OBSERVATIONAL TRIAL PROTOCOL

Use, safety and Tolerability of IntraVenous epOprostenoL (Veletri®) in patients with severe pulmonary arterIal hypertension

A 6-month, open label, multicenter, observational, non-interventional study

TIVOLI

Local Project ID: 9713228

Observational Trial Code:	TIVOLI
EudraCT No.:	non applicable
Clinical Phase:	observational study
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1 Protocol Outline

Title	Use, safety and tolerability of intravenous epoprostenol (Veletri®) in patients with severe pulmonary arterial hypertension
Short title:	TIVOLI
Local Project ID	9713228
Phase:	Observational study / "Anwendungsbeobachtung" according to § 67 subsection 6 German Medicinal Products Act (AMG)
Principal / Coordinating Investigator	Prof. Dr. med. Ekkehard Grünig Thoraxclinic at Heidelberg University Hospital 1. Centre for pulmonary hypertension Röntgenstraße 1 69126 Heidelberg
Financing	Co-financing by pharmaceutical industry: Actelion Pharmaceuticals
Indication	ICD-10 I27.0 Primary pulmonary hypertension MedDRA (V. 12.0) Pulmonary Hypertension 10037400, Level 4
Trial Population	<u>Inclusion Criteria</u> 1. male or female patients with pulmonary arterial hypertension (PAH) 2. adult patients having completed his/her 18th birthday 3. patients in need of treatment escalation with i.v. epoprostenol according to current guidelines 4. (PAH) confirmed by right heart catheter (RHC) before enrolment, i.e. mPAP ≥25 mmHg at rest, PAWP ≤15 mmHg 5. able to understand and willing to sign the Informed Consent Form <u>Exclusion Criteria</u> 1. known intolerance to epoprostenol or one of its excipients 2. participation in any clinical drug trial within 4 weeks prior to screening of this study and/or patient, who is scheduled to

	receive an investigational medicinal product (IMP) during the course of this study pregnancy or lactation
Objectives / Endpoints	<u>Primary [Objectives / Endpoints]</u> - To collect and explore real-life data on the use, safety and tolerability of a systematic drug management of intravenous epoprostenol (Veletri®) treatment in patients with PAH. Real-life safety and tolerability data will be obtained by listings of the frequency of i.v. epoprostenol (Veletri®)-associated adverse drug reactions (ADRs), serious adverse events (SAEs) during i.v. epoprostenol therapy and AEs during i.v. epoprostenol therapy. <u>Secondary [Objectives / Endpoints]</u> To assess the real world clinical effectiveness of i.v. epoprostenol (Veletri®) therapy by collection of the following data (according to clinical practice): - demography - vital signs - exercise capacity as measured by six minute walking distance - N-terminal pro-brain natriuretic peptide (NTproBNP) - World Health Organization (WHO) functional class - Borg dyspnea score - blood gas analysis - right heart size and function (presence/absence of pericardial effusion and tricuspid annular plane systolic excursion (TAPSE), right atrial and ventricular area, systolic pulmonary arterial pressure, right ventricular pump function, assessed by echocardiography) - haemodynamics (right arterial pressure (RAP); mean pulmonary arterial pressure (mPAP); cardiac output (CO), cardiac index (CI); pulmonary vascular resistance (PVR); PVR index (PVRI); pulmonary capillary wedge pressure (PCWP) assessed by right heart catheterisation and tricuspid regurgitant jet velocity (TRJV) assessed by echocardiography) - symptoms of PAH - outcome (survival, transplant-free survival)

Trial Design	This is a non-interventional, observational and prospective, multicenter study to evaluate the use, safety and tolerability of i.v. epoprostenol therapy (Veletri®) in routine practice according to the German Drug Law (AMG, §67(6)). Patients with invasively diagnosed PAH receiving targeted PAH combination treatment in need of treatment escalation with i.v. epoprostenol, according to medically indicated decision on treatment-escalation, will be included in this non-interventional, observational study. This study is performed as a non-interventional trial using a prospective, open label, multicenter clinical study design with treatment according to current medical practice. Patients will be assessed according to routine clinical examinations in their respective pulmonary hypertension expert center. According to the current guidelines, patients will be seen in the expert center about every three months. This will allow to collect data within the first 6 months of treatment and compare changes between baseline, 3 and 6 months (~24 weeks). Routine medical examinations comprise of medical history, physical examination, electrocardiogram (ECG), laboratory testing (including NT-proBNP), echocardiography at rest, and right heart catheterization according to clinical practice of the PH center. If patients fulfill the inclusion criteria they will be invited to join the study. The prospective period of data collection will comprise of a ~24-week study period a follow-up phase of about 30±7 days. Outcome (survival and transplant-free survival) of all patients will be assessed when the last patient has terminated his/her ~24 week observation period.
Medicinal product under observation	Epoprostenol i.v. (Veletri®) will be applied according to general practice. Dosage will be individually up-titrated according to the physician's and the patient's estimation.
Sample Size	In this open label, multicentre study patients with PAH will receive i.v. epoprostenol according to current clinical practice. Patients in need of treatment escalation according to the current guidelines receive at least

