nausea	44 (47)	7 (7)
Pain	30 (32)	11 (11)
Vomiting	21 (23)	5 (5)
Diarrhea	16 (17)	2 (2)
Hypotension	15 (16)	10 (10)
Injection site reaction	13 (14)	2 (2)
Back pain	10 (11)	0 (0)
Abdominal pain	9 (10)	3 (3)
Hypertonia	8 (9)	0 (0)
Nausea and Vomiting	8 (9)	1 (1)
Neck pain	8 (9)	0 (0)
Paresthesia	8 (9)	0 (0)
Injection site edema	7 (8)	7 (7)
Dizziness	6 (6)	8 (8)
Nervousness	6 (6)	4 (4)
Chills	5 (5)	0 (0)
Peripheral edema	5 (5)	3 (3)
Injection site inflammation	5 (5)	0 (0)
Injection site pain	5 (5)	2 (2)
Asthma	4 (4)	0 (0)
Dyspepsia	4 (4)	1 (1)
Dyspnea	4 (4)	1 (1)
Sweating increased	4 (4)	0 (0)

Source: Table, "Number (%) of Patients Reporting Adverse events," Study A990, p. 87

^a More than one adverse events may have been reported for any patient.

The most commonly reported events (headache, vasodilatation, nausea, [nonspecific] pain, vomiting, diarrhea, hypotension) echo what was reported with the oral and inhaled formulations.

Adverse events by dose

Inhalation

There is limited information about the relationship between dose and events. Provided one accepts the conversion factors designed by the sponsor, the following table divides adverse events by dose category.

No. and (percent) of patients

	Iloprost (ug/24 hr)			control N=133
	<30 n=35	30-45 n=58	45 n=36	
Any event	31 (88.6)	50 (86.2)	33 (91.7)	112 (84.2)
Cardiovascular- any	19 (54.3)	30 (51.7)	24 (66.7)	54 (40.6)
Vasodilatation	5 (14.3)	21 (36.2)	9 (25.0)	15 (11.3)
Hypotension	2 (5.7)	4 (6.9)	4 (11.1)	6 (4.5)
Syncope	4 (11.4)	4 (6.9)	2 (5.6)	6 (4.5)
Respiratory-any	17 (48.6)	31 (53.4)	23 (63.9)	58 (43.6)
Cough increased	10 (28.6)	22 (37.9)	14 (38.9)	31 (23.3)
Hemoptysis	2 (5.7)	2 (3.4)	2 (5.6)	2 (1.5)
Nervous -any	8 (22.9)	33 (56.9)	15 (41.7)	46 (34.6)
Trismus	2 (5.7)	9 (15.5)	5 (13.9)	5 (3.8)
Headache	6 (17.1)	17 (29.3)	9 (25.0)	23 (17.3)
Body as a whole- any	13 (37.1)	24 (41.4)	18 (50.0)	44 (33.1)
Digestive-any	11 (31.4)	20 (34.5)	16 (44.4)	46 (34.6)
Metabolic, nutritional-any	11 (31.4)	19 (32.8)	12 (33.3)	40 (30.1)
Alk phos increased	0	3 (5.2)	3 (8.3)	1 (0.8)
Skin, appendages- any	6 (17.1)	9 (15.5)	11 (30.6)	14 (10.5)
Rash	2 (5.7)	2 (3.4)	7 (19.4)	6 (4.5)
Musculoskeletal- any	1 (2.9)	7 (12.1)	6 (16.7)	11 (8.3)
Special senses-any	2 (5.7)	7 (12.1)	5 (13.9)	5 (3.8)
Hemic, lymphatic-any	2 (5.7)	3 (5.2)	0	4 (3.0)
Urogenital-any	4 (11.4)	1 (1.7)	0	10 (7.5)

14.5

The separation between doses is narrow and the sample sizes are small. According to the above table, perhaps vasodilatation, hypotension, cough increased, trismus, headache, and rash are dose related events.

Oral

Dose related: those events that had a higher reporting incidence with higher oral dose (>150 ug) compared to lower dose (<150 ug) suggesting a dose relationship include trismus (6.2% vs. 2.3%) and vasodilatation (33.1% vs. 21.0%). O5.2.

Special Populations

Adverse events by age

Inhalation

The small total sample size in the inhalation safety database make any information about the relationship between age and adverse events difficult to interpret.

Table 20 Inhaled Safety Population - Most Frequently ($\geq 10\%$ of Patients) Reported Adverse Events by Age During the Randomized Phase

HARTS Body System	< 65 Years		≥ 65 Years	
	Iloprost (n=114)	Placebo/Control (n=111)	Iloprost (n=15)	Placebo/Control (n=22)
Overall	99 (87%)	96 (87%)	15 (100%)	16 (73%)
Vasodilatation	30 (26%)	14 (13%)	5 (33%)	1 (5%)
Cough increased	43 (38%)	25 (23%)	3 (20%)	6 (27%)
Headache	28 (25%)	22 (20%)	4 (27%)	1 (5%)
Asthenia	6 (5%)	10 (9%)	3 (20%)	1 (5%)
Nausea	16 (14%)	7 (6%)	1 (7%)	3 (14%)
Diarrhea	10 (9%)	12 (11%)	3 (20%)	0
Trismus	14 (12%)	4 (4%)	2 (13%)	1 (5%)
Upper respiratory infection	11 (10%)	17 (15%)	2 (13%)	2 (9%)
Syncope	8 (7%)	3 (3%)	2 (13%)	3 (14%)
Aggravation reaction	5 (4%)	5 (5%)	2 (13%)	3 (14%)
Congestive heart failure	5 (4%)	9 (8%)	2 (13%)	4 (18%)
Peripheral edema	12 (11%)	17 (15%)	2 (13%)	4 (18%)
Pruritis	3 (3%)	2 (2%)	0	4 (18%)
Vertigo	6 (5%)	11 (10%)	0	1 (5%)

Source: ISS Table 14.6 (02Jun04)

It is not possible to argue that older patients are more (or less) at risk of an adverse event when taking inhaled iloprost.

Oral

Sample sizes are much larger in the safety database using the oral formulation. The table below is placebo subtracted incidence rates by treatment group and age for events reported by $\geq 4\%$ in either treatment or age cohort).

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Table 59 Oral Safety Population- Differences in Proportions, Iloprost Minus Placebo, in Common Adverse Events ($\geq 4\%$ in Either Treatment or Age Cohort) in Patients < 65 Years of Age and Those ≥ 65 Years of Age

Adverse Event	% Difference, Iloprost - Placebo	
	Patients < 65 years ^a	Patients ≥ 65 Years ^b
Headache	27.3% _a	33.8% _a
Dizziness	0.3% _a	5.0% _a
Trismus	5.9% _a	1.1% _a
Pain in extremity	4.1% _a	2.3% _a
Pain	2.3% _a	6.8% _a
Infection	0.2% _a	0.1% _a
Asthenia	3.9% _a	0.1% _a
Aggravation reaction	-1.2% _a	1.3% _a
Abdominal pain	1.2% _a	1.4% _a
Flu syndrome	-1.0% _a	-0.9% _a
Surgery	-1.0% _a	0.1% _a
Vasodilatation	21.0% _a	18.7% _a
Hypertension	0.5% _a	-1.8% _a
Nausea	6.7% _a	10.7% _a
Diarrhea	3.0% _a	5.0% _a
Vomiting	1.9% _a	5.4% _a
Constipation	-0.5% _a	-0.3% _a
Dyspnea	0.6% _a	-0.4% _a
Skin ulcer	-0.9% _a	-1.6% _a
Peripheral edema	-1.1	-1.2% _a

Source: ISS Table O5.3.2 02.fun04

^a n = 1726 (1092 iloprost, 634 placebo)

^b n = 1435 (941 iloprost, 494 placebo)

Events with sizable differences between older and younger patients suggestive of an age relationship include headache, dizziness, pain, nausea and vomiting. Any conclusions, however, would have to be verified with a clinical study.

Adverse events by gender

Inhalation

The table below shows frequently reported events ($\geq 10\%$ of patients) by gender and treatment group.

**Table 21 Inhaled Safety Population - Most Frequently ($\geq 10\%$ of Patients)
Reported Adverse Events by Gender During the Randomized Phase**

HARTS Body System	Male		Female	
	Iloprost (n=38)	Placebo/Control (n=46)	Iloprost (n=91)	Placebo/Control (n=87)
Overall	32 (84%)	40 (87%)	82 (90%)	72 (83%)
Cough increased	11 (29%)	8 (17%)	35 (39%)	23 (26%)
Vasodilatation	11 (29%)	5 (11%)	24 (26%)	10 (12%)
Headache	8 (21%)	4 (9%)	24 (26%)	19 (22%)
Trismus	7 (18%)	0	9 (10%)	5 (6%)
Nausea	5 (13%)	1 (2%)	12 (13%)	9 (10%)
Diarrhea	5 (13%)	5 (11%)	8 (9%)	7 (8%)
Hypotension	4 (11%)	2 (4%)	6 (7%)	4 (5%)
Aggravation reaction	4 (11%)	2 (4%)	3 (3%)	6 (7%)
Edema	4 (11%)	4 (9%)	6 (7%)	6 (7%)
Rash	4 (11%)	3 (7%)	7 (8%)	3 (3%)
Peripheral edema	3 (8%)	8 (17%)	11 (12%)	13 (15%)
Syncope	0	4 (9%)	10 (11%)	2 (2%)
Upper respiratory infection	3 (8%)	6 (13%)	10 (11%)	13 (15%)
Vertigo	3 (8%)	5 (11%)	3 (3%)	7 (8%)
Congestive Heart failure	1 (3%)	6 (13%)	0 (7%)	7 (8%)
Asthenia	1 (3%)	2 (4%)	8 (9%)	9 (10%)

Source: ISS Table 14.6.02Jun04

This data base is too small to attempt to draw conclusions about the relationship between iloprost and gender.

Oral

The table below shows the placebo subtracted incidence rates of adverse events (limited to those reported by $\geq 4\%$ in either treatment or gender cohort).

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Table 60 Oral Safety Population Differences in Proportions, Iloprost Minus Placebo, in Incidence of Common Adverse Events ($\geq 4\%$ in Either Treatment or Gender Cohort) in Male or Female Patients

Adverse Event	% Difference, Iloprost – Placebo	
	Males ^a	Females ^b
Headache	26.5%	35.6%
Dizziness	2.8%	2.2%
Trismus	3.4%	3.8%
Pain in extremity	3.0%	3.8%
Pain	5.5%	2.9%
Infection	0.1%	0.5%
Asthenia	0.5%	4.8%
Aggravation reaction	-1.5%	1.8%
Abdominal pain	1.4%	1.1%
Flu syndrome	-1.5%	-0.3%
Surgery	-0.7%	-0.2%
Vasodilatation	17.9%	23.1%
Nausea	7.1%	11.5%
Diarrhea	3.8%	4.5%
Vomiting	2.1%	5.7%
Dyspepsia	1.2%	0.1%
Skin ulcer	-1.8%	-0.2%
Myalgia	1.4%	2.8%
Peripheral edema	-2.3	0.1%
Fever	0.9%	-1.9%
Cough increased	-2.3%	0.4%

Source: ISS Table O5.3 1 02Jun04

^a n = 1813 (1188 iloprost, 625 placebo)

^b n = 1348 (845 iloprost, 503 placebo)

According to the above table, females randomized to oral iloprost had a somewhat greater tendency to report headache, asthenia, vasodilatation, nausea and vomiting compared to their male counterparts.

Adverse Events by Race

Oral

Since 94% of the 3144 study patients were white, further investigation into a relationship between race and events was not done.

Laboratory Findings

Inhalation

There were no reports of a patient who received inhaled iloprost and discontinued study medication because of an abnormal laboratory value.

Means

Mean values at baseline and weeks 4, 8, and 12 for selected parameters are shown below (studies ME98008 and ME97218).

Table 31 Inhaled Safety Population - Summary Statistics for Selected Chemistry Assays During the Randomized Phase

Assay	Mean \pm Standard Deviation				Upper Limit of Normal ^a	
	Baseline	Week 4	Week 8	Week 12	Female	Male
Liver Function Tests						
ALT (U/L)					17.0 - 19.0	22.0 - 23.0
Iloprost	15.7 \pm 12.3	14.6 \pm 15.4	14.7 \pm 11.8	14.8 \pm 17.5		
Placebo/Control	14.4 \pm 8.5	13.7 \pm 9.2	13.0 \pm 8.3	13.8 \pm 11.7		
AST (U/L)					15.0 - 18.0	18.0 - 19.0
Iloprost	13.1 \pm 5.6	12.7 \pm 5.5	13.0 \pm 4.9	13.2 \pm 7.8		
Placebo/Control	12.8 \pm 6.1	12.9 \pm 5.9	13.3 \pm 7.1	13.7 \pm 11.6		
Alk. Phosphatase (U/L)					170.0	170.0 - 175.0
Iloprost	154.1 \pm 85.2	164.1 \pm 80.2	167.1 \pm 87.2	164.6 \pm 88.7		
Placebo/Control	150.5 \pm 68.6	160.4 \pm 70.6	161.6 \pm 73.5	156.9 \pm 73.7		
Bilirubin (μ mol/L)					17.1 - 18.8	17.1 - 18.8
Iloprost	16.4 \pm 11.9	14.7 \pm 9.7	14.5 \pm 9.1	18.0 \pm 11.2		
Placebo/Control	15.7 \pm 13.4	14.9 \pm 14.4	15.9 \pm 17.7	16.9 \pm 12.3		
Gamma - GT (U/L)					18.0	28.0
Iloprost	60.4 \pm 64.1	61.1 \pm 66.1	63.3 \pm 66.9	65.6 \pm 72.6		
Placebo/Control	51.1 \pm 49.9	52.5 \pm 50.1	51.8 \pm 48.1	55.7 \pm 55.3		
Renal Function Test						
Creatinine (μ mol/L)					79.6 - 97.2	97.2 - 114.9
Iloprost	93.1 \pm 25.8	94.4 \pm 25.3	94.9 \pm 23.3	91.6 \pm 27.5		
Placebo/Control	95.0 \pm 24.8	97.9 \pm 25.1	97.9 \pm 26.4	94.1 \pm 25.2		

Table 31 Inhaled Safety Population - Summary Statistics for Selected Chemistry Assays During the Randomized Phase (Continued)

Assay	Mean ± Standard Deviation				Upper Limit of Normal ^a	
	Baseline	Week 4	Week 8	Week 12	Female	Male
Liver Function Tests						
Creatine Kinase (U/L)					700	800
Iloprost	24.8 ± 12.0	29.5 ± 16.6	32.5 ± 26.1	30.0 ± 18.1		
Placebo/Control	27.8 ± 28.75	32.0 ± 31.4	36.8 ± 33.2	31.7 ± 31.1		
LDH (U/L)					2400	2400
Iloprost	215.5 ± 68.3	230.6 ± 62.2	250.4 ± 64.2	232.5 ± 68.7		
Placebo/Control	203.2 ± 54.5	225.6 ± 73.2	213.6 ± 52.9	223.5 ± 78.7		

Source: ISS Table 16.1 03Jun04

^a Normal ranges usually differed between the two studies. The upper limit of normal for each study (98008 followed by 97218) is displayed by gender.

Table 32 Inhaled Safety Population - Summary Statistics for Selected Hematology Assays

	Mean ± Standard Error				Lower Limit of Normal	
	Baseline	Week 4	Week 8	Week 12	Female	Male
Hematocrit (L/L)					0.35	0.40
Iloprost	0.45 ± 0.05	0.46 ± 0.05	0.46 ± 0.05	0.46 ± 0.05		
Placebo/Control	0.45 ± 0.06	0.46 ± 0.06	0.47 ± 0.06	0.46 ± 0.06		
Hemoglobin (g/L)					12.0	14.0
Iloprost	14.8 ± 1.7	15.0 ± 1.6	15.2 ± 1.6	14.8 ± 1.7		
Placebo/Control	14.6 ± 2.0	14.8 ± 1.9	15.0 ± 1.9	14.7 ± 1.9		
Leukocytes (10⁹/L)					4.0	4.0
Iloprost	7.4 ± 2.1	7.8 ± 2.1	7.9 ± 2.3	7.5 ± 2.2		
Placebo/Control	7.6 ± 2.3	8.3 ± 2.5	7.9 ± 2.3	7.8 ± 2.4		
Platelets (10⁹/L)					140	140
Iloprost	230.0 ± 71.4	236.5 ± 70.2	234.2 ± 72.7	226.6 ± 72.1		
Placebo/Control	234.2 ± 84.7	241.6 ± 80.4	233.1 ± 81.3	224.9 ± 82.3		

Source: ISS Table 16.1 03Jun2004

None of the parameters revealed an abnormal increase or decrease throughout 12 weeks of treatment. Only LDH had means going above upper limit of normal (week 8); it was reversed by week 12.

Shift tables

Selected values from the laboratory shift table with baseline and maximum post-baseline values by treatment group are shown below.

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parameter	Low or normal at baseline and high at post baseline	
	Iloprost N=129*	Control-placebo N=133*
Liver function tests		
ALAT	16 (12.4)	14 (10.5)
ASAT	19 (14.7)	17 (12.8)
bilirubin	18 (14.0)	17 (12.8)
gamma GT	7 (5.4)	10 (7.5)
LDH	7 (5.4)	8 (6.0)
Hematology		
leucocytes	29 (22.5)	27 (20.3)
platelets	2 (1.6)	1 (0.8)
Other		
creatinine	23 (17.8)	29 (21.8)
potassium	19 (14.7)	12 (9.0)

parameter	high or normal at baseline and low at post baseline	
	Iloprost N=129*	Control-placebo N=133*
potassium	7 (5.4)	4 (3.0)
hematocrit	1 (0.8)	1 (0.8)
hemoglobin	5 (3.9)	9 (6.8)
leucocytes	1 (0.8)	3 (2.3)
platelets	7 (5.4)	10 (7.5)

16.2

* not all patients had all values

There are only small differences between the percent of iloprost patients and placebo patients with abnormal results.

The table below shows the incidence of substantially abnormal laboratory values (selected parameters) measured post baseline, by treatment group.

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* not all patients had all values

* not all patients had all values

Lab Test	Criterion	Variable	Iloprost (N=129)	Placebo+Control Combined (N=133)
CHEMISTRY				
Overall (>3*ULN)	Overall	N(%) abnormal	3 (2.3%)	7 (5.4%)
ALAT/GPT (U/l)	>2 * ULN	N	127	129
		N(%) abnormal	4 (3.1%)	3 (2.3%)
	>3 * ULN	N	127	129
		N(%) abnormal	2 (1.6%)	2 (1.6%)
>5 * ULN	N	127	129	
	N(%) abnormal	2 (1.6%)	1 (0.8%)	
>8 * ULN	N	127	129	
	N(%) abnormal	1 (0.8%)	0 (0.0%)	
ASAT/GOT (U/l)	>2 * ULN	N	127	129
		N(%) abnormal	2 (1.6%)	4 (3.1%)
	>3 * ULN	N	127	129
		N(%) abnormal	2 (1.6%)	3 (2.3%)
>5 * ULN	N	127	129	
	N(%) abnormal	1 (0.8%)	1 (0.8%)	
Alk.Phosphatase (U/l)	>2 * ULN	N	127	129
		N(%) abnormal	4 (3.1%)	5 (3.9%)
	>3 * ULN	N	127	129
		N(%) abnormal	1 (0.8%)	0 (0.0%)
>5 * ULN	N	127	129	
	N(%) abnormal	0 (0.0%)	0 (0.0%)	
>8 * ULN	N	127	129	
	N(%) abnormal	0 (0.0%)	0 (0.0%)	
<hr/>				
Lab Test	Criterion	Variable	Iloprost (N=129)	Placebo+Control Combined (N=133)
Bilirubin-total (umol/l)	>2 * ULN	N	127	129
		N(%) abnormal	11 (8.7%)	11 (8.5%)
	>3 * ULN	N	127	129
		N(%) abnormal	0 (0.0%)	4 (3.1%)
	>5 * ULN	N	127	129
N(%) abnormal	0 (0.0%)	2 (1.6%)		
>8 * ULN	N	127	129	
	N(%) abnormal	0 (0.0%)	0 (0.0%)	
HEMATOLOGY				
Overall	Overall	N(%) abnormal	7 (5.4%)	5 (3.9%)
Neutrophils (%)	<0.75 * LLN	N	0	0
		N(%) abnormal	0 (0%)	0 (0%)
Hemoglobin (g/l)	<0.75 * LLN	N	127	129
		N(%) abnormal	2 (1.6%)	2 (1.6%)
Hematocrit (l/l)	<0.75 * LLN	N	100	98
		N(%) abnormal	0 (0.0%)	1 (1.0%)
Platelets (10 ⁹ /l)	<0.75 * LLN	N	127	129
		N(%) abnormal	5 (3.9%)	3 (2.3%)

I6.3

There are uncommon, sporadic changes similar in both treatment groups.

Liver function

There were 3 iloprost patients with abnormally high ($\geq 3x$ ULN) liver function test (s)

Table 35 Inhaled Safety Population - Iloprost-treated Patients with Liver Function Tests $\geq 3 \times$ ULN

Study	Pt. No.	Age/Gender/Race	Lab Test	Baseline	Week 4	Week 8	Week 12	ULN	Sponsor Comments
97218	62	48/F/C	<i>ALT (U/L)</i>	8	22	24	146	19	<i>Probably heparin-induced allergic reaction at injection site</i>
			<i>AST (U/L)</i>	9	14	13	81	15	
			<i>Bilirubin (μmol/l)</i>	12.0	6.8	6.8	6.8	18.8	
			<i>Alk phos (U/L)</i>	149	226	307	348	170	
97218	237	61/F/C	ALT (U/L)	12	10	19	15	19	
			AST (U/L)	15	13	19	19	15	
			Bilirubin (μ mol/l)	22.2	22.2	22.2	22.2	18.8	
			<i>Alk phos (U/L)</i>	668	593	774	706	170	<i>Alk phos level compatible with hepatic distension</i>
98008	122	46/F/C	<i>ALT (U/L)</i>	106	173	124	139	17	<i>Chronic hepatitis of unknown origin</i>
			<i>AST (U/L)</i>	36	55	42	44	18	
			<i>Bilirubin (μmol/L)</i>	15.4	6.8	13.7	20.5	17.1	
			<i>Alk phos (U/L)</i>	80	99	77	68	170	

Source: ISSI Listing 111.1.03Jun04
 Note: italics represents $\geq 3 \times$ ULN

Patient no. 97218-62 developed a “heparin-induced allergy.” By the Week 16 follow-up visit, the ALT and AST levels had returned to within the normal range.

Patient no. 97218-237 had an elevated level of alkaline phosphatase (668 U/L) at baseline (consistent with hepatic congestion), persisted throughout the study and remained elevated at Week 16 (549 U/L).

Patient no. 98008-122 had a history of hepatitis of unspecified etiology. The patient’s ALT remained elevated (ALT 160 U/L and AST 54 U/L) despite continued iloprost treatment.

Kidney function

There were 4 iloprost and 9 placebo-control patients with elevated serum creatinine ($> 1.5 \times$ ULN) during the trial. All had baseline creatinine either at or greater than the upper limit of normal.

Patient no. 97218-79 deteriorated while receiving iloprost and was discontinued from study drug. The patient was switched to Flolan i.v. and died the next day. The cause of death was cor pulmonale with congested liver, spleen, and kidneys.

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Table 36 Inhaled Safety Population - Iloprost-treated Patients with Elevated Creatinine Levels (> 1.5 x ULN) During the Randomized Phase

Study	Pt. No.	Age/Gender/Race	Lab Test	Baseline	Week 4	Week 8	Week 12	ULN	Sponsor Comments
97218	79	59/M/C	Creatinine	123.8	114.9	132.6	194.5	123.8	Creatinine value at Week 12 is > 1.5 x ULN.
97218	135	68/F/C	Creatinine	132.6	159.1	150.3	132.6	97.2	History of chronic renal failure. Creatinine values at Weeks 4 and 8 are > 1.5 x ULN.
97218	238	66/F/C	Creatinine	194.5	159.1	176.8	203.3	97.2	Creatinine values at Week 4 and 8 are > 1.5 x ULN, and at Weeks 0 and 12 are > 2 x ULN.
97218	258	66/F/C	Creatinine	150.3	150.3	132.6	194.5	97.2	Creatinine values at Weeks 0, 4, and 8 are > 1.5 x ULN, and at Week 12 is > 2x ULN.

Source: ISS Listing 1111_03Jun04

Patient no. 97218-135 had a history of chronic renal failure. The patient's creatinine was elevated at baseline and remained elevated throughout the randomized and follow-up phases of the study.

Patient no. 97218-238 entered the study with a serum creatinine level that was elevated (194.5 µmol/L). Her creatinine level remained elevated throughout the randomized phase of the study. At the Week-16 follow-up visit, creatinine was 159.1 µmol/L.

Patient no. 97218-258 had an elevated creatinine level that remained elevated throughout the study. The investigator noted that this patient's elevated creatinine was consistent with long-standing renal dysfunction.

Hematology

There were 7 iloprost patients had substantially abnormal hemoglobin, hematocrit, or platelets at baseline that remained low throughout the study.

Table 37 Inhaled Safety Population - Iloprost-treated Patients with Substantially Abnormal Hematocrit, Hemoglobin, or Platelets

Study	Pt No	Age/Gender/Race	Lab Test	Baseline	Week 4	Week 8	Week 12	LLN
ME97218	3	52/F/C	Platelets	86	98	107	85	140
ME97218	79	59/M/C	Hemoglobin	9.5	9.6	10.7	9.3	14.0
ME97218	126	42/M/C	Platelets	107	92	113	105	140
ME97218	178	53/M/C	Platelets	102	115	101	90	140
ME97218	310	57/F/C	Platelets	100	106	106	82	140
ME97218	444	26/M/C	Platelets	107	97	83	101	140
ME98008	601	30/M/C	Hemoglobin	11.7	10.5	N/A	9.9	14.0

Oral

The table below shows the number and percent of patients on oral iloprost or placebo and had a substantially abnormal liver test.

Lab Panel	Lab Test	Criterion	Variable	Iloprost (N=2033)	Placebo (N=1126)	
Chemistry	SGPT (ALAT) (nkat/l)	>2*ULN	N (%) abnormal	1794 41 (2.3%)	990 17 (1.7%)	
		>3*ULN	N (%) abnormal	1794 15 (0.8%)	990 9 (0.0%)	
		>5*ULN	N (%) abnormal	1794 6 (0.3%)	990 3 (0.3%)	
		>8*ULN	N (%) abnormal	1794 3 (0.2%)	990 0 (0.0%)	
		SGOT (ASAT) (nkat/l)	>2*ULN	N (%) abnormal	1795 30 (1.7%)	986 12 (1.2%)
			>3*ULN	N (%) abnormal	1795 9 (0.5%)	986 3 (0.3%)
	>5*ULN		N (%) abnormal	1795 3 (0.2%)	986 0 (0.0%)	
	>8*ULN		N (%) abnormal	1795 0 (0.0%)	986 0 (0.0%)	
	alkaline phosphatase (nkat/l)		>2*ULN	N (%) abnormal	1800 57 (3.2%)	985 32 (3.2%)
			>3*ULN	N (%) abnormal	1800 17 (0.9%)	985 15 (1.5%)
		>5*ULN	N (%) abnormal	1800 9 (0.5%)	985 9 (0.9%)	
		>8*ULN	N (%) abnormal	1800 4 (0.2%)	985 2 (0.2%)	
		total bilirubin (umol/l)	>2*ULN	N (%) abnormal	1794 2 (0.1%)	991 2 (0.2%)
			>3*ULN	N (%) abnormal	1794 1 (0.1%)	991 0 (0.0%)
	>5*ULN		N (%) abnormal	1794 0 (0.0%)	991 0 (0.0%)	
	>8*ULN		N (%) abnormal	1794 0 (0.0%)	991 0 (0.0%)	
	Patients with at least one >3*ULN Abnormal Result			35	23	

08.2

There were small differences between treatment groups regarding the incidence rates of one or more substantially abnormal liver test.

