30 January 2020
EMA/CHMP/86002/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trepulmix

International non-proprietary name: treprostinil sodium

Procedure No. EMEA/H/C/005207/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

6MWD	6-minute-walk-distance
AE	Adverse event
ADR	Adverse drug reaction
ANCOVA	Analysis of covariance
ASMF	Active Substance Master File
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AUC0-inf	Area under the plasma concentration-time curve from zero to infinity
AUCss	Area under the plasma concentration-time curve at steady state
BMI	Body mass index
BMPR2	Bone morphogenetic protein receptor type 2
bpm	Beats per minute
cAMP	Cyclic adenosine monophosphate
CI	Cardiac index
CI	Confidence interval
Cmax	Maximal concentration
CO	Cardiac output
CTEPH	Chronic thromboembolic pulmonary hypertension
CTPA	Computed tomography pulmonary angiogram
CYP	Cytochrome p450
DP1	Prostaglandin D2 receptor
E2	Prostaglandin E2 receptor
ECG	Electrocardiogram
EIF2AK4	Eukaryotic translation initiation factor 2 alpha kinase 4
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
FC	Functional class
GC	Gas chromatography
GI	Gastrointestinal

GTP	Guanosine triphosphate
HIV	Human immunodeficiency virus
HPLC-MS/MS	High-performance liquid-chromatography pressure ionisation tandem mass spectrometry
HR	Heart rate
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN	International nonproprietary name
INR	International normalised ratio
IPAH	Idiopathic pulmonary arterial hypertension
IP receptor	Prostacyclin receptor
IR	Infrared spectroscopy
ITT	Intent to treat (population)
IV	Intravenous
Ki	Inhibition constant
LDPE	Low-density polyethylene
MS	Mass spectroscopy
NDA	New Drug Application
NMR	Nuclear magnetic resonance spectroscopy
NSAIDs	Nonsteroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PAPm	Mean pulmonary arterial pressure
PAWP	Pulmonary artery wedge pressure
PDE-5	Phosphodiesterase type 5
PE	Pulmonary embolism
PEA	Pulmonary endarterectomy
PGI2	Prostaglandin I2, prostacyclin
PH	Pulmonary hypertension
Ph. Eur.	European Pharmacopoeia

PK	Pharmacokinetic(s)
PP	Per protocol (population)
PT	Preferred term
PVOD	Pulmonary veno-occlusive disease
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
QoL	Quality of Life questionnaire
RAPm	Mean right arterial pressure
RCT	Randomised clinical trial
RV	Right ventricular
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAPm	Mean systemic arterial pressure
SC	Subcutaneous
sGC	Soluble guanylate cyclase
SM	Starting material
SmPC	Summary of product characteristics
SOC	System organ class
SvO2	Venous oxygen saturation
t1/2	Half-maximal time
TEAE	Treatment-emergent adverse event
TPR	Total peripheral resistance
UHPLC	Ultra high performance liquid chromatography
USP	United States Pharmacopeia
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SciPharm Sarl submitted on 8 February 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Trepulmix, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2018.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: treatment of adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment (severity classified WHO Functional Class (FC) II, III or IV), to improve exercise capacity and symptoms of the disease.

Trepulmix, was designated as an orphan medicinal product EU/3/13/1103 on 8 February 2013. Trepulmix was designated as an orphan medicinal product in the following condition: treatment of chronic thromboembolic pulmonary hypertension.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, and appropriate non-clinical and clinical data.

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Remodulin 1 mg/ml, Solution for infusion
- Marketing authorisation holder: United Therapeutics Corporation
- Date of authorisation: 10-08-2005
- Marketing authorisation granted by:
  - Member State (EEA): France
- Marketing authorisation number: FR/H/0278/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product: Remodulin 1 mg/ml

- Product name, strength, pharmaceutical form: Remodulin 1 mg/ml, Solution for infusion
- Marketing authorisation holder: United Therapeutics Corporation
- Date of authorisation: 10-08-2005
- Marketing authorisation granted by:
  - Member State (EEA): France
- Marketing authorisation number: FR/H/0278/001

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	8 February 2019
The procedure started on	28 February 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 May 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 May 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	14 June 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 October 2019
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
A GCP inspection at two clinical investigator sites and one Clinical Research Organisation site in Austria and Poland between 1 July-2 August 2019. The outcome of the inspection carried out was issued on 9 September 2019.	27 June 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	21 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 November 2019

The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	6 January 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	17 January 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Trepulmix on	30 January 2020

2. Scientific discussion

2.1. Introduction

This application concerns a centralised procedure application submitted under Article 10(3) of Directive 2001/83/EC, with Remodulin as the reference product. Remodulin is indicated for the treatment of idiopathic or inherited pulmonary arterial hypertension (PAH), to improve exercise capacity and symptoms of disease in patients with New York Heart Association (NYHA class III). The applied indication for Trepulmix is treatment of adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment (severity classified WHO Functional Class (FC) II, III or IV), to improve exercise capacity and symptoms of the disease. Remodulin is also available as a solution for infusion and the same strengths as Trepulmix.

2.2. Problem statement

2.2.1. Disease or condition

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and life-threatening form of pulmonary hypertension (PH). It is thought to be the long-term complication of pulmonary embolism (PE), although the processes are poorly understood and likely to be multifactorial. Along with other forms of PH, symptoms are non-specific and mainly related to progressive right ventricular (RV) dysfunction. Initial symptoms are typically induced by exertion. They include shortness of breath, fatigue, weakness, angina and syncope. Less commonly, patients may also describe dry cough and exercise-induced nausea and vomiting. Symptoms at rest occur only in advanced cases. Abdominal distension and ankle oedema will develop with progressing RV failure.

2.2.2. Epidemiology

Among patients with PH, the incidence of CTEPH subtype remains unknown, partly due to the difficulty in accurately diagnosing CTEPH and distinguishing it from other forms of PH (Edward and Mandras, 2017). However, CTEPH occurs in 3 out of 100 adult patients with a symptomatic pulmonary embolism (Lang and Klepetko, 2008), or presents with an incidence of 1% to 5% within 2 years after the occurrence of

symptomatic PE. The median age of CTEPH patients at diagnosis is 63 years and both genders are equally affected; cases of patients below the age of 18 are extremely rare (Galiè et al., 2016). Specifically, using an upper estimate of 1-9 per 100,000 (Orphanet, 2009) adult patients, roughly half of these cases are inoperable (Klepetko et al., 2004), and one group's (Madani et al., 2011) observation that only 1% of the patients with CTEPH that had undergone a PTE surgery were children would suggest that the prevalence of CTEPH in paediatrics may, in fact, be below one in two million (0.05 per 100,000).

If left untreated, CTEPH patients have a poor prognosis (Rich and McLaughlin, 2003). When mean pulmonary arterial pressure (PAP) is greater than 50 mm Hg, the 1-year survival rate in untreated patients with CTEPH is less than 50% (Lang and Klepetko, 2008).

2.2.3. Aetiology and pathogenesis

In CTEPH, the sequence of events leading to PH is triggered by single or recurrent pulmonary embolism arising from sites of venous thrombosis; it occurs when a clot fails to resolve completely after an acute pulmonary embolic event. The rate of resolution of clots after acute pulmonary embolism varies and is longer in patients with pre-existing cardiopulmonary disease, and anatomic resolution of acute embolism is often incomplete, but sufficient resolution restores normal haemodynamics usually by 4 to 6 weeks after an acute event. To some extent, the rate of resolution depends on the initial clot burden or the size of the acute pulmonary embolism. If the clot fails to resolve, it becomes organised before it can be completely fibrinolysed; this organised thrombus is incorporated into the wall of the pulmonary artery, becomes covered by endothelial cells and a process of vascular remodelling starts and forms a false intima. The organised material occludes the vascular lumen, which increases pulmonary vascular resistance and leads to pulmonary hypertension. It has been reported that 52% of patients had evidence of residual emboli 11 months after the acute event (Nijkeuter et al., 2006).

2.2.4. Clinical presentation, diagnosis

Early diagnosis remains a challenge in CTEPH, with a median time of 14 months between symptom onset and diagnosis in expert centres. When present, the clinical symptoms of CTEPH may resemble those of acute PE or IPAH; in the latter context, oedema and haemoptysis occur more often in CTEPH, while syncope is more common in idiopathic pulmonary arterial hypertension (IPAH) (Rich, 2011). Several clinical features and risk factors distinguish the two diseases, as briefly summarised in Table 1; CTEPH is usually confirmed by ventilation/perfusion (V/Q) lung scan.

Table 1. Summary comparison of CTEPH with idiopathic pulmonary arterial hypertension (IPAH)

Feature	CTEPH	IPAH
Gross pathology	• Organized, central thrombi	• Some thrombotic pathology
Histopathology	• Plexogenic arteriopathy	• Plexogenic arteriopathy
Symptoms	• Shortness of breath	• Shortness of breath
Signs	• PH and right heart failure	• PH and right heart failure
Family history	• No	• Seen in 6–10% of cases
Genetic basis	• None identified	• Genetic basis in up to 30% of sporadic IPAH cases (e.g., BMPR-II)
	• No sex predisposition	• Thrombophilia
		• Sex predisposition
Contributory mechanisms	• VTE/DVT (single or recurrent PE)	Endothelial/smooth muscle dysfunction
	• *In situ* thrombosis?	• *In situ* thrombosis?
	• Decreased fibrinolysis?	• Antiphospholipid antibodies
	• Endothelial dysfunction	• Prothrombotic factors?
	• Prothrombotic factors (factor VII)	
	• Non-O blood groups, plasma lipoprotein (a) and antiphospholipid antibodies	
Associated with other disorders	• Splenectomy	—
	• Hemolytic disease	
Treatment responses	• PEA/lung transplantation	• Lung transplantation
	• Anticoagulants	• Vasodilator therapy
	• Advanced therapies*	• Anticoagulants
	• Reduced vasodilator response	• Advanced therapies*

The diagnosis of CTEPH is based on findings obtained after at least 3 months of effective anticoagulation in order to discriminate this condition from 'subacute' PE. CTEPH is frequently found in adult patients without any previous clinical episode of acute PE or deep venous thrombosis (up to 50% in different series), and a clear understanding of why some patients resolve after PE and others do not is poorly understood (Rich, 2011).

2.2.5. Management

Surgery to remove the obstruction, pulmonary endarterectomy (PEA) is the treatment of choice for most patients with CTEPH: with the advent of PEA, 1-year mortality rates from European CTEPH registry studies have been reported to be less than 20%, while overall operative in-hospital mortality risk is 2.2% following PEA (Edward and Mandras, 2017). However, since an estimated one-half of CTEPH cases are inoperable (Klepetko et al., 2004), there remains a need for drugs to treat CTEPH patients where PEA is infeasible or ineffective.

Since March 2014, Adempas (riociguat) has been approved for the treatment of adult patients with WHO Functional Class (FC) II to III with inoperable CTEPH, to improve exercise capacity. There are no other approved therapeutic agents in the EU specifically indicated for the treatment of inoperable CTEPH.

About the product

Mechanism of action

The primary mechanism of action of treprostinil (a prostacyclin (PGI_2) analogue) is a reduction in pulmonary artery pressure and pulmonary vascular resistance through direct vasodilation of the pulmonary and systemic arterial vascular beds, thereby improving systemic oxygen transport and increasing cardiac output (CO) with minimal alteration of heart rate (HR).

Treprostinil, like endogenous prostacyclin (PGI_2) and other active analogues, binds to the G protein-coupled IP receptor which is linked with adenylyl cyclase. The IP receptor is present on the surface of several cell types including endothelial cells, vascular smooth muscle cells, and platelets (Tuder and Zaiman, 2002). Pulmonary vascular resistance (PVR) is thought to be reduced via activation of the IP receptor on vascular smooth muscle cells resulting in increases in intracellular cyclic adenosine monophosphate (cAMP) and, ultimately, vasodilation (Sprague et al., 2008). Furthermore, activation of the second messenger cAMP accounts for additional mechanisms of prostacyclin action, including inhibition of pulmonary artery smooth muscle cell proliferation, inhibition of platelet aggregation, and reversal of pulmonary artery remodelling (Falcetti et al., 2010; Whittle et al., 2012).

The initially proposed indication for Trepulmix was:

Treatment of adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment (severity classified WHO Functional Class (FC) II, III or IV), to improve exercise capacity and symptoms of the disease.

During the evaluation, the applicant amended the proposed indication to:

Treatment of adult patients with WHO Functional Class (FC) III or IV and:
- inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or
- persistent or recurrent CTEPH after surgical treatment to improve exercise capacity.

The recommended initial infusion rate for Trepulmix is 1.25 ng/kg/min. If this initial dose is poorly tolerated, the infusion rate should be reduced to 0.625 ng/kg/min.

The infusion rate should be increased under medical supervision in increments of up to 1.25 ng/kg/min per week for the first four weeks of treatment and then up to 2.5 ng/kg/min per week.

The dose should be adjusted on an individual basis and under medical supervision in order to achieve a maintenance dose at which symptoms improve and which is tolerated by the patient.

Type of Application and aspects on development

No scientific advice was requested by the applicant.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a solution for infusion containing 1 mg/ml, 2.5 mg/ml, 5 mg/ml or 10 mg/ml treprostinil (as treprostinil sodium) as active substance.

Other ingredients are sodium citrate, hydrochloric acid, metacresol, sodium hydroxide, sodium chloride and water for injections.

The product is available in 10 ml type I clear glass vials sealed with a rubber teflon-coated stopper and fitted with a yellow, blue, green or red cap respectively for the different strengths.

2.3.2. Active substance

General Information

The chemical name of treprostinil is [[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1- [(3S)-3-hydroxyoctyl]-1-H-benz[f]inden-5-yl]oxy]acetic acid. It corresponds to the molecular formula $C_{23}H_{34}O_5$, its relative molecular mass is 390.51 and it has the structure shown in **Figure 1**.

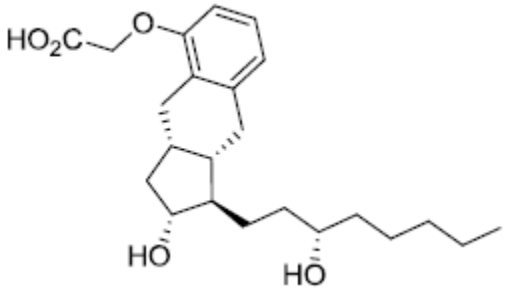


Figure 1. Structure of treprostinil

The structure of the active substance (AS) was elucidated by a combination of elemental analysis, infrared spectroscopy (IR), ^{1}H-and ^{13}C- nuclear magnetic resonance spectroscopy (NMR), mass spectroscopy (MS), specific rotation and melting point.

Treprostinil is a white or slightly yellowish hygroscopic crystalline powder. It is freely soluble in methanol, ethanol and isopropanol but practically insoluble in water and acidic solutions. Treprostinil has no known polymorphic forms. The molecule has 5 chiral centres but is synthesized as a single enantiomer. The stereochemistry of these 5 centres is derived from that of an isolated intermediate. Optical orientation cannot be further changed by subsequent chemical neither by physical manufacturing processing steps; this was further confirmed by NMR.

Manufacture, process controls and characterisation

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The manufacturing process consists of two main stages and a total 13 steps (different reactions). The selection of the regulatory starting materials is acceptable as is the control of the SM. Both SMs are

introduced early in the synthesis and their introduction is followed by multiple chemical transformations with isolated intermediates up to the final drug substance with isolated intermediates up to the final AS. Both SMs incorporate a stereogenic centre in their structure and are pure enantiomers. The stereochemical configuration of the SMs determines the stereochemical configuration of the final AS. The batch sizes have been clearly defined.

Critical steps have been specified and justified as requested. The process is sufficiently described in general and the overall control strategy (including in process controls, testing of starting material, monitoring of process parameters etc.) and the risk mitigation measures are adequate to control the process leading to an AS of intended and consistent quality. No design space has been claimed.

The characterisation of the AS and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. An adequate discussion on potential genotoxic impurities, their control and carry-over has been given. The threshold of toxicological concern (TTC) limit applied has been based on the actual maximum daily dose of the product. None of the potentially mutagenic impurities was found to carry over into the final active substance. This was further supported by actual analytical data which demonstrated that their levels are below 30% of the TTC limit. No additional control of these impurities is considered necessary. In addition, a risk evaluation has been performed on the potential of nitrosamine formation during the manufacture of the active substance, the manufacture of the finished product and/or during its storage throughout its shelf life. No relevant risk for formation of nitrosamines was identified and no further controls need to be implemented. The reassurance by the applicant to further work on the risk assessment to reassure the results obtained in this first assessment and inform EMA is noted and is considered sufficient.

Satisfactory validation study data has been presented for all the proposed batch sizes.

The packaging of the active substance has been described and is acceptable. Specification for the packaging materials has been presented and confirmation given that the primary packaging material comply with Ph. Eur. chapter 3.1.3 and EU legislation for plastic materials intended to come into contact with food.

Specification

Treprostinil active substance specification includes appropriate tests and limits for description (visual), identification (IR, UPLC), specific rotation (polarimetry), residue in ignition (Ph. Eur.), water content (Ph. Eur.), heavy metals (USP), enantiomer (chiral HPLC), related substances (UPLC), residual solvents (GC), benzene (GC) and assay (UPLC).