	dual combination treatment with two PAH-targeted drugs and have an unsatisfying long-term clinical response or are still in an intermediate or high risk group. The main analyses will be the description of use, safety data and the change of clinical data by i.v. epoprostenol during the course of the study. A sample of ~15 patients will be included into the observational study to gain insights into and collect data regarding the use, safety and tolerability of a systematic drug management of i.v. epoprostenol treatment (Veletri®).
Statistical Analysis	General Descriptive statistics: - All data (demographic and other baseline characteristics, continuous data at each visit and their change to baseline) will be listed and trial summary tables will be provided. The data from all centers will be pooled. - Descriptive statistics will be displayed (arithmetic mean, median, standard deviation, standard error, 95% confidence limits of mean and median, first and third quartiles, minimum, and maximum for quantitative variables). Frequency tables for qualitative data will be provided.

2 Introduction

2.1 Scientific Background

Chronic pulmonary hypertension (PH) is associated with impaired exercise capacity, quality of life and right ventricular function.[1] The disease is characterized by an increase of pulmonary vascular resistance and pulmonary arterial pressure, leading to right heart insufficiency.[1, 2] Within the last decade, new disease-targeted medical therapies have been approved for treatment of pulmonary arterial hypertension (PAH).[3] Combinations of these agents have shown to further improve symptoms, 6-minute walking distance (6-MWD) and hemodynamics in PAH patients.[1, 3]

The loss of endogenous prostacyclin plays an important role in the pathogenesis of PAH. Prostacyclin has vasodilatory, anti-proliferative, anti-inflammatory and anti-thrombotic properties and is therefore an important target substance in PAH-specific therapy.[4] Epoprostenol was the first specific therapy approved for the treatment of PAH, after showing a positive effect on survival in otherwise treatment naïve patients.[5] Epoprostenol is chemically unstable with a short biological half-life of 3-5 minutes, and must be continuously administered by intravenous (i.v.) infusion using an external pump and in-dwelling central venous catheter. The application of epoprostenol is therefore aggravated by its handling, which makes it a challenge for the patient to store and administer the medication.

Flolan® was the first epoprostenol drug that was made available for treatment of pulmonary arterial hypertension. Reconstituted flolan solution is stable at 2 - 8 ºC for up to 48 hours. If used immediately, reconstituted flolan is stable for up to 12 hours at room temperature (< 25 ºC), or prior to use at room temperature, reconstituted flolan may be stored at 2 - 8 ºC for up to 40 hours. In this case, flolan should not be infused for over 8 hours at room temperature.

With Veletri® an improved epoprostenol solution has been therefore developed to facilitate storage and administration of the drug. It provides a better stability upon reconstitution is self-preserving, does not allow the growth of micro-organisms and allows reconstitution with readily available diluents.

2.2 Trial Rationale/ Justification

Intravenous epoprostenol (Veletri®) is used to treat adults with certain kinds of severe pulmonary arterial hypertension (PAH) (WHO Group 1) and it has been in use worldwide for decades. It gives patients the option of up to once- weekly preparation (up to 8 cassettes at one time), and which, when prepared, stored, and used as directed, does not require ice packs. By

contract with Flolan® (epoprostenol sodium), which contains the same active pharmaceutical ingredient, it provides 24-hour room temperature stability at all concentrations.

As intravenous treatment is still complex and experience in the administration, titration and handling of i.v. application systems is rare, this non-interventional study is aimed to investigate the use of a systematically structured management of intravenous epoprostenol (Veletri®) in patients with severe pulmonary arterial hypertension within German centers according to current clinical practice.

3 Trial Objectives and Endpoints

3.1 Primary Objective and Primary Endpoint

To collect and explore real-life data on the use, safety and tolerability of a systematic drug management of intravenous epoprostenol (Veletri®) treatment in patients with PAH.

Real-life safety and tolerability data will be obtained by listings of the frequency of i.v. epoprostenol (Veletri®)-associated adverse drug reactions (ADRs), serious adverse events (SAEs) and AEs during i.v. epoprostenol therapy.

3.2 Secondary Objectives and Endpoints

2) To assess the real world clinical effectiveness of epoprostenol (Veletri®) therapy by collection of the following data (according to clinical practice), if available:

- demography
- vital signs
- exercise capacity as measured by six minute walking distance
- N-terminal pro-brain natriuretic peptide (NTproBNP)
- World Health Organization (WHO) functional class
- Borg dyspnea score
- blood gas analysis
- right heart size and function (presence/absence of pericardial effusion and tricuspid annular plane systolic excursion (TAPSE), right atrial and ventricular area, systolic pulmonary arterial pressure, right ventricular pump function, assessed by echocardiography)
- haemodynamics (right arterial pressure (RAP); mean pulmonary arterial pressure (mPAP); cardiac output (CO), cardiac index (CI); pulmonary vascular resistance (PVR); PVR index (PVRI); pulmonary capillary wedge pressure (PCWP) assessed by right heart catheterisation and tricuspid regurgitant jet velocity (TRJV) assessed by echocardiography)

- symptoms of PAH
- outcome (survival, transplant-free survival)

4 Design of the Observational Trial

This is a non-interventional, observational and prospective, multicenter study to evaluate the use, safety and tolerability of i.v. epoprostenol therapy (Veletri®) in routine practice according to the German Medicinal Products Act (AMG, §67(6)).