There were 8 oral iloprost patients who had at least one substantially abnormal laboratory value (AST and/or ALT > 5 x ULN or bilirubin >3 x ULN. These patients are briefly discussed below.

Patient no. 10706-616031, a 76-year-old male with normal SGOT and SGPT values recorded 2 weeks before treatment. Both values were > 5 x ULN on the Week 13. Bilirubin remained within the normal range. Results of a subsequent test at Week 27 were within the normal range for both SGOT and SGPT.

Patient no. 91116-314, a 38-year-old male had mildly elevated SGOT/SGPT at start of treatment. At Week 5, levels of both enzymes were within the normal range; Week 9 SGOT rose to 7.9 x ULN with normal SGPT. Iloprost administration was stopped immediately. By Week 20 both values returned to normal. Bilirubin remained within the normal range.

Patient no. 92045-177, a 71-year-old female had a marginally elevated SGOT and normal SGPT. At Week 4, about 3 weeks after iloprost was discontinued, SGOT remained normal, but SGPT rose to 9.3 x ULN. Levels were normal when measured at Weeks 12, 25, and 53. Bilirubin remained normal.

Patient no. 95102-502731, an 84-year-old female had normal SGOT and SGPT values. Values were elevated at Week 6 (SGOT 4.3 x ULN and SGPT 8.3 x ULN). During this time she was hospitalized for unstable angina pectoris congestive heart failure. She recovered and remained on iloprost. Subsequently, all values for hepatic enzymes were within the normal range. Bilirubin remained normal.

Patient no. 95102-903261, a 44-year-old male had mildly elevated SGOT and SGPT levels. At Week 6 the values were 7.3 and 11.0 x ULN, respectively. Iloprost was discontinued the following day. At Week 10 SGOT and SGPT remained high, but dropped to near normal in subsequently weeks. Bilirubin values were in the normal range at all tests.

Patient no. 95102-1103266, a 64-year-old female had normal liver enzymes until Week 22, when her SGOT rose to 3.6 x ULN and her SGPT rose to 5.5 x ULN. Bilirubin levels remained within the normal range at all tests. The patient withdrew from the study at this time.

Patient no. 95102-1403493, an 85-year-old male had normal SGOT but slightly elevated SGPT at baseline. At Week 1, SGPT had risen to 5.2 x ULN, while SGOT was 2.8 x ULN. Subsequently, after discontinuation of iloprost values were near normal. Bilirubin remained normal.

Patient no. 95102-1417501, an 81-year-old male had normal baseline SGOT, SGPT, and bilirubin. At Week 25, about a week after stopping iloprost, his SGOT was 3.2 x ULN, SGPT was 2.4 x ULN, and total bilirubin was 4.3 x ULN with an elevated alkaline phosphatase 2.6x ULN. He was hospitalized for cholelithiasis and prostate carcinoma a short time later.

It is likely that there are a small number of patients who develop elevated liver enzymes with the intake of (oral) iloprost. There were no signs of frank liver failure associated with the use of iloprost. It is expected that by withdrawing patients from iloprost will correct any drug associated elevations of liver enzymes.

Hematology

The table below shows the number and percent of patients on oral iloprost or placebo and had a substantially hematology test.

Lab Panel	Lab Test	Criterion	Variable	Iloprost (N=2033)	Placebo (N=1128)
Hematology	neutrophils (1/1)	<0.5*LLN	N N (%) abnormal	863 0(0.0%)	423 1(0.2%)
	haemoglobin (amol/l)		N	1806	997
Hematology	haemoglobin (mmol/l)	<0.75*LLN	N (%) abnormal	64(3.5%)	32(3.2%)
	haematocrit (l/l)	<0.75*LLN	N (%) abnormal	40(2.2%)	22(2.2%)
	platelets (10 ⁹ /l)	<0.75*LLN	N (%) abnormal	1785 14(0.8%)	988 10(1.0%)
Patients with at least one Abnormal Result				90	47

O8.2

As with the other tests, there were only small differences between treatment groups regarding the incidence rates of one or more substantially hematology test.

Renal function

The table below shows the number and percent of patients with baseline creatinine values either ≤ 1.5 x ULN or >1.5 x ULN and had a maximum post baseline value either normal or abnormal (up to > 8 x ULN).

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Treatment	Unit	Baseline Level	Maximum Post Baseline Value						Total
			<=1.5*ULN	>1.5*ULN	>1.5*ULN - 3*ULN	>3*ULN - 5*ULN	>5*ULN - 8*ULN	>8*ULN	
Iloprost (n=2033)	umol/l	<=1.5*ULN > 1.5*ULN	1397 (73.3%) 1 (0.1%)	298 (15.7%) 7 (0.4%)	31 (1.6%) 26 (1.4%)	3 (0.2%) 3 (0.2%)	1 (0.1%) 0 (0.0%)	0 (0.0%) 0 (0.0%)	1730 (91.0%) 37 (1.9%)
Placebo (n=1126)	umol/l	<=1.5*ULN > 1.5*ULN	760 (74.2%) 2 (0.2%)	174 (17.4%) 2 (0.2%)	28 (2.7%) 11 (1.1%)	0 (0.0%) 0 (0.0%)	1 (0.1%) 0 (0.0%)	1 (0.1%) 0 (0.0%)	968 (94.5%) 15 (1.5%)

No iloprost patient and 1 placebo patient had a post baseline creatinine value > 8 x ULN. The differences between the groups are minor.

Patients with creatinine values (> 3 x ULN) during an oral iloprost studies are discussed briefly below.

Patient no. 92045-174, a 76-year-old male had normal creatinine and BUN values at baseline. On Day 4, he had episodes of mild hypotension and became progressively anuric with an elevated creatinine level. Iloprost, atenolol, and morphine were stopped. The patient became progressively uremic and hyperkalemia of 7.6 mmol/L. The patient died on Day 7 of uremia despite dialysis.

Patient no. 92045-631, a 79-year-old male with moderately elevated creatinine levels before starting iloprost. Creatinine levels continued to increase, he suffered from a myocardial infarction. Study medication was stopped.

Patient no. 92045-1115, a 77-year-old male. Iloprost was discontinued on Day 28 because of an ongoing low hemoglobin level and an increase in pre-existing signs of renal impairment.

Patient no. 95102-902266, a 76-year-old female was discontinued from study drug because of diarrhea and dizziness. Thirty-three days after the last iloprost infusion the patient went into renal failure.

Patient no. 95102-902511, a 56-year-old male had normal creatinine values at baseline but at Week 13 his creatinine level rose to 4.0 x ULN. Iloprost was continued and the creatinine level returned to near normal.

Patient no. 95102-902769, a 50-year-old male had normal creatinine values at baseline, but at Week 9 his creatinine level rose to 3.3 x ULN. Subsequently, while he was still on iloprost, his creatinine level returned to the normal range.

Patient no. 95102-1531011, a 52-year-old male had unknown baseline creatinine values. He had an elevated creatinine level (2.7 x ULN) at Week 2. At Week 13 his creatinine level doubled to 4.3 x ULN. Continued iloprost.

It is unlikely that (oral) iloprost is a major contributor to kidney insufficiency.

Vital Signs and Cardiac Hemodynamics

Vital signs

There was evidence of a small blood pressure decrease when examining the blood pressure results from the inhalation studies (mean changes in blood pressure[@] from baseline at week 12 were -2.4/-2.8 mmHg for iloprost and -1.4/+1.0 mmHg in the placebo-control). Judging from the adverse events reports, a (short lived) vascular effect of iloprost is likely. The majority of these events, however, rarely resulted in drop out or a serious event. However, very ill patients are usually susceptible to decreases in blood pressure as was intimated by the events leading up to the death of patient #97218-28.+

[@]measured pre and post inhalation

+ Investigator reports: A 27 year old male patient enrolled in study 97218 received iloprost aerosol in the indication primary pulmonary hypertension (NYHA IV). Patient was withdrawn from treatment after second dose of study drug. Deterioration despite begin of iloprost inhalation. Despite severe illness, the patient was included in the study. The patient deteriorated after 2 inhalations on the first day of treatment. The study medication was discontinued. Two events were reported: blood pressure decrease of moderate intensity, decrease in 6-min walking distance of severe intensity. Off-label iloprost therapy was started. After a first improvement of the patient's

Heart rate increased[^] (mean change from baseline 5-7 bpm) in subjects taking compared to placebo (3 bpm) and the reporting of palpitations in the inhalation studies was slightly higher in iloprost group (2.4% placebo-control subtracted).

Oral studies

There were small changes in heart rate (1.1 bpm iloprost and 0.7 bpm placebo), diastolic blood pressure (-1.6 mmHg iloprost and -0.6 mmHg placebo), and systolic blood pressure (-3.3 mmHg iloprost and -1.9 mmHg placebo) in the combined oral trials (Table O7.1).

Cardiac hemodynamics

Pharmacokinetic/pharmacokinetic inhalation study ME98051

This was a randomized, open-label, multicenter, crossover study of hemodynamic effects and pharmacokinetics in patients with primary or secondary pulmonary hypertension following one short period of inhalation of an iloprost aerosol, for the purpose of assessing the comparability of three distinct nebulizing devices.

Pharmacodynamic effects: Hemodynamic variables of pulmonary circulation obtained with right heart catheterization

Target dose: 5 µg of iloprost at mouthpiece with approximately 9-min. to 12-min. inhalation per nebulizer and a 2-hour washout between inhalations (maximum of 3 successive nebulizer tests per patient).

The figure below shows the mean serum iloprost concentration vs time with the 3 different nebulizers.

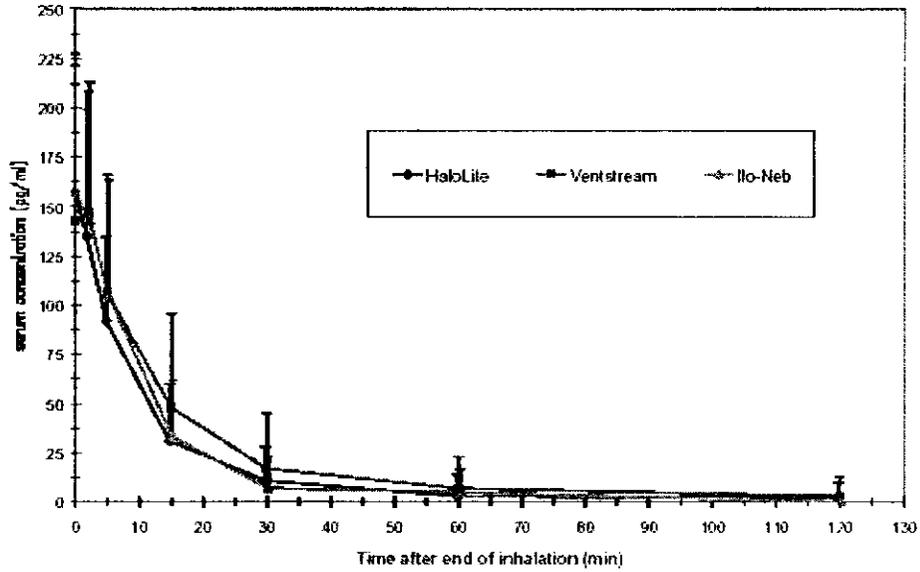
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condition, good tolerance of iloprost inhalations and increasing oxygen saturation during inhalation, acute right heart failure developed which could not be stopped by cardiopulmonary reanimation. The patient died 2 days after start of drug.

[^] see results of ECG study C200-004

TF 1

Mean iloprost serum level-time curves after the end of inhalation with three different devices

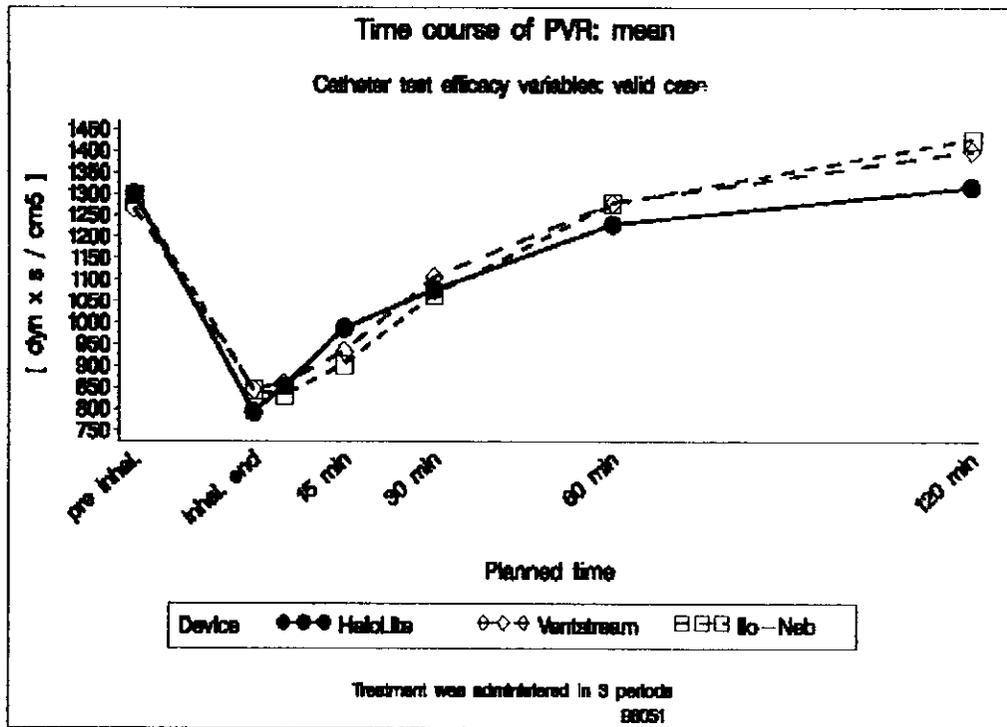


Mean serum concentrations, regardless of nebulizer, were close to zero by 30 minutes.

Pulmonary vascular resistance (PVR) was determined at baseline, at the end of inhalation and 5, 15, 30, 60 and 120 minutes after the end of inhalation. The time course of the PVR is shown below.

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Section 14 Figure 1 Mean pulmonary vascular resistance



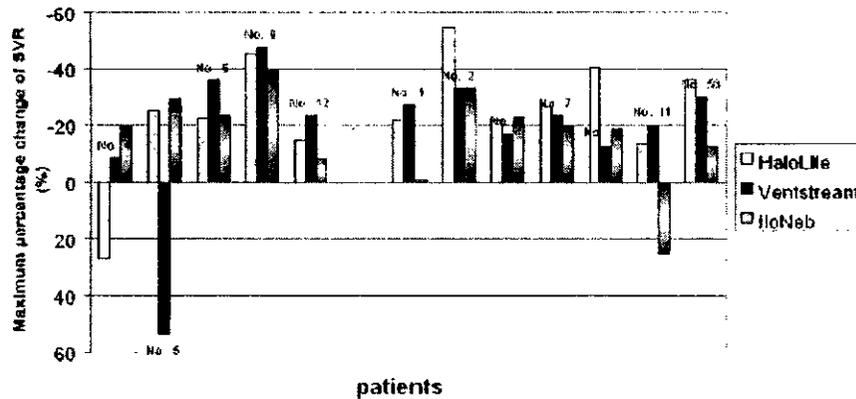
The greatest drop in pulmonary vascular resistance was observed at the end of the inhalation. This parameter slowly returned to baseline by approximately 1 hour.

Systemic vascular resistance

The maximum percentage change of SVR for each individual patient by device is shown below. Please note that the negative percentage change values plotted *above* the x-axis indicate a drop in systemic vascular resistance (SVR), while any changes amounting to greater systemic vascular resistance appear *beneath* the x-axis as positive percentage points.

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Section 14 Figure 5 Maximum percentage change of SVR after each treatment, based on Section 14 Table 19



Most patients had large decreases (up to 55%) in SVR following iloprost inhalation.

Premature withdrawals:

One patient (no. 8) was withdrawn from the study prematurely after two minutes of the first treatment period due to a 6 mmHg drop in mean systemic blood pressure. This value was lower than the prescribed stop criterion (this could have been precipitated by insertion of the catheter for right-heart catheterization).

Patients 1 and 2 had treatment disruptions:

Patient 1 was withdrawn due to the treatment stop criterion valid at the time that stipulated a decrease of 10% or more in mean arterial pressure for more than two minutes (this was later amended to allow drops less than 20%). This withdrawal occurred 8 minutes after beginning the 2nd treatment period (using treatment A, HaloLite™). The same occurrence of decrease was observed in the subsequent 3rd treatment (treatment B, Ventstream™), and this treatment was also discontinued after 7 minutes.

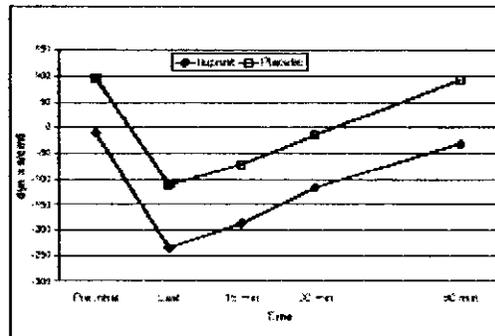
Patient 2 was also withdrawn from one treatment due to the treatment stop criterion valid at the time (first period, treatment A, HaloLite™). This patient continued with each subsequent treatment as normal and completed these. Both patients remained in the study and were included in the valid case analysis set.

Long term effect on pulmonary hemodynamics-rebound effect

Study ME97218 measured pulmonary vascular resistance at 12 weeks of inhalation therapy (measurements from patients on iloprost and those on placebo) as well as at baseline. Measurements were taken at trough (overnight).

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Figure 10 Study ME97218 - Difference in PVR at Week 12 Compared with Baseline



PVR at pre-inhalation (trough) was higher in the placebo group.

After the trough measurement, both randomized groups received one dose of inhaled iloprost to compare the hemodynamic responses to iloprost inhalation after the first dose of iloprost (placebo patients) and after 12 weeks of iloprost dosing (iloprost patients). After dosing, there was a decrease in pulmonary vascular resistance that was similar in both groups, most likely reflecting no rebound effect of iloprost.

Electrocardiograms (ECGs)

Study C200-004

This study was a partial double-blind, parallel group, positive (single oral dose of moxifloxacin) and placebo-inhalation controlled, multiple fixed and rising inhalation dose, safety, tolerance, and pharmacokinetic study of iloprost administered at 2.5 µg every 2 hours for 6 doses and at 5, 7.5, 10, 12.5, 15, and 20 µg in normal healthy male and female subjects. Inhalation therapy was double blind with respect to placebo vs. iloprost. The study was not blinded with respect moxifloxacin or to fixed vs. multiple rising doses.

The dose regimen is shown below.

Table 2.7.4.1 Dose Regimen in Study C200-004

Treatment Group (Design)	Dose Regimen
Treatment Group A (open-label)	Single oral dose of moxifloxacin (400 mg)
Treatment Group B (open-label)	Inhaled iloprost solution 2.5 µg every 2 hours for 6 dose inhalations, for a total of 15 µg
Treatment Group C (double-blind vs. D)	Increasing doses of inhaled iloprost solution every 2 hours, beginning with 5 µg and followed by 7.5, 10, 12.5, 15, and 20 µg, for a total of 6 dose inhalations (total cumulative dose of 76 µg), or up to a maximally tolerated dose (MTD) in order to maximize exposure. Please refer to Section 3.4.5 or Protocol C200-004 for rules on changes in dosing if MTD was reached
Treatment Group D (double-blind vs. C)	Inhaled placebo to match Treatment C only.

Increasing doses were obtained by using longer inhalation times rather than administration of more concentrated drug solution. (Highest dose in efficacy study was 45 ug/day.) Maximum tolerated dose was reached if any of the following occurred:

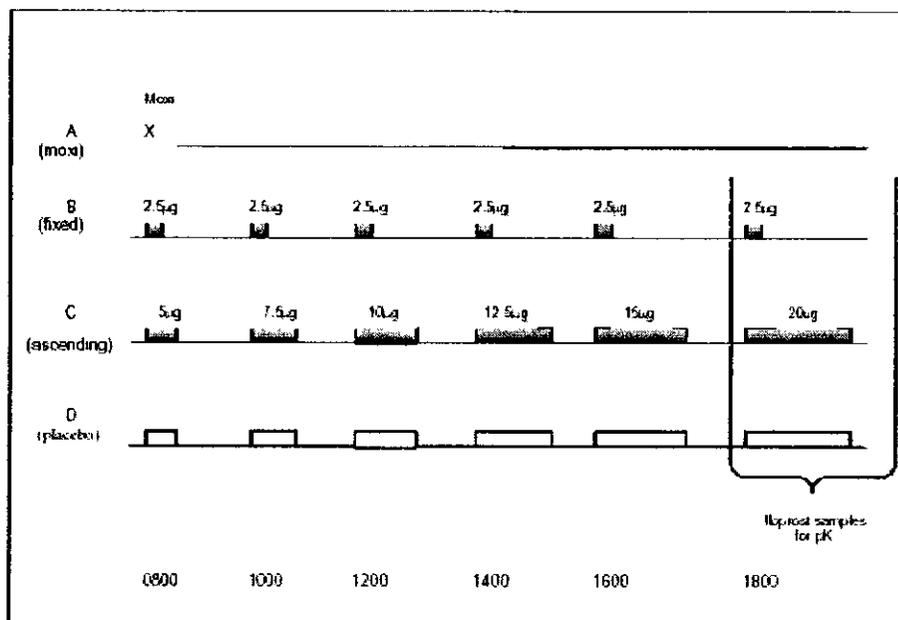
- Severe intolerability [e.g., severe headache, severe flushing, severe jaw pain (trismus)]
- ≥ 20 mmHg decrease in systolic blood pressure with symptoms
- Systolic blood pressure ≤ 80 mmHg
- Any other AE, which in the opinion of the Investigator, necessitated discontinuation of the current inhalation level

ECG procedures were as follows “The formal analysis of ECG intervals and morphology were performed using digital 12-lead Holter technology ☐

☑ Electrocardiograms to be used in the endpoint analysis were selected by predetermined timepoints, and were analyzed centrally using a high-resolution, manual, on-screen, caliper method with annotations. Three 12-lead ECGs were downloaded from the H-12 flash card approximately 1 minute apart at each defined time point. At baseline, 30 ECGs (10 timepoints x 3 ECGs at each timepoint) were collected. The total number of digitized ECGs was 69 ECGs for 120 subjects and 60 ECGs for 40 subjects, for a grand total of 10,680 ECGs. The ECG testing in this trial could detect a 5 to 10 ms QTc effect.”

Time points for sample collection for pharmacokinetic analysis: predose (before the 6th dose level), midpoint and endpoint of the inhalation, and at 5, 15, and 60 minutes postdose (a total of 6 PK doses per subject).

Figure 9.1-1 Study Design



Results

Demographics

A total of 161 subjects were studied with 81 females and 80 males. Subjects were young (mean age 25 years) and mostly white (85.1%).

There were 3 study withdrawals: # 065 (because of cough), # 096 (withdrew consent), and #126 (because of atrial flutter).

The mean changes from baseline for ECG intervals including QT with and without correction factors are shown below, by treatment group.

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Table 11.1-1 Mean Change from Baseline in ECG Parameters and Outlier Analyses

	Moxifloxacin	Iloprost fixed	Iloprost Ascending	Placebo
Total N	40	39	41	40
Heart Rate				
Heart Rate in bpm*	1	5	7	3
Heart rate using 1800-2000 hrs	-1	3	5	3
Heart Rate tachycardic outliers N (%)	8 (20%)	6 (15%)	6 (15%)	2 (5%)
Heart Rate bradycardic outliers N (%)	2 (5%)	1 (3%)	4 (10%)	6 (15%)
PR interval				
PR in msec*	-3	-2	-1	0
PR using 1800-2000 hrs	0	-1	0	0
PR outliers N (%)	1 (3%)	1 (3%)	0	0
QRS Interval				
QRS in msec N*	-1	-1	-1	-1
QRS using 1800-2000 hrs	-1	-1	-1	0
QRS outliers N	0	0	0	0
QT Interval				
QT in msec*	1	-12	-14	-10
QT from 1800-2000 hrs	10	-7	-10	-9
QT new >500 msec N (%)	0	0	0	0
QTcI Interval				
QTcI in msec* (C.I.)	3	-2	-1	-4
QTcI max mean in msec	23	17	17	14
QTcI 1800-2000 hrs	6	-2	-1	-3
QTcI new >500 msec N	0	0	0	0
QTcI new >450 msec N (%)	0	0	0	0
QTcI 30-60 msec inc N (%)	8 (20%)	4 (10%)	3 (7%)	0
QTcI >60 msec inc (N)	0	0	0	0
QTcF Interval				
QTcF in msec* (C.I.)	3	-3	-2	-4
QTcF using 1800-2000 hrs	7	-3	-1	-4
QTcF max mean in msec	23	17	17	16
QTcF new >500 msec (N)	0	0	0	0
QTcF new >450 msec N (%)	0	0	0	0
QTcF 30-60 msec inc N (%)	9 (23%)	4 (10%)	3 (7%)	3 (8%)
QTcF >60 msec inc N	0	0	0	0
QTcB Interval				
QTcB in msec* (C.I.)	4	2	4	-2
QTcB using 1800-2000 hrs	5	0	4	-2
QTcB max mean in msec	25	20	24	18
QTcB new >500 msec (N)	0	0	0	0
QTcB new >450 msec N (%)	1 (3%)	0	0	0
QTcB 30-60 msec inc N (%)	12 (30%)	7 (18%)	11 (27%)	5 (13%)
QTcB >60 msec inc N (%)	0	0	0	0

	Moxifloxacin	Iloprost fixed	Iloprost to MTD	Placebo
Other Findings				
New abnormal U waves N (%)	0	0	0	0
New ST segment elevation changes N (%)	0	0	1 (2%)	0
New ST segment depression changes N (%)	2 (5%)	1 (3%)	1 (2%)	1 (3%)
New T wave inverted N (%)	3 (8%)	2 (5%)	2 (5%)	2 (5%)
New Second Degree Heart Block N (%)	0	1 (3%)	0	0
Third Degree Heart Block, Complete RBBB & LBBB, MI N (%)	0	0	0	0

Mean change from baseline

Bpm=beats per minute; msec=milliseconds; QTcI: Individual Correction; QTcB: Bazett correction;

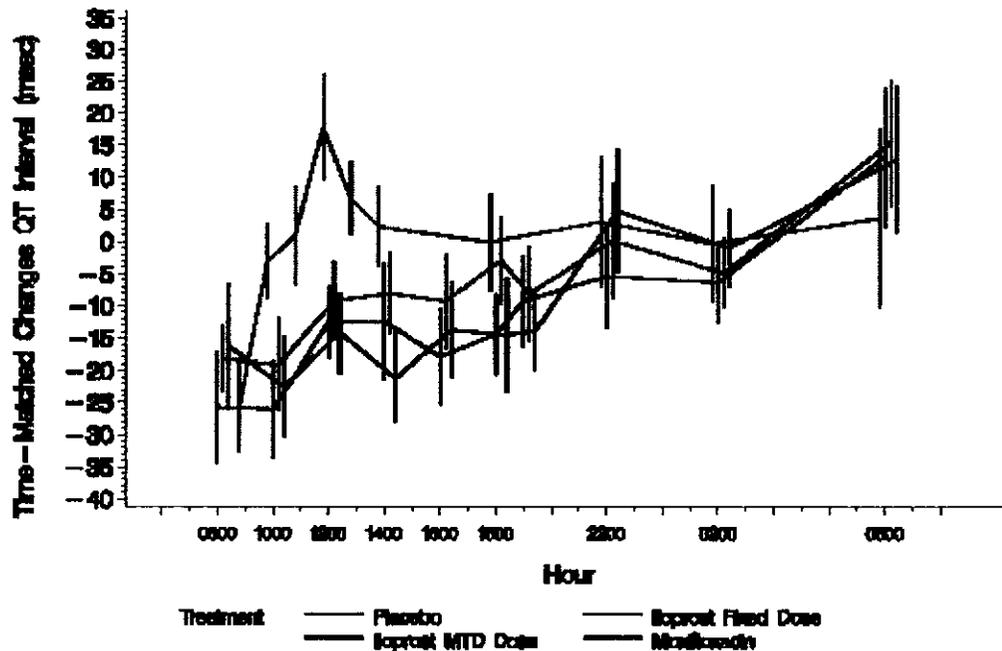
QTcF= Fridericia correction; RBBB=right bundle branch block; LBBB= left bundle branch block.

