European Medicines Agency

London, 19 November 2009
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WITHDRAWAL ASSESSMENT REPORT FOR

Tyvaso

International Nonproprietary Name:
treprostinil sodium

Procedure No. EMEA/H/C/1115

Applicant: United Therapeutics Europe Ltd., UK

Day 180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AE	Adverse Events
ANCOVA	Analysis of Covariance (statistical procedure)
ATS	American Thoracic Society
AUC	Area under Curve
AUCinf	Area under the concentration time curve from time of dosing to infinity
BNP NT-	pro-Brain Natriuretic Peptide
BP	Blood Pressure
CHD	Congenital Heart Disease
CI	Cardiac Index
Cmax	Observed peak drug concentration
CMH	Cochran-Mantel Haenszel (statistical test)
CO	Cardiac Output
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CVD	Collagen Vascular Disease
CYP	Cytochrome P450
DMC	Data Monitoring Committee
e.g.	For example
ECG	Electrocardiogram
ERA	Endothelin receptor antagonist
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
hr	Hour(s)
HR	Heart Rate
INH	Inhaled
INR	International Normalised Ratio
IPAH	Idiopathic Pulmonary Arterial Hypertension
ITT	Intent-to-Treat
iv	Intravenous(ly)
Kg	Kilogram(s)
LDPE	Low Density Polyethylene
LOCF	Last Observation Carried Forward
LRX	LungRx
LVEF	Left Ventricular Ejection Fraction
m	Metre
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
MITT	modified intent-to-treat (analysis)
mL	Milliliter
MLWHF	Minnesota Living With Heart Failure (questionnaire)
mmHg	Millimetres of Mercury
MUGA	Multigated Angiogram Multiple-Gated Aquisition
N	Number of Subjects
ng	Nanogram
NS	Not Significant
NYHA	New York Heart Association
PAH	Pulmonary Arterial Hypertension
PAPm	Pulmonary Arterial Mean Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PDEI	Phosphodiesterase Inhibitor
PGI2	Prostacyclin or Epoprostenol Sodium

PH	Pulmonary Hypertension
pITT	Pure Intent-to-Treat
PPH	Primary Pulmonary Hypertension
PVR(I)	Pulmonary Vascular Resistance (Index)
QID	Four times daily
QOL	Quality of Life
RAPm	Mean Right Atrial Pressure
SAE	Serious Adverse Event
SAP	Systemic Arterial Pressure
sc	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SvO2	Mixed Venous Oxygen Saturation
SVR(I)	Systemic Vascular Resistance (Index)
Tmax	Time of peak plasma concentration
TRE	Treprostinil sodium
TRIUMPH	Treprostinil Inhalation Used in the Management of Pulmonary Hypertension
UCSD	University of California at San Diego
US	United States
UTC	United Therapeutics Corporation
UT-15	Treprostinil sodium, TRE
UT-15C	Treprostinil diethanolamine
WHO	World Health Organization
µL	Microliter
6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
95% CI	95% confidence interval

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Tyvaso (treprostinil), in:

the treatment of pulmonary arterial hypertension (PAH; WHO Group I) to improve exercise capacity in patients receiving either a phosphodiesterase-5 (PDE-5) inhibitor or an endothelin receptor antagonist with New York Heart Association (NYHA) functional class III severity of disease. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease

is not approvable since a major objection still remains, which precludes a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of outstanding issues.

The major objection precluding a recommendation of marketing authorisation pertains to the following:

Based on the Agency inspections at two different trial sites, the pivotal TRIUMPH study is considered non-GCP compliant and therefore not in accordance with requirements of Directive 2001/83/EC. The conclusion of non-compliance was based on several critical and major findings in the two investigators sites inspected, pertaining to trial management, and quality of the data. These issues are considered to have a major impact on the reporting of both efficacy and safety data. The registration of this product is based on a single pivotal trial and therefore, the results should be compelling and the trial designed and performed impeccably (robust) [CPMP/EWP/2330/99]. This is not the case. Thus, the credibility of the data is questioned and the benefit/risk cannot be assessed based on the currently submitted data.

Proposal for Questions to be posed to additional Experts
None

Proposal for Inspection
None.

II. EXECUTIVE SUMMARY

II.1 Problem statement

United Therapeutics Europe Ltd filed a full application for a medical product using the Centralised Procedure containing a new active substance: treprostinil sodium in accordance with Article 3(1) indent 4 of Regulation (EC) No 726/2004 (Orphan designated medicinal product). The intended trade name is Tyvaso. The CHMP appointed Prof P. de Graeff from the Netherlands as Rapporteur and Dr Prieto Yerro from Spain as Co-rapporteur.

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries, characterized by vascular proliferation and remodelling. It results in a progressive increase in pulmonary arterial resistance and, ultimately, right ventricular failure and death. Conventional treatment for patients with PAH includes anticoagulants, diuretics and oxygen. There are currently three therapeutic classes approved for the treatment of PAH in the EU:

- endothelin receptor antagonists (ERA): bosentan, sitaxentan, and ambrisentan (oral)
- phosphodiesterase 5 inhibitor (PDE5-I): sildenafil (oral)
- prostacyclin / prostanoids : epoprostenol IV infusion, treprostinil SC infusion; and iloprost inhalation

Prostanoids:

Flolan (epoprostenol sodium), a synthetic prostacyclin, was the first product introduced for the treatment of pulmonary hypertension. Flolan is approved for use in patients with NYHA Class III and IV primary pulmonary hypertension. Because Flolan is unstable, it must be given by continuous IV infusion, which has been associated with side effects and serious complications related to its mode of delivery e.g. sepsis, thrombosis, pneumothorax and cardiovascular collapse due to rebound from even brief interruption.

Ventavis (iloprost) is an inhaled prostacyclin analogue approved for patients with NYHA Class III Ventavis requires inhalation regimens approximately every 2 hours while awake (6-9 times per day). The inhalation procedure takes 10-15 minutes and requires preparation and clean-up, totalling approximately 20-30 minutes for every inhalation cycle. The average frequency of inhalations is 7.5 times per day, and the primary device requires access to electricity for proper delivery. Although of a longer duration than epoprostenol, efficacy can still be minimal before the next dosing, sometimes resulting in syncope. Thus, while treatment with inhaled iloprost appeared promising, issues with treatment compliance related to dosing frequency, and "therapeutic gaps" and "insufficient efficacy" have been recognized.

Treprostinil sodium was initially developed as a parenteral formulation for the treatment of PAH, administered by the subcutaneous (SC) and later intravenous (IV) routes. Remodulin (treprostinil sodium) solution for subcutaneous infusion (same formulation as Tyvaso except for the preservative metacresol) is approved in EU through an MRP FR/H/278/01 but marketing applications were voluntarily withdrawn during the mutual recognition procedure in Ireland, Spain and the United Kingdom. However, these routes of administration have certain convenience limitations, including the need for an ambulatory infusion device for continuous delivery and pain at the site of infusion. Thus, the inhaled route of delivery of treprostinil was investigated to provide the benefits of prostacyclin therapy without these limitations. Remodulin contains the same aqueous formulation as the proposed inhaled product, Tyvaso, except Remodulin has metacresol as a preservative.

Management of PAH patients is usually initiated with oral therapy (ERA, PDE5-I). There is currently a growing interest in combination therapy based on the potential of additive or synergistic effects across the various drug pathways. Combination therapy is currently an off-label use, and long-term safety and efficacy data are lacking. There are many open questions regarding combination therapy, including the choice of combination agents, the optimal timing [initial combination (in naive patients) or sequential combination (according to the response to the first drug)], when to switch, and when to combine. According to the recent PAH treatment management guidelines (Galie et al., 2009) combination therapy of established PAH drugs is recommended for patients not responding adequately to monotherapy, and should be instituted by expert centres only. Whether the response to monotherapy is sufficient or not can only be decided on an individual basis. The main clinical trial in the current application investigated the additive effect of treprostinil inhalation in PAH patients stabilized on bosentan or sildenafil in support of the proposed add-on indication. Early studies with inhaled treprostinil showed that its longer half life (4.5 hours vs. 30 min for iloprost) could enable fewer and shorter dosing sessions per day thus improving patient compliance. It was also associated with less systemic side effects.

II.2 About the product

Tyvaso contains treprostinil sodium as active substance, a stable synthetic analogue of prostacyclin, intended to be administered as a nebuliser solution via the inhalation route. Each millilitre of solution contains 0.6 mg of treprostinil. Inhaled treprostinil is administered using the Optineb-ir ultrasonic nebuliser. This nebuliser generates a pulsed aerosol cloud of formulation. Each pulse delivers 6 µg of treprostinil from the mouthpiece.

The proposed indication is:
"Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise capacity in patients receiving either a phosphodiesterase-5 (PDE-5) inhibitor or an endothelin receptor antagonist with New York Heart Association (NYHA) functional class III severity of disease. Efficacy has been shown in idiopathic pulmonary arterial hypertension (IPAH) and PAH associated with connective tissue disease".

Tyvaso is intended to be dosed in four separate inhalation sessions each day, during waking hours being the inhalation sessions at least 4 hours apart. Therapy should begin with 3 breaths of Tyvaso (18 micrograms of treprostinil) per inhalation session and the dosage should be subsequently increased to the target maintenance dose of 9 breaths (54 micrograms of treprostinil) per inhalation session as tolerated. If adverse effects preclude titration to this target dose, treatment should be continued at the highest dose that is tolerated by the patient.

Treprostinil is available as a parenteral formulation of treprostinil sodium [Remodulin (treprostinil sodium) Solution for Infusion] and is approved for use in treating patients with PAH (NYHA Class III). Remodulin is currently approved in the United States, Argentina, Peru, Mexico, Switzerland, Israel and Canada for sc and iv administration and in Australia, Taiwan, and in most countries in the European Union (Austria, Belgium, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, and Sweden) for sc administration. Remodulin contains the same aqueous formulation as the proposed inhaled product, Tyvaso, except Remodulin has metacresol as a preservative.

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

In support of the current application, the applicant refers to 15 clinical studies: 11 studies conducted with the inhalation form and 4 conducted with an oral formulation (in support of the pharmacokinetic data). The eleven studies conducted by the inhalation route include 4 long term studies and 7 acute studies. The applicant also refers to the clinical data available from Remodulin solution for infusion (SC and IV).

The long term efficacy of inhaled treprostinil is investigated in the TRIUMPH study which is a randomised, double-blind, placebo-controlled, parallel-group study in NYHA Class III and IV PAH patients who were on stable dose of bosentan or sildenafil for at least three months prior to enrolment. Patients recruited in this 12 week study were allowed to enter a long term open-label study (ongoing). Presented data from this study have a cut-off date of January 2008, and an interim safety update with a cut-off date of July 2008 is also presented (updated data with a cut-off date of January 2009 was submitted with the day 120 responses).
Data from 2 investigator initiated studies are also submitted.

Relevant for the current application is the draft CHMP *Guideline on the Clinical Investigations of Medicinal Products for the treatment of Pulmonary Hypertension EMEA/CHMP/EWP/356954/2008*. Reference to this document will be made in the clinical assessment.