Patients with invasively diagnosed PAH receiving targeted PAH combination treatment in need of treatment escalation with i.v. epoprostenol, according to medically indicated decision on treatment-escalation, will be included in this non-interventional, observational study. This study is performed as a non-interventional trial using a prospective, open label, multicenter clinical study design with treatment according to current medical practice.

Patients will be assessed according to routine clinical examinations in their respective pulmonary hypertension expert center. According to the current guidelines, patients will be seen in the expert center about every three months. This will allow to collect data within the first 6 months of treatment and compare changes between baseline, 3 and 6 months (~24 weeks).

Routine medical examinations comprise of medical history, physical examination, electrocardiogram (ECG), laboratory testing (including NT-proBNP), echocardiography at rest, and right heart catheterization according to clinical practice of the PH center. If patients fulfill the inclusion criteria they will be invited to join the study. The prospective period of data collection will comprise of a ~24-week study period a follow-up phase of about 30±7 days.

Outcome (survival and transplant-free survival) of all patients will be assessed when the last patient has terminated his/her ~24 week observation period.

4.1 Study population

In this open label, multicenter non-interventional, observational study patients with PAH will receive medically indicated i.v. epoprostenol (Veletri®) according to a systematic drug management including initiation, administration, storage, handling of the infusion system and patient education. Patients in need of treatment escalation according to the current guidelines receiving at least dual oral combination treatment with two PAH-targeted drugs and having an unsatisfying long-term clinical response or are still in an intermediate or high risk group will be eligible for the study.

5 Trial Duration and Schedule

5.1 Study Phases

- Clinical visits and assessments will be scheduled according to the center's clinical practice about every 3 months.
- Treatment Duration: ~ 24 weeks

5.2 Trial Duration

The overall duration of the trial is expected to be approximately 3 ½ years. Recruitment of subjects will start in the fourth quarter of 2017. The actual overall duration or recruitment may vary.

Total trial duration:	[3 ½ years]
Beginning of the preparation Phase:	*[Q4 2017]*
FSI (First Subject In):	*[Q1 2018]*
LSI (Last Subject In):	*[Q2 2020]*
LSO (Last Subject Out):	*[Q3 2020]*
DBL (Data Base Lock):	*[Q4 2020]*
Statistical Analyses Completed:	*[Q1 2021]*
Trial Report Completed:	*[Q1 2021]*

6 Selection of Subjects

6.1 Number of Subjects

A sample of ~15 patients will be included into the observational study to gain insights into and collect data regarding the use, safety and tolerability of a systematic drug management of i.v. epoprostenol treatment (Veletri®).

6.2 General Criteria for Subjects' Selection

We will ascertain that only patients who are correctly diagnosed and are on PAH-targeted therapy will be included. Only patients on PAH targeted treatment in need of treatment escalation with i.v. epoprostenol will be included in this observational trial. Eligibility criteria are as follows:

6.3 Inclusion Criteria

1. male or female patients with pulmonary arterial hypertension (PAH)
2. adult patients having completed his/her 18th birthday

3. patients in need of treatment escalation with i.v. epoprostenol according to current guidelines
4. (PAH) confirmed by right heart catheter (RHC) before enrolment, i.e. mPAP ≥25 mmHg at rest, PAWP ≤15 mmHg
5. able to understand and willing to sign the Informed Consent Form.

6.4 Exclusion Criteria

1. known intolerance to epoprostenol or one of its excipients
2. participation in any clinical drug trial within 4 weeks prior to screening of this study and/or patient, who is scheduled to receive an investigational medicinal product (IMP) during the course of this non-interventational trial
3. pregnancy or lactation

6.5 Criteria for Removal or Withdrawal

6.5.1 Withdrawal of Subjects

Since the patients will be treated according to general practice and based on the medically indicated physician's decision (non-interventional trial), a patient will only be removed from this trial at his/her own request.

The reason for withdrawal must be recorded in the CRF and in the subject's medical records and the reason should be asked for as extensively as possible and documented. The patient will be informed that he/she is not obliged to give a reason for withdrawal.