MI= myocardial infarction; "new" means not present at baseline and only seen post baseline. MTD to maximum tolerated dose.

Mean heart rate was increased in the iloprost groups (5-7 bpm) compared to placebo (3 bpm) and moxifloxacin (1 bpm). There was little evidence that iloprost prolongs or shortens the PR or QRS intervals.

The unadjusted mean QT interval change was slightly increased for moxifloxacin (1 ms) compared to the other groups (all with decreases). The time matched changes in uncorrected QT interval versus time for the 4 treatment groups are shown below.

Figure 1
Change in (Time Matched) QT Interval (msec) versus Time

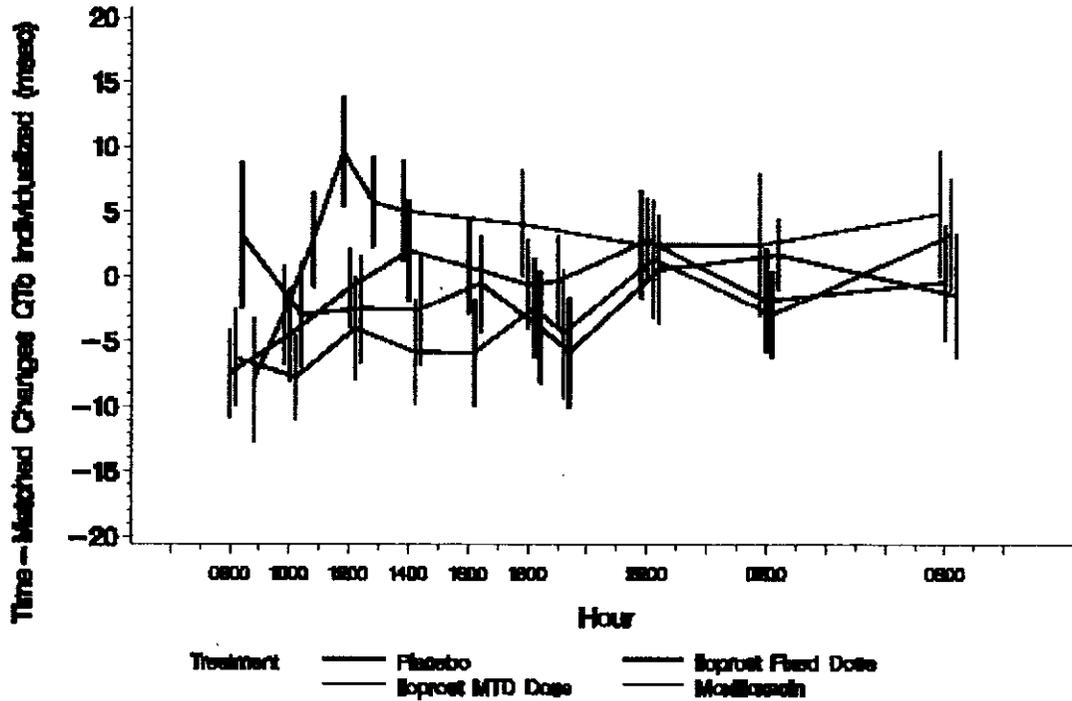


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The mean changes (ms) in QTcI (individual corrections) were +3 for moxifloxacin and -2, -1, and -4 for iloprost fixed dose, iloprost escalating dose, and placebo, respectively. No one in any of the groups had a QT >500 ms. The time-matched changes in QTcI versus time are shown below.

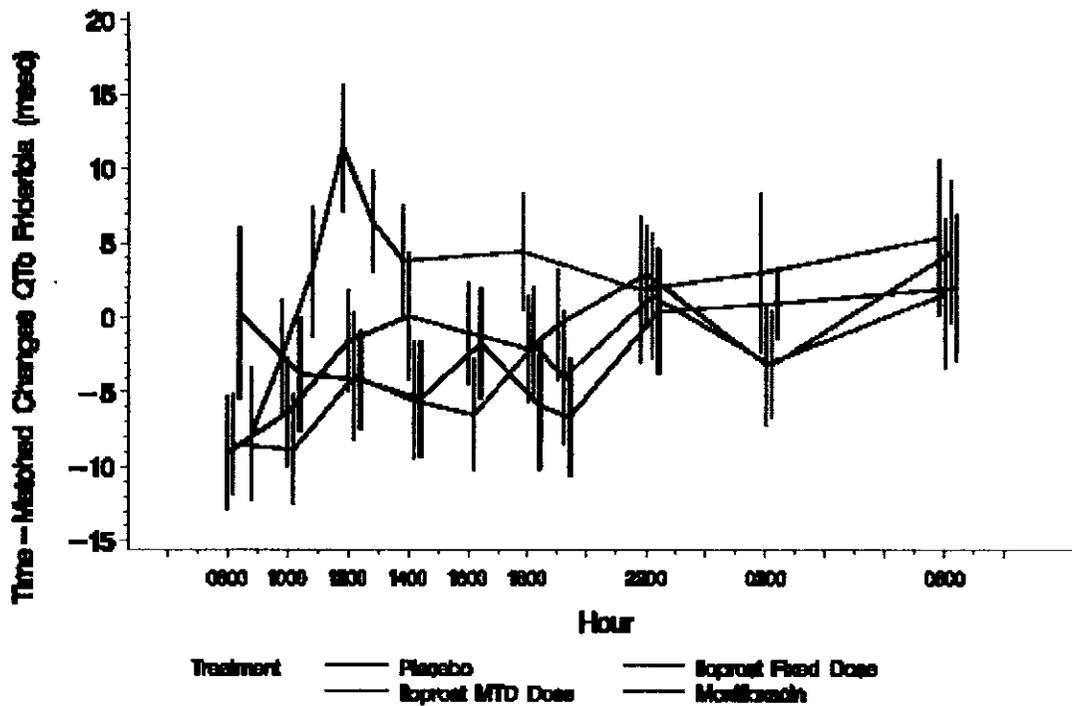
Figure 2
Change in (Time Matched) QTc Individualized (msec) versus Time



The sponsor stated that because of the increase in heart rate associated with iloprost, the best correction method was the individually corrected QT interval (QTcI). Mean changes for all groups other than moxifloxacin were below 0 (as was observed with the Fridericia correction). The time matched changes in QTcF versus time are shown below.

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Figure 3
Change in (Time Matched) QTc Flecicla (msec) versus Time

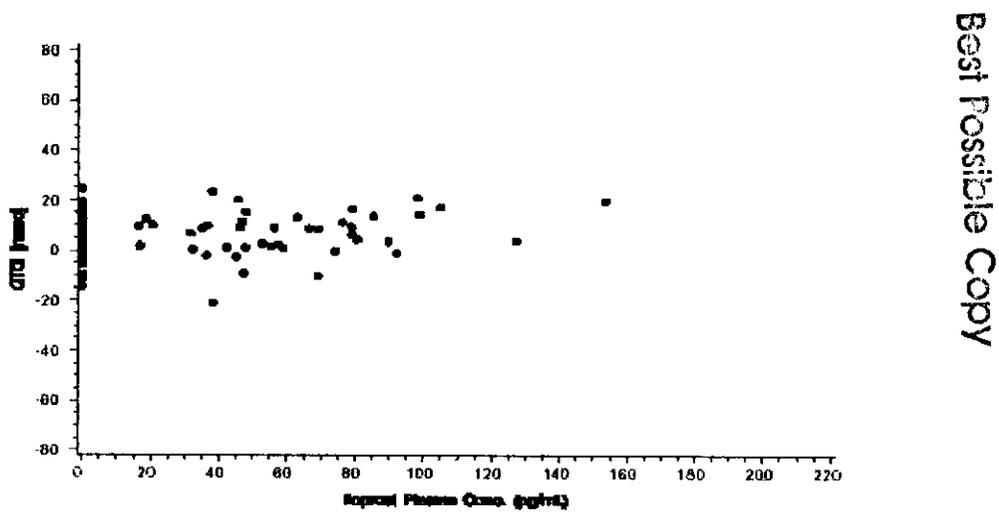


The only slightly disturbing finding was the QTcI 30-60 ms increase with 20% reported for moxifloxacin group, and 10%, and 7% for the iloprost groups compared to 0 for placebo. This finding is probably irrelevant.

The figure below shows no change in the maximal QTcI change from baseline as related to increasing iloprost blood concentration (iloprost, however, has a very short half life).

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Figure 2 Maximal Change in QTc1 (ms) Versus Peak Iloprost Plasma Concentration After the 18:00-hour Dose, to 60 Minutes Postdose



Pharmacokinetic results

The results were highly variable. Median T_{max} ranged from 5 to 20 minutes, mean t_{1/2} ranged from 8.7 min (2.5 ug dose) to 17.1 min (20 ug dose). Individual C_{max} vs. dose is shown below.

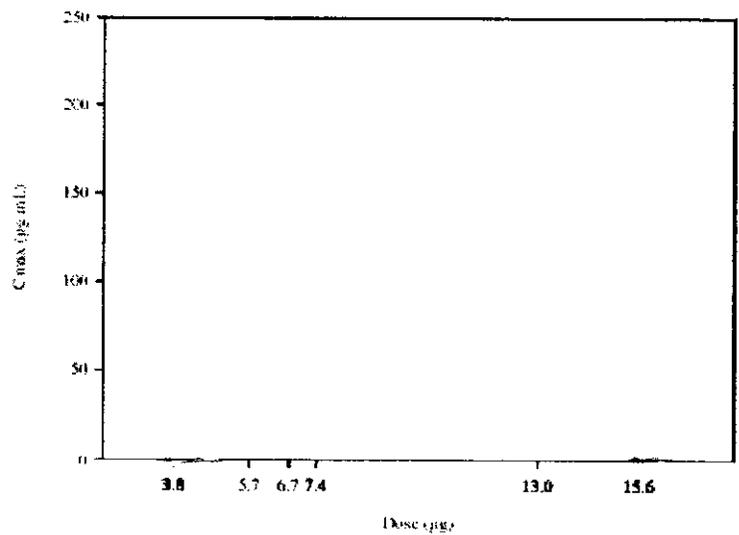


Figure 11.5-1 Individual Subject C_{max} Versus Delivered Dose

Individual AUC_{0-t} vs. dose is shown below.

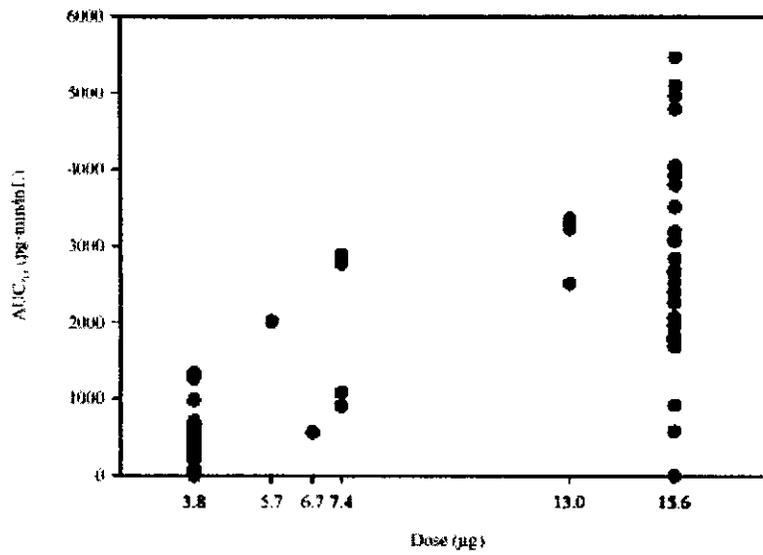


Figure 11.5-2 Individual Subject AUC₀₋₂₄ Versus Delivered Dose

Adverse events

The table below lists the adverse events reported by >3% of subjects, by treatment group (excluding moxifloxacin).

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TABLE 14.2.3-2 ADVERSE EVENTS

Study	Subject Total	Preferred Term	Total
Treatment	#	System Organ Class	Related & NR
B	40	CHEST DISCOMFORT	11 (27.5%)
		DIZZINESS	8 (20.0%)
		COUGH	7 (17.5%)
		PHARYNGOLARYNGEAL PAIN	6 (15.0%)
		FLUSHING	4 (10.0%)
		NAUSEA	3 (7.5%)
		FEELING HOT	3 (7.5%)
		DYSPNOEA	3 (7.5%)
		THROAT IRRITATION	3 (7.5%)
		CHEST PAIN	2 (5.0%)
HEADACHE	2 (5.0%)		
C	41	CHEST DISCOMFORT	15 (36.6%)
		DIZZINESS	15 (36.6%)
		FLUSHING	14 (34.1%)
		NAUSEA	12 (29.3%)
		PAIN IN JAW	8 (19.5%)
		COUGH	8 (19.5%)
		FEELING HOT	7 (17.1%)
		DRY THROAT	5 (12.2%)
		THROAT TIGHTNESS	5 (12.2%)
		ABDOMINAL PAIN UPPER	2 (4.9%)
		CHEST PAIN	2 (4.9%)
		TRISMUS	2 (4.9%)
		THROAT IRRITATION	2 (4.9%)
		HYPERHIDROSIS	2 (4.9%)
D	40	DIZZINESS	5 (12.5%)
		HEADACHE	3 (7.5%)
		FATIGUE	2 (5.0%)
		DECREASED SYSTOLIC BP	2 (5.0%)
		SOMNOLENCE	2 (5.0%)
		PHARYNGOLARYNGEAL PAIN	2 (5.0%)
		HEMORRHOID	2 (5.0%)

Treatment B = inhaled Iloprost solution (2.5 µg every 2 hours for a total of 6 dose inhalations)
 Treatment C = increasing doses of inhaled Iloprost solution every 2 hours based on randomization schedule
 Treatment D = inhaled placebo matched to Treatment C only.

Chest discomfort is the most often reported event in the 2 iloprost groups. Other events reported frequently with iloprost include dizziness, flushing, nausea, jaw pain, and cough.

There were 13 subjects (31.7%) who failed to go to the highest scheduled dose (20 ug). The reason for stopping and the dose at which they reported the events are shown below.

- 008 (nausea, 15 µg),
- 009 (chest pain, 12.5 µg),
- 027 (headache, 15 µg),
- 030 (chest discomfort, 15 µg),
- 047 (tachycardia, 5 µg),
- 066 (chest discomfort, 12.5 µg),
- 080 (headache, 12.5 µg),
- 086 (nausea, 20 µg),
- 097 (dizziness, 12.5 µg),
- 102 (chest discomfort, 15 µg),
- 114 (headache, 12.5 µg),
- 126 (atrial flutter, 5 µg),

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247 (chest discomfort, 10 µg).

There were 5 subjects who stopped the dose escalation because of chest discomfort/chest pain. These are discussed in detail below.

Subject #9: An 18 year old female noted mild chest pain with deep inspiration beginning with 5ug and continuing through 12.5 ug (dose 4), during which a decision was made to decrease the dose thereafter to 10 ug (MTD reached). The subject also had alteration in taste, facial flushing, and lightheadedness. The chest pain continued with the fifth dose associated with a cough. The 6th dose was terminated early due to a decrease in blood pressure. All adverse events were rated as mild in severity.

Subject #30: A 22 year old female noted chest discomfort rated as mild in severity beginning with the 7.5 ug dose and continuing through the 15 ug (dose 5), after which the 6th dose was reduced to 12.5 ug. Associated with the chest symptoms were mild dizziness, sore throat, and nausea. Therapy was discontinued early during the 6th dose due to the chest symptoms.

Subject #66: A 21 year old male who noted moderate chest discomfort beginning with 12.5 ug (dose 4) which resulted in reduction in dose to 10 ug with the last 2 doses. He continued to note moderate "chest discomfort" with the subsequent doses. He also noted mild transient dizziness with the 4th dose.

Subject #102: A 25 year old female who noted moderate chest tightness during 10 ug (dose 3) after experiencing dizziness, headache, and nausea with the 2nd dose. Moderate chest tightness continued through the 6th dose, and the dose was decreased to 12.5 ug after the 5th dose (15 ug). Dizziness, headache, nausea, and cough were also noted with the later doses.

Subject # 247: 23 year old female noted moderate chest discomfort with 5 ug (dose 1) that persisted throughout the entire dosing period, resulting in dose reduction from 10 ug to 7.5 ug and then to 5 ug. The subject also noted cough, headache, facial flushing, and trismus, along with diaphoresis and nausea with the final dose. The chest symptoms in these subjects were rated as mild to moderate in intensity, and were generally persistent during a portion of the dosing period.

Possible proarrhythmic events

In the inhaled studies, the overall incidence of potential proarrhythmic adverse events was 19% (24/129) in the iloprost group vs. 17% (22/133) in the placebo/control group. Serious events were reported in 7% (9/129) of iloprost-treated patients vs. 2% (3/133) of placebo/control-treated patients.

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Table 25 Inhaled Safety Population – Intensity of Potential Proarrhythmic Adverse Events of Special Interest During the Randomized Phase

HARTS Term	Severity	All Adverse Events		Serious Adverse events	
		Iloprost (n = 129)	Placebo/control (n = 133)	Iloprost (n = 129)	Placebo/control (n = 133)
Overall		24 (19%)	22 (17%)	9 (7%)	3 (2%)
	Mild	5 (4%)	9 (7%)	1 (1%)	1 (1%)
	Moderate	9 (7%)	11 (8%)	2 (2%)	1 (1%)
	Severe	10 (8%)	2 (2%)	6 (5%)	1 (1%)
Syncope		10 (8%)	6 (5%)	6 (5%)	0
	Mild	0	1 (2%)	0	0
	Moderate	2 (2%)	2 (2%)	1 (1%)	0
	Severe	8 (6%)	1 (1%)	5 (4%)	0
Palpitation		8 (6%)	5 (4%)	0	0
	Mild	3 (2%)	3 (2%)	0	0
	Moderate	3 (2%)	2 (2%)	0	0
	Severe	2 (2%)	0	0	0
Dizziness		3 (2%)	8 (6%)	0	0
	Mild	1 (1%)	3 (2%)	0	0
	Moderate	2 (2%)	5 (4%)	0	0
	Severe	0	0	0	0
Tachycardia		5 (4%)	3 (2%)	1 (1%)	1 (1%)
	Mild	2 (2%)	3 (2%)	0	1 (1%)
	Moderate	3 (2%)	0	1 (1%)	0
	Severe	0	0	0	0
Supraventricular Tachycardia		1 (1%)	2 (2%)	1 (1%)	2 (2%)
	Mild	0	0	0	0
	Moderate	0	1 (1%)	0	1 (1%)
	Severe	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Bradycardia		1 (1%)	2 (2%)	0	0
	Mild	0	0	0	0
	Moderate	1 (1%)	2 (2%)	0	0
	Severe	0	0	0	0
Arrhythmia		2 (2%)	0	1 (1%)	0
	Mild	2 (2%)	0	1 (1%)	0
	Moderate	0	0	0	0
	Severe	0	0	0	0

Source: ISS Table 14.11.1.02 Jun/04

Oral studies

The table below summarizes the incidence of any of possible potentially proarrhythmic adverse events in the double-blind, randomized phase of the 12 pooled studies that comprise the oral iloprost safety database.

Table 61 Oral Safety Population – Intensity of Potential Proarrhythmic Adverse Events of Special Interest During the Randomized Phase

HARTS Term	Intensity	All Adverse Events		Serious Adverse Events	
		Iloprost (n=2033)	Placebo (n=1128)	Iloprost (n=2033)	Placebo (n=1128)
Overall	overall	253 (12.4%)	103 (9.1%)	15 (0.7%)	10 (0.9%)
	mild	116 (5.7%)	59 (5.2%)	0 (0.0%)	0 (0.0%)
	moderate	110 (5.4%)	32 (2.8%)	3 (0.1%)	2 (0.2%)
	severe	27 (1.3%)	12 (1.1%)	12 (0.6%)	8 (0.7%)
Dizziness	overall	171 (8.4%)	67 (5.9%)	2 (0.1%)	1 (0.1%)
	mild	88 (4.3%)	47 (4.2%)	0 (0.0%)	0 (0.0%)
	moderate	71 (3.5%)	16 (1.4%)	0 (0.0%)	0 (0.0%)
	severe	12 (0.6%)	4 (0.4%)	2 (0.1%)	1 (0.1%)
Hypotension	overall	40 (2.0%)	9 (0.8%)	4 (0.2%)	0 (0.0%)
	mild	15 (0.7%)	4 (0.4%)	0 (0.0%)	0 (0.0%)
	moderate	20 (1.0%)	5 (0.4%)	2 (0.1%)	0 (0.0%)
	severe	5 (0.2%)	0 (0.0%)	2 (0.1%)	0 (0.0%)
Palpitation	overall	20 (1.0%)	12 (1.1%)	0 (0.0%)	0 (0.0%)
	mild	11 (0.5%)	5 (0.4%)	0 (0.0%)	0 (0.0%)
	moderate	8 (0.4%)	6 (0.5%)	0 (0.0%)	0 (0.0%)
	severe	1 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)
Tachycardia	overall	14 (0.7%)	7 (0.6%)	0 (0.0%)	1 (0.1%)
	mild	2 (0.1%)	4 (0.4%)	0 (0.0%)	0 (0.0%)
	moderate	9 (0.4%)	2 (0.2%)	0 (0.0%)	0 (0.0%)
	severe	3 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
Arrhythmia	overall	9 (0.4%)	7 (0.6%)	1 (0.0%)	1 (0.1%)
	mild	5 (0.2%)	6 (0.5%)	0 (0.0%)	0 (0.0%)
	moderate	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	severe	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
Bradycardia	overall	6 (0.3%)	2 (0.2%)	1 (0.0%)	2 (0.2%)
	mild	3 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	moderate	2 (0.1%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
	severe	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
Atrial Fibrillation	overall	5 (0.2%)	3 (0.3%)	2 (0.1%)	2 (0.2%)
	mild	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	moderate	3 (0.1%)	2 (0.2%)	1 (0.0%)	1 (0.1%)
	severe	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)

Table 61 Oral Safety Population – Intensity of Potential Proarrhythmic Adverse Events of Special Interest During the Randomized Phase (Continued)

HARTS Term	Intensity	All Adverse Events		Serious Adverse Events	
		Iloprost (n=2033)	Placebo (n=1128)	Iloprost (n=2033)	Placebo (n=1128)
Syncope	overall	5 (0.2%)	4 (0.4%)	1 (0.0%)	2 (0.2%)
	mild	0 (0.0%)	2 (0.2%)	0 (0.0%)	1 (0.1%)
	moderate	4 (0.2%)	2 (0.2%)	0 (0.0%)	1 (0.1%)
	severe	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Heart arrest	overall	3 (0.1%)	2 (0.2%)	3 (0.1%)	2 (0.2%)
	mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	severe	3 (0.1%)	2 (0.2%)	3 (0.1%)	2 (0.2%)
Atrial arrhythmia	overall	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	moderate	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sudden death	overall	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
	mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	severe	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Ventricular arrhythmia	overall	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	mild	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Atrial flutter	overall	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
	mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	moderate	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	severe	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)

Source: ISS Table 05.7.1 (2/Jan04)

Overall, there is no evidence that adverse events reported while subjects were receiving iloprost (and including syncope, dizziness, or hypotension) were caused by ventricular arrhythmias. While patients were on iloprost treatment, there were no reports of events (such as ventricular tachycardia or torsade de pointes) suggestive of drug-induced QT prolongation.

Concomitant medications

The only disallowed medications for patients enrolled into ME97218 were a) prostanoid or prostaglandins, b) use of beta blockers within 4 weeks of baseline, and c) new treatment with or changes doses of calcium channel blockers within 6 weeks of baseline. Approximately 80% of subjects were taking an anticoagulant and more than half were taking a diuretic. There is no indication that medications other than those listed above, should be limited in patients taking inhaled iloprost.

TT 13: Concomitant medication at screening by PHT diagnosis – ITT population
number (percent) of patients given

Medication	Treatment	PPH iloprost: n = 53 placebo: n = 55	SPH iloprost: n = 48 placebo: n = 47	Overall iloprost: n = 101 placebo: n = 102
Ca antagonists	Iloprost	22 (41.5%)	15 (31.3%)	37 (36.6%)
	Placebo	23 (41.8%)	17 (36.2%)	40 (39.2%)
Diuretics	Iloprost	31 (58.5%)	30 (62.5%)	61 (60.4%)
	Placebo	35 (63.6%)	35 (74.5%)	70 (68.6%)
Vasodilators	Iloprost	11 (20.8%)	4 (8.3%)	15 (14.9%)
	Placebo	8 (14.5%)	10 (21.3%)	18 (17.6%)
Anticoagulants	Iloprost	45 (84.9%)	42 (87.5%)	87 (86.1%)
	Placebo	42 (76.4%)	41 (87.2%)	83 (81.4%)
Steroids	Iloprost	3 (5.7%)	11 (22.9%)	14 (13.9%)
	Placebo	9 (16.4%)	8 (17.0%)	17 (16.7%)

Data based on Section 14.1, Table 8

Withdrawal Phenomena and/or Abuse Potential

There were 67 subjects (32 iloprost and 35 placebo) who abruptly stopped study drug treatment in study ME97218 ranging from 1 dose to a week of dosing. The mean PVR at trough (pre-inhalation), after an overnight period of no inhaled iloprost therapy, was essentially unchanged at Week 12 compared to baseline among iloprost patients. Additionally, hemodynamic changes following acute administration of inhaled iloprost to the iloprost group (who received 12 weeks of inhaled iloprost) and the placebo group (who were receiving their first dose of iloprost) showed a time-dependent decrease in PVR and return to pre-inhalation levels, with no evidence of overshoot after 60 minutes.

In conclusion, the sponsor states that there is no evidence of withdrawal effects or rebound such as showing signs of clinical deterioration. Although no formal study evaluated these effects, there is no reason to contradict these conclusions.

Overdose Experience

No instances of overdose of iloprost delivered via inhalation have been reported. A specific antidote is not known. Interruption of the inhalation session, monitoring, and symptomatic measures would be prudent.

Post-marketing reports of overdose have been described for the i.v. formulation of iloprost. Over a 10 year period, seven cases of overdose were reported. Four cases were associated with hypotension, with two resulting in loss of consciousness. All patients recovered with supportive measures, although one patient with advanced arteriosclerosis had a myocardial infarction a few days after. Two cases were associated with profound vasovagal effect and widespread flushing and headache. In one case, data were incomplete and the overdose could not be confirmed.

7.2 Adequacy of Patient Exposure and Safety Assessments

Introduction

Description of databases

Iloprost has been studied in over 160 clinical trials spanning two decades and involving more than 12,000 subjects in whom the drug was administered via the iv, oral, or inhaled routes.

The safety database includes data from selected clinical trials conducted with the inhalation, oral, and intravenous formulations of iloprost. Safety data from a total of 3025 recipients of iloprost by any route/formulation were made available for review. The safety data have been pooled by formulation.