The applicant sought scientific advice during the clinical development of treprostinil inhalation. Protocol Assistance has been sought from the SAWP on the chemical similarity of treprostinil to iloprost EMEA/CHMP/SAWP/420478/2005 (see section IV). This was followed by protocol assistance on some aspects in quality, pre-clinical and clinical development EMEA/CHMP/SAWP/266344/2006 and follow-up protocol assistance EMEA/CHMP/SAWP/258052/2007.

A Paediatric Investigation Plan has been submitted to the Agency (EMEA-000207-PIP01-08).

II.4 General comments on compliance with GMP, GLP, GCP

Acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product. For the site that does secondary packaging and batch release in the EU (UK), a copy is accepted of the current manufacturer authorisation, issued by the inspection service of the competent authorities as certification that acceptable standards of GMP are in place at that site. The manufacturing site of the finished product in the USA has been inspected for GMP compliance by an EEA authority less than three years ago.
GLP: The safety studies previously submitted for REMODULIN application and included in the present application have not been carried out in compliance with GLPs. However, the new cardiovascular and respiratory safety studies submitted by the applicant for Tyvaso application were GLP compliant.

GCP: Critical and major issues were identified after a routine GCP inspection requested by the Agency was performed of the single pivotal trial for Tyvaso LRX-TRIUMPH 001at two of 27 trial sites, corresponding to 38 (16%) of 235 patients randomized. Inspections were performed by the European health authorities. No particular trigger led to the GCP inspection other than that no clinical trial of this sponsor had ever been investigated. The inspection focused on procedures, documents and data from the period covered by the Clinical Study Report of the clinical study LRX-TRIUMPH 001. The inspection was performed in line with applicable guidance documents, such as CPMP/ICH/135/95: "NfG on GCP".
At the two sites inspected (one site in the United States and one in the European Union), nine major and four critical deviations were observed in the site in the United States and nine major and five critical at the European site. In addition during inspection of these sites major and critical findings were identified which were addressed to the sponsor of the study.
Inspection of the European site was performed in May 2009 and the inspection of the site in the United States was performed in June 2009. Inspection reports were sent to the sponsor and principal investigators at the study sites in July 2009, response from the inspectees was received in August 2009.
A final inspection report was written in September 2009 addressing these sponsor and investigator responses.

- Site in the EU: Two critical findings (one investigator- and one sponsor-related) were downgraded and two major findings were withdrawn, but an additional two were observed after the response.
- Site in the US: One critical finding of the investigator was downgraded to major and one critical finding related to the sponsor was withdrawn. One major sponsor-related finding was also withdrawn.

At the end of their report the Inspectors concluded on the general non-GCP compliance of the inspected centres, together with the deficiencies of the sponsor in quality management and quality control responsibilities. According to the inspectors, these deficiencies resulted in deviations and necessitated multiple data manipulations of the efficacy parameters in the clinical study report. These issues should be carefully considered during the final assessment of the submitted data.

The view of the CHMP is that these GCP findings have serious implications on the assessment of the study, in particular because the assessment of benefit/risk is based on one pivotal study. In this case the results should be compelling and the trial designed and performed impeccably (robust) [CPMP/EWP/2330/99]. Many deficiencies are identified throughout the study either attributed to the sponsor or the individual investigators casting serious doubts on data integrity and study conduct. The major question is whether a study with the following deficiencies allows any conclusions concerning efficacy and safety:

1. Poor quality of content and version management of critical study documents e.g. protocol, CRF, informed consent
2. Failure to demonstrate adequate GCP oversight and management of the trial and trial sites (e.g. protocol waivers granted, no written randomisation procedures, multiple necessary adaptations of on site elevated data compared to those listed in the study report) and

3. Lack of quality control during trial conduct (insufficient monitoring regarding frequency and outcome, no monitoring plan).

The answer appears no. These issues are considered to have a major impact on the reporting of both efficacy and safety data. If quality control and oversight of the trial was insufficient, how can these data be considered reliable? This can not be solved by, for instance, imputation strategies to correct for missing values of the measured endpoints.
According to the Introduction and general principles of the annex 1 of Directive 2001/83/EC as amended "All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use." This is not the case. A major objection is accordingly posed.

II.5 Type of application and other comments on the submitted dossier

This is an Article 8(3) Dir 2001/83/EC application for a medicinal product with a known active substance via the centralised procedure (in accordance with Regulation (EC) No 726/2004), article 3(1) annex 4 (mandatory scope as orphan designation has been asked for) Orphan designation has been granted on 14.04.2004 based on the criterion of :"significant benefit".

According to the information provided by the sponsor, pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension are considered to affect not more than 39,000 persons in the European Union.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Introduction
A centralized procedure is followed for the proposed product Tyvaso 0.6 mg/ml nebuliser solution, intended for oral inhalation using a specific device, the Optineb-ir AICI (Model ON1001/7), an ultrasonic, pulsed delivery nebuliser. It is used in the treatment of pulmonary arterial hypertension (WHO Group I). The maximum daily dose used in clinical studies was 12 breaths (72 micrograms of treprostinil).

Active substance

The active substance, treprostinil sodium, is also used in Remodulin 1-2.5-5-10 mg/ml solution for infusion, registered by MRP (FR/H/278/01-04), authorized by 23 EU members, with the same company as Marketing Authorisation Holder (United Therapeutic Europe Ltd.), for the treatment of primary pulmonary hypertension (PAH).
The active substance is a prostaglandin derivative, being an acid (the sodium salt is only formed *in situ* during the formulation of the medicinal product), soluble in various aqueous and organic solvents. Because the medicinal product is a solution, solid state properties do not have any impact on bioavailability.
Treprostinil has five chiral centres; a combination of data from chiral HPLC and specific optical rotation for the active substance, and chiral HPLC + X-Ray diffraction data from the starting material, having the same stereo-chemical configuration, and data from chiral control of several pivotal synthesis steps, demonstrates the absolute configuration of the active substance.

- Manufacture

Treprostinil is supplied by one manufacturer. The Active Substance Master File (ASMF) procedure was not used and the applicant provided full information on the active substance manufacturing process and controls, the development and control of critical steps.
The manufacture of treprostinil consists of a four step process, followed by recrystallisation to give a white solid and drying. Adequate in process controls are in place and appropriate specifications have been adopted for the starting materials, solvents and reagents used in the manufacturing process. All relevant impurities (related substances, degradation products) and residual solvents have been appropriately characterized.

- Specification

The in-house active substance specification has previously been established during the mentioned MRP for Remodulin. The active substance specification includes among others tests for related substances and assay (HPLC), residual solvents (GC), bacterial endotoxins, microbial limits, water (Karl Fischer), identification (IR, HPLC) and specific rotation.
All specifications are considered adequate and the analytical procedures have been satisfactorily described and validated in accordance with the ICH guidelines. Minor amendments to validation report for the active substance were requested. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been presented, supporting the predefined active substance specifications.

- Stability

Stability results have been provided for four validation lots of treprostinil, manufactured by the active substance manufacturer proposed for registration. Samples have been stored six months at 25°C/60% RH (accelerated) conditions and twelve months at 2-8°C (longterm) conditions. Key attributes tested during stability studies are appearance, water content, assay, and chromatographic purity. Based on

these data, an appropriate retest period was proposed for storage under the proposed storage conditions and in the proposed packaging. The stability testing of these four batches was proposed to be continued, and one batch would be put annually on a long-term stability program.

Medicinal Product

The medicinal product is an aqueous solution for inhalation that is to be administered by a portable ultrasonic nebuliser. The sodium salt of treprostinil is formed *in situ* during the formulation of the medicinal product. Treprostinil nebuliser solution is aseptically filtered and packaged into blow-fill-seal ampoules with nominal fill volumes of 2.9 ml. The filled ampoules are further packaged into foil pouches with 4 and 28 ampoules per pouch. As excipients known pharmacopoeial substances are used as osmotic agent, buffering agent, solvent (water for injections), and acid and base for pH adjustment.

- Pharmaceutical Development

As treprostinil nebuliser solution is an aqueous solution for inhalation, the pharmaceutical development focussed on obtaining a preservative free treprostinil formulation.
Treprostinil is practically insoluble in water therefore the treprostinil sodium salt is used in the formulation. Since this salt is difficult to handle (the solid is deliquescent), the sodium salt of treprostinil is formed in situ during the formulation of the medicinal product. The excipients for the treprostinil nebuliser solution are all of compendial quality.
During the development the pH and osmolality have been optimised in line with the Ph. Eur. monograph on preparations for inhalation. Treprostinil nebuliser solution is aseptically filtered and packaged into blow-fill-seal ampoules with nominal fill volumes of 2.9 ml. The filled ampoules are further packaged into foil pouches. Extractables and volatiles testing, and leachables testing have been performed, showing the compatibility between the container-closure system and the nebuliser solution.

The applicant investigated the risk of lung infections by fungi as introduced by fungi in the nebulizer apparatus. Less convincing is the argument that all parts of the nebulizer equipment are sterile and packaged in ISO 8 environment, because the daily cleaning procedure will reduce this initial clean situation of the nebulizer. Stronger is the argument that both air filters will be replaced on a daily basis (and these filters remove >99% of all aerosol particulates). It is reasonable to assume that no additional contamination by fungi will be initiated due to imperfect cleaning procedures performed by users or medical care professionals. Based on this, it is accepted that by all precaution measures taken (renewed cleaning instructions, daily replacement of the two air filters) the risk of infectious mould contamination and subsequent pulmonary infection from the use of Tyvaso with this nebuliser, is considered very low.

- Manufacture of the Product

The nebulizer solution filled ampoules (0.6 mg/ml, 2.9 ± 0.2 ml per ampoule) are manufactured by straight-forward pharmaceutical procedures involving preparation of the bulk nebulizer solution, sterilizing filtration (through double 0.1 µm filters), filling and sealing of the ampoules (by the blow-fill-seal procedure), and packaging of the filled ampoules. Also equipment cleaning and sterilizing (steam sterilization-in-place) procedures are described. All manufacturing stages have been described in detail and adequate in process controls are in place. An extensive amount of validation reports is present in the dossier. Validation protocols and reports are provided to describe the various validation activities performed. The provided full package on process validation aspects is considered to be adequate. The manufacturing process has been demonstrated to be robust and to produce a finished product of the desired quality within the agreed finished product specification.

- Product Specification

The medicinal product specification includes tests for appearance, identity, assay and related substances, pH, particulate matter, osmolality, fill weight, and sterility. All analytical methods included in the specification have been satisfactorily described and validated. Several questions have been asked regarding specification limits, both for release and shelf life. Comparative analytical

results between the test methods was requested. Batch analysis results comply with the proposed medicinal product specifications and confirm consistency & uniformity of manufacture and indicate that the process is under control.

- Stability of the Product

Stability studies have been conducted on five batches of treprostinil nebuliser solution, 0.6 mg/ml, in low-density polyethylene (LDPE) ampoules. Up to 36 months long-term stability data (25ºC/40% RH) and up to 6 months accelerated stability data (40ºC/20% RH) have been submitted. In addition, up to 6 months intermediate stability data (30ºC/35% RH) was submitted.
Two stability batches were manufactured at fullscale commercial batch size while the remaining three batches were manufactured at 1/5th of the commercial batch size. The parameters investigated were: appearance, pH, particular matters, sterility, identification (HPLC, IR and chiral HPLC), assay (HPLC), degradation products, weight loss, chiral purity (HPLC) and leachables. All stability results met the pre-defined end of shelf-life specifications. The shelf life and storage conditions proposed by the applicant are considered acceptable based on the stability data provided.