7 Medicinal Product

7.1 General Information about the Medicinal Product Under Observation (i.v. Epoprostenol)

Medicinal product under observation: i.v. epoprostenol/Veletri®, solution

International Nonproprietary Name (INN): i.v. epoprostenol

ATC code: B01AC09

Route of administration: intravenuous

Time and frequency of administration: continuous

Dosage: titration according to general practice and decision of the treating physician

Storage conditions: option to prepare and use your medicine immediately, or to prepare your medicine and store it in the refrigerator (36°F to 46°F/2°C to 8°C) for up to 8 days

Marketing authorization holder: Actelion Pharmaceuticals

7.2 Therapeutic Effects

Chronic pulmonary hypertension (PH) is associated with impaired exercise capacity, quality of life and right ventricular function.[1] The disease is characterized by an increase of pulmonary vascular resistance and pulmonary arterial pressure, leading to right heart insufficiency.[1, 2] Within the last decade, new disease-targeted medical therapies have been approved for treatment of pulmonary arterial hypertension (PAH).[3] Combinations of these agents have shown to further improve symptoms, 6-minute walking distance (6-MWD) and hemodynamics in PAH patients.[1, 3]

The loss of endogenous prostacyclin plays an important role in the pathogenesis of PAH. Prostacyclin has vasodilatory, anti-proliferative, anti-inflammatory and anti-thrombotic properties and is therefore an important target substance in PAH-specific therapy.[4] Epoprostenol was the first specific therapy approved for the treatment of PAH, after showing a positive effect on survival in otherwise treatment naïve patients.[5] Epoprostenol is chemically unstable with a short biological half-life of 3-5 minutes, and must be continuously administered by intravenous (i.v.) infusion using an external pump and in-dwelling central venous catheter.

The application of epoprostenol is therefore aggravated by its handling, which makes it a challenge for the patient to store and administer the medication.

Flolan® was the first epoprostenol drug that was made available for treatment of pulmonary arterial hypertension. Reconstituted flolan solution is stable at 2 - 8 ºC for up to 48 hours. If used immediately, reconstituted flolan is stable for up to 12 hours at room temperature (< 25 ºC), or prior to use at room temperature, reconstituted flolan may be stored at 2 - 8 ºC for up to 40 hours. In this case, flolan should not be infused for over 8 hours at room temperature.

With Veletri® an improved epoprostenol solution has been therefore developed to facilitate storage and administration of the drug. It provides a better stability upon reconstitution is self-preserving, does not allow the growth of micro-organisms and allows reconstitution with readily available diluents.

7.3 Known Side Effects

Treatment with i.v. epoprostenol/Veletri® may cause side effects. The most common side effects seen in at least 1% of patients were:

- flushing
- headache
- nausea/vomiting
- low blood pressure

- anxiety/nervousness
- chest pain
- dizziness
- slow heartbeat
- abdominal pain
- pain in the muscles and/or ligaments and bones
- shortness of breath
- back pain
- sweating
- upset stomach
- numbness/increased sensitivity
- fast heartbeat

The most common side effects in patients with PAH due to unidentified or hereditary factors with at least 10% difference between the group that received epoprostenol and the group that received conventional therapy alone were:

- flu-like symptoms
- fast heartbeat
- flushing
- diarrhea
- nausea/vomiting
- jaw pain
- pain in the muscles and/or ligaments and bones
- anxiety/nervousness
- dizziness
- headache
- numbness/increased sensitivity/tingling

The most common side effects in patients with PAH due to connective tissue disease with at least 10% difference between the group that received epoprostenol and the group that received conventional therapy alone were:

- flushing
- low blood pressure
- lack of appetite
- nausea/vomiting
- diarrhea

- jaw pain
- neck/joint pain
- headache
- skin ulcer
- rash

7.4 Dosage Schedule, Titration and Administration

This non-interventional trial aims to investigate the use and titration of i.v. epoprostenol (Veletri®) in clinical practice. To guide physicians during the titration phase, the following informations will be provided, allowing a systematic approach to dosing. Informations given to the study phasicians include initiation, titration, dosage, known side effects and administration. This information is however not binding, but shall help the treating physician to handle i.v. administration of i.v. epoprostenol (Veletri®).

Official dosage recommendations are as follows:

- Initiation of chronic infusion of i.v. epoprostenol (Veletri®) at 2 ng/kg/min (or lower if not tolerated)
- Increase in increments of 2 ng/kg/min every 15 minutes or longer until a tolerance limit to the drug is established or further increases in the infusion rate are not clinically warranted.
- Decrease of dosage if dose-limiting pharmacologic effects occur
- In clinical trials, the most common dose-limiting adverse events were nausea, vomiting, hypotension, sepsis, headache, abdominal pain, or respiratory disorder (most treatment-limiting adverse events were not serious).

In the controlled 12-week trial in PAH/SSD, for example, the dose increased from a mean starting dose of 2.2 ng/kg/min. During the first 7 days of treatment, the dose was increased daily to a mean dose of 4.1 ng/kg/min on day 7 of treatment. At the end of week 12, the mean dose was 11.2 ng/kg/min. The mean incremental increase was 2 to 3 ng/kg/min every 3 weeks.

Titration

Adjust the infusion by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes.