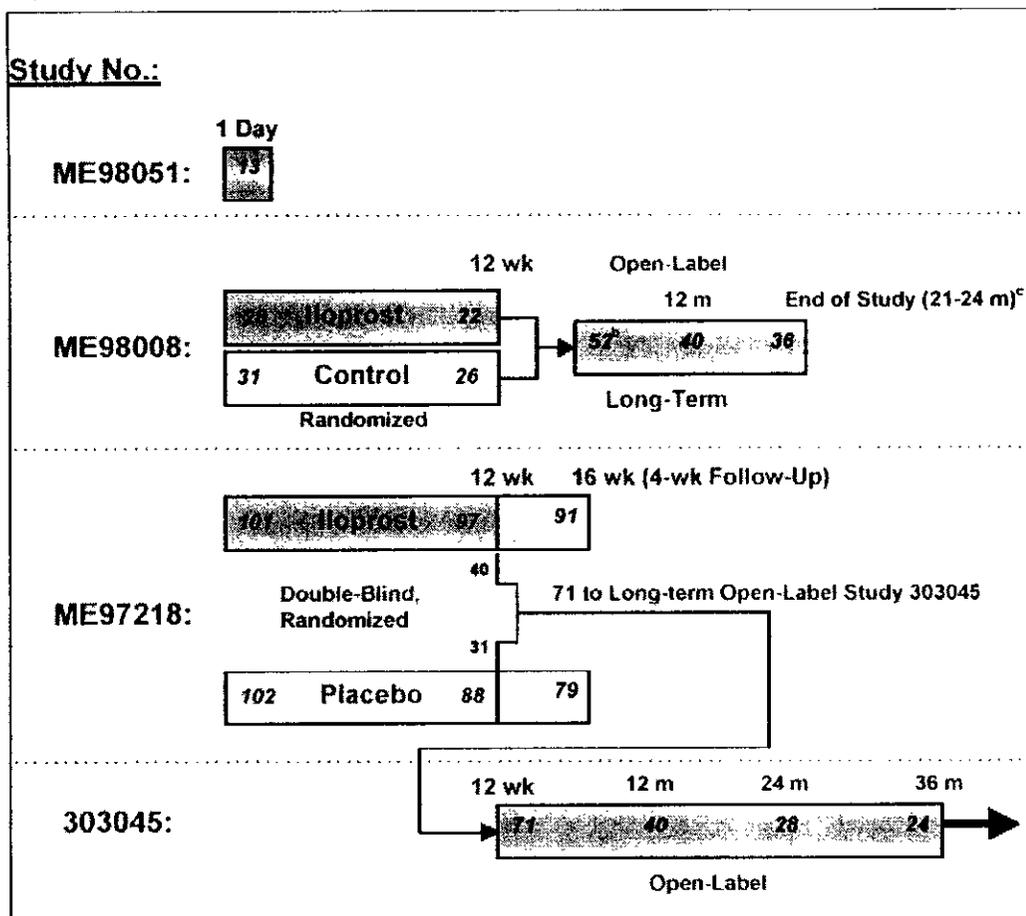
A summary of deaths, other serious adverse events, and discontinuations because of adverse events for those iv and oral studies not presented in the integrated summary of safety (approximately 106 iv studies enrolling 7489 subjects, and approximately 22 oral studies enrolling 281 subjects) was incorporated into the safety update.

Inhalation

The inhaled route of administration was evaluated in three clinical studies (a fourth safety study 303045 is ongoing and an ECG study C200-004 was recently completed) involving patients with pulmonary arterial hypertension (PAH). The duration of iloprost therapy ranged from 1 day to 3 years.

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Figure 2 Overview of Study Design of Clinical Studies with Inhaled Iloprost in PAH*



- * Includes number of patients who entered (italicized numbers preceding treatment group) and completed (other italicized numbers) each phase of the studies, as well as number of patients from each randomized treatment group who went on in open-label, long-term treatment (smaller, non-italicized numbers)
- ^b Includes 48 patients who completed the double-blind, randomized phase (22 iloprost, 26 control) plus 4 additional patients on control who opted for long-term, open-label treatment before completing 12 weeks of randomized therapy.
- ^c Depending on whether the patient was assigned to control or iloprost during the 12-week randomized period, the total duration of iloprost treatment ranged from 21 to 24 months, respectively.

Study ME98051 (AX15) was a single dose, device comparison study with 13 patients.

ME98008 (Report A02237) was a 12-week, randomized, open label, exploratory study (control group received “best supportive care”) that included a total of 63 patients. Thirty (30) were randomized to iloprost (with 2 excluded from the data base because the sponsor stated that there was no evidence that they received study drug) and 33 to control (with 2 excluded for the same reason as the iloprost patients). Of the 63 randomized patients, 52 continued in a follow up phase and received open label iloprost for up to 2 years.

ME97218 (Report A02997) was a double blind, 12-week, randomized trial with a total of 203 patients (101 randomized to iloprost and 102 randomized to placebo). A subset of 71 patients was entered into a long-term, open-label treatment study (Study 303045).

The table below shows the number of patients in the inhalation studies.

Study Number	Number of Patients	Comments
Total Patients in Inhaled Clinical Studies (N = 275)¹		
AX15	13	
ME98008	59	63 patients enrolled, 4 patients excluded from analysis, randomized but not treated
ME97218	203	
Total	275	
Total Exposure (total number of patients receiving iloprost, N = 215)		
ME98008	28	Patients who were randomized to iloprost in 12-week randomized phase
ME98008	30	Patients who were randomized to control during the 12-week randomized phase and received iloprost in long-term phase of the study
ME97218	101	Patients who were randomized to iloprost during 12-week randomized phase of the study
ME97218 (post randomized phase/study 303045)	56	Patients randomized to placebo during the 12-week randomized phase of study ME97218 who rolled into the long-term safety study 303045 OR initiated off-label Ilomedin (iloprost) during the 4-week follow-up period.
Total	215	
Total Patients Receiving Iloprost during Randomized, Controlled Phase (N = 129)		
ME98008	28	
ME97218	101	
Total	129	

¹ Total patients receiving iloprost or placebo/control

Total number of patients enrolled in an inhalation study was 275 with 215 having been exposed to iloprost. The total number of iloprost patients in randomized, controlled phase was 129.

Oral and IV

Large numbers of clinical studies were conducted over the past two decades using the intravenous and/or oral formulations of iloprost. The sponsor selected studies they considered relevant for pooling to assess the safety of inhaled iloprost. These were limited to trials that were randomized and placebo controlled, and involved dosing periods of ≥ 14 days in duration. Most had safety follow up studies. Patient population receiving i.v. and oral iloprost consisted predominantly of patients with peripheral arterial occlusive disease. Additional safety data from studies using these formulations were included in the safety update. Many of these studies date back to the 1980s, only the bodies of many reports were preserved; appendices containing patient numbers and narratives, as well as CRFs, are missing in many cases and not available.

Twelve trials were selected from the oral iloprost program. From a total of 3161 patients, 2033 were randomized to receive iloprost clathrate at doses ranging from 50 μg to 200 μg bid from 4 weeks to 1 year and 1128 were randomized to placebo. Most of the patients in the oral iloprost safety database of pooled studies had peripheral vascular disease. Overall, 66% (1341/2033) of recipients had peripheral arterial obstructive disease, 15.4% (314/2033) had Raynaud's syndrome, 10.6% (216/2033) had thromboangiitis obliterans and 6.8% (138/2033) had rheumatoid arthritis. A small study of patients with multiple sclerosis (1.2%, 24/2033 iloprost recipients) completes the oral iloprost database.

Twelve trials were selected from the iv iloprost program. From a total of 1473 patients, 764 were randomized to receive iloprost at doses up to 2 ng/kg/min over 6 hours per day from 14 to 30 days in duration. Most of the patients in these studies had peripheral vascular disease. Overall, 55.6% had PAOD, 20.2% had atherosclerotic peripheral vascular disease with ischemic ulcers and 9.7% had thromboangiitis obliterans. Two small studies completed the summary, one of diabetic patients with ulcerated or necrotic trophic lesions (7.3%) and one of critical limb ischemia (6.9%).

For those i.v. and oral studies not presented in this integrated summary of safety (approximately 106 iv studies enrolling 7489 subjects, and approximately 22 oral studies enrolling 281 subjects), a summary of deaths, other serious adverse events (SAEs) and discontinuations due to adverse events are included in the NDA safety update.

Results

Inhalation

Dosing

Average daily inhaled dose used in the 2 randomized, controlled trials is shown below.

ISS Table 11.3
Average Daily Dose (ug/24 hrs) During Randomized Phase
Safety Population

Statistic	Iloprost (N=129)	Placebo+Control Combined (N=133)
N	129	102
Mean	32.8	36.8
S.D.	9.16	8.31

N.B. 4 subjects, 2 per treatment group, were excluded from the safety data base.

According to the sponsor, doses in study 98008 were expressed as the nominal doses instilled into the nebulizer chamber; however, doses in study 97218 were expressed as the dose delivered at the mouthpiece. Thus, a conversion factor was developed based upon measured dose delivery at the mouthpiece at each of the nominal doses used in the phase 2 study. This was used to express the daily delivered dose administered in the phase 2 study as the dose delivered at the mouthpiece. The conversion was as follows.

- If nominal daily dose ≤ 100 ug, then nominal dose $\times 0.24 =$ delivered dose
- If nominal daily dose > 100 ug, then nominal dose $\times 0.30 =$ delivered dose

The delivered dose was proportionally greater with nominal daily doses greater than 100 ug because the nebulization device was not emptied after each use; thus, because the concentration of residual medication increased with more use, the amount delivered at the mouthpiece increased as more inhalations per day were administered.

If one uses the sponsor's conversion factors, the mean total daily dose of iloprost was 32.8 ug (range 5-45 ug). The top dose in the efficacy study was 45 ug and 100 ug in the open label study.

Duration of exposure

The total 215 patients includes patients who received iloprost during the randomized portion of the 2 clinical efficacy studies, the long-term portion of Study 98008, and patients who received iloprost during the Week 13-16 follow-up period of study 303045.

ISS Table 11.4
 Duration of Exposure (Weeks) During Entire Study
 Safety Population

Statistic	Iloprost (N=215)
N	215
Mean	27.4
S.D.	33.30
Median	15.4
Minimum	0.1
Maximum	117.4
<=1 week	3 { 1.4%
>1 - 4 weeks	22 { 10.2%
>4 - 12 week	47 { 21.9%
>12 - 26 wee	97 { 45.1%
>26 - 52 wee	6 { 2.8%
>52 weeks	40 { 18.6%

The mean duration of exposure was 27.4 weeks. Forty patients (18.6%) received inhaled iloprost for more than 52 weeks.

Patient disposition

The number of patients who completed and the number of patients who did not complete iloprost inhalation studies and the reasons for not completing are shown below.

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ISS Table 13.1
Patient Disposition
ITT Population

Visit	Parameter	Statistic	Iloprost (N=131)	Placebo+Control Combined (N=135)
(Randomized Phase)	*Prematurely Discontinued	No	116 (88.5%)	110 (81.5%)
		Yes	15 (11.5%)	25 (18.5%)
	Primary Reason	Adverse Events	3 (2.3%)	11 (8.1%)
		Lack of Efficacy	4 (3.1%)	4 (3.0%)
		Protocol Deviation	1 (0.8%)	0 (0.0%)
		Withdrawal of Consent	4 (3.1%)	2 (1.5%)
		Other	1 (0.8%)	4 (3.0%)
Death	2 (1.5%)	4 (3.0%)		

*Prematurely discontinued during randomized phase in study 98008 and during first 12 weeks in study 97218
Data for this table comes from the termination CRF

A lower percent of iloprost patients (11.5%) dropped out of the randomized phase prematurely compared to placebo/control patients (18.5%). More than half of the 25 placebo patients who discontinued prematurely did so either for adverse events (11) or death (4). More than half of the 15 iloprost patients dropped out because of lack of effect (8) or withdrawal of consent (4).

The table below shows the discontinuation rate all 215 iloprost patients.

Visit	Parameter	Statistic	Iloprost (N=215)
End of Study	**Prematurely Discontinued	No	174 (80.9%)
		Yes	40 (18.6%)
	Primary Reason	Discontinuation of Study Med	13 (6.0%)
		Death	7 (3.3%)
		Withdrawal of Consent	12 (5.6%)
Other	8 (3.7%)		

** Patient 245 of study 97218 died during the randomized phase and a disposition form was not completed
** and is therefore not included in this summary

Of the 215 patients who received inhaled iloprost, 40 were prematurely discontinued. Of these 40, 13 (6.0%) discontinued study medication for various reasons, 7 (3.3%) died, and 12 (5.6%) withdrew consent. The remaining 8 discontinued for a variety of reasons.

Demographics

The following table shows the mean age, percent male/female, ethnicity, etiology of pulmonary hypertension, NYHA class, and mean baseline 6-minute walk distance for the patients in the controlled inhalation studies.

Parameter	Statistic	Iloprost (N=129)	Placebo+Control Combined (N=133)
Age (years)	N	129	133
	Mean	48.9	52.0
	S.D.	13.48	12.01
	Median	52.0	54.0
	Minimum	20.0	23.0
	Maximum	70.0	78.0
Gender	Male	38 (29.5%)	46 (34.6%)
	Female	91 (70.5%)	87 (65.4%)
Ethnicity	Caucasian	128 (99.2%)	126 (94.7%)
	Black	1 (0.8%)	2 (1.5%)
	Hispanic	0 (0.0%)	3 (2.3%)
	Asian	0 (0.0%)	1 (0.8%)
	Other	0 (0.0%)	1 (0.8%)
PAH	PPH	69 (53.5%)	72 (54.1%)
	SPH	60 (46.5%)	61 (45.9%)
NYHA	II	11 (8.5%)	10 (7.5%)
	III	71 (55.0%)	75 (56.4%)
	IV	47 (36.4%)	48 (36.1%)
Baseline 6-min Walking Distance (m)	N	129	133
	Mean	337.7	321.1
	S.D.	101.83	103.79
	Median	350.0	323.0
	Minimum	49.0	84.0
	Maximum	565.0	540.0

I 2.1

Patients tended to be around 50 years of age, mostly female, and nearly all white. The PAH diagnosis was split nearly 50-50 between primary and secondary hypertension; more than half were NYHA class III and more than a third were NYHA class IV. The groups were well matched although the mean baseline walk distance was a little longer for the iloprost group (337.7 m) compared to the control (321.1 m).

Postmarketing experience

Post marketing events reported between March 16, 2004 and August 16, 2004 are shown below.

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Table 2.7.4.22 Postmarketing ADR Reports (16Mar04-16Aug04)

Case Number (Date, country)	Medication	Event	Related to Drug?	Patient	Medical Condition	Serious?	Concomitant Meds	Outcome
DE-2004-027127 (15Jan04, Germany)	Ventavis	Dyspnea, drop in systolic blood pressure, nausea	Not stated	23-y old female	Eisenmenger's syndrome	No	Not reported	recovered/resolved
DE-SHR-04-023613 (5Apr04, Germany)	Ventavis	Increasing personality change, inadequate behavior, logorrhea, worsening of pre-existing affective instability and cognitive impairment	Related	70-y old male	Severe rheumatic pulmonary fibrosis	Yes	Prochlorone, tramadol, spiropractone, leflunomide, colecalciferol, finasteride, acetylsalicylic, oxygen	recovering/resolving
DE-SHR-04-023865 (1May04, Germany)	Ventavis (given as diluted with NaCl)	Flush	Not stated	Male	Not stated	No	Sodium chloride	recovered/resolved
DE-SHR-04-025045 (4May04, Germany)	Ventavis	Sensation of lightness in chest	Not stated	Female	Not stated	No	Not reported	recovered/resolved
DE-SHR-04-025046 (4May04, Germany)	Ventavis	Sensation of lightness in chest	Not stated	Female	Not stated	No	Not reported	recovered/resolved
HU-2004-029168 (12Jul04, Hungary)	Iloprost aerosol 25-100 µg/d	Gastrointestinal adverse events, vomiting, pain	Possibly	Not stated	Primary pulmonary hypertension	Yes	Not reported	Drug discontinued
PT-2004-028134 (23Apr04, Portugal)	Ventavis, Iloprost aerosol 25-100 µg/d	Drug exposure during high-risk pregnancy (22 wk)	Related	21-y old female	Primary pulmonary hypertension	Yes	Nifedipine, carnitine, folic acid, sucralose, betaninobasem, oxytocin, warfarin	Cesarian delivery of male child with no congenital defects
PT-2004-030073 (4Aug04, Portugal)	Ventavis	Neonatal jaundice, intracostals indrawing	Related (report) Not related (specimen)	Male neonate	Drug exposure via mother	Yes	Not stated	Not stated

There were 2 reported exposures during pregnancy: one with delivery of a child with no congenital defects and the other reported a neonate with neonatal jaundice and intracostals indrawing. The first report, PT-2004-028134, was regarding a 21-year-old woman with severe primary pulmonary hypertension and 22 weeks pregnant at the start of iloprost. A male infant was born by cesarean section (oligoamnios triggered the delivery), and had no apparent congenital anomalies. PT-2004-030073 had no additional information.

The events not related to pregnancy and delivery were similar to those reported during clinical trials.

Additional post marketing reports (Aug 17, 2004-Oct 15, 2004) included one case of prolonged epistaxis and 1 fatal case of severe hypotension in a 34 year old female living in Argentina. The second case involved a severely ill patient with HIV/AIDS. One month prior to receiving iloprost she was found to have hepatomegaly, splenomegaly, ascites, right pleural effusion, and main portal thrombosis. E. coli sepsis was diagnosed. The patient experienced a hypotensive event on the day she started aerosolized iloprost. The Swan-Ganz catheter was removed at this time, possibly precipitating the event. She died that day. Complete information is lacking.

Safety Update

The update provided safety from ongoing longterm study 303045, results from ECG study C200-004 examining the effects on QT interval, and a summary of oral and intravenous and/or intra-arterial iloprost studies not submitted in the original NDA.

Inhalation studies

Study C200-004 was a placebo- and positive-controlled (moxifloxacin) study of the effects of inhaled iloprost ECG parameters (particularly the QTc interval). There was a total of 160 healthy male and female volunteers selected for this study.

Study 303045 is a long-term, open-label safety study of iloprost in a subset of patients who had completed the double blind, randomized placebo controlled study ME97218. After 12 weeks of treatment with either iloprost or placebo, patients were all started on inhaled iloprost and followed for at least 24 months or until the start of marketing the drug. The study remains ongoing.

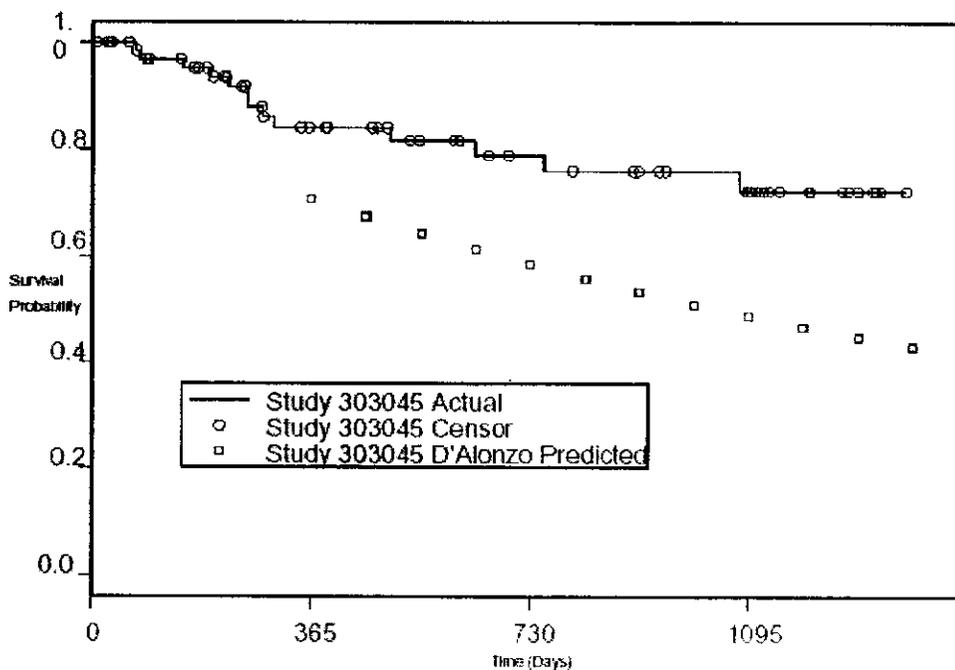
Long term study 303045

Among the 71 patients who entered Study 303045, 40 completed 12 months of treatment, 27 completed 24 months, and 24 completed 36 months.

Of the 71 patients, 47 discontinued study drug. The most common reasons for discontinuation was lack of efficacy (23), death (8), adverse events (8), withdrawal of consent (3), worsening of disease/lack of response to therapy (3) patients, poor compliance (1), and complications following thromboendarterectomy (1) patient.

There were 13 deaths: 8 during the trial and 5 who discontinued study drug prior to death. (all were reported in original NDA and are not discussed here).

Mortality estimate



Kaplan Meier plot of the time to death for patients treated with iloprost long-term. Actual time to death for these patients was compared with predicted time to death using the baseline hemodynamic data from these same patients inserted into the predicted survival model from a national prospective registry (D'Alonzo GE et al. Survival in patients with primary pulmonary hypertension. *Ann Intern Med* 1991;115:343-9).

It is reassuring that there is no evidence of a detrimental effect of iloprost on survival.

Serious adverse events

Of the 35 reports of serious adverse events, the most frequent were congestive heart failure (12), syncope (5), dyspnea (4), and aggravation reaction (4). There was 1 report of kidney failure and 2 for anemia.

Syncope/collapse

A total of 5 serious adverse events of syncope have been reported in this long terms study. The NDA discussed 4 of these events (303045-90, 303045-197, 303045-220, and 303045-474). The most recent event is described below:

#303045-106: 64-year-old female started treatment Day 70 of open-label iloprost. She complained of dyspnea at rest, collapsed, became unconscious, and underwent failed cardiopulmonary resuscitation. Concomitant drugs included cisapride.

Study drug withdrawals because of an adverse event

There were 10 patients who withdrew from iloprost treatment because of an adverse event. These are shown below:

Number of patients

Adverse event	Iloprost (n=71)
Congestive heart failure	6
Syncope	1
Dyspnea	1
Pneumonia	1
Respiratory disorder	1
Aggravation reaction	1
Total	10

The syncope event involved a 72-year-old female on iloprost aerosol 35 µg/d for over 3 months experienced an (continue) episode of syncope associated with worsening dyspnea and cyanosis. She was hospitalized on the same day and the symptoms were attributed to a worsening of PHT (NYHA functional class IV). Iloprost was discontinued, started on bosentan, and discharged from the hospital.

Adverse events

Events reported by at least 5 subjects are shown in the table below.

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HARTS Term	Iloprost (n = 71)
Overall	63 (88.7%)
Congestive heart failure	21 (29.6%)
Cough increased	20 (28.2%)
Peripheral edema	17 (23.9%)
Bronchitis	13 (18.3%)
Trismus	11 (15.5%)
Dyspnea	10 (14.1%)
Headache	7 (9.9%)
Syncope	7 (9.9%)
Asthenia	6 (8.5%)
Malaise	6 (8.5%)
Sore throat	6 (8.5%)
Aggravation reaction	5 (7.0%)
Infection	5 (7.0%)
Diarrhea	5 (7.0%)
Hypotension	5 (7.0%)
Vasodilatation	5 (7.0%)

Table 7

These events are similar to what has been reported in other trials.

Protocol C200-002 (STEP)

The STEP study, a double blind, randomized, placebo control, bosentan add on study, began enrollment June 11, 2004, and completed enrollment October 14, 2004 with a total of 67 patients. As of October 15, 8 patients have completed the 12-week randomized phase of the study, with an additional approximately 23 patients having completed at 6 weeks of randomized therapy. The study remains blinded.

To date, there were no reported deaths. A total of 4 patients have discontinued participation in the 12-week blinded phase of the study.

- Patient 04-53: 36 year old female withdrew consent, voluntarily discontinued study drug and declined participation in the open-label phase. She was hospitalized for worsening of PAH approximately 3 weeks after stopping study drug
- Patient 16-59: 59 year old female entered early into open-label phase after being hospitalized because of worsening of PAH.
- Patient 11-32: 51 year old female who discontinued participation after two days because of severe headache considered to be related to study drug.
- Patient 13-50: 60 year old female who discontinued study drug because of persistent fatigue and dyspnea thought to be related to study drug. She did not enter the open-label phase.

A total of 6 patients have reported 7 serious adverse events: deep vein thrombosis/cellulitis and right sided heart failure (patient 03-51), chest pain (16-66), and hypoxemia/dyspnea (13-72).

Oral formulation database not submitted in NDA

The sponsor has submitted for the safety update the serious safety from 20 studies with oral iloprost. This safety was not part of NDA integrated summary of safety. The studies in all but 1 instance (study AM69 was 8 weeks with 6 subjects) were short term. The largest study was 26 subjects (table 17). There were 247 subjects who received oral iloprost including 98 healthy volunteers and 149 patients with diseases. In 16 studies, there were no reported deaths, serious adverse events, or permanent discontinuations from study drug. The reported serious safety for the 4 remaining studies (all enrolled a diseased population) is shown below.

Table 18 Oral Iloprost Studies in the Safety Update: Deaths, Serious Adverse Events, and Permanent Discontinuations of Study Medication Because of Adverse Events

Report (File Name)	Deaths (n/N)	Patients with Serious Adverse Events (n/N)	Discontinuations for Adverse Events (n/N)
8179	0/5	0/5	2 (1/5 i.v.; 1/5 p.o.) ^a
AG60	0/26	1/26	2/26
AL51	0/5	0/5	1/5
AM68	0/25	0/25	5/25

^aIn this study, each patient received i.v. iloprost for 1 week, followed by oral iloprost for 3 weeks.

There were no reported deaths. The 1 serious event report was right groin pain (the patient continued oral iloprost) and the 10 discontinuations for adverse events were decrease in blood pressure/hypotension (2), giddiness/blurred vision (1), headache, nausea, muscular aches (1), headache, flush, nausea, diarrhea (1), and unknown (5).

Intravenous/intra-arterial database not submitted in NDA

The sponsor has submitted for the safety update the serious safety from 98 studies (50 controlled and 48 uncontrolled) with iv or intra-arterial iloprost that was not part of NDA integrated summary of safety. In this supplemental database, there were 5682 subjects who received iloprost (122 healthy volunteers and 5560 patients with diseases). There were reports of serious safety in 54 of the 98 studies. It was stated that there were no reports of serious safety for the remaining 44 studies.

The table below shows the serious safety for the 44 studies.

Deaths		No. of patients with serious adverse events		Discontinuations for adverse events	
Iloprost n/N (%)	Control n/N (%)	Iloprost n/N (%)	Control n/N (%)	Iloprost n/N (%)	Control n/N (%)
Placebo controlled trials					
42/1042 (4.0)	32/988 (3.2)	35/921 (3.8)	31/905 (3.4)	44/1042 (4.2)	19/988 (1.9)
Other controlled trials					
87/887 (9.8)	81/892 (9.1)	28/887 (3.2)	8/892 (0.9)	121/887 (13.6)	16/892 (1.8)

Uncontrolled trials					
299/2996 (10.0)	NA	251/2996 (8.4)	NA	300/2996 (10.0)	NA

Tables 21 and 22

In the controlled trials, the mortality rates were similar for both treatment groups. The serious events were similar for both treatment groups in the placebo controlled trials, but more than 3 times higher for the iloprost group compared to control for the other controlled trials. Discontinuations for adverse events were higher for iloprost treatment compared to placebo (4.2% vs. 1.9%) and other controls (13.6% and 1.8%).

There is no indication of increased mortality with the intravenous formulation.

8 MARKED-UP PRODUCT LABEL

B. PRESCRIBING INFORMATION

B.1 Labeling Text

Ventavis®
(iloprost) Inhalation Solution

DESCRIPTION

[

]

9 pages redacted from this section of
the approval package consisted of draft labeling



9 APPENDICES

ME97218

Overall Study Design and Plan Description

This study was a prospective, double-blind, 2-arm, parallel-group, placebo-controlled, multicenter investigation in patients with primary or secondary pulmonary hypertension (PHT). The patients were randomly assigned to inhalation of placebo aerosol or iloprost aerosol for 12 weeks in addition to their background therapy. The primary efficacy endpoint a composite that included improvement in the 6-minute walk test at 12 weeks by at least 10% compared to baseline, improvement of at least one NYHA functional class at 12 weeks compared to baseline, and no death or deterioration of PAH at any time before 12 weeks.