From chemical pharmaceutical point of view the proposed product – including the proposed type of nebuliser – can be accepted under the condition that the applicant resolves a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product, either during this procedure or post-approval.

III.2 Non clinical aspects

Remodulin Solution for Infusion has been approved in most of Europe in 2005 for subcutaneous or intravenous infusion to treat pulmonary, arterial hypertension. In that Mutual Recognition procedure, France was reference member state and the Netherlands was one of the concerned Member States (FR/H/278/01-04). Since Remodulin contains the same active substance (treprostinil sodium), the same GLP-compliant toxicology studies have been used for the present application for Tyvaso. In the assessment of these preclinical studies, the assessment of the reference member state has been followed. For Tyvaso, additional studies have been performed. The results of these studies have been evaluated below.

Pharmacology

Primary pharmacodynamics
In a haemodynamic study in anaesthetised rats, intravenous administration of UT-15C, the diethanolamine salt of treprostinil, had identical activity and potency in causing dose-dependent fall in MAP following bolus intravenous administration when compared to the parent molecule UT-15. All metabolites evaluated had very much reduced activity compared to UT-15C.
The effect of treprostinil and its metabolites on mean arterial blood pressure and heart rate has been evaluated following intravenous administration.

Secondary pharmacodynamics
The secondary pharmacodynamic effects of Tyvaso® are described under safety pharmacology.

Safety pharmacology
Treprostinil, at concentrations up to 100 µM (39,052 ng/mL), produced no inhibition of the hERG tail current in HEK293 cells transfected with hERG cDNA, whereas terfenadine, the positive control, inhibited the hERG current for 85.2 ± 2.7%. The highest concentration of treprostinil tested (100 µM) is approximately 8000 times greater than the mean Cmax in patients produced by an inhaled 45µg dose of treprostinil.
In isolated rabbit Purkinje fibres, treprostinil did not prolong action potential duration at concentrations of up to 300 µM (117, 156 ng/mL), the highest concentration tested. This concentration is approximately 234,000 times greater than the mean Cmax in patients produced by an inhaled 45-µg dose of treprostinil. Although treprostinil did slightly shorten action potential duration at higher

concentrations, its shortened action potential duration in this assay does not imply a QT prolongation risk in patients.
Intravenous bolus injection of treprostinil to conscious radiotelemetry-instrumented dogs caused an initial drop in arterial blood pressure and compensatory increase of heart rate at all doses during the first hour after dosing, although both differences were only significant for 200 µg/kg treprostinil when compared to the control group. Both effects were considered normal since they reflect the drug's primary pharmacodynamic activity. The significant shorting of PR and RR interval following 200 µg/kg treprostinil was considered reflective of the observed changes in heart rate following 200 µg/kg treprostinil. However, for 200 µg/kg treprostinil, the initial drop in arterial blood pressure was followed by an excessive and thus adverse increase in blood pressure for up to 6 hours.
Although treprostinil (2 and 200 µg/kg) induced transient atrioventricular (AV) blocks in 2 out of 4 dogs in a safety pharmacology study evaluating the cardiovascular effects of treprostinil following intravenous administration to conscious dogs, treprostinil (up to 600 ng/kg/min IV or SC, up to 1 mg/kg/day PO or up to 2.4 mg/kg/day by inhalation) did not induce AV blocks (or other ECG changes) in 8 additional studies (safety pharmacology, repeated dose and pharmacokinetic studies). Based on these findings, it is concluded that treprostinil does not affect atrioventricular conductivity.
Respiratory rate and minute volume remained decreased for duration of aerosol exposure. However, they returned to baseline and control levels within 24 hours following treatment.

Pharmacodynamic drug interactions
For Tyvaso® no additional studies evaluating its pharmacodynamic drug interactions have been performed.

Pharmacokinetics
The additional pharmacokinetic studies via the inhaled route in rats showed that treprostinil concentrations (AUC) increased in an approximate proportional manner with increasing dose. $AUC_{0-\infty}$ values were low following inhalation of treprostinil compared to oral and i.v. administration. Based on the AUCs provided following i.v. administration (449.6 ng/ml*h in females and 717.3 ng/ml*h in males), it can be estimated that the bioavailability in rats is about 5%, which indicates that most of the drug does not reach the systemic circulation. Apparent clearance values were high at all dose levels after inhalatory administration and the terminal elimination phase half-life was relatively short (19 - 90 minutes). Compared to the other routes investigated in rats, the inhaled route demonstrated a very fast absorption phase, short half-life probably due to fast tissue distribution phase, low systemic exposure and high apparent clearance. Based on the short half-life following inhalation and the resulting low plasma levels, there are no concerns about accumulation in plasma of treprostinil via systemic exposure. Following oral dosing, plasma C_{max} values of 27 and 30.4 ng equiv/ml occurred at 0.5-1 hours in male rats and 2-6 hours in female rats; plasma levels of radioactivity declined slowly but were still detectable 24 hours post dose. The apparent bioavailabilities were similar for males and females (45.3 and 46.4%).
The applicant did not provide information on concentrations of treprostinil in the lungs following inhalation and was requested to address this issue.
The target tissues after inhalation administration have been addressed clinically. Although no specific non-clinical studies were performed, Phase I and Phase III trials performed in more of 400 patients receiving treprostinil by inhalation administration have stated that 79.42% of treprostinil administered was deposited in the lungs, and 20.58% was deposited in the oropharyngeal cavity. Therefore, the question about a possible accumulation of treprostinil in the lungs has been solved.
The tissue distribution of radioactivity was examined in the rat after administration of a single 6-hour subcutaneous infusion of [^{14}C]-treprostinil. The tissues with the highest C_{max} were liver, small intestine, non-pigmented skin, kidneys, pigmented skin, and large intestine. The half-lives in tissues ranged from 1.66 hours (thyroid) to 478 hours (reproductive fat). Data suggested that treprostinil does not bind to melanin. The mean protein binding of treprostinil in human plasma was 91%.
The metabolites of treprostinil have been identified following oral and/or subcutaneous administration. The applicant was also requested to provide information on the metabolites formed following inhalation of treprostinil. The applicant states in the Responses Document that treprostinil administered by inhalation follows the same systemic metabolic fate as oral or subcutaneous administration.

This argumentation is based in the fact of the absolute systemic bioavailability for inhaled treprostinil and that the CYP450 enzymes involved in the metabolism of treprostinil are either not detectable or evident in small quantities in the lung tissue. This provides evidence that the contribution of lung metabolism to the elimination is minimal.
According to this argumentation, it can also be considered that the inhaled treprostinil follows the same metabolic pattern than the treprostinil administered by oral or subcutaneous route.
The metabolic profile of treprostinil was investigated in bile collected from rats given single, oral and i.v. 200 µg/kg doses of [^{3}H]-treprostinil. Data suggested an extensive metabolism to more polar compounds. The chemical data and the in vivo data from the rat, dog and human confirm that treprostinil is a chirally pure drug substance and does not undergo chiral inversion in vivo. Enzyme inhibition and induction studies have been conducted on treprostinil. In rats, no inducing effect on hepatic microsomal protein, total cytochrome (CYP) P450 content or on the activities of the isoenzymes - CYP1A, CYP2B, CYP3A were observed. In an in vitro study, treprostinil had no inhibitory effect on the activities of six P450 isoenzymes using human hepatic microsomal fractions.
In the rat, elimination half-lives by the i.v. and oral routes were 9.7 and 3.6 for males, respectively, and 14 and 7.4 hours for females. Clearance values were similar after oral and i.v. administration but were slower in males (440 and 441 ml/hr/kg) compared with females (276 and 272 ml/hr/kg). In rats and dogs, the great majority of radiolabelled compound is excreted in the faeces (65-82%). In contrast, the urine is the main route of excretion in humans (~ 80%) with only 13% of the dose recovered in faeces. In the study in rats, the bile was the major route of excretion accounting (67.1% of an oral dose and 91.1% of an i.v. dose).

Toxicology

Remodulin contains the same active substance as Tyvaso (treprostinil sodium). For this reason, GLP-compliant toxicology studies carried out previously for Remodulin authorisation have been used for the application of Tyvaso. These studies include single dose studies and repeated-dose toxicity studies up to 13 weeks following administration by oral gavage, continuous intravenous infusion, continuous subcutaneous infusion, reproductive and developmental toxicity studies by subcutaneous infusion, and studies on genotoxicity and local tolerance. For marketing authorization of Tyvaso additional single dose and 7-day and 3-months repeated dose toxicity studies of treprostinil sodium by inhalation were performed in rats and dogs. The formulation used in these inhalation toxicology studies was the same as the intended marketed formulation. The main findings of these studies have been evaluated below.

<u>Single dose toxicity</u>
The single dose studies carried out previously for Remodulin authorization showed a low oral and intravenous acute toxicity of treprostinil, in mice and rats. This was also found in dogs after subcutaneous administration. Clinical signs included tremor, lacrimation and irregular breathing. In addition, discolouration of the extremities occurred in rats. Hypoactivity and gastrointestinal effects (vomiting, liquid faeces) were observed in dogs. In both species darkening/congestion of the lungs was observed at necropsy. Observations are consistent with the pharmacological effects of the compound after inhalatory administration in rats, laboured breathing, respiratory rate increases and weakening. In dogs, the most significant observations were skin redness and decreased activity. The maximum tolerated dose after single oral administration was considered to be about 0.7 mg/kg/day in rats and 3 mg/kg/day in dogs.

<u>Repeated-dose toxicity</u>
The main effects observed after continuous subcutaneous or intravenous infusion toxicity studies, previously included in the Remodulin dossier, were swelling at the infusion site, redness of the nose, pinnae and paws, decreases in body weight and food consumption and haematological changes (increases in mean white blood cell counts).
Four new GLP-pivotal studies have been carried out for Tyvaso application: 7-day and 3-months repeat dose inhalation toxicity studies in rats and dogs.
In rats, drug-related findings included irritation of the respiratory tract (nasal cavity: goblet cell hyperplasia; larynx: squamous metaplasia; lungs: macrophage accumulation, haemorrhage) and effects on the heart (myocardial degeneration/fibrosis), testis (tubule degeneration, reduced epididymal sperm) and adrenals (hypertrophy of the cortex). Based on exposure intensity at the LOAEL in rats

(2.3 – 150 h*µg/L) and in that human (2.5 h*µg/L), there is no safety margin for the irritation of the respiratory tract for human. Based on systemic exposure (AUC values), there is also no safety margin for the effects in the heart, testis and adrenals. All these effects were not observed after oral administration or after continuous subcutaneous or intravenous infusion. As such, these are new toxicological findings not reported previously for Remodulin. In addition, in view of the low bioavailability after inhalation in the rat studies (about 5%), as compared to that after oral administration (30-47%), or after continuous subcutaneous (30%) or intravenous infusion (100%), these effects are not expected.
In dogs, the LOAEL for a dose-related irritation of the respiratory tract was considered to be 6 h*µg/L. At this exposure intensity, which delivered an estimated dose level of 110 µg/kg/day, a lung haemorrhage was observed in one of the three females examined. In the heart, microscopic haematocysts were observed in males and females. A slight reduction in relative heart weight was observed only in females at ≥23 h*µg/L (~320 µg/kg/day). These effects showed evidence of reversibility during the 4-week recovery period. The irritation of the respiratory tract was not completely disappeared by the presence of slight microscopic haemorrhages in the lungs of females and degenerative changes in the nasal epithelium of males.
The toxicokinetic studies were carried out after inhalation administration in rats and dogs as part of the 3-month repeat-dose toxicology studies. Based on AUC detected in the different studies there was no drug accumulation. Also, the mean plasma concentration peak after inhalation administration was higher than the observed after subcutaneous and intravenous administration. Animal/ human exposure ratios (based on C_{max}, AUC and local pulmonary exposure intensity) for the pivotal repeated dose inhalation toxicity studies had to be calculated in order to evaluate the potential risk of the toxic effects observed in these studies.