In clinical trials, incremental increases in dose occurred at intervals of 24 to 48 hours or longer. Following establishment of new chronic infusion rate, observe the patient, and monitor standing

and supine blood pressure and heart rate for several hours to ensure that the new dose is tolerated.

During chronic infusion, the occurrence of dose-limiting pharmacological events may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Make dosage decreases gradually in 2-ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Avoid abrupt withdrawal of i.v. epoprostenol (Veletri®) or sudden large reductions in infusion rates. Except in life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of i.v. epoprostenol (Veletri®) should be adjusted only under the direction of a physician.

Administration

Veletri, once prepared as directed, is administered by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. During initiation of treatment, i.v. epoprostenol (Veletri®) may be administered peripherally.

Infusion sets with an in-line 0.22 micron filter should be used.

8 Data Sources

8.1 Variables

Information will be collected as available and per clinical practice visit schedule. Data will be entered by the investigator / member of the study team into a standardized CRF.

Data will be collected for each patient an initiation of i.v. epoprostenol (Veletri®) and throughout the observational period from the existing medical record at any clinical visit on the respective CRF. If a patient's data collection is terminated, the date and reason for termination of data collection must be recorded on the CRF. Table 1 provides an overview of the variables collected at initiation of i.v. epoprostenol (Veletri®) and/or during the observation period (follow-up visits), if available, per clinical practice.

At initiation of a new i.v. epoprostenol (Veletri®) therapy, the data available at initiation of i.v. epoprostenol (Veletri®) will be collected for assesments stated above (points 8.1.1-8.1.10). Descriptions of clinical practice assessments are excplicitly not used to alter or regulate clinical assessments in the participating centres.

According to the current guidelines, patients are likely to be seen in the expert center about every three months. This will allow to collect data within the first 6 months of treatment and compare changes between baseline, 3 and 6 months (~24 weeks).

8.1.1 Physical examination and demographic data

The physical examination comprises measurement of body weight and height (height will be measured only once) and a routine internal medical examination. The results of these clinical physical examinations will be used to evaluate the inclusion and exclusion criteria and to document the health status before and following treatment with i.v. epoprostenol (Veletri®).

8.1.2 Hemodynamic parameters

According to current guidelines the right heart catheterization (RHC) is being performed at the beginning and after six months of treatment with i.v. epoprostenol (Veletri®) [6, 7]. the If performed at initiation of i.v. epoprostenol (Veletri®) therapy and after six months, right heart catheterisation (RHC) hemodynamic parameters will be collected [right atrial pressure, mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure (PAWP), cardiac output (CO), cardiac index (CI), and venous oxygen saturation (SvO2); heart rate, blood pressure.]

8.1.3 Echocardiography

If routinely conducted, following echocardiography parameters will be collected : systolic pulmonary arterial pressure (sPAP), Tei-Index, right atrial and ventricular area, tricuspid annular plane systolic excursion (TAPSE), right and left ventricular pump function will be assessed.

8.1.4 Determination of WHO functional class

As par of the routine, functional assessment of pulmonary hypertension is performed according to the WHO-Functional Class, i.e. the Evian Symposium, 1998, modified New York Heart Association (NYHA) Classification:

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea of fatigue, chest pain or near syncope.

Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

8.1.5 Lung function tests and blood gas analysis

As available and per clinical practice visit schedule following parameters will be collected:

Lung function test: Body plethysmography (preferred method) including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow (FEV), total lung capacity (TLC), diffusion-limited carbon monoxide (DLCo), residual volume), normally accounting for about 25% of TLC.

Blood gas analysis: capillary or arterial blood gas analysis; partial pressure of oxygen and carbon dioxide, oxygen saturation, supplemental oxygen "yes" or "no" (if the patient receives supplemental oxygen the amount will be recorded in the CRF in liters/minute).

8.1.6 6-minute walking distance and Borg dyspnea Score (CR 10)

As part of clinical practice visits patient is asked to walk along a prescribed path as far as possible during a 6 minute interval of time. The patient may walk at whatever pace he/she feels comfortable with the goal of walking the most distance he/she feels possible. If the patient feels the need to rest, he/she may do this. Blood pressure, heart rate and oxygen saturation are measured before and after the test. The Borg Scale (Breathlessness Scale) is commonly used to measure shortness of breath of patients or in sports medicine.

The Borg Scale comprises the following parameters according to the ATS guidelines (ATS 2002):

0	Nothing at All
0.5	Very very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat Moderate
5	Severe
6	
7	Very Severe
8	
9	Very very severe (almost maximal)
10	Maximal

8.1.7 Quality of Life (QoL):

QoL will be assessed as part of clinical practice visits using the SF 36-questionnaire (see Appendix) that will be handed out to the patients. Scoring will be carried out according to the test manual.

The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale, i.e. a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The eight sections are: vitality; physical functioning; bodily pain; general health perceptions; physical role functioning; emotional role functioning; social role functioning; mental health.

8.1.8 Vital signs

Blood pressure, heart rate and oxygen saturation will be recorded according to current clinical practice.