Dosing

The individually tolerated dose at the mouthpiece (determined within the first 7 days of randomization) was 15 ug, 22.5 ug, 30 ug, or 45 ug.

The initial total daily dose of iloprost was 30 ug divided into 6 equal-dose inhalations of 5 ug; if this dose was well tolerated, the total daily dose was increased to 45 ug divided into 9 equal-dose inhalations of 5 ug. The minimum interval between inhalations was 2 hours.

In case of poor tolerability of the single dose of 5 ug, the dose was reduced to 2.5 ug with a total daily dose of 15 ug divided into 6 equal-dose inhalations of 2.5 ug. If this dose was well tolerated, the total daily dose was increased to 22.5 ug divided into 9 equal-dose inhalations of 2.5 ug.

Dose adaptations during the following 11-week period were allowed for poor tolerability determined by the investigator. Temporary interruptions of therapy of up to two weeks were allowed as medically required

Randomization

The patients were assigned to treatment groups by central telephone randomization and prospectively stratified for pulmonary hypertension (primary or secondary) and for the New York Heart Association (NYHA) class (III or IV).

Patients receiving a lung or heart and lung transplantation were to be discontinued from study medication.

Disallowed concomitant therapy was limited to prostanoids.

Patients were to be assessed on day 8 (\pm 2 days), at week 4, at week 8 and at week 12 (\pm 5 days, respectively) for the end of treatment visit, or in the event of discontinuation of treatment at the time point of withdrawal. An additional follow-up visit was scheduled four weeks after the end of the treatment period for assessment of safety.

Inclusion criteria

- male or female patients, aged 18-70,
- with primary or secondary pulmonary hypertension presenting under consolidated background therapy,
- NYHA functional class III or IV at study entry,
- entry mean pulmonary artery pressure > 30 mmHg at rest.

Patients with secondary pulmonary hypertension could be included if the underlying cause was one of the following: chronic thromboembolic pulmonary hypertension, connective tissue disease with isolated PHI or interstitial pulmonary disease, or drug-associated PHT (e.g. fenfluramine).

Efficacy variables

Primary efficacy endpoint was the combined responder criterion defined as:

- Improvement in exercise capacity (6-minute walking test) at 12 weeks by at least 10% versus baseline, and
- Improvement by at least one NYHA class at 12 weeks versus baseline, and
- No deterioration of PHT, and
- Alive at week 12.

Exercise Capacity (6-Minute Walking Test)

Exercise capacity was measured using the unencouraged six-minute walking test (Guyatt et al. Attachment 1). The test was to be performed at the same time of day throughout the study. The primary endpoint was exercise capacity measured 30 minutes after the end of study medication inhalation at week 12.

NYHA class

The clinical classification for heart failure severity by the New York Heart Association (NYHA) was used for assessing this endpoint. The baseline assessment of NYHA class was to be performed at the screening visit. If the baseline visit took place no later than one week after the screening visit, the screening classification was to be used as baseline value. In all other cases, the classification was to have been repeated at the baseline visit and the value then obtained was to serve as the baseline value. The change of NYHA class at week 12 (end of treatment) versus the baseline assessment was to be determined, and the criterion was fulfilled if the patient has improved by at least one class.

Deterioration of PHT

Patients exhibiting 2 or more of the following criteria of deterioration (if there were clinical signs of worsening of the disease, additional examinations could have been indicated as common practice);

1. Refractory systolic arterial hypotension <85 mmHg,
2. Worsening of right heart failure as indicated by emergence of cardiac edema, ascites or pleural effusion despite adequate background therapy,
3. Rapidly progressive cardiogenic hepatic failure (e.g. leading to an increase of GOT and/or GPT to > 100 U/l, total bilirubin > 5 mg/dl),
4. Rapidly progressive cardiogenic renal failure (e.g. leading to a decrease of creatinine clearance to < 50% of baseline value; creatinine clearance calculated from serum creatinine using the Cockcroft and Gault formula),
5. PHT-related decrease of six-minute walking distance by $\geq 30\%$ of baseline value,
6. New and continued need for i.v. medication, e.g. catecholamines, diuretics,
7. Cardiac index ≤ 1.3 l/min/m² (right heart catheterization),
8. CVP ≥ 22 mmHg (via indwelling catheter) despite adequate diuretic therapy,
9. SVO₂ $\leq 45\%$ despite nasal O₂ therapy (right heart catheterization),

In the time-to-event analysis, patients were to be counted for this endpoint with the time point at which they discontinued study treatment due to deterioration of PHT.

Mortality

Defined as all-cause mortality

Secondary efficacy endpoints:

exercise capacity, NYHA class, dyspnea index (Mahler, Attachment 3), hemodynamic parameters (PVR, mPAP, CO) and gas exchange (SVO₂), deterioration of PHT, mortality, need for transplantation, and Quality of life (QoL).

Dyspnea index

The dyspnea index is defined according to Mahler, et. al. The baseline value for this index was obtained in the same manner that was used for the NYHA classification (see above).

Focal score

This index rates the severity of dyspnea at a single state. The scores for the index depend on ratings for three different categories with five grades from 0 (very severe impairment) to 4 (unimpaired) for each of the 3 categories. The ratings for each of the three categories are added to form a baseline focal score (range from 0 to 12).

Transition score

At the transition periods (study assessment time points after baseline) changes in dyspnea for the three categories used for the baseline dyspnea index are rated by seven grades, ranging from -3 (major deterioration), to +3 (major improvement). The ratings for each of the three categories are added together to form a transitional focal score (range from -9 to +9).

Hemodynamic Parameters

Hemodynamic parameters (PVR, mPAP, CO) and gas exchange (SVO₂) were measured or calculated with the aid of a right heart and pulmonary artery catheter. The time points for measurements post inhalation of study medication were 15 min, 30 min and 60 min post inhalation at baseline and week 12.

Quality of Life

The Medical Outcomes Trust Short Form-12 (SF-12), the Minnesota Living with Heart Failure (MLHF) questionnaire adapted for PHT (MLF/PHT), and the EuroQoL 12 (EQ-5D) (Attachment 4).

QoL was evaluated in a longitudinal design in all patients entered in this study. The baseline assessment was to be performed at or just after randomization. Subsequent assessments were recorded at weeks 4 and 12 after the start of treatment. At each of these assessments, the MLHF/PHT, the SF-12 and the EQ-5D was to be completed; at week 8, only the MLHF/PHT was to be completed.

Need for Transplantation

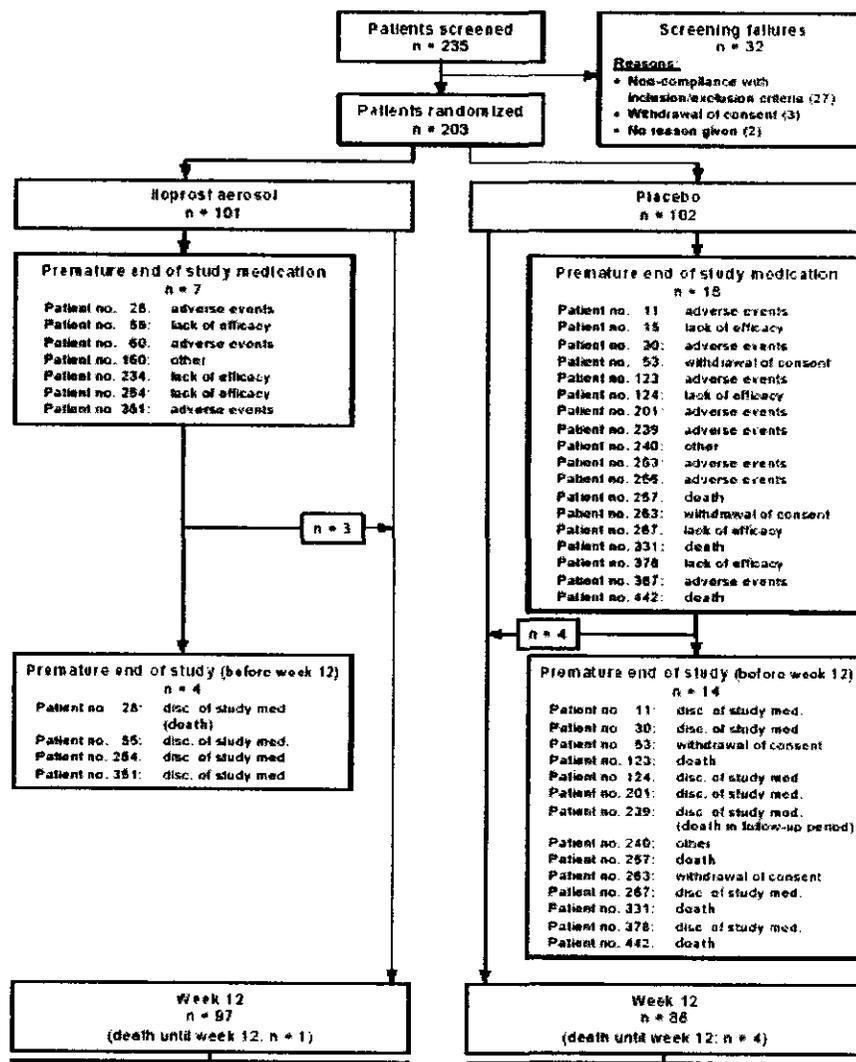
Patients who received a lung or heart and lung transplantation during the study period was considered not assessable for efficacy if this was only because of transplant availability. If a patient was newly entered into a transplantation list, his/her data were counted as having developed the "need for transplantation".

RESULTS

Patient disposition

The figure below shows the number of patients screened, randomized, discontinued study medication, discontinued study, and the final numbers of patients still in study at week 12 (end of study drug treatment). Patients were followed for an additional 4 weeks and underwent a final safety visit (week 16, end of study).

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There were 235 patients screened with 201 randomized (101 to iloprost and 102 to placebo). The numbers of subjects completing the study through week 12 were 97 (96.0%) randomized to iloprost and 88 (86.3%) randomized to placebo. Of the 7 iloprost patients who prematurely discontinued study medication before week 12, 3 remained in the study. Of the 18 placebo patients who discontinued study medication, 4 remained in the study.

The table below shows the reason for study drug discontinuation for the 7 iloprost and 18 placebo.

Table 2: Discontinuation of study medication by type of PHT and NYHA class – ITT population

PHT / NYHA class		Iloprost	Placebo
Overall	Number of patients	101 (100.0%)	102 (100.0%)
	Premature Disc. of Study Med.		
	no	94 (93.1%)	84 (82.4%)
	yes	7 (6.9%)	18 (17.6%)
	adverse events	3 (3.0%)	8 (7.8%)
	lack of efficacy	3 (3.0%)	4 (3.9%)
	protocol deviation	0 (0.0%)	0 (0.0%)
	withdrawal of consent	0 (0.0%)	2 (2.0%)
	other	1 (1.0%)	1 (1.0%)
	death	0 (0.0%)	3 (2.9%)
	NO/LINK/NA	0 (0.0%)	0 (0.0%)
	NO/UNK/NA	0 (0.0%)	0 (0.0%)

Most study drug discontinuations were for adverse events: 3 (3.0%) iloprost vs. 8 (7.8%) placebo. More deaths occurred in the placebo group (3) compared to iloprost (0). Discontinuations for lack of effect were similar between treatment groups (3% vs. 3.9%).

One iloprost subject withdrew because of difficulty taking all doses (reason was recorded as patient decision). Two placebo patients withdrew consent and 1 switched to active drug.

Selected information about the 7 iloprost patients who discontinued study medication is shown below.

2. TABLE DP.4 – Patients who prematurely discontinued study medication

Study 97218 / 300180

ITT - Population

TABLE DP.4 : Patients who prematurely discontinued study medication

Treatment: Iloprost

SUBJECT	PHT / NYHA class	Date of Randomization	Date of Last Study Med.	Duration of medication (day)	Reason for Disc. of Study Med.	Premature Disc. of Study Med. (text)
28	PPH / IV	16JUN00	16JUN00	0	adverse events	
55	PPH / III	13APR00	20JUN00	68	lack of efficacy	Deterioration of exercise, worsening of dyspnoe > NYHA 4
60	SPH / III	07SEP00	03DEC00	87	adverse events	Cough after inhalation that made inhalation impossible from []
160	SPH / IV	09OCT00	16OCT00	7	other	Difficulty for taking all doses regularly (patient decision)
234	PPH / IV	15DEC99	01MAR00	77	lack of efficacy	
254	SPH / III	27MAR00	23MAY00	57	lack of efficacy	
351	PPH / IV	31OCT00	14DEC00	44	adverse events	Right heart decompensation

Patient demographics

Age, sex, ethnic group

The table below shows the mean age (and range), percent female, and percent non white in all subjects, by iloprost (n=101) and placebo (n=102) groups.

Mean age, percent male/female, and percent nonwhite for the patient population by treatment group are shown below.

Mean age: yrs (range)		Female: %		Nonwhite: %	
Iloprost	placebo	Iloprost	placebo	Iloprost	placebo
51 (20-70)	53 (23-70)	68.3	66.7	1.0	6.9

Tables 4 and 5

The mean age was early 50s, two thirds were female, and few were nonwhite.

Patient type

Patients were stratified according to etiology (primary or secondary) of pulmonary hypertension and by baseline NYHA class. The following table shows the number of subjects according to these strata.

TT 8: Patient distribution over predefined strata (randomization) – ITT population

	PPH		SPH	
NYHA functional class III	70		50	
	Iloprost: 34	placebo: 36	Iloprost: 26	placebo: 24
NYHA functional class IV	38		45	
	Iloprost: 19	placebo: 19	Iloprost: 22	placebo: 23

Data based on Section 14.1, Table 3

Baseline walk test

There was no restriction on the distance eligible patients could cover in the 6 minute test at baseline. The table below shows baseline means and medians by strata and treatment group.

TT 19: Baseline walking distance by predefined strata – ITT population

Predefined stratum	Treatment	n	Mean	SD	Min	Median	Max
PPH/III	Iloprost	34	356.6	91.0	130.0	351.5	485.0
	Placebo	36	356.7	69.9	202.0	364.0	502.0
	Overall	70	356.6	80.3	130.0	360.0	502.0
PPH/IV	Iloprost	19	281.4	105.0	110.0	281.0	448.0
	Placebo	19	262.0	65.6	117.5	260.0	403.0
	Overall	38	271.7	86.9	110.0	262.5	448.0
SPH/III	Iloprost	26	355.0	83.4	155.0	357.5	490.0
	Placebo	24	353.7	87.4	140.0	366.5	491.0
	Overall	50	354.4	84.5	140.0	360.0	491.0
SPH/IV	Iloprost	22	312.4	76.6	150.0	329.5	488.0
	Placebo	23	254.0	111.5	84.0	237.0	477.0
	Overall	45	282.5	99.4	84.0	276.0	488.0

Data based on Section 14.2.1, Table 44

Mean walking distances for PPH/III and SPH/III were around 355 meters; for PPH/IV and SPH/IV means were around 25 meters less. Both PPH and SPH class IV placebo groups at baseline walked somewhat less than their iloprost counterparts (262.0 m vs. 281.4 m and 254.0

vs. 312.4 m, respectively). The walking distances were similar across treatment groups for the class III.

Baseline dyspnea index

This index rated severity of dyspnea at a single state. The scores are drawn from 3 categories graded 0 to 4. The worst case would be 0 and the best would be 12.

- Category 1: functional impairment - grades from 0 (very severe) to 4 (unimpaired)
- Category 2: magnitude of task - grades from 0 (none) to 4 (extraordinary)
- Category 3: magnitude of effort - grades from 0 (none) to 4 (extraordinary)

The ratings for each of the three categories are added to form a baseline focal score (range from 0 to 12).

TT 23: Baseline dyspnea focal scores by predefined strata – ITT population

Predefined stratum	Treatment	n	Mean	SD	Min	Median	Max
PPH/III	Iloprost	34	5.1	1.5	3.0	5.5	9.0
	Placebo	36	5.0	1.3	3.0	5.0	7.0
	Overall	70	5.1	1.4	3.0	5.0	9.0
PPH/IV	Iloprost	19	2.7	0.7	1.0	3.0	4.0
	Placebo	19	3.2	1.1	2.0	3.0	6.0
	Overall	38	2.9	1.0	1.0	3.0	6.0
SPH/III	Iloprost	26	5.0	1.8	2.0	5.0	11.0
	Placebo	24	5.3	1.5	2.0	6.0	8.0
	Overall	50	5.2	1.7	2.0	5.5	11.0
SPH/IV	Iloprost	22	2.7	1.2	0.0	3.0	5.0
	Placebo	23	2.9	1.9	0.0	3.0	7.0
	Overall	45	2.8	1.6	0.0	3.0	7.0

Mean baseline scores were around 5.1 for both NYHA III groups and around 2.9 for the class IV groups.

PHT diagnosis by type of PHT

Etiologies for the PHT are shown below by treatment group.

Table 13: PHT diagnosis by type of PHT – ITT population

PHT Diagnosis	Iloprost	Placebo
Overall	101 (100.0%)	102 (100.0%)
Number of patients		
Diagnosis		
sporadic	47 (46.5%)	43 (42.2%)
post partum	1 (1.0%)	1 (1.0%)
familiar	2 (2.0%)	3 (2.9%)
appetite suppressants	4 (4.0%)	5 (4.9%)
HIV	0 (0.0%)	0 (0.0%)
other PPH	1 (1.0%)	4 (3.9%)
SS	3 (3.0%)	5 (4.9%)
CREST	4 (4.0%)	13 (12.7%)
SLE	1 (1.0%)	1 (1.0%)
overlap and other	5 (5.0%)	3 (2.9%)
thromboembolic	33 (32.7%)	24 (23.5%)

The most common etiologies were sporadic PHT and thromboembolic PHT. More iloprost patients had thromboembolic (33, 32.7%) etiology compared to placebo (24, 23.5%). More placebo (13, 12.7%) than iloprost (4, 4.0%) patients were diagnosed with CREST.

Duration of disease

Table 16: Duration of PHT disease (months) by type of PHT and NYHA class – ITT population

PHT / NYHA class	Treatment	N	Mean	SD	Min	Median	Max	Miss
Overall	Iloprost	101	24.5	38.8	1	9.0	243	0
	Placebo	102	19.8	34.1	0	7.5	258	0
	Overall	203	22.2	36.5	0	6.0	258	0
PPH / III	Iloprost	34	18.3	42.7	1	5.5	243	0
	Placebo	36	15.3	22.7	0	6.5	93	0
	Overall	70	16.7	33.7	0	6.0	243	0
PPH / IV	Iloprost	19	32.6	48.5	1	6.0	169	0
	Placebo	19	6.3	9.6	1	2.0	38	0
	Overall	38	19.4	37.0	1	3.0	169	0
SPH / III	Iloprost	28	28.0	34.1	1	10.0	154	0
	Placebo	24	26.4	27.8	2	17.0	105	0
	Overall	50	26.2	30.9	1	11.5	154	0
SPH / IV	Iloprost	22	25.5	27.7	1	14.0	85	0
	Placebo	23	31.3	57.1	0	13.0	258	0
	Overall	45	28.4	44.8	0	13.0	258	0

The mean duration of disease was somewhat higher in the overall iloprost group compared to the overall placebo group (24.5 months and 19.8 months, respectively).

Mean daily dose of study medication and frequency of inhalation

The maximum allowed total daily dose was 45 ug. The mean daily dose at week 12 for the iloprost group (n=96) was 34.97 ug and 36.91 ug for the placebo group (n=85). Table 21

At week 12, most patients, regardless of treatment group, were receiving the maximum 5 ug dose (88, 90.7% iloprost and 83, 94.3%). Table 19

The maximum number of allowed inhalations was 9. Mean frequency of inhalation for both treatment groups at week 12 were similar (approximately 7.5) Table 20. At week 12, 8 iloprost and 9 placebo patients reported using the inhaler at night either occasionally or regularly. Table 19.

Concomitant PHT medications

Percents of patients by treatment group receiving medication for PHT at baseline are shown below.

Medication	Iloprost (%)	Placebo (%)
Anticoagulant	84.2	79.4
Calcium antagonist	41.6	46.1
Diuretic	65.3	68.6
Digitalis	25.7	16.7
Steroids	11.9	12.7
ACE antagonist	23.8	26.5

Long term O ₂ therapy	45.5	43.1
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Table 23 and 24

The majority of patients were receiving an anticoagulant and a diuretic. The treatment groups were well balanced.

Few patients were smokers (iloprost 6.9%, placebo 2.9%)

Efficacy

The primary efficacy endpoint was the combined responder rate. A responder was a patient who had the following changes at week 12:

- a) Improvement in exercise capacity (6-minute walking test) at 12 weeks (performed 30 minutes after inhalation) by at least 10% versus baseline **and**
- b) Improvement by at least one NYHA class at 12 weeks versus baseline **and**
- c) No deterioration of PHT, or death at any time before 12 weeks.

Patients were classified as non-responders if:

- they prematurely discontinued the study medication because of the defined criteria of deterioration or because of treatment with not allowed concomitant prostanoid medication during the study period, or
- they had missing information for the primary endpoint;

Patients who left the study prematurely for any reason were defined as non-responders for the primary endpoint.

Patients assigned a value of 0 meters for their baseline exercise capacity assessment who showed any improvement at 12 weeks satisfied the first part of the combined responder criterion (improvement by 10%).

Patients who received a lung or heart and lung transplantation during the study period were considered not assessable for efficacy if this was only due to transplant availability.

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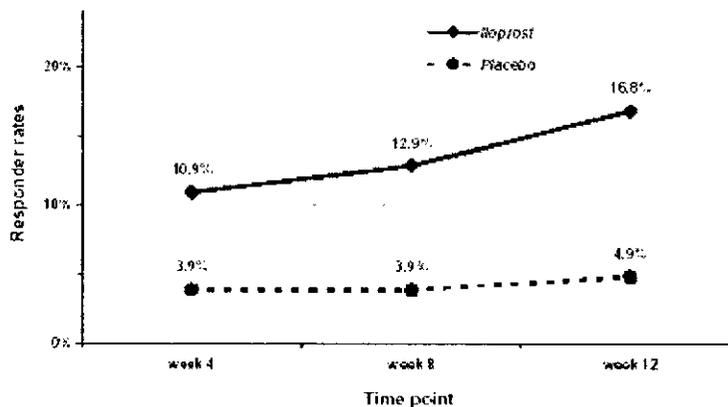
Table 28: Summary of the primary endpoint and components, statistical analysis – ITT population

Endpoint	Primary analysis	Result	Secondary analyses	Result
combined responder endpoint	stratified Mantel-Haenszel test	treatment: p = 0.007 odds ratio 3.970 {1.466;10.750}	logistic regression model	treatment: p = 0.011 other prognostic factors: n.s.
Walking distance (>10% improvement)	stratified Mantel-Haenszel test	treatment: p = 0.059		
NYHA class (≥1 class improvement)	stratified Mantel-Haenszel test	treatment: p = 0.032		
Mortality (until week 12)	Fisher's exact test (pooled data)	treatment: p = 0.369		
Deterioration	Fisher's exact test (pooled data)	treatment: p = 0.407		

The overall responder rates for the combined analysis were iloprost 16.8% (17/101) and placebo 4.9% (5/102) with two-side p=0.007.

Overall responders at individual time points

The figure below shows the percent of responders, by treatment group, at weeks 4, 8 and 12.



The difference in response rate between study groups was evident by the first 4 weeks of treatment (10.9% iloprost vs. 3.9% placebo). This difference continued to increase at the 8 week (12.9% vs. 3.9%) and 12 week (16.8% vs. 4.9%) visits.

The results by strata are shown below.

TT 33: Combined responder criterion by predefined strata – ITT population

Stratum	Iloprost (n = 101)		Placebo (n = 102)	
	Responders		Responders	
PPH/III	5/34	14.7%	2/36	5.6%
PPH/IV	6/19	31.6%	1/19	5.3%
SPH/III	5/26	19.2%	2/24	8.3%
SPH/IV	1/22	4.5%	0/23	0.0%
All	17/101	16.8%	5/102	4.9%

Placebo subtracted responder rates by etiology and NYHA class are shown below:

stratum	Response rates (%) placebo subtracted
PPH/III	9.1
PPH/IV	26.3
SPH/III	10.9
SPH/IV	4.5
Overall	11.9

The iloprost group responded better to treatment compared to the placebo group regardless of stratum.

Individual iloprost responders are shown below.

Pt no./etiology/dose	Dose No. inhal x ug	walk test baseline/ endpoint meters	Walk test improvement meters (percent)	NYHA class B/E^
12/PPH	9 x 5	330/432	102 (30.9)	IV/III
48/SPH	6 x 2.5	280/310	30 (10.7)	III/II
54/PPH	6 x 5	430/500	70 (16.3)	IV/II
59/PPH	9 x 5	304/406	102 (33.6)	III/II
67/PPH	6 x 5	470/530	60 (12.8)	III/II
82/SPH	6 x 5	431/477	46 (10.7)	III/II
90/SPH	9 x 5	432/480	48 (11.1)	III/II
92/PPH	9 x 5	410/488	78 (19.0)	III/II
93/PPH	9 x 5	370/427	57 (15.4)	IV/III
104/PPH	9 x 5	281/390	109 (38.8)	IV/III
137/SPH	8 x 5	350/444	94 (26.9)	III/II
147/SPH	6 x 5	276/315	39 (14.1)	IV/III
161/PPH	6 x 5	130/300	170 (131)	III/II
197/PPH	9 x 5	454/504	50 (11.0)	III/II
348/PPH	9 x 5	240/469	229 (95.7)	IV/III
386/SPH	9 X 2.5	318/365	47 (14.8)	III/II
397/PPH	6 x 5	210/400	190 (90.5)	IV/III

^B/E: baseline/endpoint
Tables 36 and 42

Dosing

Of the 17 iloprost responders, 8 patients received 45 µg daily (the maximum allowed dose) during the entire course of the treatment period, 1 received 40 µg, 6 patients received 30 µg daily, 1 received 22.5 µg and 1 received 15 µg. This finding tends to point to urging the use of higher doses. Only three iloprost responders changed their dosage regimen during the treatment period.

Of the 5 placebo responders, 3 patients received the highest dose of 45 µg daily, one patient received 30 µg daily and the fifth patient changed his dosage regimen twice during the treatment period.

Nonresponders because of missing data

There were 11 patients with missing information (9 placebo and 2 iloprost) and therefore counted as not reaching the combined responder endpoint. Four patients (1 iloprost and 3 placebo) did not have their walking distance assessed at week 12. These are shown below.

Table 37: Individual response according to defined criterion / patients with missing data either only for walking distance or only for NYHA class at week 12 – ITT population

SUBJECT	Treatment	PHT / NYHA class	6-min walk at baseline	6-min walk at week 12	change in walking distance[%]	NYHA Functional Class at baseline	NYHA Functional Class at week 12	Change in NYHA Class	Deterioration up to 12 weeks	Premature Disc. of Study Med.	Death Phase	Responder
176	Placebo	PPH / IV	205			IV	IV	0	no	no	alive	no
238	Iloprost	PPH / IV	204			IV	IV	0	no	no	alive	no
387	Placebo	SPH / IV	176			IV	III	-1	no	yes	death	FP
411	Placebo	PPH / III	250			III	IV	1	no	no	alive	no

*Responder definition: Improvement of exercise capacity (6-minute walking test) at 12 weeks by at least 10% versus baseline, and improvement by at least one NYHA class versus baseline at 12 weeks, and no deterioration of PHT or death at any time before 12 weeks.
RP = Randomized Phase FP = Follow-up Phase

Seven patients had prematurely discontinued the study before week 12 without prior deterioration or death: one iloprost patient (# 55 (lack of effect)) and 6 placebo patients (#11 (adverse events), #30 (adverse events), #53 (withdrawal of consent), #124 (lack of effect), #240 (other) and #267 (death)).