The applicant provides a new 13-week inhalation toxicity study in rats. Systemic drug-related adverse effects included effects on the testis (o.a.tubule degeneration), prostate (decreased weight), thymus and spleen (lymphoid atrophy), adrenals (slight hypertrophy of the zona glomerulosa). These effects were not observed at 34.1 µg/kg/day. The applicant states the No-Observable-Adverse-Effect-Level (NOAEL) to 34.1 µg/kg/day and the No-Observable-Effect-Level (NOEL) is considered to dose of 2.60 µg/kg/day. This study with its more refined dosing established a higher NOAEL with a safety margin of approximately 44-55X for C_{max} and 50X for AUC.
However, at doses up to 34.1 µg/kg/day, the proposed NOAEL, three animals were found dead. Although the applicant considered these deaths as incidental and not to be of important toxicological significance, ten animals died at higher doses and these last deaths occurred in a dose-related manner and a relation to treatment seems likely. Based on these findings, the proposed NOAEL of 34.1 µg/kg/day is not agreed. The NOAEL would therefore be lower, 2.60 µg/kg/day, so the safety margin for this NOAEL would be now 4.25X for C_{max} and 3.6X for AUC, about 10 times lower than that the applicant proposed. Therefore, there is a low safety margin for effects on the respiratory tract in human and they can not be considered sufficient to discard a potential risk of irritation of the respiratory tract.
The issue is considered solved pending on the inclusion in the Risk Management Plan a reference to the potential effects.

<u>Reproduction toxicity</u>
As shown for Remodulin, treatment in both the rat and rabbit by continuous subcutaneous infusion has produced no adverse effects on any developmental parameter measured, only maternal toxicity was detected. Furthermore, in the prenatal and postnatal development, including maternal function, the results showed that after F1 generation exposition to treprostinil there were no alterations in gestational length, number of implantation site per litter, or number of lost post-implantation. Also in the F2 generation no development and growth variations were observed. For Tyvaso, no additional reproduction toxicity studies have been performed. Nevertheless, the 3-month inhalation repeated-dose study in rats detected an increased incidence of testis degeneration, reduced epididymal sperm and atrophy of the seminiferous epithelium and to a less extent also in dogs. The applicant states that the possible explanation is that peak systemic exposure in males was greater when treprostinil was given by inhalation than when it was given by continuous infusion (C_{max}=563.7 ng/ml and C_{ss}= 24 ng/ml respectively). Studies of the excretion of treprostinil in milk have not been conducted.

Taking into account that the applicant has planned to perform a single 2-year carcinogenicity study in rats, the effect of treprostinil on male fertility could also be assessed. In the same way, the results of other carcinogenicity studies by a different administration route are of interest to help in evaluating of the clinical relevance of the findings on male reproductive organs.

Genotoxicity

An ICH-recommended 3-test battery of genotoxicity studies was submitted in the Remodulin applications which included an Ames assay, a mouse lymphoma assay, and a bone marrow micronucleus assay in rats dosed via continuous subcutaneous infusion. Treprostinil sodium was negative for genotoxic potential in all studies. No additional genotoxicity studies have been conducted to support the current marketing application for Tyvaso. This is agreed.

Carcinogenicity

For the application of Remodulin no carcinogenicity studies have been conducted. The carcinogenic potential of treprostinil sodium will be evaluated in a single 2-year carcinogenicity study in rats dosed via nose-only inhalation. No carcinogenicity study in a second species is planned. Dependent on the outcome of single 2-year carcinogenicity study in rats, this is agreed. Follow-up Protocol Assistance was given regarding this study (EMEA/CHMP/SAWP/258052/2007). The CHMP considered that it may be acceptable to complete the carcinogenicity studies after marketing approval. The following conditions should be fulfilled:

- Treprostinil diethanolamine should show a clinical benefit for the PAH patient population
- The MAA should submit the status of the single inhalation carcinogenicity study in rats at the MA filing, communicate any new fact occurring unexpectedly in the study after filing.
- If available, any final or interims report for the Treprostinil carcinogenicity studies ongoing by a different route of administration are of interest also for the inhaled formulation and should be submitted with the marketing application or as soon as they are available.

This position was endorsed in the minutes of the Agency pre-submission meeting for treprostinil sodium held on 30th May 2008.

Local tolerance

A local tolerance test was carried out for Remodulin application. Thus subcutaneous administration of treprostinil to beagle dogs at doses of 100 or 200 ng/kg/min induced lesions around the infusion site. Nevertheless, *in vitro* treprostinil did not produced haemolysis in human or dog erythrocytes (at 20 µg/ml), or precipitation of human and dog plasma proteins (at 1 mg/ml). No specific local tolerance study has been conducted after inhalation administration. However, the lack of this study is acceptable as in the repeat dose studies following inhalation route, the local tolerance have been assessed. Signs of local irritation in the respiratory tract were observed.

Immunotoxicity

The antigenicity and immunotoxicity of treprostinil sodium have not been studied. However, based on the accumulation of macrophages in long observed in repeat-dose toxicity study, it was requested to be further addressed.

In the Responses Document, the applicant states that in the treprostinil inhalation toxicity study, macrophage accumulation in the lung is considered a normal pulmonary adaptive response to an irritant and demonstrates appropriate immune response in the lung, as it is reported in the literature provided. Also it is established that there was no evidence of antigenicity, immunotoxicity or immunosuppression locally in lung tissue or systemically based on clinical pathology, bone marrow exam, or histological evaluation of a full list of tissues including lymphoid tissue systemically or in the respiratory system (BALT- bronchus-associated lymphoid tissue) following administration of inhaled treprostinil. The issue is considered solved.

Dependence

Treprostinil is not considered a CNS-active medicinal product therefore the lack of dependence studies is considered acceptable.

Haemolysis
For the marketing application of Remodulin, treprostinil has been tested in vitro for protein flocculation with type O human plasma and canine plasma and also for in vitro haemolysis using a 50% suspension of type O human erythrocytes and a 50% suspension of canine erythrocytes. Treprostinil produced neither haemolysis nor precipitation of plasma proteins. For Tyvaso, no further studies are needed.

Impurities
The impurity profile of treprostinil in Tyvaso is identical to that in Remodulin. There are eight specified impurities in treprostinil sodium drug substance (1AU90, 2AU90, 97 W86, 3AU90, Methyl-treprostinil-ester, Ethyl Ester, 750 W93, and 751 W93). The impurity 2AU90 was below the ICH qualification threshold (0.15%).The rest of impurities were qualified in the repeat-dose subcutaneous toxicity and genotoxicity studies submitted previously for Remodulin application. However, in the batches used in the inhalation studies submitted for the Tyvaso application the impurities profile was below the specified limit for all impurities, but taking into account that the toxicity studies has been carried out with the same the formulation as the intended for marketing, the toxicity of the impurities is not a concern.

Biocompatibility tests
Several parts of nebulizer to be used clinically, including the Nebu-Tec plastic (APEC 1745), the medicine cup (PETG) and sealing ring (EPDM) have been tested for biocompatibility, including cytotoxicity, intracutaneous reactivity, sensitisation, and genotoxicity according ISO 10993. The results of these tests showed no concerns.

Environmental Risk
The applicant has submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline (CHMP, 2006). The Applicant has provided a $PEC_{surfactewater}$ calculation, resulting in a $PEC_{surfacewater}$ of $1.44 * 10^{-6}$ mg/L. This value is below the action limit of 0.01 µg/L. The Applicant reports a solubility of treprostinil sodium of >10 g/L, a pKow = 1.5 (pH 7) and a pKa = 4.5. A valid study determining log K_{ow} (ion corrected; i.e. for the neutral molecule) according to OECD 107 should be submitted. If a log K_{ow} of >4 is anticipated, the slow stirring method should be used (OECD 123). The PBT assessment can not be completed.

III.3 Clinical aspects

Pharmacokinetics

Pharmacokinetics of inhaled treprostinil were established in three single dose studies, the LRX-TRIUMPH BA.001 study was a three-way cross over study in which the bioavailability of oral treprostinil was compared to two doses of inhaled treprostinil. Furthermore, there are 3 clinical studies including pharmacokinetics conducted during the development of Remodulin with SC or IV treprostinil that provide supportive data. Study P01:10 using radio-labelled treprostinil provided additional supportive data. A total of 6 drug-drug interaction pharmacokinetic studies were performed with of oral treprostinil diethanolamine (UT-15C) or subcutaneous treprostinil to healthy human volunteers. Additionally, a total of 6 *in vitro* studies were performed supporting the pharmacokinetics of treprostinil.

Treprostinil (15AU81, UT-15) is a stable tricyclic benzindene analogue of the naturally occurring prostacyclin, PGI2 (epoprostenol) Tyvaso (treprostinil sodium) 0.6 mg/mL Nebuliser Solution, has been developed as a treatment for pulmonary arterial hypertension (PAH) Tyvaso is administered using the ultrasonic nebulizer, Optineb -ir, manufactured by NebuTec. REMODULIN (treprostinil sodium) Solution for Infusion has the same formulation as Tyvaso except for the preservative metacresol.

Absorption
Mean estimates of the absolute systemic bioavailability of treprostinil after inhalation were 64 % (18 µg) and 72% (36 µg). The mean C_{max} for the 18 µg and 36 µg doses were 354 pg/mL and 698 pg/mL, respectively, with a Tmax of 0.15 hr. Treprostinil remained detectable in the plasma for up to 3.5 hours after inhalation. The mean AUC_{inf} for the 18 µg and 36 µg doses were 0.26 and 0.61 hr·ng/mL, respectively. The absolute bioavailability was 70%. This is relatively high for inhaled drugs in general. Probably, the duration of the 60 min infusion compared to the inhalation leads to a relatively low AUC as treprostinil seems to be metabolised at a fast rate. No food interaction studies were performed; this is acceptable for a product using this route of administration. Absorption via the intestines is expected to me negligible as 12 to 20 % of the dose is expected to be available in the stomach and the intestines and oral bioavailability is estimated by the applicant to be 12%.

Distribution
The steady-state volume of distribution (Vss) for treprostinil sodium administered by intravenous infusion to healthy human volunteers is approximately 0.18 L/kg. The apparent volume of distribution (Vz/F) for inhaled treprostinil sodium was between 45 – 70 L in healthy adult volunteers (with CV ranging from 40 - 100%). This is roughly comparable with the Vz/F found after s.c. administration, being 1.11 and 1.22 l/kg in studies P01:07 and P01:08. Protein-binding is approximately 91% independent of concentration.