The proposed specifications and limits are acceptable. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data has been provided for 8 validation batches covering all three proposed batch sizes. All presented batches comply with proposed specifications; consistency of active substance has been demonstrated.

Stability

Stability data on eight commercial scale batches of active substance stored in the intended commercial packaging for up to 60 months under long term conditions (-20 ± 5°C), and for up to 6 months under accelerated conditions (5 ± 3°C) was provided according to the ICH guidelines.

Parameters investigated: description, water content, related substances and assay. The analytical methods used correspond to the release methods, while acceptance criteria were those at time of testing.

At the long-term storage condition (-20°C) no clear changes or trends were seen in any of the tested parameters up to 60 months storage. At the elevated temperature of 5°C an increase in the levels of impurities was observed leading to out-of-specification (OOO) results after 6 months storage in one batch (for two of the impurities). After 3 months storage the levels were within the specification limits. No clear changes or trends were seen at 5°C for the other tested parameters. These OOS results observed at elevated temperature are not relevant for determining the retest period since the AS is intended for storage in a freezer; the retest period should be based on long-term data alone in accordance with the ICH Q1E.

Forced degradation study
A forced degradation study was performed where the AS was exposed to acid, base, oxidation, heat and photolytic conditions (ICH Q1B). Degradation was most pronounced after acid exposure and high heat. Although less pronounced, some degradation was also observed after basic, oxidation, medium heat exposure and photolytic conditions. There are no indications from the stress studies that the active substance is sensitive to light exposure as the observed degradation at this condition rather seems related to the study temperature. However, the proposed storage precaution to store the AS protected from light is acceptable. Peak purity was confirmed under all conditions demonstrating the methods are stability indicating.

Based on the presented stability data, the claimed retest period of 2 years when stored in a freezer at -20°C is considered justified.

2.3.3. Finished medicinal product

Description of the product and Pharmaceutical Development

The finished product is a clear, colourless or lightly yellowish, pH controlled, sterile and preserved solution practically free from particles. It is supplied as a multi-dose solution (10 ml) at four different strengths of 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml in 10 ml glass vials. The finished product is administered undiluted by continuous subcutaneous infusion via a subcutaneous catheter using an ambulatory infusion pump. The infusion pump system is not supplied with the product. Requirements for the infusion pump system that is to be used to administer the product have been laid down in the product SmPC.

The product has been developed with reference to the authorised product Remodulin (treprostinil) solution for infusion 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml. The proposed formulation is essentially similar to Remodulin.
Treprostinil has low bioavailability after oral administration. The AS is only very sparsely absorbed from the GI tract and can cause local irritation of the gastrointestinal mucosa. Due to these characteristics a non-oral route of administration is preferable.
The manufacturing process takes advantage of the solubility characteristics of the active substance. Because the AS is present in the finished product in dissolved form polymorphic form and particle size are not critical parameters. Information on the choice of the excipients and their functions in the formulation has been

provided. The multi-dose presentation of the formulation (to permit multiple entries for pump syringe refill) necessitates the addition of an antimicrobial preservative. Metacresol was selected based on its established use in parenteral preparations and especially its safety profile over many years in insulin preparations. The antimicrobial efficacy of the chosen concentration of metacresol (i.e. 0.3% w/v) has been demonstrated. Metacresol is compatible with the other components of the formulation and the AS is compatible with the chosen excipients. Sterile water for injections is used as solvent. The level of 0.3% w/v of the antimicrobial preservative metacresol is within the usual range of 0.15-0.3% for subcutaneous preparations according to the Handbook on pharmaceutical excipients. The antimicrobial efficacy of the chosen concentration of metacresol will also be confirmed in accordance with Ph.Eur.5.1.3 at the end of storage in the stability testing program.

Well-established excipients are used in the manufacture of the FP. No incompatibilities between the components of the formulation are to be expected. Compatibility between the components of the drug formulation and the proposed packaging material was discussed and assessed as part of ongoing stability studies. No additional studies beyond the proposed stability testing programme have been conducted. This approach is considered justified as the qualitative and quantitative composition of the drug product is essentially similar to the reference product.

The manufacturing process is relatively straightforward. The product is terminally sterilised by autoclaving using standard Ph. Eur. reference conditions (121°C for 15 minutes). Terminal sterilisation by moist heat at 121°C for 15 minutes is the preferred sterilisation method for aqueous products. The manufacturing method remained essentially unchanged throughout the manufacture of stability and clinical batches at the development site. However, during transfer to the proposed manufacturer the manufacturing process has been slightly adapted.

The in-use compatibility with the proposed polypropylene infusion pump container has been adequately demonstrated. It is stated in the SmPC that "The reservoir must be made of polypropylene or glass."; this is acceptable. There are no concerns with regard to the compatibility with glass as the product itself is stored in glass vials.

The FP is packed in 10 ml type I glass vials at a nominal filling volume of 10 ml. The vials are closed with a fluoropolymer-coated rubber stopper. The stoppers are secured onto the vials with a centre-tear crimped aluminium cap. Based on results of a stress study, it was concluded that photostability was not an issue for the drug product and therefore clear glass vials were adopted. The glass vials meet the Ph. Eur. requirements for Type I borosilicate glass. The rubber stopper conforms to the Ph. Eur. requirements for use with aqueous parenteral preparations. The suitability of the primary packaging materials is demonstrated by the results from container closure integrity testing (vacuum test) and ongoing stability studies. In addition, multi-puncture studies have been carried out on container samples from FP batches to support in-use conditions.

Manufacture of the product and process controls

The main steps of the manufacturing process are the manufacture of the bulk solution, filtration of the solution filling of the solution into the final containers, stoppering of the vials and terminal sterilisation in an autoclave using standard Ph. Eur. reference conditions; therefore the manufacturing process is considered a standard process.

There are no intermediates during drug product manufacture. No critical steps were identified in the manufacturing process. The type of sterilisation filters has been laid down in the dossier and satisfactory filter

validation studies have been performed, which address sufficiently solution compatibility and leachable filter material.

The manufacturing process is considered a standard process. The manufacturing process has been adequately validated on three production scale batches per strength as well as on six additional production scale batches that are considered as supportive. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification, analytical procedures, batch analysis

The finished product release and shelf life specifications include appropriate tests and limits for appearance (clarity, colour of solution (Ph. Eur.)), visible particles (Ph. Eur.), particulate matter (Ph. Eur.), pH (Ph. Eur.), extractable volume (Ph. Eur.), identification of treprostinil (HPLC), identification of metacresol (HPLC), assay (HPLC), related substances (HPLC), metacresol content (HPLC), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), and preservative efficacy (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. A Risk Analysis on elemental impurities according to the above guideline has been conducted by the finished product manufacturer. The determinations of the exposure limits were based on their parenteral Permitted Daily Exposure (PDE) values. The elemental impurities assessment showed that all elemental impurities are well below the parenteral PDE limits as provided in the ICH Q3D guideline.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis data on three production scale batches of each product strength have been provided in the dossier, demonstrating compliance with the drug product release specification, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Formal stability data have been provided on six production scale batches (two per strength) that have been manufactured at the commercial manufacturing site and were packed in the commercial packaging configuration. The batches were stored at 25 °C /60% RH (36 months), 30 °C /65% RH for 36 months and 40 °C /75% RH for 6 months; only the 1 mg/ml and 10 mg/ml products. The storage conditions are in accordance with the ICH recommendations.

The following parameters have been investigated: appearance, sub-visible particles, pH, assay of treprostinil, related substances, the content of metacresol, sterility and preservative efficacy. A reduced testing design has been applied; the testing design is considered justified. No differences were seen with different orientations. The stability results showed no clear trends or changes in any of the tested parameters at both storage conditions.

Results of a formal photostability study as per ICH 1QB showed that the product in its container closure system without outer carton was not sensitive to light exposure.

An in-use stability study after first opening, with repeated puncture of the vial was performed on a 1 mg/ml batch (representing worst-case). Supportive in-use study results with repeated puncture have also been

provided in the dossier for 1 mg/ml and 10 mg/ml batches manufactured at the development site showing no changes or trends under the same conditions. The claimed in-use shelf-life after first opening of 30 days when stored at or below 30 °C (SmPC sections 6.3), is considered justified based on the in-use study results.

The product is administered undiluted by continuous subcutaneous infusion via a subcutaneous catheter using an infusion pump. In-use stability was investigated for the undiluted solution with continuous subcutaneous infusion. Except for a clear decrease in metacresol content, the data showed no trends or changes in any of the tested parameters. Chemical, physical and microbial in-use stability of a single container (syringe) of undiluted Trepulmix administered subcutaneously has been demonstrated for 72 h at 37°C (SmPC sections 6.3). Preservative efficacy was confirmed after 72 hours at the lowest metacresol level.

The presented stability data are sufficient to support the claimed shelf-life of 3 years without any special storage conditions (SmPC sections 6.3).

Adventitious agents

No excipients of human or animal origin are used in the manufacturing of the FP.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

None.

2.4. Non-clinical aspects

2.4.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.4.2. Ecotoxicity/environmental risk assessment

Table 2. Summary of main study results

Substance (INN/Invented Name): treprostinil			
CAS-number (if available): 81846-19-7			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log Kow	**OECD107 or …**	**TBD***	**Potential PBT (Y/N)**
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	**log Kow**	**No original study available**	**No conclusion**
	BCF	**No study available**	**No conclusion**
Persistence	**DT50 or ready biodegradability**	**No study available**	**No conclusion**
Toxicity	**NOEC or CMR**	**The substance is not a CMR. No study on ecotoxicity available.**	**No conclusion**
PBT-statement:	**It is not possible to perform a PBT assessment due to lack of original studies on persistence, logKow and BCF.**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, with refined Fpen of 0.000052	**0.0003**	**μg/L**	**> 0.01 threshold (Y)**
Other concerns (e.g. chemical class)	**Interacts with the PPARγ pathway**		**No further action needed.**

*TBD = to be determined.

2.4.3. Discussion on non-clinical aspects

As treprostinil is a well-known active substance, no further studies concerning pharmacodynamic, pharmacokinetic and toxicological properties of this active substance are required. Therefore the submitted overview based on literature review was considered appropriate by the CHMP.

In terms of the Environmental Risk Assessment, using the refined Fpen of 0.000052, a PECsw of 0.00031 µg/L was obtained, which is below the action limit of 0.01 µg/L.

The applicant conducted a literature search but was not able to find a reliable log *Kow* value. In the absence of such data, PBT-assessment is not possible. Therefore, the CHMP recommended that the applicant should perform an OECD TG 107 test.

This study has been initiated and the applicant should submit an updated ERA as soon as the study report is available.

2.4.4. Conclusion on the non-clinical aspects

The CHMP agreed that there are no objections to the approval of Trepulmix from a non-clinical point of view.

The applicant should submit to the Agency an updated ERA as soon as the report from the ongoing OECD TG 107 test is available.

2.5. Clinical aspects

2.5.1. Introduction

This is an application for a solution for infusion containing treprostinil. To support the marketing authorisation application in the applied indication the applicant conducted a comparator-controlled, double-blind prospective 24-week study in 105 patients with CTEPH (study CTREPH 116-02). This study was the pivotal study for the assessment of this application.

GCP

A routine GCP inspection at two clinical investigator sites and one CRO site was requested by the CHMP.

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Exemption

The formulation of treprostinil solution for infusion can be considered virtually identical to the commercially available product Remodulin. In accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, bioequivalence studies between the two products were not submitted as these are generally not required if the test product is to be administered subcutaneously and contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved.

Clinical studies

- Tabular overview of clinical studies

Reference	Study type	Dose at EOT, Duration	Patients	Mean age ± SD, years	Outcome vs. baseline
CTREPH 116-02	2-arm, double-blind, prospective RCT (high vs. low dose treprostinil, TRE)	~3 ng/kg/min, ~30 ng/kg/min 6M	Severe inoperable CTEPH (n=105, high TRE: 53, low TRE: 52)	Mean: 64 y Range: 18-88	Increase in 6MWD (ITT population, p<0.001); WHO/NYHA-FC improvement (p=0.0012); improvements in haemodynamic parameters (PVR, p<0.001; mPAP, p=0.04; CO, p<0.001; CI, p<0.001) and pro-BNP values (p= 0.032)
Skoro-Sajer et al.,2007	Open-label uncontrolled study (TRE vs. vs. historical control [conventional therapy: oral anticoagulation, supplemental O_2, digitalis])	11-30 ng/kg/min 24M (mean)	Inoperable CTEPH (n=25)	59±13 (TRE) 62±15 (control)	Increase in 6MWD (p=0.01); decrease in PVR (p=0.01) and NT-proBNP (p=0.02); WHO-FC improvement (p=0.001)
Lang et al., 2006	Open-label, uncontrolled retrospective study (TRE vs baseline)	≤ 40 ng/kg/min 36M	PAH (n=99) and CTEPH (n=23); pts. pooled for efficacy analysis	49 (12–81)	Increase in 6MWD (p=0.0001); WHO/NYHA-FC improvement (p=0.0001); results consistent across all types of PH

2.5.2. Pharmacokinetics

No pharmacokinetic studies were submitted by the applicant. The formulation of treprostinil solution for infusion used in clinical study CTREPH 116-02 can be considered identical to that of the reference medicinal

product Remodulin. It was therefore considered that pharmacokinetic studies with the proposed formulation were not necessary.

2.5.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.6. Clinical efficacy

2.6.1. Dose response study

Dose response studies were not submitted by the applicant.

The determination of target doses was based on published literature and the clinical experience of investigators with the use of treprostinil in PAH patients.

Long-term data have shown a positive outcome of exercise capacity after three years at an average dose of 40 ng/kg/min in PAH and CTEPH patients (Lang et al., 2006). A significant increase of long-term survival in PAH patients was observed after one year at an average dose of 26 ng/kg/min in another analysis (Barst et al., 2006). In contrast, doses of < 5 ng/kg/min showed no clinical improvement (Simonneau et al., 2002).

In the study by Skoro-Sajer et al. (2007) effectiveness and safety at mean doses of 21 ng/kg/min (range: 11-30 ng/kg/min) and 28 ng/kg/min (range: 12.5-42 ng/kg/min) at 6 and 12 months, respectively, has been shown. Nevertheless, in this study doses up to 100 ng/kg/min were reached after 29 ± 15 months.

A prospective registry (Sadushi-Kolici et al., 2012), evaluating the efficacy and safety of long-term treatment of SC treprostinil in severe PH (N=111; 42 subjects with CTEPH) reported doses of over 100 ng/kg/min within an observation period of 8 years. Earlier terminations in 13 patients due to intolerable drug side effects, such as infusion site pain, occurred at < 6 months of treatment at a median dose of just 14 ng/kg/min. The registry showed that it is essential to up-titrate an observed attrition rate and a 12 % drug intolerance rate within the first 6 months.

Several other publications confirm that SC treprostinil requires up-titration and dose adaptions over time driven by clinical symptoms and objective criteria (6MWD, WHO FC, NT-proBNP) (Simonneau et al., 2002, Lang et al., 2006, Barst et al., 2006, Benza et al., 2011).

The selected doses included target dose of ~ 30 ng/kg/min (high dose) versus ~3 ng/kg/min (low dose; comparator). A placebo-controlled design was considered not feasible due to the characteristic smell of the treprostinil solution and the anticipated local site reactions induced by s.c. administered treprostinil. As such, the low dose of ~3ng/kg/min was used as a comparator in order to facilitate complete double blinding.

Thereafter, in the open label phase dosing was not stipulated by the study protocol but was at the discretion of the investigator in order to maintain a stable condition with an acceptable adverse event profile. A summary of the doses achieved in the open-label extension phase of CTREPH 116-02 up until the latest data cut-off date is summarised in **Table 3**.

Table 3. Dosages during open-label extension phase of CTREPH 116-02, cut-off date: 31st October 2018.

	Months									
Timepoint (baseline = start of up-titration to effective doses)	6	12	18	24	30	36	42	48	54	60
Sample Size (available data at timepoint)	41	36	32	30	23	19	15	10	6	2
Mean Dose	26,4	30,9	32,8	33,1	35,3	39,4	36,9	37,7	39,7	34,7
Std.	9,7	8,7	9,3	11	9,7	8	10	7,8	6,1	3,3
Min	2,7	8,2	12,2	3,6	12,2	21,9	15,4	21,9	32,4	32,4
Max	44,4	51,7	52,6	53,8	48,7	49,8	50	49,2	48,5	37

2.6.2. Main study

Study CTREPH 116-02: A double blind controlled clinical study to investigate the efficacy and tolerability of subcutaneous Treprostinil sodium in patients with severe non-operable Chronic Thromboembolic Pulmonary Hypertension (CTREPH).

Methods

This was a double blind, multi-centre, randomised, controlled, parallel-group study in patients with severe non-operable CTEPH. Assessments were done at Baseline (Randomisation, start of therapy), week 6, week 12, week 18 and week 24 (end of study).

The study included four periods:

- A baseline period of 2 weeks consisting of a screening visit (Visit 1/ between day -14 and day 1) and a randomisation visit (Visit 2: at day 1). Both visits could be on one day. During this period baseline assessment were performed and baseline status for eligibility was assessed. Patients who met all inclusion/exclusion criteria were scheduled for visit 2/ randomization 1:1.
- A randomized double-blind treatment period of 24 weeks in which patients received sc infusion of treprostinil (target dose of 3 ng/kg/min (low dose) or target dose of 30 ng/kg/min (high dose)). Assessments were performed at week 6, 12, 18 and 24, whereas 6MWT were performed at week 12 and 24.