Secondary endpoints

The following secondary endpoints were listed in the following order in the protocol: exercise capacity, NYHA class, dyspnea index, hemodynamic parameters (PVR, mPAP, CO) and gas exchange (SVO2), deterioration of PHT, mortality, need for transplantation, quality of life (QoL). There was no statistical plan for analyzing these endpoints.

Walk test

Walk test responders (defined as improvement in 6-minute walking test at 12 weeks by at least 10% versus baseline) are shown below. Those unable to walk because of defined deterioration or death were assigned a value of 0 meters.

Table 29: Response in walking distance by predefined strata –ITT population

Stratum	Iloprost (n = 101)		Placebo (n = 102)		Overall (n = 203)	
	response	no response	response	no response	response	no response
PPH/III (n=70)	16 47.1%	18 52.9%	10 27.8%	26 72.2%	26 37.1%	44 62.9%
PPH/IV (n=38)	10 52.6%	9 47.4%	7 36.8%	12 63.2%	17 44.7%	21 55.3%
SPH/III (n=50)	9 34.6%	17 65.4%	7 29.2%	17 70.8%	16 32.0%	34 68.0%
SPH/IV (n=45)	3 13.6%	19 86.4%	2 8.7%	21 91.3%	5 11.1%	40 88.9%
All strata (n=203)	38 37.6%	63 62.4%	26 25.5%	76 74.5%	64 31.5%	139 68.5%

Data based on Section 14.2.1, Table 39

Compared to placebo, there were more walk responders in the iloprost group, regardless of stratum (all patients: 37.6% iloprost versus 25.5% placebo).

The absolute changes from baseline in walking distance for the 2 treatment groups are shown below. (There was a statistically significant imbalance in the baseline walk distance: iloprost 356.5 m and the placebo 331.0 m. (report page 72)

Table 45: 6-minute walk : absolute change to baseline by type of PHT – ITT population

PHT Diagnosis	Timepoint	Treatment	N	Mean	SD
Overall	Week 4 after	Iloprost	99	24.433	51.184
		Placebo	99	6.125	63.235
		Overall	198	15.280	58.115
	Week 8 after	Iloprost	99	24.058	68.155
		Placebo	90	4.081	63.828
		Overall	189	14.544	66.754
	Week 12 before	Iloprost	91	14.589	67.759
		Placebo	82	0.177	67.298
		Overall	173	7.757	67.730
	Week 12 after	Iloprost	95	22.262	71.441
		Placebo	85	-3.319	74.204
		Overall	180	10.150	73.671
PEOT before		Iloprost	1	55.000	
		Placebo	4	85.250	74.799
		Overall	5	79.200	66.176
PEOT after		Iloprost	2	-50.000	63.640
		Placebo	7	-97.286	53.027
		Overall	9	-87.889	54.432

before = before inhalation after = after inhalation
 PEOT = pressure end of study treatment
 change to baseline = post - pre

Best Possible Copy

Peak

The iloprost group walked about 22-24 m longer compared to baseline 30 minutes after inhalation (peak effect) at weeks 4, 8 as well as at 12. Placebo group walked 4-6 m longer except at week 12 when they walked less compared to baseline (-3.3 m).

Trough

The trough effect (before inhalation) for iloprost at week 12 produced a smaller increase in walk distance (14.6 m) compared to peak (22.4 m). In contrast, the placebo group at trough walked about the same distance as they had walked at baseline (0.2 m).

16 iloprost and 17 placebo patients did not have walk test at endpoint

The sponsor investigated the influence of different variables on the changes in walk distance. They found that those receiving iloprost and those with a higher baseline test predicted a longer walk test at endpoint.

Walk test by strata

TT 39: Six-minute walking distance – absolute change from baseline to week 12 by type of PHT – ITT population

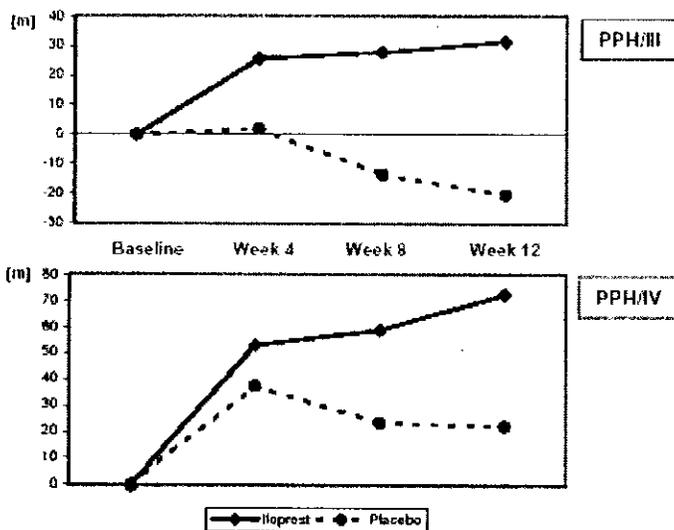
Time point*	Treatment	n	Mean	SD	Median
PPH	Iloprost	49	44.7	74.0	31.0
	Placebo	46	-7.4	90.0	2.0
SPH	Iloprost	46	-1.8	60.7	10.5
	Placebo	39	1.5	50.3	0.0

Data based on Section 14.2.1, Table 45

Only available patients appear in this table (cf. Figure TF 2).

* The walking test was performed after inhalation.

Only the patients with PPH improved their (mean) walk test. The figure below shows changes in the walk test for the PPH group at the various time points, by NYHA class.



Data based on Section 14.2.1, Table 46

Only the values for the walking tests after the end of inhalation are shown.

TF 8: PPH groups: six-minute walking distance – mean absolute change to baseline – ITT population

NYHA class III patients who received placebo walked either the same or a shorter distance compared to baseline at every time point. The iloprost group improved their walk distance at week 4 with the effect leveling off by week 8.

On the other hand, NYHA class IV patients who received iloprost experienced a greater increase in walk distance at all time points. The placebo group had an initial response followed by a decline starting at week 4.

Classified percent change

Classified percent change from baseline is shown below (table 48) at week 12 after inhalation (peak) and before inhalation (trough), by treatment group.

PHT / NYHA class	Timepoint		iloprost	Placebo
Overall	Week 12 after	change in walking distance[%]		
		Number of subjects	101 (100.0%)	100 (100.0%)
		< -50	3 (3.0%)	2 (2.0%)
		-50 to -10	11 (10.9%)	24 (24.0%)
		-10 to +10	45 (44.6%)	33 (33.0%)
		+10 to +50	28 (27.7%)	20 (20.0%)
		> +50	8 (7.9%)	6 (6.0%)
missing	6 (5.9%)	15 (15.0%)		
	Week 12 before	change in walking distance[%]		
		Number of subjects	101 (100.0%)	100 (100.0%)
		< -50	0 (0.0%)	2 (2.0%)
		-50 to -10	12 (11.9%)	22 (22.0%)
		-10 to +10	47 (46.5%)	33 (33.0%)
		+10 to +50	27 (26.7%)	19 (19.0%)
		> +50	5 (5.0%)	6 (6.0%)
missing	10 (9.9%)	18 (18.0%)		

Peak

The incidence rates for patients who walked < 10 m longer at endpoint (peak) were nearly identical for the 2 treatment groups: 58.4% (59/101) for iloprost and 57.8% (59/102) for placebo. The rates for those who walked \geq 10 m were 35.6% (36/101) for iloprost and 25.5% (26/102) for placebo.

Trough

The incidence rates for patients who walked < 10 m longer at trough were similar for both treatment groups. Of the iloprost group, 31.7% (32/101) of patients had > 10% improvement over baseline at week 12. This was greater than that for placebo patients (24.5%, 25/102). The numbers of patients with missing data were high for both groups.

NYHA classification

Patients eligible for the study were limited to those in NYHA class III or IV at baseline. (Baseline assessment of NYHA class was performed at the screening visit if the baseline visit took place no later than one week after the screening visit. If the baseline visit took place more than one week after the screening visit, the classification was to be repeated at the baseline visit and that value served as the baseline value.)

Response is defined as improving at least 1 step in the NYHA class. The changes in class by etiology, baseline NYHA class, and treatment group are shown below.

Table 30: Response in NYHA class by predefined strata – ITT population

Stratum	Iloprost (n = 101)		Placebo (n = 102)		Overall (n = 203)	
	response	no response	response	no response	response	no response
PPH/III (n=70)	7 20.6%	27 79.4%	2 5.6%	34 94.4%	9 12.9%	61 87.1%
PPH/IV (n=38)	6 31.6%	13 68.4%	2 10.5%	17 89.5%	8 21.1%	30 78.9%
SPH/III (n=50)	8 30.8%	18 69.2%	4 16.7%	20 83.3%	12 24.0%	38 76.0%
SPH/IV (n=45)	4 18.2%	18 81.8%	5 21.7%	18 78.3%	9 20.0%	36 80.0%
All strata (n=203)	25 24.8%	76 75.2%	13 12.7%	89 87.3%	38 18.7%	165 81.3%

Data based on Section 14.2.1, Table 39

In all groups, iloprost was shown to be superior to placebo. The response rate for the iloprost groups ranged between 18.2% and 30.8%. For all iloprost strata, the rate was 24.8% with a nonresponse rate of 75.2% meaning the vast majority did not improve despite receiving iloprost.

The response rate for the placebo groups ranges between 5.6% and 21.7%. For the all placebo strata, the rate was 12.7%. An iloprost recipient was about twice as likely to improve their NYHA class as the placebo patient.

Baseline NYHA III

Changes in patients with NYHA class III heart failure at baseline are shown below by treatment group at weeks 4, 8, and 12.

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Class III at baseline: no. and (percent) of patients

	NYHA class [^]	Iloprost	placebo
Week 4	No. of subjects	60	58
	II	6 (10.0)	1 (1.7)
	III	52 (86.7)	54 (93.1)
	IV	2 (3.3)	3 (5.2)
Week 8	No. of subjects	60	55
	II	7 (11.7)	5 (9.1)
	III	47 (78.3)	43 (78.2)
	IV	6 (10.0)	7 (12.7)
Week 12	No. of subjects	58	54
	II	15 (25.9)	6 (11.1)
	III	37 (63.8)	40 (74.1)
	IV	6 (10.3)	8 (14.8)

[^]no patient at any time point was classified as NYHA class I

Table 54

Ten percent of iloprost patients shifted from class III to class II by 4 weeks compared to 1.7% placebo. By week 12, the percent of improved iloprost patients more than doubled (25.9% compared to placebo 11.1%).

By week 12, 10.3% of the iloprost patients had become worse (i.e., shifted to class IV). The incidence rate of the placebo patients who became worse was 14.8%.

Baseline NYHA IV

Changes in patients with NYHA class IV heart failure at baseline are shown below by treatment group at weeks 4, 8, and 12.

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Class IV at baseline: no. and (percent) of patients

	NYHA class+	Iloprost	placebo
Week 4	No. of subjects	40	41
	II	1 (2.5)	1 (2.4)
	III	8 (20.0)	7 (17.1)
	IV	31 (77.5)	33 (80.5)
Week 8	No. of subjects	40 [^]	36
	II	3 (7.5)	0
	III	8 (20.0)	6 (16.7)
	IV	28 (70.0)	30 (83.3)
Week 12	No. of subjects	39 [^]	34
	II	1 (2.6)	0
	III	9 (23.1)	7 (20.6)
	IV	28 (71.8)	27 (79.4)

[^]1 iloprost patient missing

+no patient at any time point was classified as NYHA class I

Table 54

There were small differences between the treatment groups regarding improvement in this patient population at all time points. However, even these small differences always favored iloprost.

Dyspnea index

The dyspnea index was measured using an instrument referred to as Mahler². The value of this score is unknown.

The baseline value for the dyspnea index was obtained in the same manner that was used for the NYHA classification (see above).

Focal score

Briefly, this index rates the severity of dyspnea at a single state. The scores for the index depend on ratings for three different categories with five grades from 0 (very severe impairment) to 4 (unimpaired) for each of the 3 categories. The ratings for each of the three categories are added to form a baseline focal score (range from 0 to 12).

Transition score

At the transition periods (study assessment time points after baseline) changes in dyspnea for the three categories used for the baseline dyspnea index are rated by seven grades, ranging from -3 (major deterioration), to +3 (major improvement). The ratings for each of the three categories are added together to form a transitional focal score (range from -9 to +9).

² Mahler DA, Weinberg DH, Wells CK, and Feinstein AR. The Measurement of Dyspnea. Chest 1984; 85 (6): 751-758.

Table 58: Change to baseline dyspnea Index / focal score by type of PHT – ITT population (continued)

Examination: Week 12

PHT Diagnosis	Treatment	N	Mean	SD	Min	Median	Max	Miss	
Overall	absolute change	Iloprost	96	0.448	1.091	4.00	0.000	5.00	5
		Placebo	86	0.174	1.365	4.00	0.000	3.00	4
		Overall	182	0.319	1.548	4.00	0.000	5.00	21
Overall	percent change	Iloprost	95	22.262	70.815	100.00	0.000	>100.00	8
		Placebo	85	7.776	36.963	100.00	0.000	100.00	17
		Overall	180	15.421	57.892	100.00	0.000	>100.00	24

The percent change in the improvement in dyspnea score for the iloprost group (22.3%) at week 12 was 3 times better than the placebo group (7.8%).

TT 49: Descriptive statistics for Mahler dyspnea index at baseline and week 12 – ITT population

Index by subgroup	Iloprost						Placebo					
	baseline			week 12			baseline			week 12		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
focal score - PPH/III	34	5.1	1.5	33	5.7	1.6	36	5.0	1.3	33	5.1	2.0
focal score - PPH/IV	19	2.7	0.7	17	3.8	1.8	19	3.2	1.1	15	3.5	1.1
focal score - SPH/III	26	5.0	1.8	25	4.9	1.7	24	5.3	1.5	21	5.2	1.8
focal score - SPH/IV	22	2.7	1.2	21	3.4	1.5	23	2.9	1.9	17	3.3	1.9
focal score - all strata	101	4.1	1.8	96	4.6	1.9	102	4.3	1.8	86	4.5	2.0
transition score - PPH/III				33	1.5	2.3				33	0.1	3.0
transition score - PPH/IV				17	1.6	2.6				15	1.0	2.2
transition score - SPH/III				25	1.2	2.7				21	0.3	2.2
transition score - SPH/IV				21	1.5	3.0				17	0.1	1.8
transit. score - all strata				96	1.4	2.6				86	0.3	2.5

Data based on Section 14.2.1, Tables 57 and 61

Only available patients appear in this table (cf. Figure TF 2).

Cardiac hemodynamic parameters (PVR, mPAP, CO) and gas exchange (SVO2)

Effects on hemodynamic parameters and the gas exchange were measured during the week 12 catheter examination (trough and peak) and compared to baseline catheter findings.

Trough

The table below shows mean and percent changes in trough (preinhalation) variables at week 12, by treatment group.

TT 51: 12-week treatment effects in hemodynamic variables at trough drug effect
 – ITT population
 pre-inhalation values at week 12 compared to baseline
 absolute and percent change, mean ± SD

Variable	Iloprost		Placebo	
	n		n	
PVR ^a [dyn·s·cm ⁻⁵]	76	-9.2 ± 274.9	77	96.2 ± 322.8
[%]	76	2.4 ± 26.5	77	8.7 ± 29.6
PVR ^a [%]	76	-4.9 ± 156.8	75	61.0 ± 209.1
[%]	76	2.4 ± 26.8	75	9.5 ± 30.1
mPAP [mmHg]	93	-0.2 ± 7.3	82	-0.1 ± 6.9
[%]	93	0.6 ± 13.9	82	0.6 ± 14.1
CO [l/min]	91	0.1 ± 0.9	80	-0.2 ± 0.8
[%]	91	3.4 ± 25.2	80	-4.4 ± 19.4
SVO ₂ [%]	72	-1.1 ± 7.6	63	-3.2 ± 6.7
[%]	72	-1.2 ± 13.1	63	-5.2 ± 11.3

Data based on Section 14.2.1 Table

Only available patients appear in this table (cf. Figure TF 2).
 Trough values of the acute drug effect were obtained before inhalation.

Compared to placebo, the iloprost group tend to show improvement in the hemodynamic variables measured at trough.

Peak

The table below shows the hemodynamic values obtained at the end of inhalation (the last minute of inhalation) compared to week 12 pre-inhalation findings, the iloprost group only.

TT 52: Week 12 changes to baseline of hemodynamic variables at peak drug effect
 – ITT population
 absolute and percent change, mean ± SD

Variable	Iloprost aerosol (peak [†])	
	n	
PVR [dyn·s·cm ⁻⁵]	70	-238.7 ± 278.6
[%]	70	-22.7 ± 21.2
mPAP [mmHg]	90	-4.6 ± 9.3
[%]	90	-8.6 ± 17.2
CO [l/min]	89	0.5 ± 1.1
[%]	89	17.3 ± 30.8
SVO ₂ [%]	70	1.8 ± 8.3
[%]	70	3.9 ± 14.6

Only available patients appear in this table (cf. Figure TF 2).

[†] Change from baseline to last minute of inhalation at week 12 (at peak of acute drug effect)

As expected, the peak effects of iloprost on cardiac hemodynamic variables are better than the trough values.

Acute effects

All available patients regardless of treatment assignment received iloprost aerosol inhalation in order to evaluate the acute effect of iloprost aerosol at week 12.

TT 59: Analysis of acute hemodynamic response at week 12 – ITT population

Variable			Iloprost			Placebo		
			n	mean	p-value	n	mean	p-value
PVR [^]	[dyn·s·cm ⁻⁵]	abs. change	72	-211.8	0.0001	73	-204.7	0.0001
		% change						
mPAP	[mmHg]	abs. change	90	-4.5	0.0001	81	-4.9	0.0001
		% change						
CO	[l/min]	abs. change	89	0.5	0.0001	80	0.3	0.0001
		% change						
SVO ₂	[%]	abs. change	75	3.0	0.0001	64	3.8	0.0001
		% change						
SVR [^]	[dyn·s·cm ⁻⁵]	abs. change	74	-228.7	0.0001	71	-210.5	0.0001
		% change						
PVR / SVR ratio [^]		abs. change	64	-0.05	0.0001	65	-0.05	0.0001
		% change						
Blood pressure mean	[mmHg]	abs. change	87	-2.3	0.0220	76	-2.9	0.0016
		% change						
Heart rate	[beats/min]	abs. change	92	-0.5	0.4735	80	-1.0	0.1515
		% change						

Data based on Section 14.2.1, Table 66

Only available patients appear in this table (cf Figure TF 2)

t-test for comparing the mean to 0.

Absolute/percent change as compared to pre-inhalation values.

[^] Derived variable

Both groups improved their cardiac hemodynamics dramatically immediately after inhaling iloprost. The difference between groups was negligible.

Deterioration of PHT

Deterioration of the underlying disease was defined as exhibiting two or more of the following:

1. Refractory systolic arterial hypotension < 85 mmHg,
2. Worsening of right heart failure as indicated by emergence of cardiac edema, ascites or pleural effusion despite adequate background therapy,
3. Rapidly progressive cardiogenic hepatic failure (e.g. leading to an increase of SGOT and/or SGPT to > 100 U/l, total bilirubin ≥ 5 mg/dl),
4. Rapidly progressive cardiogenic renal failure (e.g. leading to a decrease of creatinine clearance to ≤ 50% of baseline value; creatinine clearance calculated from serum creatinine using the Cockcroft and Gault formula),
5. PHT-related decrease of six-minute walking distance by ≥ 30% of baseline value,
6. New and continued need for i.v. medication, e.g. catecholamines, diuretics,
7. Cardiac index ≤ 1.3 l/min/m² (right heart catheterization),
8. CVP ≥ 22 mmHg (via indwelling catheter) despite adequate diuretic therapy,
9. SVO₂ ≤ 45% despite nasal O₂ therapy (right heart catheterization).

The percent of patients who met the above criteria for deterioration are shown in the table below.

Table 70: Patients deteriorated [%] by type of PHT and NYHA class – ITT population

PHT/ NYHA class		Iloprost	Placebo	Overall
Overall	Deterioration during 12 weeks			
	Number of subjects	101 (100.0%)	102 (100.0%)	203 (100.0%)
	no	95 (94.1%)	87 (85.3%)	182 (89.7%)
	yes	5 (5.0%)	9 (8.8%)	14 (6.9%)
	not available	1 (1.0%)	6 (5.9%)	7 (3.4%)
PPH / III	Deterioration during 12 weeks			
	Number of subjects	34 (100.0%)	36 (100.0%)	70 (100.0%)
	no	32 (94.1%)	31 (86.1%)	63 (90.0%)
	yes	1 (2.9%)	4 (11.1%)	5 (7.1%)
	not available	1 (2.9%)	1 (2.8%)	2 (2.9%)
PPH / IV	Deterioration during 12 weeks			
	Number of subjects	19 (100.0%)	19 (100.0%)	38 (100.0%)
	no	17 (89.5%)	15 (78.9%)	32 (84.2%)
	yes	2 (10.5%)	1 (5.3%)	3 (7.8%)
	not available	0 (0.0%)	3 (15.8%)	3 (7.9%)
SPH / III	Deterioration during 12 weeks			
	Number of subjects	26 (100.0%)	24 (100.0%)	50 (100.0%)
	no	24 (92.3%)	23 (95.8%)	47 (94.0%)
	yes	2 (7.7%)	0 (0.0%)	2 (4.0%)
	not available	0 (0.0%)	1 (4.2%)	1 (2.0%)
SPH / IV	Deterioration during 12 weeks			
	Number of subjects	22 (100.0%)	23 (100.0%)	45 (100.0%)
	no	22 (100.0%)	18 (78.3%)	40 (88.9%)
	yes	0 (0.0%)	4 (17.4%)	4 (8.9%)
	not available	0 (0.0%)	1 (4.3%)	1 (2.2%)

Overall, there were fewer iloprost patients who deteriorated (5, 5.0%) compared to placebo (9, 8.8%).

Mortality

The number and percent of patients who died for any reason during the 12 weeks of treatment with study drug are shown below.

Table 32: Death for any reason (until week 12) by predefined strata – ITT population

Stratum	Iloprost (n = 101)		Placebo (n = 102)		Overall (n = 203)	
	died		died		died	
PPH/III (n = 70)	0	0.0%	1	2.8%	1	1.4%
PPH/IV (n = 38)	1	5.3%	1	5.3%	2	5.3%
SPH/III (n = 50)	0	0.0%	1	4.2%	1	2.0%
SPH/IV (n = 45)	0	0.0%	1	4.3%	1	2.2%
All strata (n = 203)	1	1.0%	4	3.9%	5	2.5%

There were fewer deaths in the iloprost group (1, 1.0%) compared to the placebo group (4, 3.9%).

Newly scheduled for transplantation

Patients newly entered into a transplantation list were counted as having developed the "need for transplantation". The number and percent of patients who were scheduled (and/or accepted) by 12 weeks and by 16 weeks are shown below, by treatment group.

PHT Diagnosis		Iloprost	Placebo
Overall	Number of patients	101 (100.0%)	102 (100.0%)
	scheduled up to 12 weeks		
	no	96 (95.0%)	90 (88.2%)
	yes	2 (2.0%)	4 (3.9%)
	not available	3 (3.0%)	8 (7.8%)
	scheduled up to 16 weeks		
	no	91 (90.1%)	84 (82.4%)
	yes	3 (3.0%)	2 (2.0%)
	not available	7 (6.9%)	15 (15.7%)
	accepted up to 12 weeks		
	no	98 (97.0%)	91 (89.2%)
	yes	0 (0.0%)	3 (2.9%)
	not available	3 (3.0%)	8 (7.8%)
	accepted up to 16 weeks		
	no	93 (92.1%)	84 (82.4%)
	yes	1 (1.0%)	2 (2.0%)
	not available	7 (6.9%)	16 (15.7%)

Table 74

The results for the 2 groups are similar.

Quality of life

The vehicles used to assess quality of life included the Minnesota Living with Heart Failure Questionnaire adapted for PHT (MLHF/PHT), the 12-Item Short Form Health Survey (SF-12) and the EuroQoL (consisting of EQ-5D and EQ-VAS).

TT 62: Descriptive statistics for quality of life scales at baseline and week 12 – ITT population

Scale	Iloprost						Placebo					
	baseline			week 12			baseline			week 12		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
MLHF/PHT total score	100	36.05	16.9	96	34.72	20.7	100	36.86	17.9	85	33.88	17.0
MLHF/PHT physical score	100	26.96	8.8	96	23.63	10.7	100	26.87	10.9	85	24.52	10.5
MLHF/PHT emotional score	99	14.84	7.5	95	13.89	7.8	99	14.93	7.7	84	13.68	8.0
SF-12 physical score	88	30.64	8.5	84	31.88	8.9	81	29.54	7.7	70	32.30	8.5
SF-12 mental score	88	43.89	12.4	84	46.46	11.7	81	45.68	12.0	70	44.34	12.3
EQ-5D health state	98	0.493	0.28	93	0.578	0.27	99	0.558	0.29	83	0.560	0.31
EQ-5D visual analog scale	100	46.88	15.9	96	52.79	19.1	100	48.57	16.9	83	47.39	21.1

Data based on Section 14.2.1, Tables 76, 78 and 82

Only available patients appear in this table (cf. Figure TF 2).

The scores for the 3 vehicles at baseline and week 12 are similar for both treatment groups.

SAFETY

Serious Safety

Deaths

During the first 12 weeks there were 5 deaths (1 iloprost and 4 placebo)

Patients who died during first 12 weeks

Study treatment	Pt#/age/sex/NYHA class	Comments
Iloprost	28/27/M/IV with dyspnea at rest	Decrease in blood pressure and in 6 min walk distance after 2 nd dose. Drug discontinued. Died 2 days later.
Placebo	257/47/M/IV	MI experienced about 1 week after start of placebo
Placebo	331/52/M/III	Possible pulmonary embolism after 12 weeks on placebo
Placebo	442/60/F/IV	Respiratory failure followed by cardiac arrest after 10 weeks on placebo.
Placebo	123/24/F/	On placebo for 8 weeks. Developed right heart failure with widespread edema, dyspnea, anuria, hypoxia. Died 10 days later.

From 14.3.3 narratives

Patient #28 with NYHA class IV heart failure at baseline was withdrawn from study after receiving the 2nd dose of iloprost because of drop in blood pressure and exercise intolerance. The patient's pre dosing blood pressure was 105/70 mmHg and a heart rate 97 bpm and at baseline he was described as being "severely ill". After the first dose, his blood pressure was recorded as 100/70 mmHg with heart rate 120 bpm. The second dose was given 2hr 15 min later and this was followed by a decrease in blood pressure of "moderate intensity" (value not given) and decrease in 6 min walk test. He was discontinued from the study and started on off-label iloprost 100 ug/day and furosemide. Improvement was reported but acute right heart failure developed and despite a resuscitation attempt he died 2 days later. Autopsy reported cause of death as acute decompensated cor pulmonale.

There were 4 deaths (2 iloprost and 2 placebo) between weeks 12 and 16.

Iloprost patient #79 died 2 days after the 12 week visit. His condition deteriorated about 11.5 weeks into the study during which he became edematous, declined mentally, and was hospitalized. Cause of death was reported as cor pulmonale.

Iloprost patient #245 died of bronchopneumonia and pulmonary fibrosis about month after finishing the trial.

Serious adverse events

The table below shows the serious adverse events that were reported by ≥ 2 iloprost patients and the incidence rate for the iloprost patients was $\geq 2\%$ more compared to placebo patients.

Number and (percent) of patients

Serious event	Iloprost n= 101	Placebo n=102	Placebo subtracted %
Any serious event	28 (27.7)	25 (24.5)	3.2
Syncope	5 (5.0)	0	5.0
Abnormal lab test	2 (2.0)	0	2.0
Pneumonia	2 (2.0)	0	2.0

Table 136

The incidence rate of serious adverse events was slightly higher for iloprost patients. Syncope was the only noteworthy event.