Elimination
Studies of treprostinil sodium administered by subcutaneous or intravenous infusion have shown that the elimination of treprostinil is biphasic, with a terminal elimination half-life of approximately 4 hours. Given the relatively low systemic plasma concentrations achieved following treprostinil inhalation, a multi-compartment model cannot be applied and, therefore, the terminal elimination half-life cannot be readily estimated. The apparent half-life for treprostinil is ranged from 0.54 to 0.76 hours.
The apparent clearance (Cl/F) for inhaled treprostinil sodium was between 60 – 90 L/hr in healthy adult volunteers (with CV ranging from 25 - 100%). This is somewhat increased compared with the Cl/F observed after s.c. administration, which ranged from 586.2 to 646.9 ml/h/kg.
After subcutaneous infusion, it was shown that renal excretion was the main route of elimination with 75.6% of the radioactivity being eliminated 8 hours after the infusion. Total recovery within 224 hours after the infusion was 92.2% (urine 78.6%, faeces 13.4%). Only 3.7% of the drug was excreted unchanged.
Only 3.7% of the drug was excreted unchanged indicating that renal excretion plays a minor role in the metabolic fate of treprostinil in humans. It is likely that most of the dose was metabolised by the liver before excretion, with the cytochrome P450 isoenzyme 2C8 being primarily responsible (see also below). Five metabolites were detected in the urine, ranging from 10.2% to 15.5% of the dose administered and accounting for a combined total of 64.4%. Four are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuro-conjugated derivative (treprostinil glucuronide). The metabolism pattern was studied after subcutaneous administration.

General pharmacokinetics
Inter-conversion is no issue as treprostinil is a chirally pure drug substance and does not undergo chiral inversion in *vivo*. The applicant should discuss the consequences of possible genetic polymorphism on the pharmacokinetics of treprostinil focusing on CYP 2C8. Inhaled treprostinil shows dose linear pharmacokinetics in a dose range of 18-90 µg, this comprises the therapeutic dose-range. No pharmacokinetics after repeated doses of inhaled treprostinil were determined. As plasma concentrations of treprostinil become undetectable in most healthy volunteers and patients with PAH approximately four hours following a single inhaled dose it is not likely that any accumulation will occur. Inhaled treprostinil has moderate inter-individual variability with a CV ranging between 20-67%. No data is available with regard to intra-individual variability. Pharmacokinetics in patients with PAH seems to be comparable with pharmacokinetics in healthy volunteers, based on C_{max} and T_{max}.

Special populations:
Renal excretion is known to be a major route of elimination for treprostinil metabolites. However, this is unlikely to be of clinical significance, given that less than 5% of a treprostinil dose is excreted

unchanged in the urine and the metabolites have been shown to have minimal biological activity. Caution should be advised when inhaled treprostinil is used in patients with renal impairment.
The plasma clearance of treprostinil was reduced by 61% and 80%, respectively, in patients with mild and moderate hepatic dysfunction, compared with healthy volunteers Treprostinil pharmacokinetics are not influenced by gender. Therefore, the initial dose of inhaled treprostinil should be up-titrated with caution in patients with hepatic impairment, to reduce the risk of dose-dependent adverse effects.
The influence of race on the pharmacokinetics of treprostinil was not formally investigated, making a reliable conclusion difficult. However, an additional analysis performed by the applicant showed that the influence of race on pharmacokinetics is small. Obesity influences the pharmacokinetics of treprostinil, with reduced clearance compared to non-obese patients. We agree with the applicant that as treatment with inhaled treprostinil is started at a low dose (18 µg QID) and then up-titrated in accordance with clinical response and tolerability, there should be no requirement to alter this dosing strategy for obese patients.
Elderly patients seem to have a reduced clearance. However the clinical significance is not clear. However, the CHMP agrees that no dose adjustments are necessary in elderly patients as treatment with inhaled treprostinil is started at a low dose (18 µg QID) and then up-titrated in accordance with clinical response and tolerability.

Interactions:
Treprostinil shows *in vitro* no potential to inhibit cytochrome P450 (CYP) isozymes 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Moreover, treprostinil does not induce hepatic microsomal proteins, total CYP content or the isozymes 1A2, 2B6, 2C9, 2C19 and 3A4. As CYP2C8 is known to play a major role in the metabolism of treprostinil, drugs that either inhibit or induce the activity of this enzyme may alter the pharmacokinetic profile of treprostinil. Treprostinil does not significantly affect the plasma protein binding of clinically relevant concentrations of warfarin and digoxin.
The potential for drug interactions with treprostinil was evaluated *in vivo* with oral treprostinil diethanolamine. The plasma levels attained in these studies were higher than the plasma levels observed for inhaled treprostinil at clinical levels. Oral treprostinil was co-administered with bosentan, sildenafil, gemfibrozil, fluconazole, and rifampicin in drug-drug interaction studies to determine if a pharmacokinetic or pharmacodynamic interaction exists. Two additional drug interaction studies (warfarin and acetaminophen) plus a multivariate analysis of two Phase III trials were also conducted to determine the potential for drug interactions with treprostinil. Co-administration of treprostinil with bosentan or sildenafil resulted in no pharmacokinetic interaction. Co-administration of treprostinil with gemfibrozil (CYP2C8 inhibitor) resulted in a pharmacokinetic interaction with a 92% and 96% increase in AUC_{inf} and C_{max}, for treprostinil, respectively. When co-administering treprostinil with gemfibrozil or other known inhibitors of CYP2C8, a dose reduction is most likely necessary to account for the increased concentrations observed with co administration of treprostinil with these types of agents. Treprostinil has no clinical significant interaction with fluconazole (CYP2C9 inhibitor). No dose adjustments for treprostinil are necessary with co-administration of treprostinil with fluconazole or other CYP2C9 inhibitors. Co-administration of treprostinil with rifampicin (CYP2C8/2C9 inducer) resulted in a pharmacokinetic interaction with a 22% and 17% decrease in AUCinf and Cmax, for treprostinil, respectively. In conclusion, the potential for drug interactions with treprostinil via any route of administration are limited to agents that are known inducers or inhibitors of CYP2C8, as this isozyme is primarily responsible for treprostinil's metabolism.

Pharmacodynamics

The so-called thorough QT study was a double-blind, randomized, parallel group trial using a clinical (54 µg) and supra-therapeutic dose (84 µg) compared to placebo and moxifloxacin (400 mg, a positive control) in healthy controls. The choice of the 84 µg treprostinil dose as supratherapeutic is based on preliminary studies indicating that a dose of 90 µg was not tolerated in healthy volunteers due to adverse events. Regarding the actual results, it can be seen that neither treprostinil (54 or 84 µg) nor the positive control (moxifloxacin 400 mg) produced any significant effects on QTcF. This indicates that the study was not sensitive to show any relevant QT prolongations. The current results are inconclusive. However, considering that no adverse QT events are reported with treprostinil SC, which is expected to give a higher systemic exposure than treprostinil inhalation and as pre-clinical data do not indicate an adverse effect for treprostinil on cardiac repolarisation, the issue is considered solved.

Study LRX-TRE-INH-0007 investigated the pharmacodynamic interaction of treprostinil inhalation on top of sildenafil in sildenafil-naïve patients or patients administered sildenafil for 3 months on haemodynamic parameters. The choice of 50 mg sildenafil is not justified considering that the recommended dose is 20 mg t.i.d, however, it was probably based on clinical practice of the investigators (not company sponsored study). The study showed a definitive additive response of treprostinil on top of sildenafil. It is postulated that the effect may have even been greater with lower doses of sildenafil as an additive effect may be more readily detected. Efficacy was more pronounced in the group chronically administered sildenafil than in the sildenafil-naïve group. No plausible explanation was given.

Clinical efficacy

In support of the clinical efficacy of treprostinil Inhalation, two company-sponsored studies are submitted: TRIUMPH and its long term open-label extension study. The target dose, concentration and mode of nebulisation in the pivotal study were based on a series of pilot clinical investigator-initiated studies. Reference is also made to Remodulin SC which is approved in several European countries through an MRP FR/H/278/01.

Dose finding studies

The dose selection in the company sponsored studies is based on 4 investigator-initiated studies for which abbreviated study reports were submitted. Studies LRX-TRE-INH-0001, LRX-TRE-INH-0002, and LRX-TRE-INH-0004 were collectively published by Voswinckel et al., 2006[1] and the current assessment is based on this publication as it integrates these three studies. Study LRX-TRE-INH-0003 is presented separately.

Studies LRX-TRE-INH-0001, LRX-TRE-INH-0002, and LRX-TRE-INH-0004 were conducted on a total of 123 patients by means of right heart catheterization. Haemodynamic data are an acceptable endpoint for the dose finding studies; with the pulmonary vascular resistance PVR considered to be a valid marker for agents used in PAH.

LRX-TRE-INH-0001 is a randomized crossover study comparing the acute haemodynamic effects and the systemic side effects of inhaled treprostinil (TRE) with inhaled iloprost (ILO),
1 a = 7.5 µg ILO versus 7.5 µg TRE,
1 b = 7.5 µg ILO versus 15 µg TRE (6-min inhalation time),
1 c =7.5 µg ILO versus 15 µg TRE (3-min inhalation time).
The choice of iloprost as the active comparator is a good choice allowing for good characterization of the efficacy of treprostinil. However, the administered dose is 50% higher than that recommended. It would have been more relevant to use the 5 µg dose. The cross-over design minimizes possible inter-patient variability, but with only 1 hour in-between the administrations, a carry-over effect could not be ruled out.

LRX-TRE-INH-0002 is a randomized, open-label, single-blind, placebo-controlled study aiming to describe the pharmacodynamic and pharmacokinetic effects of inhaled treprostinil at a well-tolerated dose (30 µg) and to explore the highest tolerated single dose: a = placebo inhalation, b = 30 µg TRE, c = 60 µg TRE, d = 90 µg TRE, e = 120 µg TRE.

LRX-TRE-INH-0004 is a randomized, open-label, single-blind study. The primary objective was to explore the shortest possible inhalation time for a 15-µg inhaled treprostinil by using higher concentrations of TRE (metacresol-free):
a = 18 pulses of 100 µg /ml TRE,
b = 9 pulses of 200 µg /ml TRE,
c = 3 pulses of 600 µg /ml TRE,

[1] Voswinckel, et al.: Favorable Effects of Inhaled Treprostinil in Severe Pulmonary Hypertension Results From Randomized Controlled Pilot StudiesJ Am Coll Cardiol 2006;48: 1672–81

d = 2 pulses of 1,000 µg /ml TRE,
e = 1 pulse of 2,000 µg /ml TRE.

Results of the first study LRX-TRE-INH-0001 show that both 7.5 and 15 µg treprostinil have comparable effects to iloprost 7.5 µg on the pulmonary vessels. The main differences were in the onset of action (significantly delayed in case of treprostinil) and the duration of action: returns to baseline in case of iloprost and extended beyond the 1 hour observation with treprostinil (Fig E1). However the favourable effects on the pulmonary circulation were not translated into an increase in CO that was observed with iloprost. On the other hand, reduction in SAP and other systemic side effects (transient flush, headache) were reported only with iloprost possibly indicating more systemic absorption than with treprostinil.