- A dose reduction period of up to 2 weeks for patients who completed last visit or who had to withdraw at an earlier stage of the study and who did not enter the follow-up open label extension period. In this period the investigator created a down titration schedule (infusion pump setting). The down titration period did not need to take two weeks but should not exceed this time. During this period, the investigator was still obliged to track all adverse events which continued or started during this time.
- A follow up open label extension phase was added in order to give patients the possibility to be treated with treprostinil after finishing 24 weeks of the randomized double-blind phase of the clinical trial.

Study Participants

Inclusion criteria (selection):

- Age over 18 year
- Patient must have a current diagnosis of CTEPH, as defined by the following criteria:
    - A test result of perfusion scintigraphy and pulmonary angiography and/or multislice CT not older than 6 months, consistent with the diagnosis CTEPH. In case of recurrent PH after PEA, test results from before the surgery are acceptable if a typical specimen was harvested during PEA substantiating the diagnosis of CTEPH.
    - A right heart catheterization, not older than 6 months, consistent with the diagnosis CTEPH but specifically with a mPAP of > 25 mmHg, and a PVR of > 300 dyn.s.cm-5
    - At least three months of effective anticoagulation therapy (without improvement/to exclude subacute pulmonary emboli)
- Patient must have a CTEPH classified as severe, as defined by the following criteria:
    - An un-encouraged 6MWT of between 150 and 400 meters
    - Classification in the WHO/NYHA functional class III or IV
- The patient must not be suitable to undergo a PEA and is therefore defined as non-operable, due to at least one of the following reasons:
    - Clot is not accessible
    - Discrepancy between severity of PH and morphologic lesion
    - Patient is not a good surgical candidate for other reasons:
        - PVR > 1500 dynes.s.cm-5
        - Age
        - Comorbidity
        - No functional lung parenchyma
        - Unsuccessful PEA in the past with residual/recurrent CTEPH
        - No consent for PEA given by the patient

Exclusion Criteria (selection):

- Patient with any form of pulmonary arterial hypertension or any disease known to cause PAH (WHO Group I)
- Patients with a total lung capacity (TLC) of < 70% predicted or a forced expiratory volume/forced capacity (FEV1/FVC < 50%)
- Patient who received any prostanoids, within the 30 days before Screening or be scheduled to receive prostanoids during the course of the study
- Patient with a new type of chronic therapy (a different category of vasodilator or diuretic) for PAH added within the last month, except anticoagulants
- Patient with an increased risk for haemorrhage or stroke or with a major cardiovascular event during the past 6 months
- Unstable patients for any reason (according to the investigators discretion)
- Patient who received any investigational medication within 30 days prior to the Screening visit of this study or be scheduled to receive another investigational drug during the course of this study
- Patient who has any musculoskeletal disease or any other disease that would limit ambulation
- Patient with other cardiovascular, liver, renal, hematologic, gastrointestinal immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the investigator, may adversely affect the safety of the patient and /or efficacy of the study drug or limit the lifespan of the patient

Treatments

The study included two treatment groups:

- Low Dose Group: Doses were planned to be titrated to a target dose of 3 ng/kg/min. The dose was escalated to an approximate target dose of 3 ng/kg/min after the first 12 weeks and was maintained for another 12 weeks. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1, 2 and 3. This depended on the patient's exact weight and was caused by the limited infusion rate setting possibility of the infusion pump. This dose was anticipated not to have an effect on efficacy and was used as a comparator instead of placebo in order to obtain blinding.
- High Dose Group: Doses were planned to be titrated to a target dose of 30 ng/kg/min. The dose was escalated to an approximate target dose of 30 ng/kg/min after the first 12 weeks and was maintained for another 12 weeks. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min could be reached.

The dosing schedule ensured that there were no differences in the up-titration of study medication and changes of vials between high dose and lose dose grouped patients in order to guarantee blinding. Patients

with the same weight followed the same dosing schedule regardless their randomization group. The vials for patients in the low dose group contained only solution with a dosage of 1mg/ml of treprostinil sodium while the strengths of the vials for the high dose group were raised continuously during the first 12 weeks (Period I – 1 mg/ml; Period II – 2.5 mg/ml; Period III – 5 mg/ml; Period IV-VIII – 10mg/ml).

Objectives

The primary objective of the study was to determine the effect of subcutaneously administered treprostinil sodium on 6MWT distance after 24 weeks in patients with severe non-operable chronic thromboembolic pulmonary hypertension.

The secondary objectives were:

1.To assess clinical worsening defined as a decrease of 6MWT distance of more than 20% from baseline due to CTEPH, as decrease of NYHA functional class, hospitalization with the requirement for additional PH specific treatment or death due to worsening CTEPH

2. To assess the effect on maximal Borg score, heart rate and oxygen saturation during 6MWT

3. To assess the effect on WHO NYHA functional class 4. To assess the effect on QOL by the MINNESOTA instrument

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline in 6MWT distance after 24 weeks.

The secondary efficacy endpoints were:

- Clinical worsening defined as a decrease of 6MWT distance of more than 20% from Baseline due to CTEPH, decrease of NYHA functional class, hospitalization with the requirement for additional PH specific treatment or death due to worsening CTEPH
- Change in 6MWT after 12 weeks
- Change in maximal Borg score, heart rate and oxygen saturation during 6MWT
- Change in WHO functional class
- Change in MINNESOTA QOL instrument

The exploratory efficacy endpoints were:

- Change in pro-BNP levels after 24 weeks
- Change in hemodynamic parameters (PVR, mPAP, mRAP, CO, CI)
- Change in signs & symptoms

Sample size

Sample size was calculated based on the primary endpoint, i.e. the 6MWT distance in walk test. Using results on the baseline variability in previous trials in patients with pulmonary hypertension for the 6MWT distance (Simmoneau, 2002, Olschewski, 2002, Barst, 2004, Galie, 2005, McLaughlin, 2006, Rubin, 2002, Hoeper, 2006). An equal standard deviation of 83m was assumed. A sample size of 46 patients per group was

therefore required to detect a difference in mean 6MWT distance of 50m (effect size 0.6) at 80% power (when applying the 2-sided t-test for the 6MWT at the two-sided significance level of 0.05). Since an analysis of covariance adjusting for Baseline levels of 6MWT distance was pre-planned for evaluating the primary efficacy outcome the actual power was expected to be larger than 80%.

An interim analysis was planned to be performed after 23 patients per treatment group applying O´Brien-Fleming critical boundaries. The interim analysis had the following goals:

a) if the efficacy boundary is crossed recruitment is stopped and a thorough statistical analysis will be performed for regulatory submissions.

b) If there is no positive trend at all the investigators can stop the study for futility. A stopping for futility is not considered when calculating for critical boundaries. Therefore, stopping for futility cannot inflate the type I error rate.

c) If neither a) nor b) occurs the study goes on.

Sample Size Recalculation for the Stage II

As a result of the interim analysis after 26 patients in the control group and 28 patients in the test group the study was continued following option c) of the goals of the interim analysis. Based on the results of the interim analysis it was decided to continue the study and proceed with the originally planned sample size for stage II of n=23 per treatment group.

Keeping the sample size of 23 patients per group in stage II seemed to be sufficient considering conditional and predictive power arguments. The same statistical model has been used to derive the second stage p-value as it was used for the first stage data.

The study was planned with a boundary calculation using an alpha spending function of O'Brien-Fleming type. Overall significance-level was 5% two-sided symmetric (so 2.5% one-sided). One interim analysis was done when 50% of information was collected. Bound for discontinuation after interim analysis was 2.797 with alpha = 0.0052 (0.0026 one-sided). Bound for end-analysis was 1.977 with alpha = 0.048 (0.024 one-sided), which allows to control the overall alpha level below 0.05 (0.025 one-sided).

A dropout rate of 17% was observed in stage I. Therefore, a maximum of 29 patients per group was planned to be recruited unless 23 patients per group were appropriate for the analysis of the primary objective. Recruitment was planned to stop if 23 patients per group were evaluable for the primary objective or at a maximum of 29 patients per group (assuming a drop-out rate of about 20%).

Randomisation

Patients were randomized in a 1:1 ratio either to the low dose or high dose group.

Blinding (masking)

This was a double-blind study.

Statistical methods

The primary endpoint was change from Baseline in 6MWT distance after 24 weeks, defined as difference between Baseline and 24 weeks.

The hypothesis to be tested was superiority regarding the change of the primary efficacy variable "6MWT" (difference between 24 weeks and Baseline) in the "High dose" group in comparison to the "Low dose" group.

To derive a stage-wise p-value, the same statistical model was planned to be used for the first and second stage. A parametric analysis of covariance was planned to be used for the analysis of the 6MWT distance after 24 weeks using as covariate the Baseline levels of 6MWT distance. To account for repeated significance testing, an alpha spending function of O'Brien-Fleming type was planned to be used.

Using a two-sided overall significance-level of 5% (2.5% one-sided), using an inverse normal function with equal weights (i.e., the Interim-analysis was planned to be done when about 50% of information is collected), this results in O´Brien & Fleming bound for the interim-analysis of 2.797 with alpha = 0.0052 (0.0026 one-sided). Bound for end-analysis was 1.977 with alpha = 0.048 (0.024 one-sided), which allows to control the overall alpha level below 0.05 (0.025 one-sided).

For the final statistical test of the primary endpoint the one-sided stage-wise p-values will be combined using the inverse normal function with equal weights. This means in the final stage the one-sided null hypothesis for the primary endpoint can be rejected if the combination test statistics Z*(2) exceeds 1.977, whereby

$$Z^{*(2)} = \sqrt{\frac{23}{46}}\Phi^{-1}\{1 - p^{(1)}\} + \sqrt{\frac{23}{46}}\Phi^{-1}\{1 - p^{(2)}\}$$

and p(1) and p(2) denotes the one-sided p-value of stage I and II, respectively.

Furthermore, as sensitivity analysis, the first and second stage data were planned to be pooled and the same ANCOVA model applied for the pooled data.

In case the data were not normally distributed (Shapiro-Wilk test) and/or the homogeneity of variances (homoscedasticity) could not be assumed (Levene test), an additional non-parametric testing was planned to be performed, using the Wilcoxon-Mann-Whitney U- test.

The main analysis with respect to the primary efficacy variable was planned to be done using the ITT population with missing values imputed by the last observation carried forward (LOCF).

Supportive analysis

The ANCOVA analysis on the pooled data was planned to be repeated using the PP population.

In addition, analysis for the primary efficacy variable was planned to be repeated by using an alternative imputation rule for missing values: worst observation carried forward (WOCF) was planned to be used for missing values due to clinical worsening, i.e. imputing a 0-meter distance at the missing time point.

Statistical Analysis Performed on Secondary Efficacy Variables

The secondary efficacy variables were planned to be analysed only for the ITT set of patients. Missing values of the secondary efficacy variables were not planned to be imputed except of change in 6MWT after 12

weeks. The statistical tests and the resulting p-values are to be interpreted in an exploratory sense and not as confirmatory tests of formal statistical hypotheses.

Data were planned to be summarized by treatment group using the following descriptive statistics: number, mean, standard deviation (SD), minimum, lower quartile (if appropriate), median, upper quartile (if appropriate) and maximum.

All secondary analysis was based on pooling the data of the first and second stage. All secondary variables are considered as exploratory only. No further multiplicity adjustment was planned to be performed. Missing data were not to be imputed, except for a LOCF imputation for 6MWT at 12 weeks.

The following analyses were planned to be performed:

- Clinical worsening of CTEPH: Number of patients/group with clinical worsening were planned to be compared using Fisher Exact test. Separate analyses were planned to be done for decrease of 6MWT distance of more than 20% from Baseline due to CTEPH, decrease of NYHA functional class, hospitalization with the requirement for additional PH specific treatment or death due to worsening CTEPH.
- Change to Baseline in 6MWT after 12 weeks: analogous ANCOVA to primary efficacy endpoint.
- Change in maximal Borg score during 6MWT, difference between Baseline and Week 24: Wilcoxon-Mann-Whitney U- test.
- Change in heart rate during 6MWT, difference between Baseline and Week 24: Wilcoxon-Mann-Whitney U- test.
- Change to Baseline in oxygen saturation during 6MWT, difference between Baseline and Week 24: analogues to primary endpoint.
- Change in WHO functional class (Week 24 versus Baseline): Chi-square test
- Change in MINNESOTA QOL instrument (Week 24 versus Baseline): Wilcoxon-Mann-Whitney U- test.

Adverse events and safety:

Adverse events were summarised descriptively by body system and preferred term. Additional tables summarise adverse events by severity and relationship to the study drug, as well as separate tables for adverse events leading to withdrawal from the study, and SAEs.

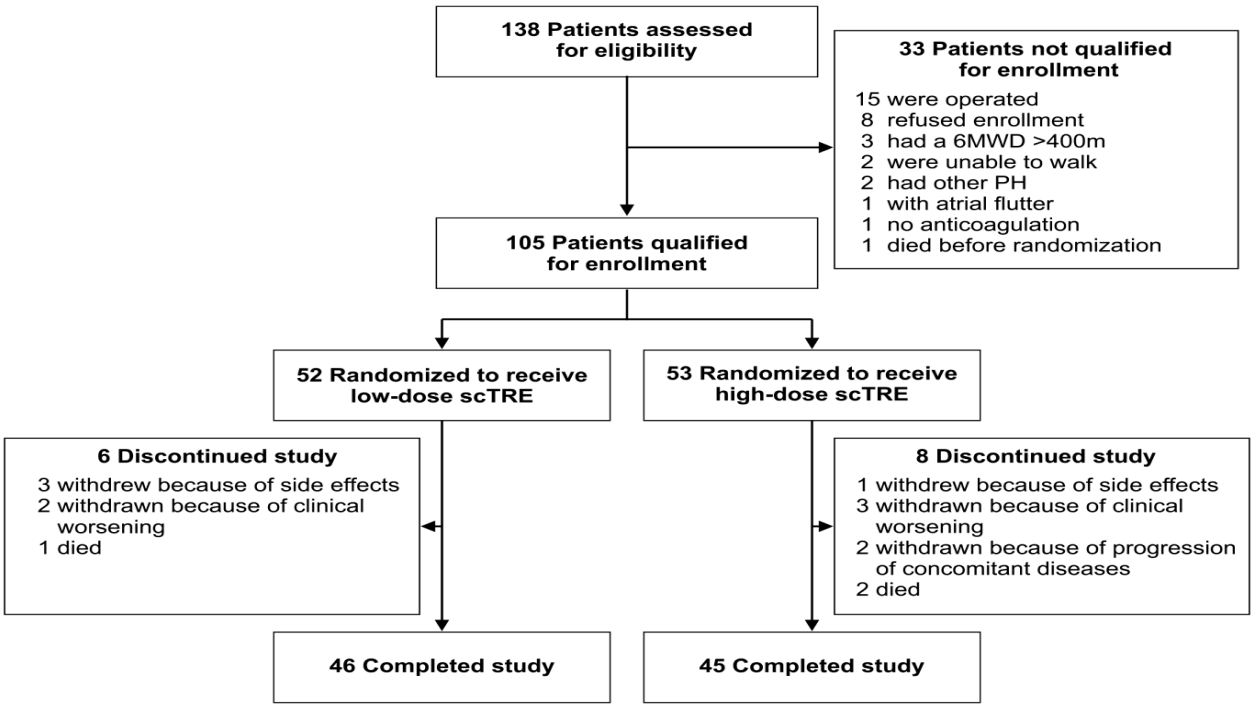
Physical examination findings, clinical laboratory data and vital signs were summarised over the complete treatment period and analysed using tests appropriate for the data (e.g. U-test, Chi square tests). The statistical tests and the resulting p-values were interpreted in a descriptive sense.

Results

Participant flow

Patient disposition is summarized in **Figure 2**.

Figure 2. Patient disposition in Study CTREPH 116-02



Recruitment

Study start: 9 December 2009 (First patient enrolled)

Study finish: 24 November 2016 (Last patient completed)

Conduct of the study

There were resulted 726 documented protocol deviations of which 649 were rated as minor and 77 as major. Of the 77 issues rated as major protocol deviation, only three cases were confirmed as significantly impacting the completeness, accuracy and reliability of the study data in course of data cleaning session by the independent data cleaning board.

One patient was included in the study even though the diagnosis of CTEPH was subsequently determined as wrong. In the second case the primary endpoint measurement was not performed during termination visit and in the third case the patient was unblinded before the primary endpoint measurement was performed. Data of all three patients were excluded from PP analysis.

Baseline data

The demographics of the patient population per study arm are shown in **Table 4**.