8.1.9 Electrocardiography

If performed as part of clinical practice visits, data from a 12-lead electrocardiogram (ECG) will be reviewed for potential AEs.

A continuous 3-lead ECG monitoring will be applied during right heart catheterization.

8.1.10 Clinical laboratory data

As available and determined locally on-site, following clinical laboratory data will be collected:

Hematology	Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets
Substrates	Bilirubin, LDL/HDL, cholesterol, triglycerides, creatinine, uric acid, urea, total protein, albumin, glucose
Electrolytes	Sodium, potassium, calcium, chloride
Enzymes	SGOT/ASAT, SGPT/ALAT, Gamma-GT, GLDH, AP, LDH, CK
Others	INR, PTT, β-HCG test for women with childbearing potential at initial screening, Vistit 3 and Vistit 4
Biomarkers	CRP, NT-proBNP

8.2 Data Collection Schedule

Patients will be assessed according to routine clinical examinations in their respective pulmonary hypertension expert center. According to the current guidelines, patients will be seen in the expert center about every three months. This will allow to collect data within the first 6 months of treatment and compare changes between initiation of new i.v. epoprostenol (Veletri®) therapy, after 3 and 6 months (~24 weeks).

Routine medical examinations comprise of medical history, physical examination, electrocardiogram (ECG), laboratory testing (including NT-proBNP), echocardiography at rest, and right heart catheterization according to clinical practice of the PH center. If patients fulfill the inclusion criteria they will be invited to join this non-interventional trial. The prospective period of data collection will comprise of a ~24-week observation period and a follow-up phase of about 30±7 days.

No additional assesments will be performed due to the study. All decisions regarding treatment and titration of i.v. epoprostenol (Veletri®) are based on the treating physicians decision.

Table 1 provides an overview of the variables collected at initiation of i.v. epoprostenol (Veletri®) therapy and/or during the observation period (follow-up visits), if available, per clinical practice.

Table 1: CRF data collection (as available per clinical practice from the existing medical record)		
Variable / Clinical characteristics	**Initiation of i.v. epoprostenol (Veletri®) therapy**	**Follow-up (at any clinical practice visit)**
Informed consent	X	
Medical History	X	
Inclusion/Exclusion Criteria Review	X	
Demographics (age, gender, country)	X	
Physicial examination and vital signs	X	X
WHO classification	X	X
Electrocardiogram - ECG	X	X
Echocardiography at rest	X	X
Right heart catheterization	X	X
6MWD-test	X	X
(Lung function test	X	X
Patient Questionnaire 1 (QoL)	X	X
Patient Questionnaire 2 (Borg dispnoe score)	X	X
Lab tests/assay 1 (including NT-proBNP)	X	X
Lab tests/assay 2 (Pregnancy test)	X	

9 Adverse Events

9.1 Definitions

9.1.1 Adverse Event

According to Good Clinical Practice GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the IMP.

An AE may be:

- New symptoms/ medical conditions

- New diagnosis
- Significant changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening (change in nature, severity or frequency) of medical conditions/ diseases existing before trial start
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.
- Events related or possibly related to concomitant medications

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

AEs are classified as "non-serious" or "serious".

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the subject was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe)
- Requires subject hospitalization or prolongation of existing hospitalization (unless the admission results in a stay of less than 12 hours or the admission is pre-planned or the admission is not associated with an adverse event)
- Results in persistent or significant disability/ incapacity or
- Is a congenital anomaly/ birth defect.
- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious (e.g. treatment at home for allergic bronchospasm).

9.1.3 Expectedness

An ‘unexpected’ adverse event is one the nature or severity of which is not consistent with the applicable “Summary of Product Characteristics” (SmPC) or scientific literature. Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute ‘unexpected’ events.

9.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to IMP and ‘unexpected’, i.e. the nature and/ or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs). The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

In case, either the investigator who primarily reported the SAE or the second assessor classify the SAE as ‘suspected’ (i.e. either definitely or *probable* or *possible related* to the IMP *or not assessable*) and the SAE is unexpected it will be categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent higher federal authority, i.e. Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), and to all participating investigators.

9.1.5 Grading of AEs

The **grading** of an AE should be assessed by the investigator according to the 5-grade scale defined in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 established by the National Cancer Institute (NCI) of the United States of America (USA) as follows:

Grade 1: mild AE, temporary event which is tolerated well by the subject

Grade 2: moderate AE; event which results in discomfort for the subject and impairs his/ her normal activity

Grade 3: severe AE; event which results in substantial impairment of normal activities of subject

Grade 4: life-threatening AE or AE causing disablement

Grade 5: death related to AE

9.1.6 Relationship and outcome of AEs, action taken

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the observed medicinal product (Veletri ®) that was ongoing at the time of AE onset, and reported as either related or unrelated. The determination of the likelihood that the observed medicinal product (Veletri ®) caused the AE shall be provided by an investigator who is a qualified physician.