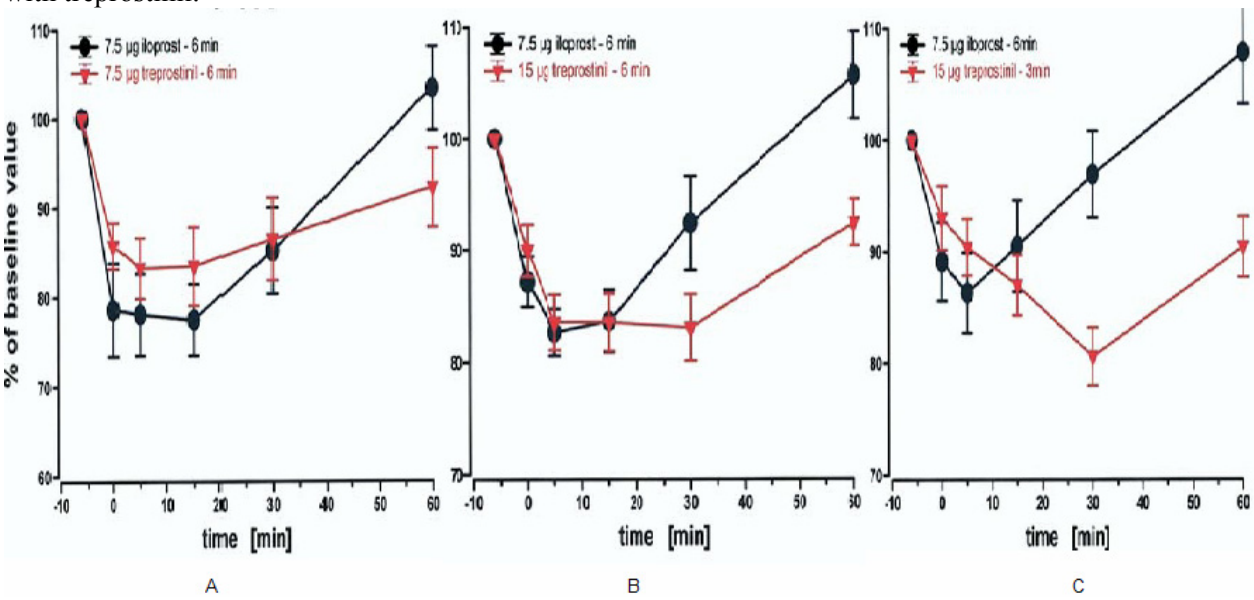


Figure E1: PVR response to inhalation of iloporost 7.5 µg in 6 minutes versus treprostinil A. 7.5 µg, B. 15 µg in 6 minutes or C. 15 µg in 3 minutes

Rapid administration (3 min) was associated with a more delayed maximum response accompanied with fewer fluctuations in SAP. Many variables could have influenced the haemodynamic response e.g. dose, duration or PH aetiology. Importantly, the administered treprostinil in this study is different from that used in the pivotal study in that in the latter it was administered as mesocresol-free preparation and in the pulsed mode which is more accurate according to the applicant. The submitted SPC currently contains relevant information regarding use. However further patient and prescriber education is necessary to ensure better administration. This should be addressed in the Risk Management Plan (RMP). The initial dose of 18 µg in TRIUMPH study appears acceptable based on the current results.

In the second study LRX-TRE- INH-0002, doses of 30, 60 and 90 µg exerted comparable haemodynamic effects, but only the latter 2 doses resulted in sustained beneficial effects beyond three hours. There was no associated increase in CO (Fig E2).

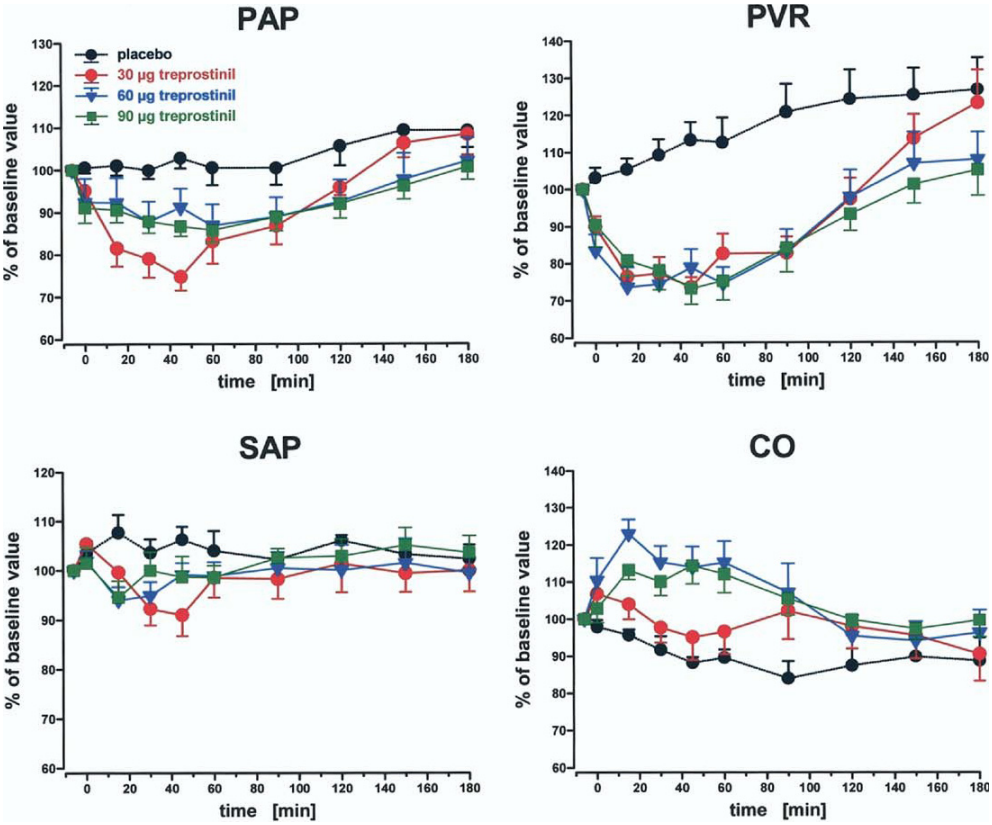


Figure E2: Pulmonary arterial pressure PAP, pulmonary vascular resistance PVR, systemic arterial pressure SAP and cardiac output CO following placebo treprostinil 30, 60 and 90 µg.

The maintenance dose 56 µg administered in TRIUMPH could be justified based on the presented haemodynamic data. This dose can also be defended based on PK data which showed that the 60 µg dose resulted in a Cmax of 1.59±0.17 ng/ml which is comparable to Cmax following treprostinil SC administration of 15 ng/kg/min (1.57±0.31 ng/ml). The clinically efficacious Remodulin SC dose is reported to be 10-20 ng/kg/min.

In the third study LRX-TRE-INH-0004, changing the inhalation time by using different concentrations of treprostinil (up to 2000 µg /ml) did not affect the haemodynamic response. The applicant chose to further use the 600 µg /ml as higher concentrations could be associated with possible variability and shorter duration of action. The choice appears plausible.

In a fourth study LRX-TRE-INH-0003, the effect of different inhalation periods on the haemodynamics was tested. Inhalation over 2 minutes showed better results than over 1 minute.

In **conclusion**, efficacy of treprostinil inhalation on pulmonary haemodynamics was shown to be comparable to that of equivalent doses of iloprost, but of a slower onset and a longer duration of action; possibly associated with fewer systemic side effects. No dose response was adequately shown on the haemodynamic parameters in the dose range tested between 7.5 µg and 90 µg. An advantage of doses of 60 µg and higher would be the associated longer duration of actions. The proposed initial dose of 18 µg appears adequate. The choice of the maintenance dose of 60 µg could be accepted based on haemodynamic data, and PK data showing comparability between the Cmax achieved with this dose and that following 15 ng/kg/min treprostinil SC.

Main Clinical Studies

TRIUMPH I was an international (USA, EU and Israel), randomized, double- blind, placebo-controlled, parallel-group study in NYHA Class III and IV PAH patients who were on stable doses of bosentan or sildenafil for at least three months prior to enrolment. The double-blind treatment phase of the study was 12 weeks in duration. Patients were randomized (1:1) to receive either active treatment

(inhaled treprostinil sodium, TRE) or placebo vehicle, administered by the OptiNeb ultrasonic nebulizer. The first patient was randomized in June 2005 and the last patient completed the double-blind phase of the study in October 2007. (*Please look above for the GCP inspections performed on 2 of the investigator sites*).
TRIUMPH 1 recruited patients on stable doses of bosentan or sildenafil, in distinction to other pivotal PAH studies which mainly recruited treatment naïve patients. This supports the proposed indication as an add-on therapy. Inclusion of patients on background bosentan or sildenafil therapy implies that patients with moderate (bosentan) to severe hepatic impairment (both bosentan and sildenafil) or with baseline liver transaminases > 3 times ULN (bosentan) were already excluded. Currently, the applicant proposes to contraindicate patients with severe hepatic insufficiency, but it is also recommended to propose dose adaptations in cases of mild to moderate liver impairment, in line with the SPC of Remodulin. Otherwise, the inclusion and exclusion criteria are generally in line with those of other pivotal PAH studies.

Drug Administration
Treprostinil was administered by the OptiNeb ultrasonic nebuliser. This nebuliser generates an aerosol cloud of formulation in a pulsatile fashion (each pulse delivers 6 μg of treprostinil). Patients initiated treprostinil at three breaths (18 μg) four times daily (0, 4, 8, and 12 hours). At the discretion of the study investigator, patients could increase their dosing regimen by up to three breaths at each of the four scheduled daily doses to a maximum target of nine breaths (54 μg) four times daily, as clinically tolerated, during the 12 week period. Considering the new nebulizer used, SPC changes are currently proposed by the applicant to improve its utilization, however specific educational material addressing both the patient and the prescriber should also be submitted in the RMP.
It was already commented in the CHMP advice in 2006, that contrary to bosentan, no clear dosage recommendation is given for the sildenafil dose. Although in clinical practice higher doses may be used the licensed recommended maintenance daily dose is three times 20 mg sildenafil. This issue could have impacted the results as will be discussed below.
In the TRIUMPH, the **primary endpoint** was the change in the 6-MWD at 12 weeks, which is the most frequently used primary endpoint in PAH pivotal clinical trials. Though not encouraged to be used as a sole primary endpoint, it allows a good comparison of efficacy among PAH drugs considering the wide experience. However, this is not the case here considering that the recruited patients are already on stable doses of other PAH drugs and that there is limited experience with the 6-MWT in such patients. Among the **secondary endpoints**, clinical outcomes were investigated as time to clinical worsening. The proposed definition is generally in line with the draft guideline EMEA/CHMP/EWP/356954/2008. Although the measurement of time to clinical worsening is strongly encouraged, it is not expected with a trial duration of 12 weeks that a clinically relevant result could be demonstrated in such a short duration.
It must be acknowledged though that the CHMP has already approved these proposed primary and secondary endpoints in a scientific advice EMEA/CHMP/SAWP/266344/2006.