Table 4. Patient demographics, CTERPH 116-02

Patient demographic	High dose (N = 53)	Low dose (N=52)	Total (N=105)
Male (%)	34 (64.2%)	22 (42.3%)	56 (53.3%)
Female (%)	19 (35.8%)	30 (57.7%)	49 (46.7%)
Mean age in y (range)	68.06 ± 11.16 (30 – 88)	60.58 ± 14.59 (18 – 82)	64.35 ± 13.44 (18 – 88)
Mean weight in kg (range)	76.94 ± 15.17 (46 – 133)	80.42 ± 16.99 (45 – 130)	78.66 ± 16.11 (45 – 133)
Mean height in cm (range)	168.72 ± 9.26 (152 – 190)	168.31 ± 9.30 (148 – 187)	168.51 ± 9.24 (148 – 190)
Ethnicity (%) Caucasian Iran Middle	 52 (98.1) 1 (1.9)	 52 (100.0) 0	 104 (99.0) 1 (1.0)
Mean BP, systolic in mmHg (range)	123.87 ± 16.63 (91 – 178)	120.9 ± 16.82 (86 – 160)	122.38 ± 16.71 (86 – 178)
Mean BP, diastolic in mmHg (range)	78.02 ± 13.07 (48 – 115)	76.02 ± 10.36 (58 – 102)	77.02 ± 11.78 (48 – 115)
Pulse frequency in bpm (range)	77.73 ± 12.87 (52 – 113)	79.82 ± 9.83 (63 – 100)	78.77 ± 11.46 (52 – 113)
Respiratory frequency (breaths/min)	16.20 ± 3.60 (11 – 31)	16.41 ± 3.69 (12 – 27)	16.30 ± 3.62 (11 – 31)
Blood pressure systolic after 5 min sitting in mmHg (range)	120.52 ± 15.6 (90 – 165)	118.08 ± 16.06 (85 – 152)	119.3 ± 15.81 (85 – 165)
Blood pressure diastolic after 5 min sitting in mmHg (range)	75.75 ± 11.92 (45 – 100)	73.58 ± 8.74 (60 – 92)	74.66 ± 10.46 (45 – 100)
Pulse frequency after 5 min sitting in bpm (range)	75.81 ± 11.58 (52 – 113)	79.08 ± 9.68 (61 – 100)	77.43 ± 10.76 (52 – 113)
Respiratory frequency after 5 min sitting in breaths/minute (range)	16.2 ± 3.6 (11 – 31)	16.41 ± 3.69 (12 – 27)	16.3 ± 3.62 (11 – 31)

Patient demographic	High dose (N = 53)	Low dose (N=52)	Total (N=105)
WHO NYHA functional class at baseline (number, %)			
Class II	3 (5.7%)	3 (5.8%)	6 (5.7%)
Class III	47 (88.7%)	44 (84.6%)	91 (86.7%)
Class IV	3 (5.7%)	5 (9.6%)	8 (7.6%)

Notes: Demographics and baseline values. Statistical comparisons of high dose vs. low dose were significant for gender (p= 0.025, Chi-square test) and age (P= 0.003, Mann-Whitney U test), other comparisons were not significant (p > 0.05).

Thirty-three patients were pre-treated with other PH specific medications (bosentan, sildenafil, riociguat, macitentan) for a mean duration of 33 months prior to study inclusion and were kept on stable doses throughout their study participation:

- Bosentan: 12
- Sildenafil: 14
- Riociguat: 4
- Sildenafil and Bosentan: 2
- Macitentan and Riociguat: 1

Numbers analysed

Full Analysis (intention to treat) population: This analysis set included patients randomized who received at least one dose of study medication. Analyses of the primary efficacy variable was performed on the "intention to treat" set of patients.

Per-protocol (PP) set: This analysis set comprised all patients of the Full Analysis Set for whom valid data are available.

Safety population: All patients randomized with at least one application of the study drug constituted the safety population.

Outcomes and estimation

Primary endpoint

6MWT values at baseline, weeks 12 and 24 are summarised in **Table 5**, and change from baseline after 24 weeks and the the statistical analysis of combined stage I and stage II data are shown in **Table 6.**

Table 5. 6MWT values in study CTREPH 116-02 (ITT population)

Time	Baseline	Week 12	Week 24
High dose			
Mean ± S.D.	307.66 ± 68.77	340.36 ± 100.75	353.09 ± 101.95
Range	(168 – 426)	(66 – 527)	(66 – 520)
Median	317	333	355
Number (n)	53	53	53
Low dose			
Mean ± S.D.	299.13 ± 85.7	326.44 ± 110.38	302.96 ± 111.85
Median	330	345	340
Minimum	150 - 400	68 - 600	0 - 470
Number (n)	52	52	52

Table 6. Primary efficacy endpoint 6MWT (m), differences between baseline and week 24 in study CTREPH 116-02 (ITT population)

	high dose	low dose	TOTAL
Mean	45.43	3.83	24.83
S.D.	71.29	56.21	67.29
Median	36	0.5	19
L.Quartile	9	-28	-3
U.Quartile	90	35	60
Minimum	-264	-150	-264
Maximum	185	120	185
Number	53	52	105
	Dose effect	ANCOVA	p=0.002
	Normality	Shapiro-Wilk	p<0.0001
	Homoscedasticity	Levene	p=0.32
	Dose effect	MW U-test	p=0.0003

All p-values are two-sided

In the PP population, the mean improvement in the high dose group was 60.3 meters and 4.83 meters in the low dose group, resulted in a p-value of 0.00002 in favour of the high dose group.

The interaction between the PH specific concomitant medication (bosentan, macitentan, sildenafil and riociguat) and dose effect of treprostinil was added to the ANCOVA model to check if the dose effect is significantly different between the pre-treated and not pre-treated populations at weeks 12 and 24. This analysis was also performed by type of PH specific concomitant medication. Whereas the effect of dose at week 24 remains significant in both pre-treated and not pretreated populations separately, the difference between the dose effects within the two populations is not significant, for all the four medication types (data not shown).

Additionally, centre effect on the primary outcome was also assessed by comparing the p-values of dose effect between those obtained by fitting the model to the data with and without centre effect. The analyses showed that significance of the dose effect remains unchanged (significant for week 24 and not significant- for week 12) when corrected for centre effect (data not shown).

Subgroup Analysis NYHA classification

An ANCOVA analysis was conducted to compare the effect of the dose of Treprostinil on the change of 6MWD from baseline after 24 weeks in different NYHA classes as subgroups. The effect was evaluated by including additional terms NYHA class at BL and interaction between NYHA class at BL and dose (low/high), in addition to dose and baseline 6MWD, that were previously included in the main efficacy assessment (**Table 7**).

Table 7. Dose effects (high-low dose) in each NYHA subgroup and in the main efficacy assessment, 6MWT distance in meters

ANCOVA Model	Dependent	Subgroup	n	Upper CL	EMMs difference	LowerCL	P-value
Main Efficacy Assessment	6MWD difference from BL after 24 weeks [m]	All NYHA classes	105	15.86	40.70	65.53	0.0016
Main Efficacy Assessment incl. NYHA classes	6MWD difference from BL after 24 weeks [m]	NYHA =2	6	-56.19	48.22	152.62	0.3617
		NYHA =3	91	11.16	37.96	64.76	0.0060
		NYHA =4	8	-33.83	59.73	153.30	0.2082

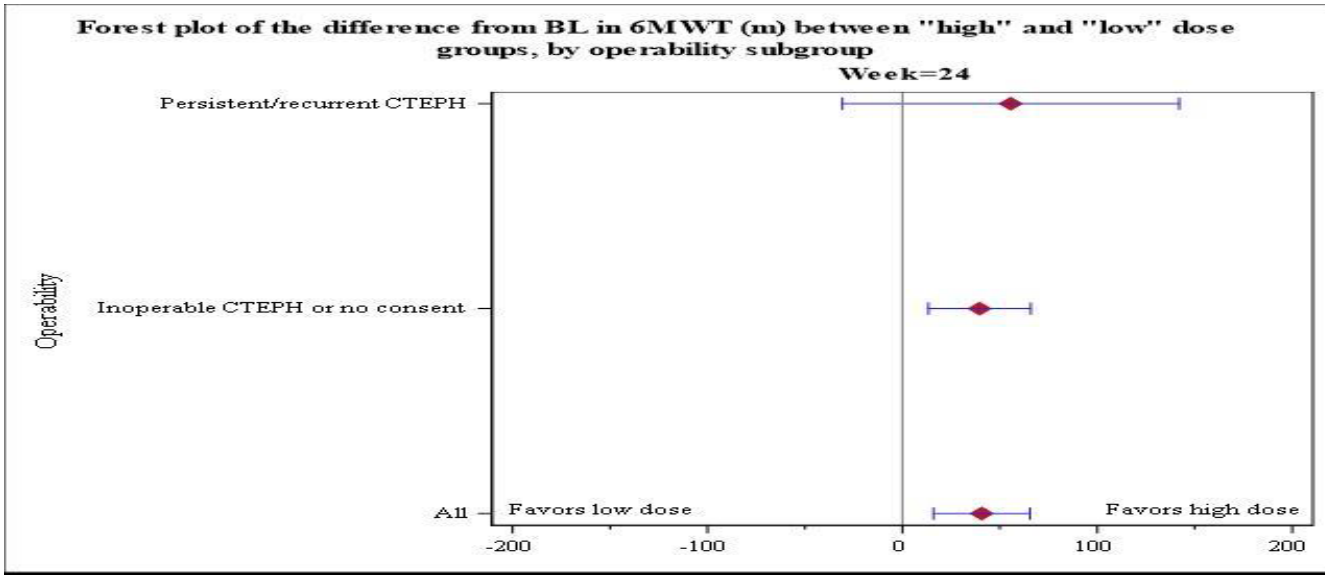
Subgroup Analysis non-operability

An ANCOVA analysis was also conducted to compare the effect of the dose of treprostinil on the change of 6MWD from baseline after 24 weeks in the different CTEPH type subgroups. The effect was evaluated by including additional terms in the ANCOVA model – CTEPH operability (inoperable/persistent) and interaction between CTEPH operability and dose (high/low) in addition to baseline 6MWD (BL) and dose (high/low) (**Table 8**) and a Forest plot was generated to visualise the differences in change from BL after 24 weeks in 6MWD by CTEPH subgroup (**Figure 3**).

Table 8. ANCOVA model fit p-values of covariates in the CTEPH subgroups of the operability assessment

Model	Dependent	Source	DF	SS	MS	FValue	ProbF
Main Efficacy Assessment incl. Operability assessment	6MWD difference from BL after 24 weeks [m]	BL-6MWD	1	7178.58	7178.58	1.73	0.1917
		Dose group	1	18325.00	18325.00	4.41	0.0382
		Operability	1	2532.10	2532.10	0.61	0.4369
		Operability*Dose group	1	505.49	505.49	0.12	0.7280

Figure 3. Forest plot of difference in change from BL after 24 weeks in 6MWD by CTEPH subgroup



Secondary endpoints

Clinical worsening

Clinical worsening was defined as a reduction of 6MWD of 20% compared to baseline, worsening of WHO NYHA functional class and/or hospitalization due to CTEPH with the need of additional PH specific treatment (including additional diuretics therapy) or death due to worsening CTEPH.

Two subjects in the high dose and seven in the low dose group showed a reduction of more than 20 % in 6MWT. Two subjects in the high dose and four in low dose group experienced a worsening of WHO NYHA functional class and four subjects in the high dose and six subjects in the low dose group had to be hospitalized due to CTEPH during study period and needed additional PH specific treatment. None of these patients needed additional vasodilators but received diuretic treatment. In total seven subjects receiving high dose treprostinil and twelve subjects receiving low dose treprostinil developed a clinical worsening during the study period (p=0.189).

Change in 6MWT after 12 weeks

The improvement in 6MWT between baseline and week 12 was 32.7 meters in high dose subjects and 27.31 meters in low dose subjects (ANCOVA p=0.72, Mann-Whitney U-test p=0.27).

Change in maximal Borg score, heart rate and oxygen saturation during 6MWT

The Borg Dyspnoea Score (measured during the 6MWT) was reduced by 0.44 score points in high dose group and 0.13 points in low dose group. A trend for reduction of the Borg Dyspnoea Score could be evaluated in both treatment groups but the difference was not clinically relevant (Mann-Whitney-U p=0.307).

Change in NYHA class

An improvement in NYHA (WHO) functional class was observed in 27 subjects (50.9 %) of the high dose group and in 9 subjects (17.3 %) of the low dose group whereas 2 subjects (3.8 %) experienced a worsening of NYHA functional class in the high dose group and 3 subjects (5.8 %) in the low dose group (Chi-square: p=0.0019; Fisher exact test: p=0.0012). No change was reported in 22 subjects (41.5%) vs. 36 subjects (69.2%) in the high and low dose group, respectively. These results are summarised by dose group in **Table 9**.

Table 9. WHO NYHA functional class, change between baseline and week 24

No change | worsening | improvement

Group high dose:

	Week 24					
Baseline	Class I	Class II	Class III	Class IV	not done	total
Class I	0					
Class II	2	1				3
Class III	2	21	21	2	1	47
Class IV			2	0	1	3
Not done					0	
total	4	22	23	2	2	53

Group low dose:

	Week 24					
Baseline	Class I	Class II	Class III	Class IV	not done	total
Class I	0					
Class II		1	1		1	3
Class III		6	33	2	3	44
Class IV			3	2		5
Not done					0	
total	0	7	37	4	4	52

Change in MINNESOTA QOL instrument

There was no clinically relevant change in the score sum of quality of life assessment by Minnesota Living with Heart Failure Questionnaire.

Exploratory endpoints

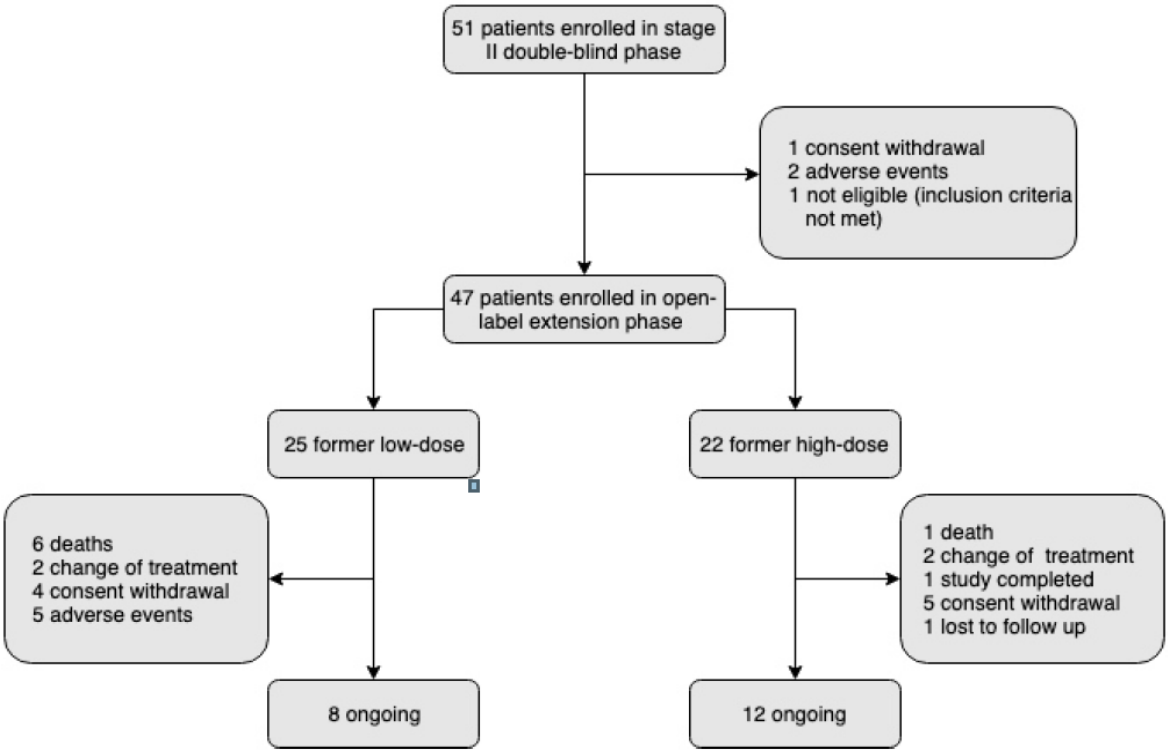
Treatment with a high dose of treprostinil resulted in significant improvements in haemodynamic parameters compared with the low dose. Mean pulmonary vascular resistance (PVR) decreased by a mean of 214.23 dyn.s.cm-5 (-25.3%) in the high dose and increased by 72.96 dyn.s.cm-5 (+9.02%) in the low dose group. Mean pulmonary arterial pressure (PAP) decreased by a mean of 3.36 mm Hg (-6.7%) in the high dose and by 0.4 mm Hg (-0.80%) in the low dose group. Mean cardiac output (CO) increased by 0.63 L/min (+14.7%) in high dose subjects and decreased by 0.22 L/min (-5.0%) in low dose subjects. Mean cardiac index (CI) increased by 0.42 L/min/m² (+18.5%) in the high dose and decreased by 0.16 L/min/m² (-7.0%) in the low dose group. Systemic vascular resistance (SVR), which was evaluated in only 65 patients, decreased by a mean of 362.74 dyn.s.cm-5 (-19.6%) in the high dose group and increased by a mean of 40.4 dyn.s.cm-5 (+2.4%) in the low dose group. No differences were found in right atrial pressure (RAP) and pulmonary capillary wedge (PCWP).

Furthermore, in the high dose group, a slight deterioration in pro-BNP of 0.84% vs an increase of 41.68 % in the low group was observed.