9.2 Period of Observation and Documentation

All AEs reported by the patient or detected by the treating physician / investigator, are routinely being documented in the subject's medical records. For the pupose of this observational trial all AEs that occur after the initiation of i.v. epoprostenol (Veletri®) up to the last visit will also be documented on the pages provided in the CRF. AEs will be assessed by the investigator using no-leading questions or observed during any visit during the whole observation. The patient should be motivated to report any AEs by phone to the investigator occurring between clinical visits.

Each event should be described in detail along with start and stop dates, severity, relationship to the observed product, action taken and outcome.

9.3 Reporting of Serious Adverse Events

Once an AE/ adverse drug reaction (ADR) is identified, the prescriber / investigator / study coordinator will complete an AE form within 1 working day of the investigator's/ prescriber's knowledge that will be transferred electronically and/or by fax to the PH Centre Heidelberg and Actelion using the Actelion Global Drug Safety (GDS) contact information:

E-mail: drugsafetyCH@actelion.com

Fax: +41 61 565 64 90

The AE / ADR form shall include following information:

- Patient/subject demographics
- Protocol number
- Start and end date of treatment with i.v. epoprostenol (Veletri®)
- Nature of the AE including date of onset, severity, chronicity and treatment (including hospitalization)
- Final diagnosis (if available)
- Action taken with respect to the observed medicinal product
- Relationship to the observed medicinal product in the opinion of the investigator
- Concomitant drug therapy at the time of the adverse event
- Outcome (if available)
- Recovery date (if available)
- In the case of death, the cause and post-mortem findings (if available).

The original SAE-reports and all other reports will be kept by the investigator.

10 Statistical Procedures

10.1 Sample Size Calculation

A sample of ~15 patients will be included into the observational study to gain insights into and collect data regarding the use, safety and tolerability of a systematic drug management of i.v. epoprostenol treatment (Veletri®).

10.2 Analysis Variables

Primary Outcome variable:

1. The main parameters are the listing and frequency of safety and tolerability parameters of i.v. epoprostenol (Veletri®).

Secondary outcome variables:

2. demography (sex, age, height, weight)
3. vital signs (blood pressure, heart rate)
4. exercise capacity as measured by six minute walking distance
5. N-terminal pro-brain natriuretic peptide (NTproBNP)
6. World Health Organization (WHO) functional class
7. Borg dyspnea score
8. blood gas analysis
9. right heart size and function (presence/absence of pericardial effusion and tricuspid annular plane systolic excursion (TAPSE), right atrial and ventricular area, systolic pulmonary arterial pressure, right ventricular pump function, assessed by echocardiography)
10. haemodynamics (right arterial pressure (RAP); mean pulmonary arterial pressure (mPAP); cardiac output (CO), cardiac index (CI); pulmonary vascular resistance (PVR); PVR index (PVRI); pulmonary capillary wedge pressure (PCWP) assessed by right heart catheterisation)
11. symptoms of PAH
12. outcome (survival, transplant-free survival)

According to the current guidelines, patients will be seen in the expert center about every three months. This will allow to collect data within the first 6 months of treatment and compare changes between baseline, 3 and 6 months (~24 weeks).

10.3 Definition of Trial Population to be Analyzed

In this open label, multicenter non-interventional, observational study patients with PAH will receive medically indicated i.v. epoprostenol (Veletri®) according to a systematic drug management including initiation, administration, storage, handling of the infusion system and

patient education. Patients in need of treatment escalation according to the current guidelines receiving at least dual oral combination treatment with two PAH-targeted drugs and having an unsatisfying long-term clinical response or are still in an intermediate or high risk group will be eligible for the study.

10.4 Statistical Methods

10.4.1 General

Descriptive statistics

All data (demographic and other baseline characteristics, continuous data at each routine visit and their change to baseline) will be listed and trial summary tables will be provided. Data of all centres will be pooled.

Descriptive statistics will be displayed, including the usual location and scale statistics (mean, median, standard deviation, standard error, first and third quartiles, minimum and maximum) and 95% confidence limits of mean and median.

Frequency tables for qualitative data will be provided.

If not mentioned otherwise, all statistical tests will be performed with a type I two-sided error rate of $\alpha = 0.05$

Primary endpoint

The main parameters are safety and tolerability parameters of i.v. epoprostenol (Veletri®). Data regarding safety and tolerability will be collected by listings of adverse reactions during the course of the medically indicated treatment.

Secondary efficacy variables will be formally tested for statistical significance of a difference between baseline and 3 months; baseline and 6 months, respectively.

Secondary efficacy analysis comprises hemodynamics, echocardiography, lung function tests, 6MWD, Borg Dyspnea index, Modified Rodnan Skin Score, laboratory parameters, quality of life and safety parameters.

WHO functional class is supposed to either remain the same, improve by one or two categories, or deteriorate by one category in most cases. A change score (baseline minus end of study) will be calculated, which could go from -3 (class 4 at baseline and class 1 at end of study) to +1 (class 3 at baseline and class 4 at end of study). This will be analyzed using the Wilcoxon test.