Statistical analysis. For the primary efficacy analysis of change in 6MWD at Week 12 in the ITT population, a non-parametric analysis of covariance (ANCOVA) was performed, with adjustment for baseline walk and disease aetiology. The median difference between treatment groups was determined by the Hodges-Lehmann estimate. The statistical methods are justified. Considering the distribution of the outcome variable, using the median difference between the treatment groups is appropriate.

The applicant requested scientific advice regarding amendment 4, relating to increasing the power of the study from 80% to 90 %, addition of patients on a background therapy of sildenafil and inclusion of interim analysis at 100 and 150 patients. In their advice EMEA/CHMP/SAWP/2663344/2006, the CHMP approved the power increase and the addition of the sildenafil arm provided the study design should allow differentiation between the two background therapies. It was considered important to stratify the analysis by background therapy and by time of inclusion of the additional sildenafil background treatment arm. A demonstration that the treatment effect is consistent across the two subgroups was considered beneficial. However, with hindsight, this amendment was not adequately executed. The CHMP advised against the interim analysis and this was implemented by the applicant as shown in amendment 5.

Results

Two-hundred thirty five (235) patients were enrolled, 212 patients (90%) remained on study drug through study completion (table E1).

Table E1 : Disposition of Study Patients

Study Disposition	Treatment		
	Inhaled Treprostinil n = 115	Placebo n = 120	Total n = 235
Completed Study n (%)	**102 (89)**	**110 (92)**	**212 (90)**
Did Not Complete Study n (%)	**13 (11)**	**10 (8)**	**23 (10)**
Death	0	1 (<1)	1 (<1)
Worsening PAH	3 (3)	0	3 (1)
Adverse Event	7 (6)	4 (3)	11 (5)
Withdrawal of Consent	3 (3)	5 (4)	8 (3)

The active and placebo groups were well balanced across the demographic indices (table E2). The recruited patients are considered representative of PAH population: majority was females, with a mean age of 54 years, and a diagnosis of iPAH. Seventy per cent of the patients were on bosentan and the rest on sildenafil.

Table E2: Baseline Demographics in TRIUMPH 1

Characteristic	**Inhaled TRE** (n = 115)	**Placebo** (n = 120)	**Total** (n = 235)
Age in Years: mean (range)	55 (20-75)	52 (18-75)	54 (18-75)
Gender: Male / Female (n)	22/93	22/98	44/191
PAH* Etiology: n (%)			
IPAH†	64 (56)	67 (56)	131 (56)
CVD‡	40 (35)	37 (31)	77 (33)
Other	11 (10)	16 (13)	27 (11)
Background PAH* Therapy: n (%)			
Bosentan	77 (67)	88 (73)	165 (70)
Sildenafil	38 (33)	32 (27)	70 (30)
Time on Background Therapy: Mean Weeks ± SD			
Bosentan	98 ± 79	90 ± 75	94 ± 77
Sildenafil	65 ± 60	77 ± 69	70 ± 64
Baseline NYHA§ Class: III / IV (n)	112 / 3	118 / 2	230 / 5
Baseline 6MWD‖: Mean ± SD (meters)	346 ± 63	351 ± 69	348 ± 66

* Pulmonary Arterial Hypertension † Idiopathic Pulmonary Arterial Hypertension ‡ Collagen Vascular Disease
§ New York Heart Association ‖6-Minute Walk Distance

For patients receiving bosentan as background therapy, 92% and 98% of subjects in the active and placebo group respectively were receiving bosentan at a dose of 125 mg twice daily. For patients receiving sildenafil as background, there appears to be some in-balance in the active and placebo groups in the administered doses of sildenafil e.g. 55% and 34% of the active and the placebo group

respectively were administered the recommended dose of 20 mg t.i.d. versus 16% and 9% administered the 80 mg t.i.d respectively.

Baseline double-blind sildenafil dosing

Baseline Sildenafil Dose	Baseline Double-Blind Dosing n (%)		
	Active n = 38	Placebo n = 32	Overall n = 70
20 mg BID	2 (5)	0 (0)	2 (3)
20 mg TID	19 (50)	11 (34)	30 (43)
25 mg BID	0 (0)	2 (6)	2 (3)
25 mg TID	0 (0)	1 (3)	1 (1)
30 mg TID	0 (0)	1 (3)	1 (1)
40 mg TID	1 (3)	4 (13)	5 (7)
50 mg TID	6 (16)	8 (25)	14 (20)
60 mg TID	2 (5)	1 (3)	3 (4)
75 mg TID	1 (3)	1 (3)	2 (3)
80 mg TID	6 (16)	3 (9)	9 (13)

Patients recruited with background bosentan therapy had the drug administered for a longer duration (94 weeks) compared to patients on sildenafil (70 weeks). The recruited patients were mainly in NYHA III correlating with the baseline 6-MWD of 348 meters. Background therapy was balanced between the active and placebo treated groups. Approximately a 70% of patients in TRIUMPH study received diuretics, 50% received oral anticoagulants and a 25-30% of patients received calcium channel blockers.

By week 12, only 72% of the recruited patients had reached the recommended dose of 54 μg treprostinil per inhaled dose; a point that could have affected the efficacy results. The possibility of underdosing could not be excluded and the applicant was asked to address the currently recommended dose in relation to that of Remodulin SC.

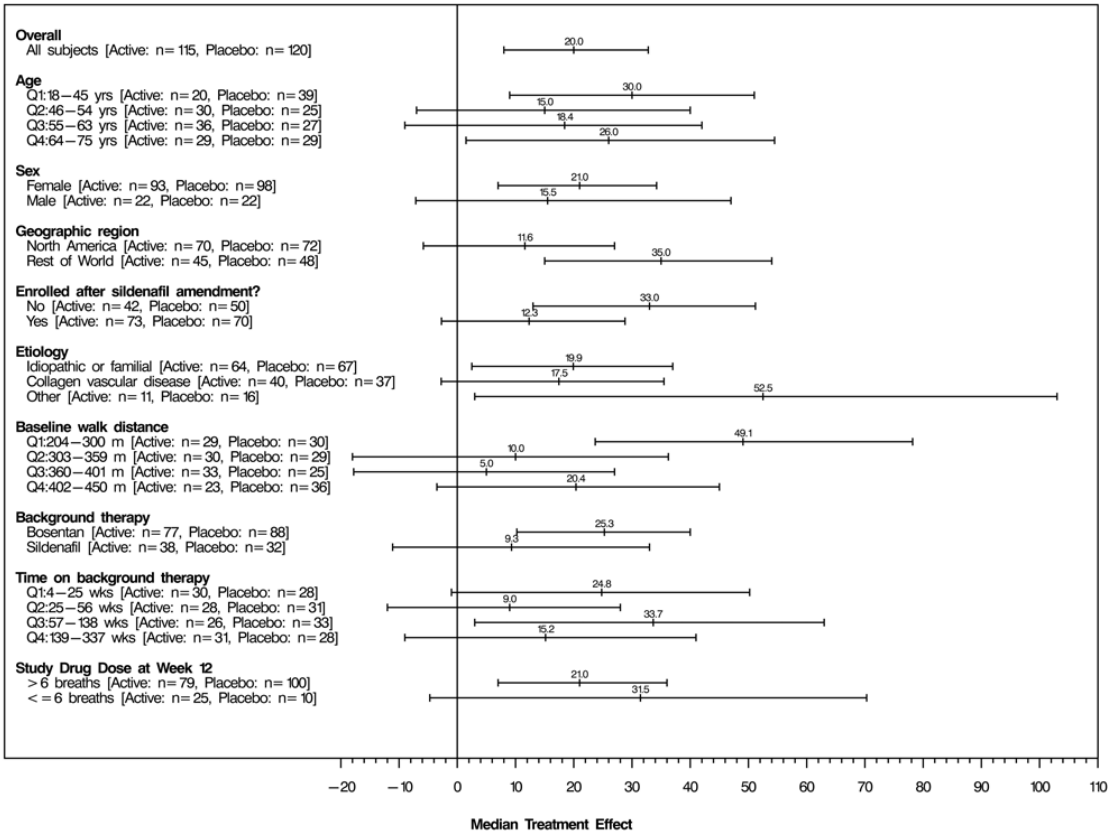
Efficacy Results. At Week 12, patients receiving inhaled treprostinil had a median improvement of +21.6 meters in 6-MWD as compared to +3.0 meters in the placebo group. The Hodges-Lehmann placebo corrected median change from baseline in peak 6-MWD was +20.0 meters (p=0.00044). These results are consistent with those performed on the PP population, or using different imputation methods for missing data.
Several combinations of PAH medications have already been investigated in RCTs: iloprost on top of existing bosentan therapy, sildenafil on top of epoprostenol, and various doses of tadalafil on top of bosentan. The observed effect on the 6-MWD in these studies is in line with the effect currently shown with Tyvaso, that is around +20 m. This emphasizes that with combination therapy the expected gain in the 6-MWD is going to be less than that observed with earlier conducted monotherapy RCTs. However, none of these combinations are yet officially approved, though their off-label used can not be ignored, which emphasizes a medical need for such combinations.
Combination therapy administered to stable PAH patients would be expected to stabilize their condition and prevent clinical worsening as captured in the endpoint of time to clinical worsening. This endpoint was investigated in TRIUMPH as a secondary endpoint, with equivocal results. A clinical trial duration of 12 weeks is probably too short to capture any positive results. Other investigated endpoints: NT-Pro-BNP and Quality of Life were statistically significant at 12 weeks, but their value is still only supportive to the primary endpoint.

In the initial assessment the clinical relevance of the above results was posed as a major objection. In their responses the applicant did not present new data. However, with the publishing of the new guideline for the diagnosis and treatment of PAH (Galie et al., 2009), the need for investigating combination therapy is further emphasized. The current results can be considered of medical importance considering it will be the first authorized combination therapy, fulfilling such medical need. Also the pathogenesis of PAH is not fully understood and the rationale of a combination therapy

targeted against two different pathophysiological pathways appears plausible especially in such a fatal disease like PAH. The combination of Tyvaso with either bosentan or sildenafil did not show relevant PK interactions, increasing the feasibility of such a combination where no dose adjustments are anticipated. This is in contrast with the PK interactions seen when sildenafil and bosentan, or tadalafil and bosentan are co-administered. The clinical experience with other prostanoids in particular Remodulin (SC infusion) and Ventavis (inhalation) lends further support to the efficacy of treprostinil, though as a monotherapy. Tyvaso has an obvious advantage of easier application than Remodulin, and the applicant expects better compliance than with Ventavis because of lesser daily applications. However, the target population who can benefit from this combined therapy should be more clearly defined. According to the current guidelines, patient status can be defined as: stable satisfactory, stable and not satisfactory or unstable and deteriorating. It can be assumed that patients recruited in TRIUMPH were "stable and not satisfactory" patients based on their 6-MWT of around 350 m and WHO FC III. If this assumption is correct, then the combination therapy has not really achieved the desirable goal i.e stable and satisfactory status as defined by the guidelines, but rather only improved exercise capacity (and as proposed in the indication). This could be acceptable as outlined before, after adequately defining the target population in section 4.1 as clinically stable patients. This will also prevent using Tyvaso as a substitute for epoprostenol, which is the first choice in the more severe or unstable patients. Also due to the novelty of combination therapy or the expected treatment goals, initiation, regular assessment of patients and decisions about the feasibility of the combination should be done by specialists otherwise it may be a lost chance for the patient to benefit from other possible combinations.