Open label extension phase

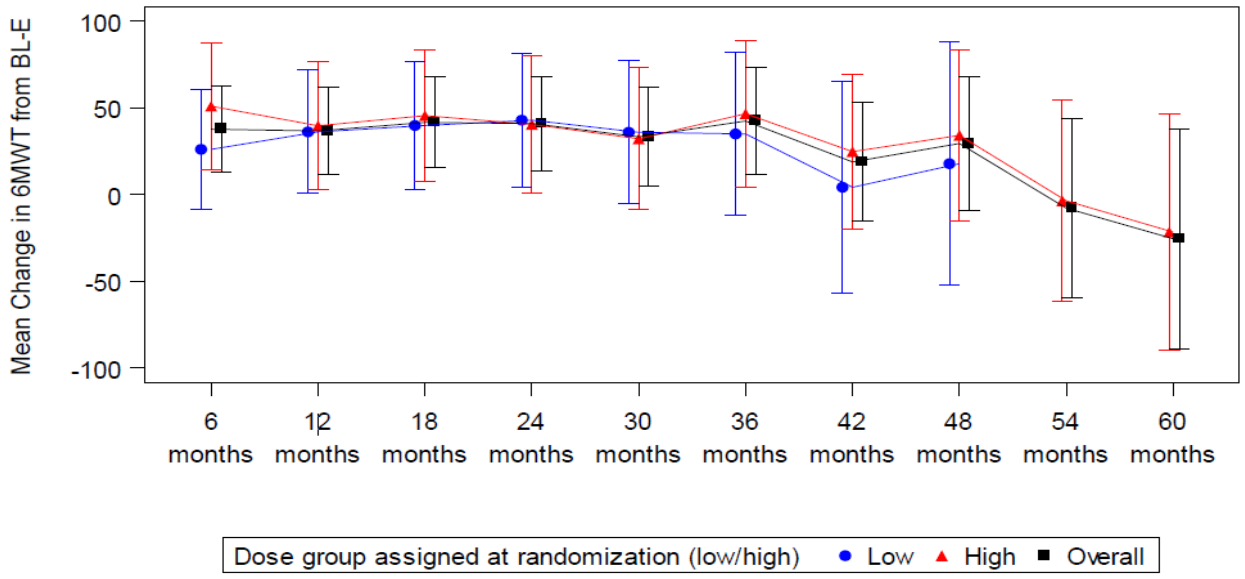
In total 51 patients were enrolled in stage II in the blinded phase. 47 patients were eligible to participate the open-label extension phase and gave consent for the follow-up treatment. In total 27 patients (10 former high dose / 17 former low dose) withdrew from the follow-up phase until data collection break (31st October 2018).

Figure 4. Disposition of patients in open label extension phase of study CTREPH 116-02



The change in 6 MWT results from BL-E were analysed by 6-monthly periods on the FAS-FU population.(**Figure 5**).

Figure 5. LS-means and 95% Confidence Intervals of change in 6MWT distance from BL-E plotted by 6-monthly periods in open-label extension phase of study CTREPH 116-02



An improvement in 6 MWT was observed between 6 months and 36 months (p-value < 0.0227).

Ancillary analyses

Not applicable.

Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10. Summary of Efficacy for trial CTREPH 116-02

Title: A double blind controlled clinical study to investigate the efficacy and tolerability of subcutaneous Treprostinil sodium in patients with severe non-operable Chronic Thromboembolic Pulmonary Hypertension (CTREPH II).		
Study identifier	CTREPH 116-02	
Design	Randomized, multicenter, double-blind, comparator-controlled study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks n.a. On-going

Hypothesis	Superiority of high dose of treprostinil over low dose of treprostinil		
Treatments groups	High dose group		Target dose of 30 ng/kg/min, dose will be escalated to an approximate target dose of 30 ng/kg/min after the first 12 weeks and will stay stable for another 12 weeks, n= 53
	Low dose group		Target dose of 3 ng/kg/min, dose will be escalated to an approximate target dose of 3 ng/kg/min after the first 12 weeks and will stay stable for another 12 weeks, n= 52
Endpoints and definitions	Primary endpoint	6MWT	Change from baseline in 6MWT after 24 weeks
	Secondary endpoints	Clinical worsening, change in 6MWT after 12 weeks, change in maximal Borg score, heart rate, oxygen saturation during 6MWT, change in WHO functional class, change in MINNESOTA QOL The secondary endpoints were not controlled for multiplicity.	
	Exploratory endpoints	Change in pro-BNP levels after 24 weeks, change in haemodynamic parameters (PVR, mPAP, mRAP, CO, CI), change in signs & symptoms	
Database lock	Not mentioned		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis set (all randomized patients), Intention to treat 24 weeks			
Descriptive statistics and estimate variability	Treatment group		High dose	Low dose
	Number of subjects		N = 53	N = 52
	6MWT (m) change from baseline to 24 weeks (S.D.)		45.43 (71.29)	3.83 (56.21)
	ANCOVA Mann-Whitney U-test		p = 0.002 p = 0.0003	
Analysis description	**Secondary Analysis**			
	Clinical worsening (N/%)		7 (13.2%)	12 (23.1%)
	6MWT (m) change from baseline to 12 weeks		32.7	27.31
	Borg sore change from baseline to 24 weeks		0.44	0.13
	Improvement in NYHA functional class (N/%)		27 (50.9%)	9 (17.3%)
	Deterioration in NYHA functional class (N/%)		2 (3.8%)	3 (5.8%)
	MINNESOTA QOL score		- 6.36	- 4,63
	Exploratory Analysis			
	Pro- BNP (%)		0.84	41.68
	PVR (%)		-25.3	9.0
	PAP (%)		-6.7	0.80
	CO (%)		14.7	- 5.0
	CI (%)		18.5	- 7.0

Clinical studies in special populations

Table 11. Summary of age classes by dose

Age class	65-74		75-84		85+	
(Older patients number /total number)	35/105		27/105		1/105	
Dose	low	high	low	high	low	high
(Older patients number /total number)	15/52	20/53	10/52	17/53	0/53	1/53

An ANCOVA analysis was conducted to compare the effect of age class on the observed dose effect of Treprostinil, i.e. on the change of 6MWD from baseline (BL) after 24 weeks. The effect was evaluated by including additional terms age class and interaction between age class and dose (low/high), in addition to dose (low/high) and baseline 6MWD, that were previously included in the model within the main efficacy assessment.

The effect of age class on the dose effect was not statistically significant (as p-value of interaction between "age class" and "dose" was 0.1543), suggesting that the effect of dose on the 6MWT outcome was not impacted by patients` age class. This is also confirmed by non-significant difference in dose effects between the age class subgroups at 24 weeks. After 24 weeks a significant dose effect in the age class 75+ was detected, whereas the dose effect in the age class 65-74 showed non-significant p-value.

Supportive studies

Skoro-Sajer et al., 2007

The study was a prospective non-controlled open-label phase II study to investigate the effect of up to 24 months treatment of treprostinil s.c. in 25 patients with severe inoperable CTEPH (WHO functional class III or IV).

Criteria for inclusion were inoperable CTEPH (distal disease or persistent/recurrent PH following PEA, and severe comorbidities precluding a surgical approach) in WHO functional classes (as modified for PAH from the New York Heart Association classification) III and IV, 6-MWD ≤ 380 m and at least one hospitalisation for right heart decompensation within the previous six months, not within one month before treatment start, mean pulmonary artery pressure (MPAP) > 25 mmHg, a PVR > 500 dynes.s.cm^{-5}, in the presence of a pulmonary wedge pressure < 15 mmHg.

A historical group of 31 patients (diagnosed between September 1994 and September 1999, and who did not receive any specific PH medication) matched for disease severity by haemodynamic assessment, WHO functional class and 6-MWD served for comparative survival analyses.

With respect to the dose, patients started at 2 ng/kg/min and doses were increased over 12 weeks to a maximum dose with an acceptable side effect profile. Dose adjustments were performed every three months from then on and were based on signs and symptoms of PH. Infusion site changes were performed every 26 ± 8 days.

Patients were followed for a mean period of 24 ± 18 months (range: 6-72 months). Mean treprostinil dose at six months was 21 ± 5 ng.kg^{-1}.min^{-1} (range: 11-30 ng/kg/min). Functional class improved in 13 patients and

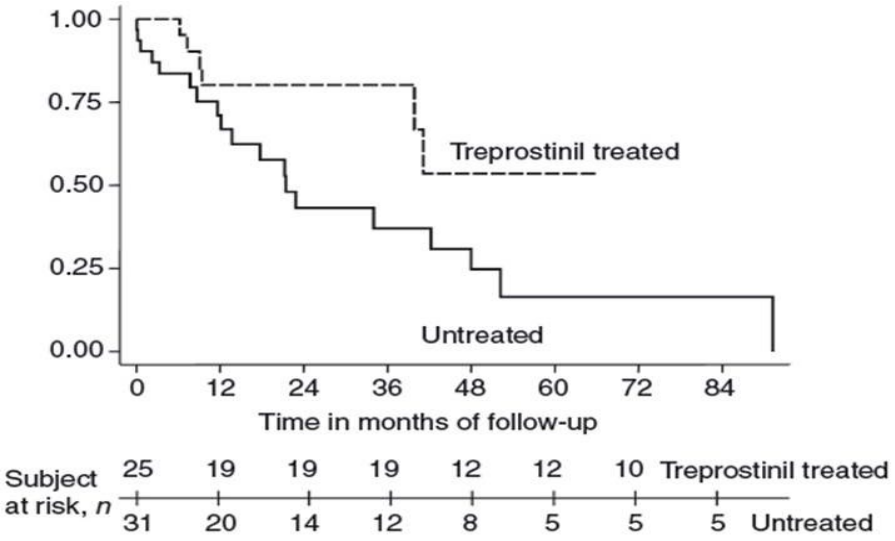
was unchanged in 12 patients. At 6 months, treprostinil therapy resulted in a mean increase in 6MWD of 59 m compared to baseline (260 ± 111 m at baseline and 319 ± 117 m at follow up, p= 0.01). WHO functional class improved in 13 patients and was unchanged in 12 patients (P ≤ 0.001).

At 12 months, the mean treprostinil dose was 28 ± 10 ng/kg/min (range: 12.5–42 ng/kg/min, n= 19). The mean increase in the 6MWD was 105 m (from 271 ± 107 to 376 ± 89 m). Five patients were classified as functional class II, 13 patients remained in class III and one patient in class IV.

Furthermore, treprostinil therapy was associated with significant improvements in cardiac output (CO; 3.8 ± 0.9 to 4.6 ± 1.5 L min-1, P = 0.007), CI (2.1 ± 0.5 to 2.4 ± 0.6 L min-1 m-2, P = 0.02) and PVR (924.6 ± 347 to 808.1 ± 372.5 dynes s cm-5, P = 0.01), whereas systolic PAP, diastolic PAP and MPAPs did not change significantly from baseline. BNP plasma levels had decreased from 270 ± 197 pg/mL to 180 ± 78 pg/mL (p=0.02). Changes in BNP plasma levels correlated with changes in functional class (r = 0.407, P < 0.01) and right ventricular end-diastolic pressure (r = 0.46, P < 0.05).

Kaplan-Meyer survival estimates for the treprostinil treated patients and the historical controls are shown in **Figure 6**.

Figure 6. Survival rates of inoperable CTEPH patients, Skoro-Sajer et al., 2007



Notes: Kaplan–Meier survival estimates in 25 patients with inoperable CTEPH, starting at the initiation of treprostinil therapy. For comparison, survival data are also shown for an untreated control group with inoperable CTEPH matched for disease severity, who did not receive vasodilator therapy.

In the group of patients treated with treprostinil the overall survival rates at one, two, three and five years were 80%, 80%, 80% and 53%, respectively, compared with 67%, 43%, 37% and 16% (p = 0.02). In the univariate and multivariate analyses, baseline functional class and treprostinil treatment were predictors of survival. While class IV was associated with high overall mortality, treprostinil treatment significantly reduced the risk of death in these patients. These associations were independent of gender, age, PVR, CI or 6-MWD.

Lang et al., 2006

This was a multicentre retrospective non-controlled study to investigate the effect of s.c. infused treprostinil in the treatment of PAH and CTEPH.

Patients with either PAH or distal CTEPH were considered for analysis. Diagnosis was established according to standard criteria, including a mean pulmonary artery pressure (PAPm) ≥ 25 mm Hg at rest, a pulmonary capillary wedge pressure < 15 mm Hg, and a pulmonary vascular resistance > 3 Wood units.

With respect to dose, treprostinil sodium was initiated in the hospital at a starting dose of 1.25 to 4 ng/kg/min and up-titrated in an outpatient setting at least once a week by dose increment of 1.25 ng/kg/min with a target dose of at least 20 ng/kg/min at 3 months. Further increments were essentially governed by symptom progression and/or side effects. All changes in conventional therapy were monitored and recorded.

In this long-term study of patients with PAH (n=99) and CTEPH (n=23), treprostinil showed improvements in NYHA-FC scores, exercise capacity and survival when compared with historical data for untreated patients. At 3 years, significant improvements from baseline were observed in mean 6MWD (305 ± 11 to 444 ± 29 m, p=0.0001), Borg dyspnoea score (5.7 ± 0.3 to 5.2 ± 1.5, p=0.0006), and NYHA class (3.20 ± 0.04 to 2.1 ± 0.1, p=0.0001). These changes were observed under a mean dose of subcutaneously-infused treprostinil at 40 ± 2.6 ng/kg/min (range, 16 to 84 ng/kg/min).

Survival rates by Kaplan Meier analysis reached 88.6%, 70.6%, and 65.6% after 1 year, 3 years, and 4 years, respectively. The probability of event-free survival, defined as survival without hospitalization for clinical worsening, transition to IV epoprostenol, and need for combination therapy or atrial septostomy, were similar to overall survival rate.

2.6.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on efficacy data obtained from the pivotal phase III study CTREPH 116-02. Additional data came from two published open-label non-controlled clinical studies (Skoro-Sajer et al., 2007 and Lang et al., 2006).

The selection of the high target dose (~30 ng/kg/min) and the low target dose (~3 ng/kg/min) used in the pivotal study is based on published literature (both in patients with CTEPH and PAH) and clinical experience of investigators with the use in PAH patients; this is acceptable, considering the similar pathophysiologic and clinical features of CTEPH and PAH. The dose will be up-titrated according to a predefined infusion rate setting schedule to improve tolerability (e.g. hypotension). Moreover, the predefined infusion rate setting schedule, which has also been proposed in the SmPC, is in line with the recommended posology for Remodulin (treprostinil) for the treatment of PAH and therefore acceptable.

The low dose of 3 ng/kg/min, which did not show clinical improvement in patients with PAH, has been used as a comparator since it was considered not feasible to conduct a placebo controlled design due to the characteristic smell of the treprostinil solution and the anticipated local site reactions induced by s.c. administered treprostinil; this approach is considered appropriate.

According to the Applicant, the maximum dose for treprostinil is not strictly defined as patients are titrated to a dose where symptoms improve but treprostinil is still tolerable. The SmPC proposes no maximum dose which is in line with that of the reference product Remodulin. The Applicant provided data from the open label phase of CTREPH 116-02 in which treprostinil was up-titrated to doses of up to 53.84 ng/kg/min which was

required to maintain stable condition with an acceptable adverse event profile. Additional information in support of the maximum dose, was provided by the studies of Skoro-Sajer et al., 2007 and Sadushi-Kolici et al., 2012 in which doses up to 100 ng/kg/min were reached. The CHMP noted that there is no defined maximum dose for treprostinil in PAH but it is rather adjusted on an individual basis and under medical supervision. As there is no evidence to suggest that the adverse event profile of treprostinil is different between CTEPH and PAH the CHMP considered the omission of a maximum dose acceptable.

General inclusion /exclusion criteria of the pivotal study were generally appropriate to reflect inoperable CTEPH patients or persistent or recurrent CTEPH patients for whom an indication is sought. The CHMP however noted that persistent or recurrent CTEPH after surgical treatment and WHO Functional Class (FC) II and IV were underrepresented in the main clinical program (see also section Efficacy data and additional analyses).

The design of the CTREPH 116-02 study is appropriate to address the objective of the study. The double-blind treatment period of 24 weeks is sufficient to evaluate efficacy of s.c. infusion of treprostinil of ~30 ng/kg/min (high dose arm) vs ~3 ng/kg/min (low dose arm; comparator), although the treatment period of 24 weeks may be considered limited for information on long term efficacy and safety of treprostinil. For long-term maintenance of effect reference is made to the two published studies of Skoro-Sajer et al., 2007 and Lang et al., 2007. Inclusion of a dose reduction period at the end of the study is considered appropriate given the rebound effects of pulmonary hypertension. Furthermore, a follow-up open label extension phase was present in order to give the patients the possibility to be treated with treprostinil after finishing the treatment period of 24 weeks provides additional support on the long-term efficacy of treprostinil.

The efficacy primary endpoint was the change from baseline in 6MWT distance after 24 weeks, which is considered appropriate for the claim of the orphan CTEPH indication for improvement of exercise capacity. As the relevant CHMP guideline (EMEA/CHMP/EWP/356954/2008) does not specifically address CTEPH, developing a clinical program in line with that recommended for PAH products is acceptable due to the disease similarities. This guideline indicates that the 6MWT can be used as a primary endpoint when the proposed indication is restricted to exercise capacity, if no negative impact on survival is observed. Further, the use of other clinical endpoints is encouraged to support the findings of the primary analysis.