Discontinuation because of adverse event

Patients who discontinued because of an adverse event are shown below.

Study treatment	Pt#/age/sex/NYHA class	Comments
Iloprost	28/27/M/IV	Had 2 doses of drug on day 1 with decrease in BP and decreased walking distance. Died 2 days later.
Iloprost	55/67/M/III	Reported deterioration of exercise and breathlessness at week 8. ECG showed supraventricular tachycardia.
Iloprost	351/22/F/IV	Developed edema, syncope, hypotension at week 8
Placebo	11/34/F/	Worsening of symptoms at week 5
Placebo	30/35/F	Worsening of symptoms at week 7
Placebo	123/24/F	Developed edema, hypoxemia and hepatomegaly at week 8. Progressed to worsening renal function. See death
Placebo	201/62/F	Developed edema, toxic digoxin levels at week 10.
Placebo	239/68/F/III	Anxiety and breathlessness. Switched to iloprost and died 1 month later
Placebo	253/38/M/III	Pleuritic chest pain, lethargy, sweats, headache at week 3.
Placebo	256/54/F/III	Supraventricular tachycardia after 2 days of

		treatment
Placebo	387/70/M/IV	worsening edema after 20 days of treatment

Table 1 and 14.3.3 narratives

Adverse events were the reason for premature discontinuation of study medication in 3.0% (3/101) of iloprost patients and 7.8% (8/102) of placebo patients. Mostly, patients had worsening symptoms of their underlying PHT. Patient #28 withdrew after second dose of iloprost because of decreasing blood pressure and decreasing walk capacity. He was started on off-label iloprost with some improvement, but died of acute right heart failure 2 days later.

All adverse events

The following table shows events reported by at least 2 iloprost patients and reported by at least 2% more iloprost patients compared to placebo patients.

Number and (percent) of patients

Adverse Event	Iloprost n=101	Placebo n=102	Placebo subtracted %
Any event	91 (90.1)	90 (88.2)	1.9
Vasodilation	27 (26.7)	9 (8.8)	17.9
Cough increased	39 (38.6)	26 (25.5)	13.1
Headache	30 (29.7)	20 (19.6)	10.1
Trismus	12 (11.9)	3 (2.9)	9.0
Insomnia	8 (7.9)	2 (2.0)	5.9
Nausea	13 (12.9)	8 (7.8)	5.1
Hypotension	11 (10.9)	6 (5.9)	5.0
Vomiting	7 (6.9)	2 (2.0)	4.9
Alk phos increased	6 (5.9)	1 (1.0)	4.9
Flu syndrome	14 (13.9)	10 (9.8)	4.1
Back pain	7 (6.9)	3 (2.9)	4.0
Abnormal lab test	7 (6.9)	3 (2.9)	4.0
Tongue pain	4 (4.0)	0	4.0
Palpitations	7 (6.9)	4 (3.9)	3.0
Syncope	8 (7.9)	5 (4.9)	3.0
GGT increased	6 (5.9)	3 (2.9)	3.0
Muscle cramps	6 (5.9)	3 (2.9)	3.0
Hemoptysis	5 (5.0)	2 (2.0)	3.0
Pneumonia	4 (4.0)	1 (1.0)	3.0
Tachycardia	5 (5.0)	3 (2.9)	2.1
Aggravation reaction	8 (7.9)	6 (5.9)	2.0
Abdominal pain	8 (7.9)	6 (5.9)	2.0
Accidental injury	2 (2.0)	0	2.0
Face edema	2 (2.0)	0	2.0
GI disorder	3 (3.0)	1 (1.0)	2.0

WBC abnormal	2 (2.0)	0	2.0
Myalgia	2 (2.0)	0	2.0
Pharyngitis	3 (3.0)	1 (1.0)	2.0
Rhinitis	2 (2.0)	0	2.0
Pleural effusion	2 (2.0)	0	2.0
Gynecomastia	2 (2.0)	0	2.0
Rash	8 (7.9)	6 (5.9)	2.0
Burning sensation-skin	2 (2.0)	0	2.0
Dry skin	2 (2.0)	0	2.0
Hair disorder	2 (2.0)	0	2.0
Eye pain	2 (2.0)	0	2.0

Table 135

The events reported by at least 8 iloprost patients and reported by $\geq 5\%$ more iloprost than placebo patients include vasodilation, cough increased, headache, trismus, insomnia, nausea, and hypotension.

Laboratory abnormalities

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14.3.4 Abnormal laboratory value listing (each patient)

Table 171: Abnormal laboratory values reported as AEs at any time point during the treatment period (until week 12) and during the study period (until week 16)

Event		Iloprost n = 101	Placebo n = 102
Laboratory test abnormal	Treatment period	7/101 (6.9%)	3/102 (2.9%)
Liver function test abnormal	Treatment period	4/101 (4.0%)	5/102 (4.9%)
	Study period	4/101 (4.0%)	6/102 (5.9%)
Thrombocytopenia	Treatment period	0/101 (0.0%)	1/102 (1.0%)
Thrombocytopenia	Study period	0/101 (0.0%)	1/102 (1.0%)
Erythrocytes abnormal	Treatment period	0/101 (0.0%)	1/102 (1.0%)
Polycythemia	Treatment period	1/101 (1.0%)	1/102 (1.0%)
Leukopenia	Treatment period	0/101 (0.0%)	1/102 (1.0%)
WBC abnormal	Treatment period	2/101 (2.0%)	0/102 (0.0%)
Alkaline phosphatase increased	Treatment period	6/101 (5.9%)	1/102 (1.0%)
	Study period	6/101 (7.9%)	2/102 (2.0%)
Creatine phosphokinase increased	Treatment period	1/101 (1.0%)	1/102 (1.0%)
Gamma-GT increased	Treatment period	6/101 (5.9%)	3/102 (2.9%)
	Study period	7/101 (6.9%)	3/102 (2.9%)
SGOT increased	Treatment period	1/101 (1.0%)	0/102 (0.0%)
Electrolyte abnormality	Treatment period	0/101 (0.0%)	1/102 (1.0%)
Hyperkalemia	Treatment period	2/101 (2.0%)	2/102 (2.0%)
Hypokalemia	Treatment period	2/101 (2.0%)	3/102 (2.9%)
Creatinine increased	Treatment period	0/101 (0.0%)	1/102 (1.0%)
Hyponatremia	Treatment period	0/101 (0.0%)	1/102 (1.0%)
	Study period	0/101 (0.0%)	2/102 (2.0%)
Bilirubinemia	Treatment period	3/101 (3.0%)	3/102 (2.9%)
Globulin decreased	Treatment period	1/101 (1.0%)	0/102 (0.0%)
Hyperuricemia	Treatment period	0/101 (0.0%)	3/102 (2.9%)

Data based on Section 14.3.1, Tables 149 and 150

Number of patients with event/number of patients at risk are given.

Events occurred during the treatment period, except when indicated for the study period

Laboratory abnormalities that were reported as adverse events by at least 2 iloprost patients and the iloprost patients had $\geq 2\%$ incidence rate compared to the placebo group include abnormal WBC (2%)³, alkaline phosphatase increase (4.9% after 12 weeks and 5.9% after 16 weeks), and gamma GT increase (3% after 12 weeks and 4% after 16 weeks).

Abnormal laboratory changes tended to be minor and mostly reversible at follow up (table 172).

Vital signs

Abnormal vital signs reported as adverse events are shown in the table below.

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³ Rates are placebo subtracted

Table 174: Incidence of abnormal vital signs reported as AEs (syncope, hypotension, hypertension, arrhythmia) at any time point during the treatment period (until week 12) and during the study period (until week 16)

Event		Iloprost n = 101	Placebo n = 102
Hypotension	Treatment period	11/101 (10.9%)	6/102 (5.9%)
	Study period	11/101 (10.9%)	8/102 (7.8%)
Syncope	Treatment period	8/101 (7.9%)	5/102 (4.9%)
	Study period	9/101 (8.9%)	6/102 (5.9%)
Palpitation	Treatment period	7/101 (6.9%)	4/102 (3.9%)
	Study period	7/101 (6.9%)	5/102 (4.9%)
Tachycardia	Treatment period	5/101 (5.0%)	3/102 (2.9%)
Hypertension	Treatment period	3/101 (3.0%)	4/102 (3.9%)
	Study period	4/101 (4.0%)	4/102 (3.9%)
Postural hypotension	Treatment period	1/101 (1.0%)	2/102 (2.0%)
Arrhythmia	Treatment period	1/101 (1.0%)	0/102 (0.0%)
	Study period	2/101 (2.0%)	0/102 (0.0%)
Bradycardia	Treatment period	1/101 (1.0%)	1/102 (1.0%)
	Study period	1/101 (1.0%)	2/102 (2.0%)
Supraventricular tachycardia	Treatment period	1/101 (1.0%)	2/102 (2.0%)
Heart arrest	Treatment period	0/101 (0.0%)	1/102 (1.0%)
Shock	Treatment period	0/101 (0.0%)	1/102 (1.0%)
	Study period	1/101 (1.0%)	1/102 (1.0%)
Weight gain	Treatment period	1/101 (1.0%)	1/102 (1.0%)
Weight loss	Treatment period	0/101 (0.0%)	1/102 (1.0%)

Data based on Section 14.3.1, Tables 149 and 150

Number of patients with event / number of patients at risk are given.

Events occurred during the treatment period, except when indicated for the study period.

Hypotension/syncope were reported more often in the iloprost group (18.8%) compared to placebo (10.8%). This was also the case with palpitation/tachycardia (11.9% iloprost and 6.9% placebo).

	Baseline		Week 12	
	Iloprost N=101	Placebo N=102	Iloprost N=94	Placebo N=85
Mean SBP/DBP (mmHg)	117/76	116/74	117/76	115/76
Heart rate (bpm)	83	81	82	84

^N is approximate

Table 181

The means of scheduled reading of blood pressure and heart rate were similar across time points and treatments.

ME98998

The sponsor revised the study report because of correction of walking distance, missing data for patient disposition, and drug dosing.

Introduction

This was an open-label, multicenter, randomized, parallel-group comparative safety study. A total of 60 clinically stable patients were randomized and treated for 3 months either with iloprost or with any conventional treatment that was deemed to be appropriate for each respective patient (prostanoids and beta-blockers were excluded). All patients were to receive their usual common background therapy. At the end of the 12 week randomization phase, patients were allowed to receive iloprost for up to 2 years.

Patient population

The study population comprised patients with primary or secondary pulmonary hypertension depending upon etiology:

Group A: Primary pulmonary hypertension, comprising the sporadic, familial and post-partum form as well as drug associated (e.g., appetite suppressant drugs), provided there was no clinical manifestation other than pulmonary hypertension.

Group B: Isolated pulmonary hypertension, comprising patients with collagenosis but without involvement of internal organs or clinical manifestation other than pulmonary hypertension.

Group C: Secondary pulmonary hypertension, comprising patients with thromboembolic disease, and pulmonary hypertension secondary to diseases of heart, lung, liver, or other organs. These patients were eligible for study entry only if best available therapy for the underlying disease had been used and pulmonary hypertension was the main limiting factor for exercise tolerance and/or prognosis.

The groups B and C were later pooled into the category secondary pulmonary hypertension (SPH)

Inclusion criteria

Male or female patients, aged 18-70 years, with primary or secondary pulmonary hypertension and a mean pulmonary artery pressure ≥ 30 mmHg (groups A and B) or ≥ 40 mmHg (group C) while resting during appropriate conventional treatment.

Exclusion criteria

Prohibited previous or concomitant drugs for all groups

1. Current or previous use of prostanoids by any route
2. Beta-blockers were to be discontinued 4 weeks before entry into the study
3. Warfarin (or other coumarins) in combination with acetylsalicylic acid; warfarin (or other coumarins) alone was eligible, or acetylsalicylic acid alone was eligible.

Patients whose PHT worsened (as defined by the criteria listed below) had to change therapy (adding iloprost if patient was not already receiving it). These patients were designated as drop outs.

- Cardiac index < 1.5,
- CVP > 20 mmHg despite adequate diuretic therapy.
- Hypoxemia with pO₂ < 50 mmHg despite maximum nasal O₂ therapy.
- Walking distance (6-minute walk) < 50 m.
- Progressive refractory cardiogenic edema, particularly pleural effusion and ascites.
- Cardiogenic hepatic failure (transaminase increase, ASAT/GOT and/or ALAT/GPT > 100 U/L or LDH > 500 U/L; bilirubin > 3 mg/dl),
- Cardiogenic renal failure (oligo-anuresis) or requiring dialysis.
- Significant increase in heart size despite restricted physical activity and adequate diuretic therapy. The increase is considered significant, if > 2 cm in the transversal diameter within an interval of less than 3 months in patients with preexisting enlarged heart in the chest x ray.
- Rapid deterioration of exercise capacity in the preceding 4 weeks (for example, > 3 Mahler index points per month, > 30 % decrease in 6-min walk per month).
- Need of increase in the chronic dose of diuretics by more than 100% within the last 3 months. This criterion could only be applied in patients with a pre-existing dose of at least 25 mg of hydrochlorothiazide + 50 mg triamterene, 40 mg furosemide, or equivalent doses of other diuretics.

Stratification

Patients were randomized within the following strata:

- primary or secondary pulmonary hypertension,
- use of calcium antagonist, and
- 6-minute walk (>500 m, 150-499 m, < 150 m).

Dosing

The initial targeted total daily dose was 100 µg (range 50 µg - 200 µg based on tolerability) divided into 6 (up to 12) inhalation sessions.

Prohibited concomitant medication

1. Current or previous use of prostanoids by any route,
2. Beta-blockers (had to be discontinued 4 weeks before entry into the study),
3. Warfarin (or other coumarins) in combination with aspirin; warfarin (or other coumarins) alone was eligible, or aspirin alone was eligible.

Evaluation

The study was designed to assess the following variables in an exploratory manner:

- Tolerability and adverse events
- Mortality and transplantation
- Exercise capacity
 - Walking distance (6-min walk)

TT 5 Scheduled measurements of 6-minutes walking distance		
	Time point of measurement relative to inhalation	
	Before	After
Baseline	•	see text
RP month 1		•
RP month 2	•	
EOR	•	•
LT month 1		•
LT month 2	•	
LT month 3	•	•
LT month 6	•	
LT month 9	•	•
LT month 15		•
PEOT	•	•
EOS	•	•

EOR = end of randomized phase; EOS = end of study;
 LT = long-term phase; PEOT = premature end of treatment; RP = randomized phase

- Mahler dyspnea index
- Acute effects of iloprost inhalation on hemodynamic and gas exchange
 - PVR, SVR, CO, MPAP, SAP, RVEF, CVP
 - SVO₂, SAO₂
- Long-term effect of hemodynamic and gas exchange
 - PVR, SVR, CO, MPAP, SAP, RVEF, CVP
 - SVO₂, SAO₂
- Quality of life
 - EuroQoL
 - Karnofsky index
 - Borg index.

A total sample size of 60 patients (30 iloprost and 30 controls) was considered sufficient for this exploratory study. This sample size was not selected for the purpose of hypothesis testing.

Study procedures

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TT 4

Flow chart of study assessments

Study phase	Randomized phase			Long-term iloprost continuation																			Prem. EOT
	Month Visit	0 ^a	1 A	2 B	3 EOR	4	5	6	7	8	9	10	11	12	14	16	18	20	22	24 ^b EOS			
Enrollment / randomization																							
Demographics	X																						
Medical history	X																						
PHT diagnosis and history	X																						
Inclusion / exclusion criteria	X																						
Randomization	X																						
Effect assessments																							
NYHA class	X	X	X	X	X ^c	X ^e	X															X	X
5-min walk	●○	○●	●○	●●	X ^c	X ^e	X															X	X
Lung function	X	X	X	X	X ^c	X ^e	X															X	X
HRQL (EQ-5D, Borg scale)	X	X	X	X	X ^c	X ^e	X															X	X
Karnofsky index	X	X	X	X	X	X	X	☎	☎	X	☎	☎	X	☎	☎	X	☎	☎	X	☎	☎	X	X
Catheter tests	X	X	X	X	X	X	X															X	(X)
Hospitalization, work status	X	X	X	X	X ^c	X ^e	X															X	X
Safety / tolerability assessments																							
Physical examination	X			X																		X	X
Vital signs and body weight	X	X	X	X	X ^c	X ^e	X															X	X
Laboratory and pregnancy test	X	X	X	X	X ^c	X ^e	X															X	X
ECG	X	X	X	X	X ^c	X ^e	X															X	X
X-ray	X	X	X	X	X ^c	X ^e	X															X	X
AEs, Concomitant medication	X	X	X	X	X	X	X	☎	☎	X	☎	☎	X	☎	☎	X	☎	☎	X	☎	☎	X	X

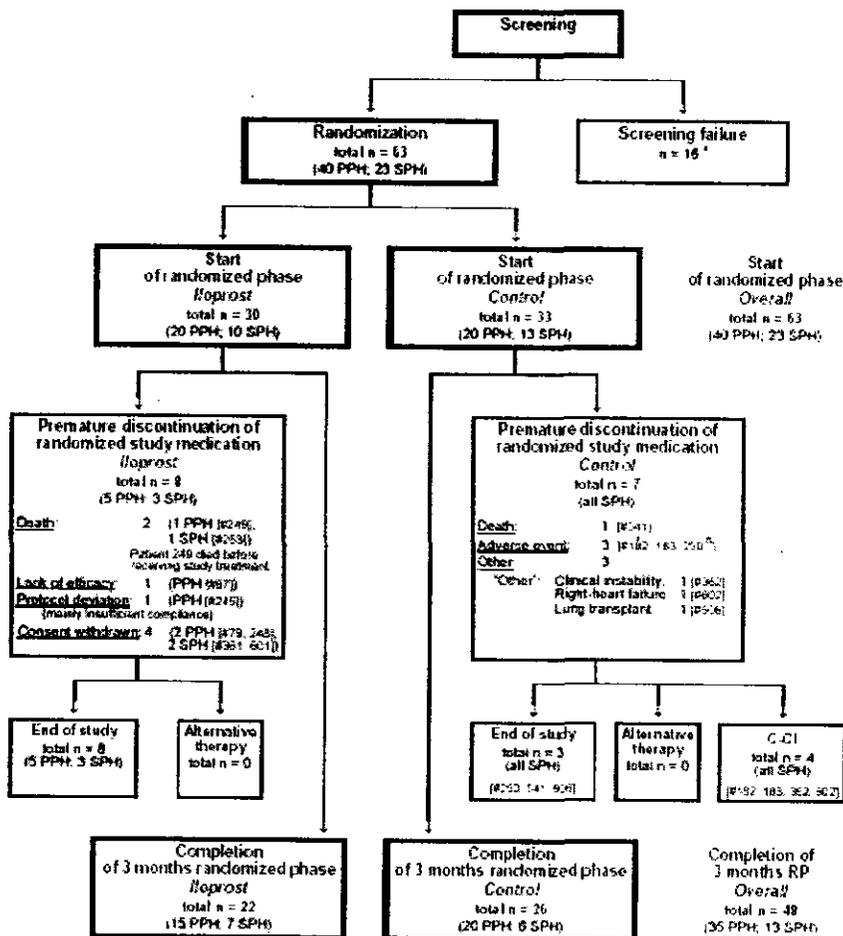
^a Visit at Week 0 (= screening and baseline) should have been done within 14 days before randomization
^b If the randomized study phase was discontinued prematurely, then the long-term study phase was continued until the end of the planned 24 months.
^c Only for patients who had newly started iloprost inhalation
^e If the end of study phase or end of study treatment visit coincided with a scheduled study visit, these examinations would replace the regular visit
 ●○ : before inhalation; ○● : after inhalation; ●● : before and after inhalation; ☎ : telephone contact (no visit at the study center)
 EOR = end of randomized study phase; Prem: EOT = premature end of treatment; EOS = end of study

RESULTS

Patient disposition

A total of 63 patients were randomized in this exploratory study.

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TF 1 Disposition chart - Randomized study phase

Figures denote number of patients. Patient identification numbers are given in squared brackets (e.g. [182, 183]).

* One screening failure (pre-randomized, 3006) was not included in the database.

* Subsequent death.

C-CI = "control-clinical instability" (Patients randomized to the control group who developed clinical instability during randomized treatment could begin long-term iloprost inhalation therapy prematurely); LT = long-term continuation study phase; PPH = primary pulmonary hypertension; RP = randomized study phase; SPH = secondary pulmonary hypertension.

Of the 30 subjects randomized to iloprost, 22 (73.3%) completed the 3-month study. Of the 33 subjects randomized to control 26 (78.8%) completed the study. Four of the seven control patients who were discontinued from the study were then started on iloprost.

Patient no. 249 (iloprost group) died soon after randomization without receiving any study treatment.

Age, sex, ethnic group

The table below shows the mean age (and range), percent female, and percent non white in all subjects, by iloprost (n=30) and control (n=33) groups.

Mean age, percent male/female, percent nonwhite

Mean age: yrs (range)		Female: %		Nonwhite: %	
Iloprost	control	Iloprost	control	Iloprost	control
42 (24-63)	48 (32-78)	76.7	63.6	0	0

Tables T6 and T7

The control group was somewhat older and a little less likely to be female. All patients were white.

Patient characteristics

The original table TT8 was revised because of an apparent programming error. The table below displays the original baseline 6 minute walk test results (shown as struck out) as well as the corrected entries.

TT 8 (amended) Baseline characteristics: PHT diagnosis, calcium antagonists, walking distance			Figures denote number / percentage of patients					
			Iloprost total n = 30		Control total n = 33		Overall total n = 63	
PHT diagnosis* at baseline	original algorithm	PPH	20	66.6%	20	60.6%	40	63.5%
		SPH	10	33.3%	13	39.4%	23	36.5%
	alternative algorithm	PPH	21	70.0%	24	72.7%	45	71.4%
		SPH	9	30.0%	9	27.3%	18	28.6%
Six-minute walking distance at baseline		0 m	0	-	0	-	0	-
		1 - < 150 m	3	10.0%	4	12.1%	7	11.1%
		150 - < 300 m	20 5	76.7 16.7%	26 9	76.9 27.3%	46 14	76.2 22.2%
		300 - < 500 m	4	13.3%	16	48.5%	20	31.7%
		≥ 500 m	4	13.3%	4	12.1%	8	12.7%
Calcium antagonists			12	40.0%	18	54.5%	30	47.6%

* See section 9.8.2.4 for details of both algorithms. Unless otherwise indicated, all classifications of the PHT diagnosis are based on the original algorithm. The alternative algorithm is used for additional analyses of walking distance and NYHA class only.

Source: Biometrical tables NY.1-2 (diagnosis), BS.1 WT.1 (walking distance), BS.20 (previous therapy)

The treatment groups were fairly well balanced between PPH and SPH, regardless of algorithm. There were more patients walking further at baseline in the iloprost group compared to control, but the difference is only with 2 patients (18 vs. 16). Fewer iloprost patients were taking calcium antagonists compared to control (40% vs. 54.5%). The control group was a little older and perhaps a little sicker.

Walk distance

The table below shows the distance covered at baseline by the patients according to baseline NYHA class, by treatment group.

T14 6 minutes walking test at baseline, descriptive statistics, stratified by re-assessed NYHA class
ITT-population

Group of IMP	Baseline reassessed NYHA class	Treatment	N	Mean	SD	Min	Median	Max	Missing
Overall	II (9-12)	Iloprost	11	419.135	81.552	336.00	429.000	555.00	0
		Control	10	418.900	124.122	189.00	470.000	540.00	0
		Overall	21	420.509	102.284	195.00	439.000	555.00	0
Overall	III (5-8)	Iloprost	14	148.538	95.662	200.00	309.000	460.00	0
		Control	17	174.235	95.864	120.00	310.000	464.00	0
		Overall	30	149.433	94.354	120.00	309.000	460.00	0
Overall	IV (9-4)	Iloprost	6	193.833	130.769	49.00	195.000	379.00	0
		Control	6	172.000	86.124	70.00	196.000	289.00	0
		Overall	12	187.917	107.796	49.00	195.000	379.00	0

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In each NYHA class, the mean distances walked by iloprost patients were a little greater compared to the placebo group.

NYHA classification

Initially, the patient's NYHA class was defined and entered in the CRF by the individual investigator. The sponsor developed an algorithm that used the Mahler Dyspnea Score (focal score) and the Karnofsky Index recorded at the time of the patient visit and retrospectively made a separate NYHA re-assessment. The table below shows the number and percent of both the original and reassessed NYHA classes, by treatment group.

T19 Baseline characteristics: NYHA functional classes
Figures denote number / percentage of patients.

Baseline NYHA class	Iloprost n = 30		Control n = 33		Overall n = 63	
	Original entry ¹	Re-assessed ²	Original entry ¹	Re-assessed ²	Original entry ¹	Re-assessed ²
II	8 (26.7%)	11 (36.7%)	6 (18.2%)	10 (30.3%)	14 (22.2%)	21 (33.3%)
III	19 (63.3%)	13 (43.3%)	24 (72.7%)	17 (51.5%)	43 (68.3%)	30 (47.6%)
IV	3 (10%)	6 (20%)	3 (9.1%)	6 (18.2%)	6 (9.5%)	12 (19.0%)

¹ Investigators' original CRF entries.

² Re-assessment based on CRF entries for Mahler focal score and Karnofsky index.

Source: Biometrical tables NY.1 (re-assessed)

The investigator based entry had more class III in the control group compared to the iloprost group (17 vs. 13); class IV groups were similar.

Hemodynamics and gas exchange

Baseline cardiac hemodynamic parameters are shown below by treatment group.

TT 10 Baseline characteristics: Hemodynamic findings					
Data presented as mean \pm SD. Owing to missing values, actual sample sizes may be lower than total Ns.					
Variable	Unit	Normal range	Iloprost total N = 30	Control total N = 33	Overall total N = 63
mPAP	[mmHg]	< 21	57.17 \pm 15.14	54.12 \pm 13.00	55.57 \pm 14.03
mSAP	[mmHg]	> 70	94.43 \pm 15.53	93.03 \pm 9.25	93.70 \pm 12.55
PVR	[dyn s cm ⁻⁵]	< 250	1094.33 \pm 467.67	1065.25 \pm 403.28	1078.56 \pm 430.33
SVR	[dyn s cm ⁻⁵]	800 - 1200	1933.70 \pm 621.41	1943.58 \pm 533.35	1938.87 \pm 572.25
CI	[l/min/m ²]	2.4 - 3.8	2.24 \pm 0.62	2.14 \pm 0.60	2.19 \pm 0.60
RVEF	[%]	> 70	17.22 \pm 9.02	16.11 \pm 10.34	16.65 \pm 9.60
CVP	[mmHg]	< 8	5.80 \pm 4.90	6.09 \pm 5.18	5.95 \pm 5.01
Hf	[beats/min]	60 - 80	84.07 \pm 14.71	84.12 \pm 13.00	84.10 \pm 13.73
SaO ₂	[%]	> 90	94.95 \pm 4.78	95.45 \pm 3.34	95.21 \pm 4.05
SvO ₂	[%]	> 70	62.81 \pm 7.47	62.69 \pm 10.24	62.75 \pm 8.98

Source: Biometrical table HD.1

Cardiac hemodynamic parameters were similar for the 2 treatment groups.

TT 11 Baseline characteristics: Borg scale, EuroQol EQ-5D, Visual analog scale and Karnofsky index									
	Iloprost			Control			Overall		
	n	mean	SD	n	mean	SD	n	mean	SD
Borg scale	30	15.1	2.3	33	14.5	2.5	63	14.8	2.4
EuroQol EQ-5D	30	0.529	0.299	33	0.502	0.351	63	0.515	0.325
Visual analog scale	25	48.8	22.8	30	41.3	20.2	55	44.7	21.6
Karnofsky index	30	70.5	12.2	33	70.8	11.0	63	70.6	11.5

Source: Biometrical tables BO.1 (Borg), EQ.1 (EuroQol incl. VAS), KI.1

These scales evaluating the clinical condition of the patients were similar between the treatment groups.