Safety analysis

All tabulations will be descriptive only. Tables will be produced for adverse events and serious adverse events.

Mortality in the 6 month period of the study will be summarized descriptively. Any deaths in the study period will be listed, with day of death relative to start and stop of study drug and cause of death. Vital signs will be summarized by visit and treatment group.

11 Data Management

11.1 Data Collection

A paper-based case report form (CRF) will be used in this study. All entries made in the CRF must be verifiable against source documents.

All findings including clinical and laboratory data will be documented in the subject's medical record and in the CRF. The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data. Any errors should have a single line drawn through them so that the original entry remains legible. The correct data should be entered at the site with the investigator's signature, date and reason for change to confirm the correctness of entries in the CRF. Self-explanatory corrections need not to be justified.

The correctness of entries in CRF will be confirmed by dated signature of the responsible investigator. The original CRF will be transferred to the data management, one copy will be kept by the investigator.

11.2 Data Handling

After first check for plausibility by eye, all data will be entered in a database as recorded in the CRF. After completion of data entry, checks for plausibility, consistency, and completeness of the data will be performed. Based on these checks, queries will be produced combined with the queries generated by visual control.

All missing data or inconsistencies will be reported back to the centre and clarified by the responsible investigator. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

11.3 Storage and Archiving of Data

According to the Joint Recommendations of BfArM and PEI on planning, execution and evaluation od observational trials (current version from 7th July 2010) all important trial documents (e.g. CRF) will be archived for at least 10 years after the termination of the observation.

12 Ethical and Legal Aspects

12.1 Good Clinical Practice

The procedures set out in this observational protocol, pertaining to the conduct, evaluation, and documentation of this observational trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

12.2 Subject Information and Informed Consent

Before being admitted to this observational trial, the subject must consent to participate after the nature and scope of the observation have been explained in a form understandable to him or her. The subject must give consent in writing. The signed Informed Consent Form will be filed by the investigator.

A copy of the signed informed consent document must be given to the subject. The documents must be in a language understandable to the subject and must specify who informed the subject.

The subjects will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

Patients will be informed of the right to refuse to participate in the trial or to withdraw consent to participate at any time without reprisal. Upon request, already collected data can be deleted.

12.3 Confidentiality

The data obtained in the course of the trial will be treated pursuant to relevant European and national legal requirements on data protection

During the observational trial, subjects will be identified solely by year of birth and an individual identification code (subject number, randomization number). Trial findings stored on a computer will be stored in accordance with relevant European and national legal requirements on data protection and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The subject consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, inspectors) may inspect the subject-related data collected during the trial.

The investigator will maintain a subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

Subjects who did not consent to circulate their pseudonymized data will not be included into the observational trial.

12.4 Responsibilities of the Investigator

The investigator should ensure that all persons assisting with the observational trial are adequately informed about the protocol, any amendments to the protocol and their trial-related duties and functions.

The investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.5 Approval of Trial Protocol and Amendments

Before the start of the observational trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) and the trial will as well be reported to the competent higher federal authority (BfArM), the Federal Association of Panel Doctors, the Central Federal Association of the health insurance funds, as well as the Association of Private Health Insurance Funds. A written favorable vote of the EC is a prerequisite for initiation of this trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

Before the first subject is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes will be submitted in writing as protocol amendments to EC and the relevant authorities mentioned above.

The investigator will keep a record of all communication with the EC and the relevant authorities.

12.6 Information to Independent Ethics Committee

The EC and the regulatory authorities must be informed of the end of the trial within one year following the completion of the data collection process.

12.7 Notification of Regulatory Authorities

The local regulatory authorities responsible for each particular investigator will be informed before the beginning and at the end of the trial according to the applicable regulations. Each investigator is obliged to notify his/ her local regulatory authority.

12.8 Registration of the Trial

Prior to the beginning of the observational study the coordinating/ principal investigator will register the trial according to the applicable regulations.

13 Quality Assurance

13.1 Quality checks

Quality checks will be done by review of the entries into the CRFs. This will include checking of the CRF/data for completeness and clarity, cross-checking for plausibility.

13.2 Inspections/ Audits

Regulatory authorities may request access to all source documents, CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities.

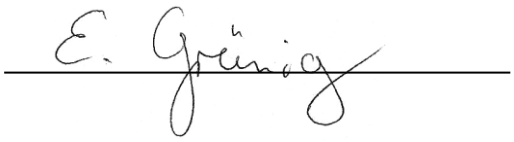
14 Financing of the Trial

The trial will be co-financed using funds of Actelion pharmaceuticals.

This funding source had no role in the design of this study and will not have any role during analyses, interpretation of the data, or decision to submit results.

15 Signature

Date: _____03.05.2018_____

Signature: 

Name (block letters): Prof. Dr. med. Ekkehard Grünig

Function: Coordinating Investigator/ Investigator

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