The investigated secondary endpoints of clinical worsening, change in 6MWT after 12 weeks, change in Borg score, heart rate and oxygen saturation during 6MWT, change in NYHA/WHO FC, and MINNESOTA QOL are relevant and provide further insight on the effects of the drug under investigation and are in line with the CHMP guideline EMEA/CHMP/EWP/356954/2008. However, as the secondary endpoints were not controlled for multiplicity they will be considered as exploratory.

The analysis populations and the statistical analysis of primary and secondary endpoints were considered acceptable. Missing data were handled with LOCF (or BOCF if only baseline measurement was available), which is not the most appropriate method for imputing missing data in this setting since it assumes treatment effects remain stable. However, sensitivity analyses using other imputation methods (data not shown) also resulted in statistically significant differences, with the more conservative methods leading to smaller differences.

The planned interim analysis was performed twice because the first was not performed according to protocol. Furthermore, after the first performance of the interim analysis, several changes were made to the protocol. Although this practice is not ideal, the applicant confirmed that the blind was not broken except for the

interim analysis statistician and any protocol amendments were the result of a careful review of the protocol, SAP and interim analysis report, leading to clarifications.

Efficacy data and additional analyses

In the primary analysis, treatment with a high dose of treprostinil resulted in a significant improvement in 6MWT from baseline to week 24 as compared to low dose in the ITT analysis set (41.6 m, ANCOVA p=0.002; Mann-Whitney U-test p=0.0003) from a baseline level of 308 m and 299 m for the high and low dose group, respectively. This increase is comparable to the 6MWT results observed for riociguat of 46 m from a baseline level of approximately 350 m after 16 weeks of treatment also in patients with CTEPH, although more patients with NYHA II were included. Subgroup analyses regarding concomitant therapy PH medication, showed a consistent beneficial effect in 6MWD. Additionally, primary outcome analysis regarding centre effect showed that significance of the dose effect remains unchanged (significant for week 24 and not significant- for week 12) when corrected for centre effect. At 12 weeks of treatment, the increase in 6MWT from baseline was not significant different between the high and low dose group (32.7 m vs 27.31 m, respectively; ANCOVA p=0.72, Mann-Whitney U-test p=0.27).

Treatment with treprostinil also resulted in a trend of a beneficial effect in other secondary or exploratory endpoints. 11 patients (6 low dose / 5 high dose) developed clinical worsening during the study and needed additional treatment. In all cases, additional diuretics were added to treat the clinical worsening symptoms. The subgroup without additional diuretic treatment had a slightly better 6MWT outcome after 24 weeks compared to the full analysis set. The difference is not considered large enough to have substantially influenced the overall results.

Further, significant improvements are also shown in WHO functional class with 27 subjects (50.9 %) of the high dose group and in 9 subjects (17.3 %), whereas 2 subjects (3.8 %) experienced a deterioration of NYHA functional class in the high dose group and 3 subjects (5.8 %) in the low dose group (Chi-square: p=0.0019; Fisher exact test: p=0.0012).

The beneficial effect of treprostinil was further supported by improvements in haemodynamic parameters (exploratory endpoint). PVR shows a reduction of -25.3% in the high dose group (vs +9.02% in the low dose group), PAP a reduction of -6.7% (vs -0.80% in the low dose group), whereas CO was increased by +14.7 % (vs -5.0% in the low dose group) and CI by +18.5% (vs -7.0 % in the low dose group). With respect to pro-BNP, in the high dose group, a slight deterioration of +0.84% vs +41.68 % in the low group was observed, which is reassuring.

Other clinical measurements like QOL and Borg Dyspnoea score also showed a non-significant positive trend for treprostinil treatment.

The applicant had initially applied to include "to improve symptoms of the disease" as part of the indication of the product. However, this was not supported by the available data in which an effect was observed only for functional class, whereas the effects on clinical worsening and QOL only showed a trend for improvement. Moreover, type I error was only controlled at the primary endpoint level (exercise capacity as measured by 6MWT and there was no formal hypothesis testing for the other component; symptoms of the disease. The claim "to improve symptoms of the disease" was therefore not considered justified by the CHMP. This statement was then removed from the claimed indication.

Several subgroup analyses were performed in the different sub-populations of the initially claimed indication.

Only 6 subjects (5.7%) with WHO NYHA class II were included, while according to the inclusion criteria only patients with FC III or IV should be enrolled in study CTREPH 116-02. This was due to the fact that in the first stage of the CTREPH study the study protocol stipulated to include patients with severe CTEPH but NYHA classification was not part of the inclusion/exclusion assessment. The number of patients with NYHA IV included in the study was also low (three patients received the therapeutic dose in the NYHA Class IV subgroup, and five the sub-therapeutic low dose), and this can possibly be explained by the fact that patients had to be capable of walking for enrolment in the study, while a significant proportion of patients in NYHA IV are confined to bed or not able to walk at least 150 m in 6 minutes.

The effect of the dose of treprostinil on the change of 6MWD from baseline after 24 weeks in different NYHA classes and the different CTEPH type subgroups was also investigated.

This analysis showed a comparable effect in favour of the high dose group in all three NYHA classes. The wide confidence intervals for NYHA classes 2 and 4 reflected the small sample sizes in these subgroups. Nevertheless, a trend for positive treatment effect was detected in both subgroups.

The effect of CTEPH type (inoperable/persistent) on the dose effect was not statistically significant (as p value of the interaction between "dose" and CTEPH operability was 0.7280) suggesting that the effect of dose on the 6MWT outcome is not impacted by patient`s operability classification and comparable dose effect in favour of the high dose group was observed in all three CTEPH types. In patients with an inoperable CTEPH the EMMs difference showed a significant effect (p=0.0016) in comparison to patients with a persistent CTEPH, but it was considered that this difference might be due to the small sample size. Overall, it was agreed that available evidence supported the use of Trepulmix in persistent or recurrent CTEPH after surgical treatment.

The small number of WHO NYHA class II patients included in the study and available data in this sub-population is too limited to draw conclusions about efficacy and safety in this sub-group. Taking also into account the available clinical guideline from the European Society of Cardiology/European Respiratory Society (ESC/ERS) guideline for the diagnosis and treatment of PH, which does not recommend prostacyclin treatment for NYHA II patients (Galie et al. 2015), the applicant agreed to exclude patients with NYHA class II from the indication.

The number of patients with NYHA IV included in the study was also low and this could possibly be explained by the fact that patients had to be capable of walking for enrolment in the study, while patients in NYHA IV are commonly confined in bed or not able to walk at least 150 m in 6 minutes. The CHMP noted that treatment options are very limited in patients in this subgroup of patients. Moreover, efficacy in this subgroup was also supported by literature data (Lang et al 2006) with all available results suggestive of consistent treatment effect between WHO FC III and FC IV. The CHMP concluded that patients with WHO FC III and IV should therefore be included in the target population for Trepulmix.

Evidence of longer-term efficacy for the use of treprostinil in CTEPH comes from the open- label extension phase of the pivotal trial, which included 47 patients. The change in 6 MWT results from BL-E were analysed by 6-monthly periods on the FAS-FU population. A significant positive change from BL-Ein 6MWT was observed for the FAS-FU population all across the period between 6 months and 36 months (p-value < 0.0227).

The small prospective open-label uncontrolled study of 25 subjects with inoperable CTEPH (Skoro-Sajer et al. 2009) supports the beneficial effect of treprostinil in 6MWD observed in the CTREPH 116-02 study but also provides some evidence of long term maintenance of the effect of treprostinil in 6MWD and beneficial effect on clinical outcomes, i.e. survival rates, compared with historical controls (overall survival rates at one, two,

three and five years of 80%, 80%, 80% and 53% compared with 67%, 43%, 37% and 16%, respectively (p = 0.02). In the study of Lang et al. which was retrospectively performed and included both PAH and CTEPH patients long term maintenance of effect was also observed.

2.6.4. Conclusions on the clinical efficacy

The use of treprostinil in CTEPH is supported by one pivotal phase III study and two published open-label studies in which efficacy is well established in terms of improvement in exercise capacity. The beneficial effect of treprostinil is further supported by improvements in NYHA class, haemodynamic parameters, and pro-BNP. The long-term maintenance of effect of treprostinil in CTEPH is supported by available data from the open-label extension phase of the pivotal study and one small prospective open-label uncontrolled study from the literature.

2.6.5. Clinical safety

Patient exposure

Study CTREPH 116-02

In this study, 105 CTEPH patients were divided into a high dose group (n=53) and a low dose group (n= 52) and treated up to 24 weeks. The mean exposure was 22.8 weeks in the high dose and 22.5 weeks in the low dose groups.

After 12 weeks, patients in the high dose group reached a mean dose of treprostinil of 29.15 ng/kg/min, whereas patients in the low dose group reached a mean dose of 2.99 ng/kg/min. After 24 weeks, the mean dose of treprostinil in the high dose group was 29.11 ng/kg/min (**Table 12**).

Table 12. Mean dosage per group (ng/kg/min), CTREPH 116-02

Dosing [ng/kg/min]	High Dose	Low Dose
Week 3 (mean)	4.78	2.82
Week 6 (mean)	11.56	2.97
Week 9 (mean)	19.66	2.37
Week 12 (mean)	29.15	2.99
Week 24 (mean)	29.11	2.99

The target dose of 30 ng/kg/min was achieved by 27 out of 53 patients (50.9%) randomized to the high dose group. One patient was excluded prior week 12 and was therefore not up-titrated to the target dose at time of withdrawal. Eleven patients experienced adverse drug reactions (infusion site pain) leading to decrease of the infusion rate. Five patients gained weight within study period without adaptation of the dose. Nine patients didn't achieve the target dose due to limitation of infusion rate settings.

Open-label extension phase (data cut-off: 31st October 2018)

47 patients were eligible to participate the open- label extension phase and gave consent for the follow-up treatment. In total 27 patients (10 former high dose / 17 former low dose) withdrew from the follow-up phase until data cut-off.

Supportive studies

In the study of Skoro-Sajer et al., 2007, actual patient exposure was not reported in the study but can be assumed from a maximal continuous exposure in 25 CTEPH patients to a 30 ng/kg/min continuous SC infusion for 24 months.

In the study of Lang et al., 2006, actual patient exposure was not reported in the study, but worst-case exposure can be estimated assuming 99 PAH and 23 CTEPH (122 total) patients to a 40 ng/kg/min continuous SC infusion for 36 months.

Adverse events

Study CTREPH 116-02

During the study 104 of 105 patients (low dose: 51/52 (98%), high dose: 53/53 (100%)) experienced at least one TEAE (**Table 13**).

Table 13. Overview of adverse event profile: Treatment emergent adverse events (Safety population, CTREPH 116-02)

Patients with … **n(%)**	**Low dose N= 52**	**High dose N = 53**
any TEAE	51 (98.1%)	53 (100%)
any treatment emergent SAE	10 (19.3%)	9 (17.0%)
any TEAE leading to death	1 (1.9%)	2 (3.8%)
TEAE related to study drug	47 (90.4%)	50 (94.3%)
treatment emergent SAE related to study drug	1 (1.9%)	0
any TEAE leading to permanent treatment discontinuation	3 (5.8%)	1 (1.9%)

A total of 513 TEAEs, 220 in the low dose group and 293 in the high dose group, were documented during the 24 weeks study period (**Table 14**).

Table 14. Adverse events, grouped by SOC and treatment, Safety population study CTREPH 116-02

SOC	Low Dose	High Dose	Total
N patients total	52	53	105
Patients with at least one AE	51	53	104
Total number of AEs	220	293	513
Blood and lymphatic system disorders	1	1	2
Cardiac disorders	23	25	48
Ear and labyrinth disorders	1	0	1
Eye disorders	0	5	5
Gastrointestinal disorders	23	52	75
General disorders and administration site conditions	90	100	190
Infections and infestations	17	19	36
Injury, poisoning and procedural complications	0	3	3
Investigations	3	1	4
Metabolism and nutrition disorders	12	9	21
Musculoskeletal and connective tissue disorders	11	27	38
Neoplasms benign, malignant and unspecified	0	1	1
Nervous system disorders	7	17	24
Psychiatric disorders	1	7	8
Renal and urinary disorders	2	1	3
Reproductive system and breast disorders	0	1	1
Respiratory, thoracic and mediastinal disorders	6	7	13
Skin and subcutaneous tissue disorders	9	7	16
Vascular disorders	14	10	24
Total	**220**	**293**	**513**

Most of the AEs observed during the study were mild (low dose: 139/220 (63.2%), high dose: 182/293 (62.1%)) or moderate (low dose: 68/220 (30.9%), high dose: 87/293 (29.7%)) in intensity. Twelve AEs in the low dose (5.5%) and 21 AEs (7.2%) in the high dose group were severe in intensity.

Most of the TEAEs (190/513 = 37.0%) came from the "General disorders and administration site conditions system organ class" (SOC), with "infusion site pain" being the most commonly reported (95/513 = 18.5%) preferred term (PT).

Treatment related AEs

In study CTREPH 116-02, 273 TEAEs were classified as related to the study drug (low dose: 118, high dose: 155) (**Table 15**).

Table 15. Treatment related adverse events according to the body system, preferred term and treatment – one of the same PT per patient

SOC / PT with Relation yes	Low Dose	High Dose	Total
N patients total	52 (100)	53 (100)	105 (100)
Patients with at least one AE	51 (98.0)	53 (100)	104 (100)
Total number of AEs	220	293	513
Total number of related AEs	118	155	273
Total number of related AEs, PT counted 1 time /patient	**97**	**132**	**229**
Eye disorders	**0**	**1**	**1**
Eyelid oedema	0	1 (1.9)	1 (1.0)
Gastrointestinal disorders	**15**	**36**	**51**
Diarrhoea	13 (25.0)	31 (58.5)	44 (41.9)
Dyspepsia	0	1 (1.9)	1 (1.0)
Nausea	2 (3.8)	3 (5.7)	5 (4.8)
Vomiting	0	1 (1.9)	1 (1.0)
General disorders and administration site conditions	**71**	**73**	**144**
Decreased appetite	0	4 (7.5)	4 (3.8)
Fatigue	0	1 (1.9)	1 (1.0)
Flushing	4 (7.7)	4 (7.5)	8 (7.6)
Infusion site reaction at least one finding of:	24 (46.2)	25 (47.2)	49 (46.7)
- *Infusion site abscess one of same PT per patient*	*0*	*1 (1.9)*	*1 (1.0)*
- *Infusion site erythema one of same PT per patient*	*20 (38.5)*	*18 (34.0)*	*38 (36.2)*
- *Infusion site haemorrhage one of same PT per patient*	*1 (1.9)*	*0*	*1 (1.0)*
- *Infusion site infection one of same PT per patient*	*0*	*2 (3.8)*	*2 (1.9)*
- *Infusion site inflammation one of same PT per patient*	*2 (3.8)*	*3 (5.7)*	*5 (4.8)*
- *Infusion site irritation one of same PT per patient*	*0*	*1 (1.9)*	*1 (1.0)*
- *Infusion site pruritus one of same PT per patient*	*6 (11.5)*	*4 (7.5)*	*10 (9.5)*
- *Infusion site rash one of same PT per patient*	*1 (1.9)*	*0*	*1 (1.0)*
- *Infusion site reaction one of same PT per patient*	*0*	*1 (1.9)*	*1 (1.0)*
- *Infusion site swelling one of same PT per patient*	*3 (5.8)*	*4 (7.5)*	*7 (6.7)*
Infusion site pain	42 (80.8)	39 (73.6)	81 (77.1)
Pain	1 (1.9)	0	1 (1.0)
Musculoskeletal and connective tissue disorders	**3**	**13**	**16**
Arthralgia	1 (1.9)	2 (3.8)	3 (2.9)
Back pain	1 (1.9)	0	1 (1.0)
Pain in extremities	1 (1.9)	9 (17.0)	10 (9.5)
Pain in jaw	0	2 (3.8)	2 (1.9)
Nervous system disorders	**4**	**8**	**12**
Headache	4 (7.7)	7 (13.2)	11 (10.5)
Vertigo	0	1 (1.9)	1 (1.0)
Skin and subcutaneous tissue disorders	**4**	**1**	**5**
Exanthema	1 (1.9)	0	1 (1.0)
Pruritus	1 (1.9)	0	1 (1.0)
Rash	2 (3.8)	1 (1.9)	3 (2.9)
Total	**97**	**132**	**229**

Open-label extension phase (data cut-off: 31st October 2018)

106 TEAEs were classified as related to the study drug and reported for 26 out of 47 patients in the open-label extension phase. Most frequently infusion site pain (19.8%), other infusion site reactions (29.2%), diarrhoea (17.0), headache (5.7%), pain in extremities (4.7) and nausea (4.7) were reported.

Treatment related diarrhoea was reported for 13 patients (27.7%), from which 9 were previously randomized to the high dose group and 4 to the low dose group.