SAFETY

Duration of exposure

TT 40		Duration of treatment					
Figures denote number / percentage of patients. Note that patients randomized to the control group started to receive inhaled iloprost only after the beginning of the long-term phase (i.e., 90 days after baseline).							
		Iloprost		Control		Overall	
Randomized phase	Days post baseline	30	100.0%	33	100.0%	63	100.0%
	0 - 90 days	16	53.3%	14	42.4%	30	47.6%
	91 - 180 days	14	46.7%	19	57.6%	33	52.4%
Long-term phase	Days post baseline	21 ^a	100.0%	29 ^c	100.0%	50	100.0%
	≤ 180 days	0	-	3	10.3%	3	6.0%
	181 - 270 days	3	14.3%	2	6.9%	5	10.0%
	271 - 360 days	0	-	1	3.4%	1	2.0%
	361 - 450 days	2 ^b	9.5%	1	3.4%	3	6.0%
	451 - 540 days	0	-	1 ^b	3.4%	1	2.0%
	541 - 630 days	0	-	1 ^b	3.4%	1	2.0%
	631 - 720 days	2 ^{b,c}	9.5%	7 ^b	24.1%	9	18.0%
	≥ 721 days	14 ^{b,c}	66.7%	13 ^{b,c}	44.8%	27	54.0%

^a Owing to missing CRF pages, two patients are missing in this analysis (Pats. 481 iloprost, 602 control; both discontinued prematurely during LT, no treatment duration was recorded). See disposition charts TF 1 and TF 2 in section 10.1 for a complete account of all patients.

^b Iloprost exposure at least 1 year.

^c Iloprost exposure at least 631 days.

Of the 29 iloprost patients who entered the longterm phase, 14 (66.7%) were treated for at least 721 days. Of the 29 control patients who entered the longterm phase, 13 (44.8%) were treated with iloprost for at least 541 days (721-180).

Dose

The mean total daily iloprost dose was 108.3 ug (range 50 µg to 150 µg) at the end of the 12 week randomized phase with a mean of 6.7 inhalations per day. During the long-term phase (up to 630 days), the maximum dose was 300 µg daily during the later months of the trial. The mean dose was 118.8 ug, higher than at week 12. Most patients received iloprost only during the day. Table 56

Serious safety

Deaths

There were 4 deaths (2 per treatment group) reported during the 12 week randomized phase.

Study treatment	Pt#/age/sex/dose	Comments
iloprost	249/62/M/NA	Developed purulent bronchitis prior to receiving study medication. Died about 2 weeks later.
Control	250/49/F/NA	Underlying condition worsened 2 months into study. Death attributed to right heart failure.
iloprost	253/64/F/100 ug	Underlying condition worsened 2 months into study. Death attributed to right heart failure with suspected bronchopneumonia.
Control	541/32/F/100-150 ug	Pulmonary embolus 7 days after

		randomization. Died 7 days later of right hear failure.
--	--	---------------------------------------------------------

14.3.3 and 14.3.4

The 4 deaths that occurred during the long-term phase are shown in the table below.

Patient no./age/sex/duration of iloprost rx	comments
65/35/M/15 months	Cardiac arrest in patient with advanced AIDS
302/42/M/3 months	Worsening underlying disease started 3 weeks after iloprost initiation. Died of right heart failure 2 months after stopping iloprost
602/57/M/3 months	Developed right ventricular failure during randomization phase, started on iloprost and died of underlying disease 3 months later.
604/48/f/11 months	Worsening underlying disease, hospitalization, cardiogenic shock followed by death. History of alcoholic liver cirrhosis.

Deaths in both phases seem to be attributed to underlying disease.

Serious adverse events (excluding deaths)

The number and percent of patients reporting serious adverse events is shown below, by treatment group

Randomization phase

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TT 48 Serious adverse events: Frequencies during randomized phase

Figures denote number (no. of patients with respective event / no. of patients at risk) / percentage of patients.

HARTS	Iloprost		Control		Overall	
Any SAE	7/30	23.3%	7/33	21.2%	14/63	22.2%
Congestive heart failure *	2/30	6.7%	4/33	12.1%	6/63	9.5%
Death	2/30	6.7%	2/33	6.1%	4/63	6.3%
Peripheral edema	1/30	3.3%	1/33	3.0%	2/63	3.2%
Hemoptysis	1/30	3.3%	-	-	1/63	1.6%
Skin melanoma	1/30	3.3%	-	-	1/63	1.6%
Syncope	1/30	3.3%	-	-	1/63	1.6%
Upper respiratory infection	-	-	1/33	3.0%	1/63	1.6%
Lung disorder	-	-	1/33	3.0%	1/63	1.6%
Thrombophlebitis	-	-	1/33	3.0%	1/63	1.6%
No drug reaction	1/30	3.3%	-	-	1/63	1.6%

* HARTS mnemonic term: 'Heart fail right'.

Source: Biometrical table AE 23

Note:

The underlying database contains five deaths during RP. However, patient 602 died after discontinuation of RP and soon after initiation of LT treatment (C-CI group); for technical reasons only, this death had been recorded in the CRF of RP, although it occurred after its termination. Therefore, in the light of these circumstances, it is felt that this death should be assigned to LT rather than to RP.

There were 7 (23.3%) iloprost patients and 7 (21.1%) control patients reporting at least 1 serious adverse event. The event congestive heart failure (right heart failure) was reported nearly twice as much by the placebo group (12.1%) compared to iloprost (6.7%). Syncope was reported as a serious adverse event by one iloprost patient. This patient (#301) reported 2 episodes of syncope after 5.5 weeks of therapy with iloprost. The first event occurred 2 hours after inhalation of study medication. Concomitant events included psychological stress, nausea and tinnitus and leading to a syncope for 2-3 minutes. A second episode occurred six days later. There were typical acral and perioral paresthesias. The patient was hospitalized for one week because of these events. The diagnosis of hyperventilation as cause of syncope was confirmed by provocation test.

Entire study

**Appears This Way
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TT 49

**Serious adverse events: Frequencies during whole study,
by randomized treatment and by diagnosis subgroup (PPH – SPH)**

Figures denote number ('no. of patients with respective event / no. of patients at risk') / percentage of patients.

HARTS	Iloprost		Control	
	no. / at risk	%	no. / at risk	%
Any SAE	16/30	53.3%	20/33	60.6%
Congestive heart failure *	5/30	16.7%	10/33	30.3%
Death	2/30	6.7%	6/33	18.2%
Surgery	3/30	10.0%	4/33	12.1%
Peripheral edema	1/30	3.3%	4/33	12.1%
No drug reaction	3/30	10.0%	2/33	6.1%
Infection	3/30	10.0%	1/33	3.0%
Aggravation reaction	3/30	10.0%	1/33	3.0%
Syncope	3/30	10.0%	-	-
Asthenia	-	-	2/33	6.1%
Edema	-	-	2/33	6.1%
Accidental injury	-	-	2/33	6.1%
Lung disorder	-	-	2/33	6.1%
Sinusitis	1/30	3.3%	1/33	3.0%
Carcinoma	-	-	1/33	3.0%
Convuls grand mal	-	-	1/33	3.0%
Dyspnea	-	-	1/33	3.0%
Gastroenteritis	-	-	1/33	3.0%
Headache	-	-	1/33	3.0%
Hemorrhage	-	-	1/33	3.0%
Hematemesis	-	-	1/33	3.0%
Hematuria	1/30	3.3%	-	-
Hemoptysis	1/30	3.3%	-	-
Hernia	-	-	1/33	3.0%
Hyperkalem	1/30	3.3%	-	-
Infect upper resp	-	-	1/33	3.0%
Kidney failure	-	-	1/33	3.0%
Skin melanoma	1/30	3.3%	-	-
Occlusion	1/30	3.3%	-	-
Back pain	-	-	1/33	3.0%
Pneumonia	1/30	3.3%	-	-
Tachycardia	-	-	1/33	3.0%
Retinal vein thrombosis	-	-	1/33	3.0%
Thrombophlebitis	-	-	1/33	3.0%
Thrombophlebitis leg	-	-	1/33	3.0%
Tooth disorder	1/30	3.3%	-	-
Vertigo	-	-	1/33	3.0%

* HARTS mnemonic term: 'Heart fail right'.

Source: Biometrical table AE.2 Patients with any serious adverse event at any timepoint for PPH/SPH subgroups, 19MAR02

Events reported by more than 2 patients include congestive heart failure, death, surgery, peripheral edema, no drug reaction, infection, aggravation reaction, and syncope.

Discontinuations for adverse events

Discontinuation of study medication because of lack of efficacy or adverse event was more frequent in the control group (iloprost 3%; control 9%).

All adverse events

Randomized phase

Events reported by at least 2 patients in iloprost group and reported more often by iloprost than placebo during the randomized phase are shown below.

No. and (percent) of patients

Adverse event	Iloprost N=30	Control N=33	control subtracted %
Any event	25 (83.3)	25 (75.8)	7.5
Vasodilation	8 (26.7)	4 (12.1)	14.6
Cough increase	8 (26.7)	6 (18.2)	8.5
Nausea	4 (13.3)	2 (6.1)	7.2
Fever	3 (10.0)	1 (3.0)	7.0
trismus	3 (10.0)	1 (3.0)	7.0
Flu syndrome	2 (6.7)	0	6.7
Creatinine pk inc	2 (6.7)	0	6.7
dyspnea	2 (6.7)	0	6.7
hemoptysis	2 (6.7)	0	6.7
Chest pain	4 (13.3)	3 (9.1)	4.2
Headache	4 (13.3)	3 (9.1)	4.2
Palpitations	2 (6.7)	1 (3.0)	3.7
diarrhea	2 (6.7)	1 (3.0)	3.7
syncope	2 (6.7)	2 (6.1)	0.6
edema	2 (6.7)	2 (6.1)	0.6
Back pain	2 (6.7)	2 (6.1)	0.6

T58

The events reported by at least 7.0% more in the iloprost group than the control group included vasodilation, cough increase, nausea, fever, and trismus.

Randomized and long term phases

Event reported throughout the entire study are shown below (limited to those reported by more than 3 iloprost patients and reported more often in the iloprost group than the control group).

No. and (percent) of patients

Adverse event	Iloprost N=30	Control N=33	control subtracted %
Any event	28 (93.3)	32 (97.0)	-3.7
Vasodilation	12 (40.0)	7 (21.2)	18.8
Fever	5 (16.7)	1 (3.0)	13.7
Sore throat	5 (16.7)	2 (6.1)	10.6
Cough increase	13 (43.3)	11 (33.3)	10.0
Nausea	9 (30.0)	7 (21.2)	8.8
Syncope	5 (16.7)	3 (9.1)	7.6
Skin disorder	4 (13.3)	2 (6.1)	7.2
Infection	11 (36.7)	10 (30.3)	6.4
Bronchitis	7 (23.3)	6 (18.2)	5.1
Edema	7 (23.3)	6 (18.2)	5.1
Flu syndrome	5 (16.7)	4 (12.1)	4.6
Dyspnea	4 (13.3)	3 (9.1)	4.2
Trismus	4 (13.3)	3 (9.1)	4.2
Diarrhea	4 (13.3)	4 (12.1)	1.2
Rash	3 (10.0)	3 (9.1)	0.9
Aggravation rxn	3 (10.0)	3 (9.1)	0.9

TT 43

The incidence rate for reporting adverse events was higher in the control group (97.0%) compared to the iloprost group (93.3). Events reported by $\geq 7.0\%$ of the iloprost group compared to control include vasodilation, fever, sore throat, cough increase, nausea, syncope, and skin disorder.

Clinical laboratory evaluations

Shift tables

Abnormal shifts from baseline at endpoint for both the randomized and long term phases were not obvious. T66-68.

Abnormal individual results

Table below provides a summary of the frequencies of laboratory findings reported as an adverse event by diagnosis (PPH, SPH) and by treatment.

TT 52 Laboratory findings: Adverse events, frequency during whole study by diagnosis and treatment

Figures denote number / percentage of patients.

HARTS description	PPH		SPH		Iloprost		Control		Overall	
Hypokalemia	2/40	5.0%	2/23	8.7%	2/30	6.7%	2/33	6.1%	4/63	6.3%
Creatine PK increased	3/40	7.5%			2/30	6.7%	1/33	3.0%	3/63	4.8%
Laboratory test abnormal	3/40	7.5%			1/30	3.3%	2/33	6.1%	3/63	4.8%
Liver function test abnormal	3/40	7.5%			1/30	3.3%	2/33	6.1%	3/63	4.8%
Bilirubinemia	2/40	5.0%			1/30	3.3%	1/33	3.0%	2/63	3.2%
GGTP increased			1/23	4.3%			1/33	3.0%	1/63	1.6%
Hyperkalemia	1/40	2.5%			1/30	3.3%			1/63	1.6%

Sporadic cases of abnormal laboratory values were similar across treatment groups.

Abnormal laboratory values reported by iloprost patients as adverse events are shown below.

T69 Laboratory findings: Adverse events, patient listing						
Pat.	Variable	Laboratory data			HARTS term	
		Baseline value	Most extreme value			Last recorded value
<i>Iloprost</i>						
64 male	K ⁺ (mmol/l)	3.9	5.7	LT month 15	6.7 H EOS (> month 15)	Hyperkalemia
	ALAT/GPT [U/l]	7	26	RP month 2	6 EOS (> month 15)	Liver function abnormal
	ASAT/GOT [U/l]	6	29	RP month 2	22 H EOS (> month 15)	
	AP [U/l]	146	196	LT month 3	132 EOS (> month 15)	Laboratory test abnormal
	Bilir. tot [mg/dl]	1.9 H	6.7	LT month 15	6 H EOS (> month 15)	
	γ-GT [U/l]	52 H	65	LT month 3	39 H EOS (> month 15)	Laboratory test abnormal
	LDH [U/l]	227	502 H	EOS (> month 15)	502 H EOS (> month 15)	
	CRP [mg/l]	14.2 H	45.4	LT month 9	18.2 H EOS (> month 15)	Laboratory test abnormal
70 fem.	K ⁺ (mmol/l)	4	2.9 L	LT month 9	2.9 L LT month 9	Hypokalemia
78 fem.	Bilir. tot [mg/dl]	0.6	1.4 H	LT month 9	1.3 H EOS (> month 15)	Bilirubinemia
301 fem.	Creat. kin. [U/l]	29	104 H	RP month 1	81 H EOS (> month 15)	Creatinine PK increased
303 male	Creat. kin. [U/l]	17	113 H	RP final	31 EOS (> month 15)	Creatinine PK increased
605 fem.	K ⁺ (mmol/l)	3.4 L	2.1 L	RP final	4.1 LT month 9	Hypokalemia

There were 5 iloprost patients (1 with increased LFTs, potassium, and CRP, 2 with only decreased potassium, 1 with increased total bilirubin, 2 with increased creatinine phosphokinase) with abnormal laboratory values reported as adverse events.

#64 had abnormal liver function test with increase in total bilirubin (2.7 mg/dl at the end of the randomized phase) with further increase to 6 mg/dl at end of study. LDH also increased and remained increased at the end of the study. Hyperkalemia (5.7 mmol/l) at end of study also was reported. Potassium levels responded concomitant spironolactone dose was reduced. (N.B. 2 control patients (#69 and #81) had elevated liver function tests during the trial, 1 patient (#65) had elevated LDH, and 1 (#182) had elevated GGT.)

EFFICACY

NYHA class

The table below shows the number and percent of patients who improved their classification status by at least 1, by treatment group.

TT 12 NYHA class: Improvements during the randomized phase

Based on re-assessed NYHA classes. Figures denote number / percentage of patients who, during the randomized phase, improved by at least one class compared with baseline.

Time point	Iloprost N = 30	Control N = 33
Week 4	8 (26.7%)	3 (9.1%)
Week 8	9 (30.0%)	2 (6.1%)
EOR	6 (20.0%)	2 (6.1%)

EOR=Last examination or data recorded at end of randomized phase, not necessarily equal to actual week 12 but used synonymously in certain listings (other synonyms for EOR include "month 3" and "final" examination of the randomized phase).

The incidence rate for improvement at EOR (end of randomization phase) was more than 3 times higher in the iloprost group (20.0%) compared to the control group (6.1%). This difference in improvement between the treatment groups was seen by week 4.

Mahler dyspnea index

TT 14 Mahler Dyspnea Index: Focal score and sum of transition scores during randomized phase, descriptive statistics

		Focal score			Sum of transition score Changes to baseline		
		Iloprost	Control	Overall	Iloprost	Control	Overall
Baseline	N	30	33	63	<i>not applicable</i>		
	Mean	4.767	4.758	4.762			
	SD	2.128	1.601	1.855			
	Median	5.500	5.000	5.000			
Month 1	N	26	30	56	26	30	56
	Mean	5.077	5.267	5.179	2.115	-0.200	0.875
	SD	2.448	1.893	2.150	2.389	2.107	2.509
	Median	6.000	5.500	6.000	3.000	0.000	0.000
Month 2	N	23	27	50	23	27	50
	Mean	5.217	5.296	5.260	1.478	-0.667	0.320
	SD	2.173	2.072	2.098	3.058	2.236	2.832
	Median	6.000	6.000	6.000	0.000	0.000	0.000
EOR	N	24	30	54	24	30	54
	Mean	5.000	4.867	4.926	1.125	-1.100	-0.111
	SD	2.226	2.315	2.256	2.437	2.657	2.772
	Median	6.000	5.000	6.000	0.000	0.000	0.000

Focal score ranges from 0 (worst condition) to 12 (best condition).

Transition score ranges from -9 (least favorable change) to 0 (no change) to 9 (most favorable change).

Source: Biometrical tables D1 3 (focal score), D1 8 (transition score)

There was a small improvement in the mean focal score for the iloprost group (4.7 at baseline to 5.0 at end of randomization phase). There was little change for the control group.

There was some improvement in the transition score in the iloprost group compared to placebo.

These results were classified according to improved, unchanged, deteriorated. The incidence rates are shown below, by treatment group.

TT 15 Mahler Dyspnea Index: Focal score and transition score (classified results at EOR)
Results refer to changes from baseline to EOR. Figures denote number / percentage of patients.

		Iloprost n = 24		Control n = 30		Overall n = 54	
Focal score, classified changes	Improved	10	41.7%	5	16.7%	15	27.8%
	Unchanged	8	33.3%	18	60.0%	26	48.1%
	Deteriorated	6	25.0%	7	23.3%	13	24.1%
Sum of transition score, classified values	Positive	8	33.3%	3	10.0%	11	20.4%
	Zero	14	58.3%	17	56.7%	31	57.4%
	Negative	2	8.3%	10	33.3%	12	22.2%

The results favor iloprost.

6 minute walk

Absolute changes in the mean walk distance at trough at the end of the randomization (EOR) phase are shown below, by treatment group. (T28 shows the same information only with patients who died (n=4, 2 per treatment group) being assigned a walk distance of 0 m). N.B. post-inhalation examination (peak) was not conducted at baseline, the corresponding pre-inhalation (trough) examination was taken as baseline value for all change-from-baseline analyses of post-inhalation examinations.

T25 Walking distance: absolute changes, descriptive statistics (strict LOCF)

ITT-population

time point	stratum	Iloprost				control				overall			
		n	mean	median	sd	n	mean	median	sd	n	mean	median	sd
EOR (before)	PPH	20	23.6	6.5	69.3	20	67.9	53.0	109.9	40	45.7	37.0	93.4
	SPH	10	73.3	31.3	169.1	13	-16.4	0.0	99.8	23	22.6	15.5	138.6
	all strata	30	48.1	27.3	112.2	33	34.7	30.0	112.5	63	37.3	27.5	111.5

T28 Walking distance: absolute changes, descriptive statistics (LOCF with death = 0 m)

ITT-population

time point	stratum	Iloprost				control				overall			
		n	mean	median	sd	n	mean	median	sd	n	mean	median	sd
EOR (before)	PPH	20	4.1	6.5	115.8	20	67.9	53.0	109.9	40	36.0	37.0	115.9
	SPH	10	64.9	27.3	173.3	13	-35.6	-10.0	125.5	23	8.1	10.0	153.2
	all strata	30	24.3	20.0	137.6	33	27.1	30.0	125.4	63	25.8	27.0	130.3

In both cases, the mean absolute change was much better for the PPH group receiving control compared to iloprost (67.9 m vs. 4.1 m). On the other hand, the SPH group performed better if

they were randomized to iloprost (mean increase 64.9 m) compared to placebo (mean decrease 35.6m). The clinical relevance of these results is unknown.

Mortality

There were 4 deaths, 2 per group.

Responders

A retrospectively defined composite response criterion was applied in order to explore the benefit for the patient: response was defined as (i) an improvement in physical capacity measured by an improvement of the NYHA class, (ii) by an improvement of the walking distance by at least 10% compared to baseline], and (iii) the patient still had to be alive at the respective time point. Patients fulfilling this composite criterion were called "responders".

TT 17 Composite response criterion: Response rates during randomized phase						
Figures denote number / percentage of patients with response.						
Visit	Time point of measurement relative to inhalation	Iloprost n = 30		Control n = 33		Overall n = 63
Month 1	after	4	13.3%	0	0.0%	4 6.3%
Month 2	before	7	23.3%	2	6.1%	9 14.3%
EOR	before	4	13.3%	0	0.0%	4 6.3%
	after	4	13.3%	1*	3.0%	5 7.9%

* Assessment after iloprost inhalation.

The trend favors iloprost.

Hemodynamics

At baseline and at end of randomization, patients of both treatment groups received an acute test with inhaled iloprost.

Changes from baseline at end of randomization at peak (iloprost group only) and trough for the study groups are shown below.

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TT 18 Hemodynamic effects at EOR (peak and trough values)

Recorded data given as mean \pm SD.

	Changes from baseline (pre-inhalation)		
	to pre-inhalation at EOR	to last minute of inhalation at EOR	to pre-inhalation at EOR
	Iloprost (trough) expected minimum drug effect	Iloprost (peak) expected maximum drug effect	Control (trough) expected minimum drug effect
mPAP [mmHg]	1.86 \pm 7.24 $p = 0.316, n = 22$	-7.09 \pm 8.18 $p = 0.00^*, n = 22$	-3.71 \pm 10.24 $p = 0.097, n = 28$
mSAP [mmHg]	-0.82 \pm 9.36 $p = 0.671, n = 22$	-3.41 \pm 10.93 $p = 0.148, n = 22$	-4.86 \pm 10.42 $p = 0.022^*, n = 28$
PVR [dyn s cm ⁻⁵]	144.84 \pm 315.68 $p = 0.111, n = 19$	-216.56 \pm 326.54 $p = 0.003^*, n = 18$	-23.30 \pm 340.19 $p = 0.815, n = 27$
SVR [dyn s cm ⁻⁵]	100.57 \pm 446.34 $p = 0.448, n = 21$	-201.10 \pm 458.78 $p = 0.078, n = 21$	-50.18 \pm 533.78 $p = 0.216, n = 28$
CI [l/min/m ²]	0.12 \pm 0.55 $p = 0.388, n = 21$	0.19 \pm 0.54 $p = 0.199, n = 21$	-0.02 \pm 0.55 $p = 0.404, n = 28$
Hf [beats/min]	-3.50 \pm 7.90 $p = 0.081, n = 22$	-5.18 \pm 8.68 $p = 0.013^*, n = 22$	-2.57 \pm 11.02 $p = 0.195, n = 28$
SvO ₂ [%]	-2.17 \pm 6.32 $p = 0.120, n = 21$	5.39 \pm 7.46 $p = 0.002^*, n = 21$	-2.43 \pm 10.24 $p = 0.191, n = 27$
CVP [mmHg]	0.14 \pm 4.85 $p = 0.857, n = 22$	-1.05 \pm 4.91 $p = 0.307, n = 22$	0.75 \pm 5.45 $p = 0.244, n = 28$
RVEF [%]	-1.38 \pm 9.92 $p = 0.150, n = 16$	1.81 \pm 10.66 $p = 0.803, n = 16$	2.18 \pm 7.28 $p = 0.634, n = 17$

At peak, the iloprost group showed evidence of decreasing mPAP (8 mmHg), PVR (217 dyns cm⁻⁵) and increasing CI (0.19 l/min/m²).

Quality of life assessments

Compared to baseline, the health related quality of life outcomes tended to show greater improvements in the iloprost group as compared with the control group. Selected results are shown below.

EuroQuol EQ-5D

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TT 19 EuroQol EQ-5D during randomized phase:
Health state classification and visual analog scale, descriptive statistics

	Iloprost				Control				Overall				
	n	mean	median	SD	n	mean	median	SD	n	mean	median	SD	
Health state classification *													
Baseline	recorded values	30	0.529	0.604	0.30	33	0.502	0.585	0.35	63	0.515	0.587	0.33
EOR	recorded values	24	0.582	0.690	0.30	30	0.510	0.620	0.41	54	0.542	0.620	0.36
	absolute changes	24	0.048	0.019	0.24	30	-0.018	0.000	0.34	54	0.011	0.000	0.30
Visual analog scale **													
Baseline	recorded values	25	48.8	40.0	22.8	30	41.3	46.0	20.2	55	44.7	46.0	21.6
EOR	recorded values	22	56.9	60.0	21.1	27	42.6	40.0	23.7	49	49.0	50.0	23.5
	absolute changes	22	6.7	2.5	16.0	27	0.0	0.0	17.2	49	3.0	0.0	16.8

* The recordings for the five dimensions of the health state classification are combined to one score ranging from -0.59 (worst condition) to 1.0 (best condition).

** The VAS ranges from 0 (worst condition) to 100 (best condition).

Karnofsky index

TT 20 Karnofsky index, descriptive statistics and classified changes from baseline to EOR

	Iloprost				Control				Overall				
	n	mean	median	SD	n	mean	median	SD	n	mean	median	SD	
Descriptive Statistics													
Baseline	recorded values	30	70.5	70.0	12.2	33	70.8	70.0	11.0	63	70.6	70.0	11.5
EOR	recorded values	24	72.7	80.0	14.2	31	65.5	70.0	17.7	55	68.6	70.0	16.5
	absolute changes	24	-0.625	0.0	12.26	31	-5.968	0.0	14.52	55	-3.637	0.0	12.26
Classified changes from baseline to EOR													
	Improved	6	25.0%		2	6.5%			8	14.5%			
	Unchanged	12	50.0%		18	58.1%			30	54.5%			
	Deteriorated	6	25.0%		11	35.5%			17	30.9%			
	Sum	24	100.0%		31	100.0%			55	100.0%			

Karnofsky index ranges from 0 (worst condition) to 100 (best condition).

Negative changes indicate an improvement, positive changes indicate deterioration.

Borg scale

TT 21		Borg Scale, descriptive statistics and classified changes from baseline to EOR											
		Iloprost				Control				Overall			
		Descriptive Statistics											
		n	mean	median	SD	n	mean	median	SD	n	mean	median	SD
Baseline	recorded values	30	15.1	15.0	2.3	33	14.5	15.0	2.5	63	14.8	15.0	2.4
EOR	recorded values	24	14.4	13.0	2.7	30	14.5	15.0	2.7	54	14.5	14.5	2.7
	absolute changes	24	-0.63	-2.0	2.67	30	0.20	0.0	2.38	54	-0.17	0.0	2.52
		Classified changes from baseline to EOR											
	Improved	13	54.2%		9	30.0%		22	40.7%				
	Unchanged	2	8.3%		9	30.0%		11	20.4%				
	Deteriorated	9	37.5%		12	40.0%		21	38.9%				
	Sum	24	100.0%		30	100.0%		54	100.0%				

Borg scale ranges from 20 (worst condition) to 6 (best condition).

Negative changes indicate an improvement, positive changes indicate deterioration.

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/s/

Maryann Gordon
11/12/04 12:24:31 PM
MEDICAL OFFICER