In the follow up phase four patients experienced TEAEs related to study drug (infusion site pain) which led to consent withdrawal, all of them were previously randomized to the low dose group in the blinded study phase. Overall eight patients were withdrawn from the study due to treatment related adverse events after a mean time of 97.25 ± 84.59 days. Mean dose at withdrawal was 7.4 ng/kg/min ± 11.25 (min. 0.51 ng/kg/min – max. 33.3 ng/kg/min, median: 2,9 ng/kg/min).

Supportive studies

Skoro-Sajer et al., 2007

In the 25 patients with severe, inoperable CTEPH who were treated up to 24 months with SC treprostinil, abdominal infusion site pain was the most common adverse event (86%), followed by infusion site erythema (76%) and hematoma (34%). Other frequent ADRs were diarrhoea (12%), infusion site abscesses (8%), jaw pain (4%), flushing (4%). There were two cases of infusion site abscesses (8%) requiring surgical incision and treatment with oral antibiotics, with no serious adverse consequences.

Lang et al., 2006

In Lang et al., 2006, the most common AEs/ADRs (relation to study drug / drug application were not reported in the publication) were infusion site pain (4.9%), abscesses (13.1%), cellulitis (8.2%), and bleeding (7.4%).

Serious adverse event/deaths/other significant events

During the study, 19 patients (10 (19.2%) in the low dose group and 9 (17.0%) in the high dose group) experienced a total of 28 serious AEs (SAEs). 5 subjects (9.6%) in the low dose group and 6 subjects (11.3%) in the high dose group developed SAEs related to the underlying disease CTEPH (**Table 16**).

Table 16. Serious adverse events, groups by SOC / severity and treatment

SOC / PT	Low Dose	High Dose	Total
N patients total	52	53	105
Patients with at least one SAE	10	9	19
Total number of SAE	12 (42.9)	16 (57.1)	28 (100)
Cardiac disorders	**4**	**8**	**12**
Cardiac failure	1 (3.6)	2 (7.1)	3 (10.7)
Dyspnoea	1 (3.6)		1 (3.6)
Right ventricular failure	1 (3.6)	6 (21.4)	7 (25.0)
Syncope	1 (3.6)		1 (3.6)
Gastrointestinal disorders	**2**		**2**
Diarrhoea	1 (3.6)		1 (3.6)
Nausea	1 (3.6)		1 (3.6)
General disorders and administration site conditions	**1**	**1**	**2**
General physical health deterioration		1 (3.6)	1 (3.6)
Incarcerated hernia	1 (3.6)		1 (3.6)
Infections and infestations	**2**	**1**	**3**
Appendicitis	1 (3.6)		1 (3.6)
Escherichia bacteraemia	1 (3.6)		1 (3.6)
Sepsis		1 (3.6)	1 (3.6)
Metabolism and nutrition disorders	**1**		**1**
Hypokalaemia	1 (3.6)		1 (3.6)
Neoplasms benign, malignant and unspecified		**1**	**1**
Polycythaemia vera		1 (3.6)	1 (3.6)
Nervous system disorders		**1**	**1**
Syncope		1 (3.6)	1 (3.6)
Renal and urinary disorders	**1**		**1**
Acute kidney injury	1 (3.6)		1 (3.6)
Respiratory, thoracic and mediastinal disorders		**1**	**1**
Haemoptysis		1 (3.6)	1 (3.6)
Vascular disorders	**1**	**3**	**4**
Aortic stenosis		1 (3.6)	1 (3.6)
Haematoma		1 (3.6)	1 (3.6)
Worsening of Pulmonary Hypertension	1 (3.6)	1 (3.6)	2 (7.1)
Total	**12 (42.9)**	**16 (57.1)**	**28 (100)**

Deaths

Three subjects died during the study (low dose: 1, high dose: 2). None of the deaths were rated as related to study drug.

Supportive studies

Skoro-Sajer et al., 2007

Five of 25 participants died during the 24 months study. Cause of death was right heart failure in 4 patients, and one patient died from breast cancer. No other information was available from the publication

Lang et al., 2006

Thirty-one of 122 participants (mixed PAH and CTEPH) died during the 36 months study. No other information was available from the publication.

AEs of special interest

Hypotension.

No events of hypotension were observed in study CTREPH 116-02.

Bleeding events.

No events of bleeding were observed in study CTREPH 116-02.

QT prolongation

In a retrospective analysis the ECG data of 202 PAH patients were compared to data of an age and sex-matched control group with normal ECGs (Rich et al. 2013). 42 patients (20.8%) of the PAH cohort received

prostacyclin (epoprostenol or treprostinil) therapy, 35 patients (17.3%) a prostacyclin and PDE5-inhibitor combination therapy. Thus, a total of 77 patients (38.1%) of the PAH cohort received epoprostenol or treprostinil therapy.

The ECGs were evaluated for QT interval, QTc interval, QRS duration, presence of RV hypertrophy and presence of right axis deviation. The analysis resulted in a significantly longer QTc interval (454.8±29 ms vs. 429.8±18 ms, p<0.001) and QRS duration (96.5±16 ms vs. 84.4±8 ms, p<0.001) for PH patients as compared to controls. No significant difference in QTc interval could be seen for patients receiving prostacyclin therapy compared to other PAH patients.

Laboratory findings

No clinically relevant shifts in laboratory parameters during the study could be detected except 9 cases of hypokalaemia (low dose: 5, high dose: 4) which were considered not related to study drug but related to concomitant diuretics therapy.

Safety in special populations

Age

Adverse events by age group are summarised in **Table 17**.

Table 17. Adverse events according to the body system or preferred term grouped by age

SOC /PT	Age <65 42 (40.0%)	Age 65-74 35 (33.3%)	Age 75-84 27 (25.7%)	Age 85+ 1 (1.0%)
N patients total	42 (100)	35 (100)	27 (100)	1 (100)
Patients with at least one AE	41 (97.6)	35 (100)	27 (100)	1 (100)
Total AEs	196	183	129	5
Total number of AEs, one of the same PT per patient	182	162	109	5
Patients with at least one SAE	7 (16.7)	6 (17.1)	6 (22.2)	0 (0)
Serious AEs – Total	8	9	11	0
- Fatal	*0*	*2*	*1*	*0*
- Hospitalization/prolong existing hospitalization	*7*	*7*	*9*	*0*
- Life-threatening	*0*	*0*	*1*	*0*
- Disability/incapacity	*0*	*0*	*0*	*0*
- Other (medically significant)	*1*	*0*	*0*	*0*
AE leading to drop-out (Infusion site pain)*	3 (7.1)	1 (2.9)	0 (0)	0 (0)
Psychiatric disorders*	1 (2.4)	2 (5.7)	2 (7.4)	0 (0)
Nervous system disorders*	6 (14.3)	7 (20.0)	5 (18.5)	0 (0)
Accidents and injuries*	0 (0)	3 (8.6)	0 (0)	0 (0)
Cardiac disorders*	11 (26.2)	11 (31.4)	6 (22.2)	0 (0)
Vascular disorders*	9 (21.4)	5 (14.3)	8 (29.6)	0 (0)
Infections and infestations*	12 (28.6)	15 (42.9)	5 (18.5)	0 (0)
Musculoskeletal and connective tissue disorders*	15 (35.7)	4 (11.4)	4 (14.8)	0 (0)
Skin and subcutaneous tissue disorders*	3 (7.1)	8 (22.9)	2 (7.4)	0 (0)
Worsening of Pulmonary Hypertension*	5 (11.9)	2 (5.7)	6 (22.2)	0 (0)
Infusion site pain*	32 (76.2)	29 (82.9)	19 (70.4)	1 (100)
Infusion site reaction (inclusion redness, swelling, itching, etc.)*	22 (52.4)	19 (54.3)	7 (25.9)	1 (100)
Diarrhoea*	15 (35.7)	15 (42.9)	15 (55.6)	1 (100)
Headache*	5 (11.9)	7 (20.0)	4 (14.8)	0 (0)

*One count per patient for same PT/SOC

Renal or hepatic impairment

Out of 105 patients enrolled in the study, nine patients had renal impairment defined as renal insufficiency (2 patients), chronic renal insufficiency (1 patient), chronic renal failure (2 patients), chronic kidney disease (2 patients) and chronic kidney failure (2 patients).

Four patients had hepatic impairment defined as congestive hepatopathy (1 patient), hepatic steatosis (1 patient), liver haemangioma (1 patient), liver test elevation (at time of baseline) (1 patient). Additionally, for two patients both renal and hepatic impairment was document as medical history (1 patient with congestive hepatopathy and renal insufficiency and 1 patient hepatopathy and chronic interstitial nephritis).

No difference in safety profile of treprostinil for patients with forms of hepatic and/or renal impairment documented as medical history could be observed. Furthermore, no difference in the rate of occurrence of specific adverse events were detected.

Safety related to drug-drug interactions and other interactions

Thirty-three patients were pre-treated with other PH specific medications (bosentan, sildenafil, riociguat, and macitentan) and were kept on stable doses throughout their study participation. The data observed in the study did not indicate drug-drug interactions between treprostinil and concomitant medication.

Discontinuation due to adverse events

In this study, 14 patients (8 high dose/ 6 low dose) discontinued study treatment. Ten subjects experienced SAEs which lead to withdrawal; however, none was classified as related to the study drug. Four subjects experienced TEAEs related to study drug (infusion site pain) which lead to consent withdrawal or withdrawal due to subject non-compliance.

2.6.6. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.6.7. Discussion on clinical safety

Treprostinil is a prostacyclin analogue which is currently approved for the treatment of pulmonary arterial hypertension (PAH). The primary safety data for the current dossier are derived from the pivotal phase III CTREPH 116-02 study. Additional safety data came from the two published open-label non-controlled studies of Skoro-Sajer et al., 2007 and Lang et al., 2006. Information on the safety profile of treprostinil can also be extrapolated from the use of the reference product, Remodulin, in PAH.

Study CTREPH 116-02 was a comparator-controlled study in which a low dose of treprostinil, which was anticipated not to have an effect on efficacy, was used as a comparator in order to obtain blinding. A classical placebo-controlled design was not feasible due to the characteristic smell of treprostinil and the anticipated local site reactions, which is plausible. As such safety data compared to placebo are not available.

Comparator controlled safety data is available for 53 patients administered the high dose of treprostinil (~30 ng/kg/min) compared to 52 patients in the low dose group (~3 ng/kg/min) for at least 24 weeks (mean exposure of 22.8 weeks in the low dose group and 22.5 weeks in the high dose group). The numbers of CTEPH patients exposed is very limited, however, expected considering the orphan designation.

The mean dose of treprostinil in the high dose group at week 24 was 29.11 ng/kg/min, which indicates that not all patients achieved the target dose of 30 ng/kg/min. Out of 53 patients, 26 patients (49.1%) didn't achieve the target does at week 24. The common reason was adverse drug reactions (11 patients (20.8%)) and weight gain (5 patients (9.4%)). However, In the open label follow up phase doses of up to 53.84 ng/kg/min were reached. Supported by toxicological investigations no maximum dose of treprostinil has been defined and no evidence is available that the adverse event profile differs in CTEPH compared to PAH. The dose should be adjusted on an individual basis and under medical supervision in order to achieve a maintenance dose at which symptoms improve and which is tolerated by the patient. The applicant presented additional data from a prospective registry (Sadushi-Kolici et al 2012), evaluating the efficacy and safety of long-term treatment of SC Treprostinil in severe pulmonary hypertension (N=111; 42 patients with CTEPH) which reported doses of over 100 ng/kg/min within an observation period of 8 years. Earlier terminations in 13 patients due to intolerable drug side effects, such as infusion site pain, occurred at < 6 months of treatment at a median dose of just 14 ng/kg/min. Based on this information the CHMP agreed that even though not used during the pivotal trial, the inclusion of no maximum subcutaneous infusion delivery rate of treprostinil as proposed in the dose recommendations in the SmPC was acceptable.

The adverse event profile as reported in the pivotal safety data is in line with the safety profile of the approved Remodulin product and with other prostacyclin analogues. Infusion site pain and infusion site reactions were also mentioned and based on the documentation of Remodulin well-known adverse events of treprostinil. The number of TEAEs considered treatment-related was slightly higher in the high dose group (155) compared with the low dose group (118), which was mainly due to a higher incidence in diarrhoea in the high dose group (33 vs 15 in the low dose group). The most common reported adverse events related to study drug were infusion site pain (73.6% of the patients in the high dose group vs 80.8% of the patients in the low dose), other infusion site reactions (47.2% vs 46.2%), diarrhoea (58.5% vs 25.0%), headache (13.2% vs 7.7%), pain in extremities (17.0% vs 1.9%) and flushing (7.5% vs 7.7%).

The incidences of serious adverse events were relatively high (n=19, 18.1%), however a slightly lower percentage of subjects in the high dose group experienced SAE compared with the low dose group (17.0% vs 19.2%), which is reassuring. No pattern indicative for a safety signal could be identified among the types of adverse events. Importantly, only one of the SAEs reported (hospitalization due to mild diarrhoea and nausea) was considered related to study drug.

Discontinuations due to AE were relatively low and even lower in the high dose group (1/53 (1.9%) compared with the low dose group (5.8%), which is reassuring. All discontinuations due to TEAE were associated with infusion site pain. Discontinuations because of clinical worsening were reported in 3 subjects in the high dose group 3/53 (5.7%) and 2 subjects in the low dose group (3.8%), emphasizing disease progression and the severity of the disease.

Three deaths were reported in the study (2 in the high dose group and 1 in the low dose group), however, none were related to study drug. Nevertheless, the study was too small to provide definitive data on mortality. Longer-term data in the Skoro-Sajer et al. 2007, do not indicate any imbalance in mortality when compared with historical controls, which is reassuring.

Events of hypotension were not observed in the pivotal study, probably due to the low number of patients included. Considering the mode of action of treprostinil as a potent pulmonary and systemic vasodilator and that hypotension is a known adverse event of Remodulin, information on the risk of hypotension has been included in sections 4.4 and 4.8 of the proposed SmPC and as an important identified risk in the RMP.

Bleeding events were not observed in study CTREPH 116-02, most likely due to the limited number of patients included but have been reported in the study of Lang et al, 2006 and are included in the Product monograph of Remodulin. Additional mechanisms of prostacyclin action include inhibition of platelet aggregation which may increase the risk of bleeding. As such, information on the risk of bleeding has been included in the SmPC, in line with the SmPC of Remodulin and bleeding tendencies is classified as an important potential risk in the RMP.

No thorough QT study has been performed. Preclinical data do not raise concerns of a QT prolongation effect. Furthermore, supportive data are submitted relating to PAH patients associated with an impaired right ventricular function (Rich et al. 2013). In this higher risk patient population, longer QTc interval and QRS duration were observed in PAH, patients compared to sex-matched controls. However, no differences could be found for patients on prostacyclin therapy compared to other PAH patients, although the dataset is quite limited. Moreover, Trepulmix can rely on the safety profile of Remodulin for which there are no concerns in relation to QT prolongation.

No clinically relevant shifts in laboratory parameters during the study could be detected except 9 cases of hypokalaemia (low dose: 5, high dose: 4) which were rated as not related to study drug but induced by diuretics therapy.

Most of the patients were > 65 years of age (60%). For the data observed, a comparable number of events could be observed in comparison to the patients < 65% group, except that diarrhoea and headache events were higher in the older age groups and that events related to musculoskeletal and connective tissue disorders were lower in the older age groups.

Furthermore, no pattern indicative for a safety signal could be identified among the types of adverse events between patients with renal or hepatic impairment compared with patients without renal or hepatic impairment, although firm conclusion cannot be made due to the limited database (9 patients with renal impairment and 4 patients with hepatic impairment) and therefore use in patients with hepatic and / or renal impairment is included in the RMP as missing information.

Nevertheless, Trepulmix, as a hybrid product of Remodulin, could rely on the study results from Remodulin that indicate that plasma treprostinil exposure increases in mild to moderate hepatic impairment and therefore caution is advised when treating patients with hepatic impairment. However, as treprostinil and its metabolites are excreted mainly through the urinary route, caution is recommended when treating patients with renal impairment.

Available data from study CTREPH do not indicate drug-drug interactions between treprostinil and concomitant PAH medication. However, as metabolism of treprostinil is suspected to be influenced by the enzyme CYP2C8, a recommendation to adjust treprostinil dose when used with concomitant CYP2C8 inhibitors or inducers has been included in Section 4.4 of the SmPC. Furthermore, co-administration with CYP2C8 inhibitors / inducers is regarded as missing information in the RMP.

Long-term safety is based on the open-label extension phase of the study and the published studies of Skoro-Sajer et al., 2007 and Lang et al., 2006. The most commonly reported TEAS in this phase of the study were infusion site pain , other infusion site reactions (29.2%), diarrhea (17.0), headache (5.7%), pain in extremities (4.7) and nausea (4.7) which are expected and in accordance to the well-known side-effect profile of treprostinil sodium from its use in PAH.

2.6.8. Conclusions on clinical safety

Despite the limited size of the safety database which is justified due to the rarity of CTEPH, the overall safety profile of treprostinil is in line with what is known from Remodulin. The main safety concerns identified are addressed adequately through appropriate routine risk minimisation measures.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hypotension
Important potential risks	Bleeding tendencies
Missing information	Use in patients with hepatic and / or renal impairment Co-administration with CYP2C8 inhibitors/inducers

Pharmacovigilance plan

No additional pharmacovigilance activities will be conducted. Routine pharmacovigilance is considered sufficient to identify and characterise the important risks and missing information of the product.

Risk minimisation measures

Safety concern	**Risk minimisation measures**
Hypotension	Routine risk minimisation measures: SmPC sections 4.4, 4.5, 4.7, 4.8 and 4.9. PL sections 2, 3 and 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Special medical prescription. Additional risk minimisation measures: None.
Bleeding tendencies	Routine risk communication: SmPC sections 4.4, 4.5 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: None.

Safety concern	Risk minimisation measures
	Other routine risk minimisation measures beyond the Product Information: Legal status: Special medical prescription Additional risk minimisation measures: None.
Use in patients with hepatic and / or renal impairment	Routine risk communication: SmPC sections 4.4, 4.5 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Dosage instruction in SmPC Section 4.2 and Warnings in Section 4.4. Contraindication for Child Pugh C in Section 4.3 Other routine risk minimisation measures beyond the Product Information: Legal status: Special medical prescription Additional risk minimisation measures: None.
Co-administration with CYP2C8 inhibitors/inducers	Routine risk communication: SmPC sections 4.4, 4.5 and 4.8 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to adjust treprostinil dose when used with concomitant CYP2C8 inhibitors or inducers in Section 4.4 of the SmPC. Other routine risk minimisation measures beyond the Product Information: Legal status: Special medical prescription Additional risk minimisation measures: None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the product information. The existing EURD list entry for treprostinil including the forthcoming Data Lock Point and submission date as per published EURD list will be used for the PSUR submission of Trepulmix.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication for Trepulmix was the treatment of adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment (severity classified WHO Functional Class (FC) II, III or IV), to improve exercise capacity and symptoms of the disease. CTEPH is defined as pre-capillary pulmonary hypertension (PH) as assessed by right heart catheterization (mean PAP ≥25 mmHg, PCWP ≤15 mmHg) in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least three months of effective anticoagulation. CTEPH is a rare debilitating, life-threatening disease characterized clinically by dyspnoea, fatigue, chest pain, dizziness, peripheral oedema, coughing, haemoptysis, and in advanced stages, fainting and syncope. CTEPH is thought to result from isolated or recurrent pulmonary thromboembolism and has been estimated to occur in 3% of patients who survive pulmonary embolism (Lang and Klepetko 2009). Using an upper estimate, CTEPH affects 1-9 patients per 100.000 (Orphanet, 2009). If left untreated, CTEPH patients have a poor prognosis. When mean pulmonary arterial pressure (PAP) is greater than 50 mm Hg, the 1-year survival rate in untreated patients with CTEPH is less than 50% (Lang and Klepetko, 2008).

3.1.2. Available therapies and unmet medical need

Pulmonary endarterectomy (PEA) is the treatment of choice for patients with CTEPH as it is a potentially curative treatment option. However, it is estimated that in 50% of CTEPH, PEA is infeasible or ineffective (Klepetko et al. 2004). Since March 2014, Adempas (riociguat, a soluble guanylate cyclase stimulator) has been approved for the treatment of adult patients with WHO Functional Class (FC) II to III with inoperable CTEPH, or persistent or recurrent CTEPH after surgical treatment to improve exercise capacity. There are no other approved therapeutic agents specifically indicated for the treatment of inoperable CTEPH.

According to the ESC ERS guideline for the diagnosis and treatment of pulmonary hypertension (2015), off-label use of drugs approved for PAH may be considered in symptomatic patients who have been classified as having inoperable CTEPH by a CTEPH team including at least one experienced PEA surgeon, indicating the unmet medical need.

3.1.3. Main clinical studies

Treprostinil has been investigated in a double-blind, comparator-controlled, 24-week phase 3 study in 105 patients with severe non-operable CTEPH (CTREPH 116-02 trial). Patients were selected based on perfusion scintigraphy and pulmonary angiography and/or multi-slice CT, right heart catheterization, effective anticoagulation therapy, baseline 6MWT between 150-400 m, WHO/NYHA FC III or IV and inoperable or persistent/recurrent CTEPH. During the double-blind treatment period, CTEPH patients received s.c. infusion of treprostinil to a target dose of 30 ng/kg/min (high dose group) or the target dose of 3 ng/kg/min (low dose group: comparator). The low dose, which did not show clinical improvement in patients with PAH has been used as a comparator since it was considered not feasible to conduct a placebo-controlled design due to the characteristic smell of the treprostinil solution and the anticipated local site reactions induced by s.c. administered treprostinil. Treprostinil was titrated to the target dose based on a predefined infusion rate setting schedule. In both the high and the low dose group, the dose was escalated to the target dose after the first 12 weeks and was stable thereafter for another 12 weeks. The primary endpoint was the change from baseline in 6MWT distance after 24 weeks. Important secondary endpoints included clinical worsening, change in 6MWD after 12 weeks, change in WHO functional class, while changes in haemodynamic parameters and pro-BNP were included as exploratory endpoints.

The effect of treprostinil in CETPH was supported by two published clinical studies (Skoro-Sajer et al., 2007 and Lang et al., 2007). The study of Skoro-Sajer et al. was a prospective open-label non-controlled phase II study to investigate the effect of up to 24 months treatment of treprostinil s.c. in 25 patients with severe inoperable CTEPH (WHO functional class III or IV). The study of Lang et al. was a multicentre retrospective study to investigate the effect of up to 36 months of s.c. infused treprostinil on exercise capacity and survival benefits in patients with PAH (n= 99) and CTEPH (n=23). Both studies used historical controls for comparative survival analysis.

3.2. Favourable effects

In the pivotal study CTREPH 116-02, the high dose of treprostinil (30 ng/kg/min) resulted in a significant improvement in 6MWD from baseline to week 24 compared to the low dose group (3 ng/kg/min) (45.43 vs 3.83 m; ANCOVA p =0.002; Mann-Whitney U-test p = 0.0003).

Significant improvements are also shown in NYHA/WHO functional class for 27 subjects (50.9 %) in the high dose group and 9 subjects (17.3 %) in the low dose group, whereas 2 subjects (3.8 %) experienced a

deterioration increase of NYHA functional class in the high dose group and 3 subjects (5.8 %) in the low dose group (Chi-square: p=0.0019; Fisher exact test: p=0.0012). A lower number of subjects in the high dose group compared with the low dose group developed a clinical worsening during the study period (7 (13.2%) vs. 12 (23.1%) in the high and low dose group, respectively), however, this difference was not significant (p=0.189). Of the patients with clinical worsening, 2 vs 7 subjects showed a reduction of more than 20% in 6MWT, 2 vs 4 subjects experienced a worsening of WHO NYHA FC and 4 vs 6 subjects had to be hospitalized due to CTEPH and needed additional PH-specific treatment. Also, a non-significant positive trend on the clinical secondary endpoint Borg Dyspnoea and MINNESOTA QOL was observed.

The effect of dose on the 6MWT outcome was not impacted by CTEPH type (inoperable/persistent) (p value of the interaction between "dose" and CTEPH operability 0.7280) as expected. The subgroup analysis (forest plot) with respect to the type of CTEPH (inoperable or persistent/recurrent CTEPH), and NYHA/WHO FC at baseline supported the primary analysis.

Comparable results were recorded in the study of Skoro-Sajer et al. where 6 months of treatment with treprostinil (mean dose of 21 ± 5 ng/kg/min (range: 11-30 ng/kg/min)) resulted in a mean increase in 6MWD compared to baseline of 59m in patients with severe inoperable CTEPH. In addition, this study demonstrated long term maintenance of the effect of treprostinil in 6MWD and a beneficial effect on clinical outcomes, i.e. survival rates, compared with historical controls (overall survival rates at one, two, three and five years of 80%, 80%, 80% and 53% compared with 67%, 43%, 37% and 16%, respectively (p = 0.02).

3.3. Uncertainties and limitations about favourable effects

The pivotal study included only a limited number of patients with CTEPH NYHA FC II and IV. Even though subgroup analyses showed a comparable effect for treprostinil in all three NYHA classes. As patients with NYHA class II are only slightly limited in physical activity, available data are too limited to draw conclusions about efficacy and safety, and available clinical guidelines advice against the use of prostacyclin treatment in such patients, it was agreed to remove this patient group from the approved indication. Although the number of patients with NYHA IV was also low, the CHMP noted that treatment options are very limited in patients unable to carry out any physical activity. Moreover, the data in this subgroup was supported by literature data (Lang et al 2006). As all available results seem to confirm consistent efficacy between FC III and FC IV, the CHMP agreed on the inclusion of this group of patients in the indication.

The proposed SmPC provides guidance for subcutaneous infusion delivery rates of treprostinil with no defined maximum dose, although in study CTREPH 116-02, patients in the high dose group received s.c. treprostinil infusions up to a target dose of 30 ng/kg/min in the blinded phase. The Applicant however presented literature data to demonstrate that in this setting, higher doses than those used in the clinical trial have been used and that the maximum dose is defined for each individual patient based on their needs and tolerability to treprostinil. Considering that the product will be administered under close medical supervision with continuous adjustment of the dose, and there is no evidence to suggest that the adverse event profile of treprostinil is different between CTEPH and PAH, the CHMP agreed to maintain the dosing instructions consistent with those of the reference product Remodulin.

3.4. Unfavourable effects

The primary safety data are derived from the pivotal phase III CTREPH 116-02 study. Additional safety data are available from the two published open-label non-controlled studies of Skoro-Sajer et al., 2007 and Lang et al., 2006 and available published data for the reference product Remodulin. Comparator controlled safety

data is available for 53 patients administered the high dose of treprostinil (~30 ng/kg/min) compared to 52 patients in the low dose group (~3 ng/kg/min) for at least 24 weeks (mean exposure of 22.8 weeks and 22.5 weeks in the high and low dose group, respectively).

The system organ classes mostly affected and with a higher rate of reported adverse events in the high dose group were "General disorders and administration site conditions" (190/513 (37.0%); low dose 90 and high dose 100) and "Gastrointestinal disorders" (75/513 (14.6%); low dose 23 and high dose 52). The most frequently reported adverse events (PT) with a higher rate in the high dose group were diarrhoea (33 subjects (62.3%) in the high dose group vs 13 subjects in the low dose group (25.0%)), headache (12 (22.6%) vs 4 (7.7%)) and pain in extremities (11 (20.8%) vs 1 (1.9%)).

Other frequently reported adverse events with a similar rate between the groups were infusion site pain (39 subjects (73.6%) in the high dose group vs 42 subjects in the low dose group (80.8%) and infusion site erythema (18 (34.0%) vs 20(38.5%)).

The most common reported adverse events related to study drug were infusion site pain (73.6 % of the patients in the high dose group vs 80.8% of the patients in the low dose group), other infusion site reactions (47.2% vs 46.2%), diarrhoea (58.5% vs 25.0%), headache (13.2% vs 7.7%), pain in extremities (17.0% vs 1.9%) and flushing (7.5% vs 7.7%).

A slightly lower percentage of subjects in the high dose group experienced SAE compared with the low dose group (17.0% vs 19.2%). No pattern indicative for a safety signal could be identified among the types of adverse events. Importantly, all but one (hospitalization due to mild diarrhoea and nausea) of the SAEs were considered not related to study drug. Most of the SAEs were related to the underlying disease CTEPH.

The incidence rate of death was numerically higher in the high dose group (n=2, 3.8%) compared with the low dose group (n=1, 1.9%), however, none of the deaths was rated as related to study drug.

Treprostinil up to doses of 30ng/kg/min was well tolerated. TEAEs leading to discontinuations were relatively low, despite the frequently reported infusion site reactions and even lower in the high dose group (n= 1, 1.9%) compared with the low dose group (n=3, 5.8%), which were all related to infusion site pain.

3.5. Uncertainties and limitations about unfavourable effects

The numbers of CTEPH patients exposed in study CTREPH 116-02 is limited, however this is to be expected considering the orphan designation. Additionally, the double-blind treatment phase of 24 weeks, was too short to assess long-term safety. Therefore, reference is made to open-label extension phase of the pivotal study and the published studies of Skoro-Sajer et al., 2007 and Lang et al., 2006. Although these are non-controlled and open-label, the safety profile of the published studies is comparable to the safety profile observed in study CTREPH 116-02.

Events of hypotension were not observed in the pivotal study, probably due to the low number of patients included. Considering the mode of action of treprostinil as a potent pulmonary and systemic vasodilator and that hypotension is a known adverse event of treprostinil, information on the risk of hypotension has been included in sections 4.4 and 4.8 of the proposed SmPC and as an important identified risk in the RMP.

A known mechanism of prostacyclin action is inhibition of platelet aggregation. Due to this effect, treprostinil may increase the risk of bleeding as observed by an increased incidence of epistaxis and gastrointestinal (GI) bleeding in controlled clinical studies for treprostinil in PAH and in the study of Lang et al. Bleeding events were not reported in the study CTREPH 116-02, most likely due to the limited number of patients,

emphasizing the limited dossier of Trepulmix, nevertheless bleeding tendencies has been included in the RMP as an important potential risk to ensure adequate monitoring of these type of events.

3.6. Effects Table

Table 18. Effects Table for treprostinil in the treatment of adult patients with WHO FC III or IV inoperable, persistent or recurrent CTEPH (data cut-off 31st October 2018)

Effect	Short Description	Unit	High dose (30ng/kg/min)	Low dose group (3 ng/kg/min)	Uncertainties/ Strength of evidence
Favourable effects					
		N	53	52	
6MWD	Change from baseline to 24 weeks (S.D.)	m	45.43 (71.29)	3.83 (56.21)	SoE: p= 0.002 (ANCOVA) Unc: Maximum effect (clinical stabilization) and maintenance of effect have not been demonstrated.
Clinical worsening	Clinical worsening at 24 weeks	N (%)	7 (13.2)	12 (23.1)	Unc: P= 0.189 (Chi-square-test); Trend to improvement in clinical worsening
Unfavourable effects					
Deterioration in NYHA functional class		%	3.8	5.8	
Diarrhoea		%	58.5	25.0	
Headache		%	13.2	7.7	
Pain in extremities		%	17.0	1.9	

Abbreviations: WHO FC: World Health Organization Functional Class, CTEPH: Chronic Thromboembolic Pulmonary Hypertension, 6MWD: 6-Minute Walking Distance, S.D: Standard Deviation, SoE: Strength of Evidence, ANCOVA: Analysis of Covariances, Unc: Uncertainties, NYHA: New York Heart Association

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment with treprostinil (Trepulmix) is targeted at patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment. Subcutaneous infusions with high dose treprostinil of 30 ng/kg/min resulted in a clinically relevant and statistically significant improvement in 6MWT after 24 weeks of treatment when compared with low dose treprostinil of 3 ng/kg/min. The presented results are nominally comparable to the results of the other authorised product for CTEPH (Adempas (riociguat)). The 6MWT is considered an acceptable surrogate according to the CHMP PAH guideline to apply for an indication including improvement in exercise capacity.

The beneficial effect on the primary endpoint is supported by improvements in other relevant endpoints of WHO (NYHA) functional class and pulmonary haemodynamics. Beneficial trends were also observed in other (exploratory) endpoints including clinical worsening and QOL. The use of the primary endpoint and the other (secondary and exploratory) endpoints is generally in line with endpoints used in several PAH dossiers and

also in the approved riociguat dossier for CTEPH (only the analysis of *the percentage of patients with clinical worsening* is not in accord with the guideline-recommended *time to* worsening). This is acceptable considering the in principal comparable disease characteristics and treatment goals for CTEPH vs PAH. The effect of dose on the 6MWT outcome was not impacted by CTEPH type (inoperable/persistent). The subgroup analysis with respect to the type of CTEPH (inoperable or persistent/recurrent CTEPH) at baseline supported the primary analysis.

Safety data are based on one pivotal active-controlled study, providing a mean exposure of 22.8 weeks for 53 patients treated with treprostinil 30 ng/kg/min and supported by two published open-label and non-controlled studies). Also, the safety data of Remodulin in PAH, can be considered supportive to assess safety. This is considered sufficient, especially for an orphan indication. The common AEs are mainly related to the route of administration, including infusion site pain and other infusion site reactions, and to the mechanism of action of vasodilation, including headache, nausea, vomiting and flushing. Overall, treprostinil up to doses of 30 ng/kg/min is well tolerated, despite the frequently reported infusion site reactions, and displays an acceptable safety profile with very limited patients discontinuing treatment due to adverse events.

Also, data on clinical worsening do not indicate a negative effect on morbidity. The reported adverse event profile is in line with the safety profile of Remodulin in PAH patients and of other prostacyclin analogues.

3.7.2. Balance of benefits and risks

The main clinical data are limited due to the rarity of the disease but do show a clinically relevant and significant effect on exercise time after 24 weeks. This clinically relevant benefit is further supported by improvement in functional class and haemodynamic parameters. For the proposed indication provided safety was acceptable, generally well tolerated and appears in line with the known safety profile of other prostaglandin analogues, including treprostinil in PAH. The demonstrated clinical benefit outweighs the risks related to the product.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of treprostinil is positive.

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Trepulmix is not similar to Adempas within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Trepulmix is favourable in the following indication:

Treatment of adult patients with WHO Functional Class (FC) III or IV and:

- inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or
- persistent or recurrent CTEPH after surgical treatment

to improve exercise capacity.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.