Of the baseline covariates, only the baseline 6-MWD showed a significant interaction with treatment, where patients walking the shortest distance at baseline, gained the most in the 6-MWT (p=0.043) (fig E3).

Figure E3: Overall median placebo corrected treatment effect and relationship with selected baseline covariates



According to the applicant, this could indicate that patients with such low 6-MWD in spite of adequate doses of bosentan or sildenafil are probably non-responders to these treatments, and thus these patients responded in a similar manner as 'monotherapy' patients. This explanation is plausible though the

limited numbers preclude any robust conclusions. A comparable effect was already observed with Remodulin SC where the more sick patients showed better improvements than the less sick patients.

The following trends can be observed from the results: patients on background bosentan therapy showed better results (median=25.3 m) than patients on background sildenafil (median=9.3 m). The Applicant attributes the differences to different duration and dose of the background therapy. Both groups were balanced regarding baseline demographic characteristics and the background therapy remained stable in the majority of the patients (100% on bosentan and 95% on sildenafil). However, patients in the bosentan group were on therapy a mean of 24 weeks longer than patients in the sildenafil group and the majority of them (92-98%) were adequately treated with the recommended dose (125 mg bid). This contrasts with the sildenafil group where any prescribed dose of sildenafil was allowed in the protocol and only 50% in the active vs 34% in the placebo groups were adequately treated according to the recommended doses (20 mg tid). The administered doses in the rest of the sildenafil group were outside the recommended dose and a higher number of patients in the placebo group received higher doses than the recommended one. However, given the amplitude of the range of these different doses (20 mg bid up to 80 mg tid) and the low number of patients in each subgroup (0-8) it is difficult to draw any conclusions about differences in effect in these subgroups. Generally, the explanation of the applicant could be plausible. However certain comments need to be made. The mean difference in the duration of background use of bosentan and sildenafil of 24 w. is admittedly a difference of long duration, but still for sildenafil, the mean duration of administration is around 70 weeks. After a mean 17 months of therapy, one would expect that the patient is already stabilized. It is of note that the pivotal studies of PAH are of 12-18 weeks duration, where the maximal effect of the drug on the 6-MWT is expected to be attained.
According to the applicant, the administered dose of sildenafil could have confounded the results. The presented data show that almost half of the patients were administered the recommended dose of 20 mg t.i.d while the rest were mostly administered higher doses. It is not expected that higher doses would have a negative impact on the results.
Accordingly, it is considered that the recruiting of patients on background sildenafil was not a well planned amendment. In their advice regarding this amendment (EMEA/CHMP/SAWP/2663344/2006), the CHMP approved the addition of the sildenafil arm provided the study design should allow differentiation between the two background therapies. It was considered important to stratify the analysis by background therapy and by time of inclusion of the additional sildenafil background treatment arm. It is currently difficult to estimate the influence of duration or dose of sildenafil on the lower efficacy when combined with Tyvaso compared to the combination of Tyvaso/bosentan. The possibility of a pharmacodynamic interaction can not be excluded either. Meantime, reference to section 5.1 should be included in section 4.1. In section 5.1, efficacy results based on the background therapy should be mentioned.

Surprisingly, patients on doses ≤6 breaths showed better results (median=31.5 m) than patients on >6 breaths (median=21.0). The results should be cautiously interpreted considering the fewer numbers of patients administered the lower dose (n= 35; 25 active, 10 placebo) precluding robust conclusion. A difference in the treprostinil effect was observed between the geographic regions: a median treatment effect of 11 metres is shown in North America vs 35 m in the rest of the world. This difference could not be attributed to either difference in baseline characteristics or different clinical management between regions.

A requested responder analysis also confirmed the general results as shown in the following table.

Categorical Outcome Analyses (Overall Population and by Background PAH Therapy)

Background PAH Therapy	Outcome	Treatment: Active		Treatment: Placebo		p-value
Bosentan	n	77		88		
	Wk 12 6MWD >=10% above baseline AND no clinical worsening	32	(42%)	17	(19%)	0.00214
	Wk 12 6MWD >=15% below baseline OR clinical worsening	5	(6%)	14	(16%)	0.08565
Sildenafil	n	38		32		
	Wk 12 6MWD >=10% above baseline AND no clinical worsening	13	(34%)	4	(13%)	0.05007
	Wk 12 6MWD >=15% below baseline OR clinical worsening	5	(13%)	6	(19%)	0.74308
Overall	n	115		120		
	Wk 12 6MWD >=10% above baseline AND no clinical worsening	45	(39%)	21	(18%)	0.00027
	Wk 12 6MWD >=15% below baseline OR clinical worsening	10	(9%)	20	(17%)	0.07948

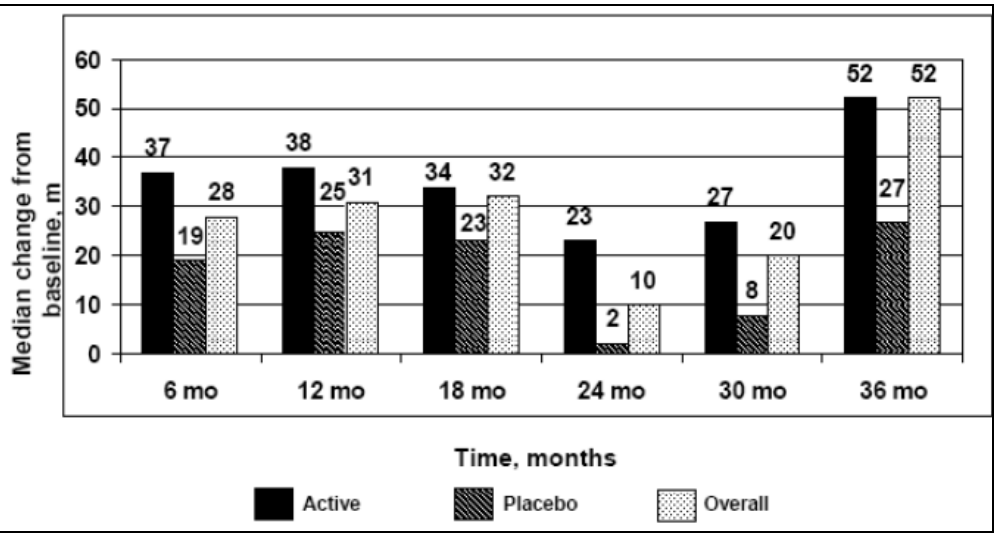
The applicant also submitted data showing that similar to 6-MWT at peak, 6-MWT at trough showed a statistically significant difference improvement of +14 m.

Long term extension TRIUMPH. Patients who completed the double-blind phase of TRIUMPH I were allowed to enter the open-label extension phase to either start or continue receiving inhaled treprostinil. Study visits were performed every 3 months and several efficacy assessments were obtained at each visit, including 6-MWT, NYHA functional classification and time to clinical worsening. There was no control group in this phase of the study limiting the interpretations of the results. Descriptive comparisons were made between the assessments conducted at each time point (over 27 months) and those recorded at baseline. Two-hundred thirty-five (235) patients entered the double-blind phase of TRIUMPH I, and 212 completed the Week 12 visit. Of these 212 patients, 206 enrolled into the open label phase. Six patients (5 active, 1 placebo) elected not to enter the open label phase. As of 01 January 2008, 149 (72%) of the patients that enrolled into the open label phase remained in the study; the most frequent cause of discontinuation was adverse events (28 %). By the 12th month, 83 % of the patients (n=90) were administered ≤ the target dose of 54µg QID.

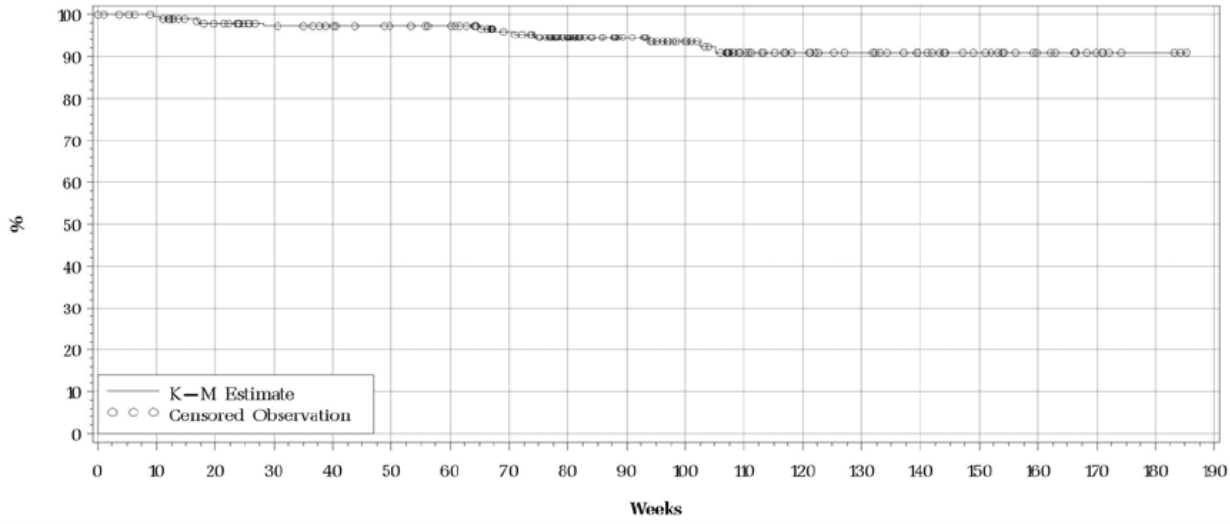
An update of the open label phase of TRIUMPH has been submitted with the day 120 responses. In the January 1, 2009 interim data analysis showed that 57% (n=117) of the enrolled patients remained in the study. Eighty-nine (43%) patients discontinued due to adverse events (17%), disease progression (9%), and withdrawal of consent (7%). Worsening pulmonary hypertension, cough, and headache were the most commonly AEs leading to study discontinuation. After 36 months a tendency to a median increase in 6MWD versus baseline is observed but this increase is not constantly achieved at all time points and the number of patients who achieved 36 months on study is small (15 patients). Patients originally randomized to active treatment demonstrated a median increase from Baseline in 6MWD of 37, 38, 34, 23, 27 and 52 meters at 6, 12, 18, 24, 30, and 36 months, respectively. Patients originally randomized to placebo demonstrated a median increase from Baseline in 6MWD of 19, 25, 23, 2, 8 and 27 meters at 6, 12, 18, 24, 30, and 36 months, respectively.

Change in 6MWD									
Time (months)	Original Randomization								
	Active			Placebo			Overall		
	n	Mean Baseline 6MWD m	Median Change 6MWD m (SE)	n	Mean Baseline 6MWD m	Median Change 6MWD m (SE)	n	Mean Baseline 6MWD m	Median Change 6MWD m (SE)
6	92	359	37 (6)	78	377	19 (6)	170	365	28 (4)
12	74	353	38 (7)	78	375	25 (6)	152	365	31 (5)
18	64	359	34 (10)	58	373	23 (10)	122	364	32 (7)
24	37	359	23 (14)	32	386	2 (14)	69	359	10 (10)
30	17	359	27 (25)	21	366	8 (14)	38	363	20 (13)
36	11	368	52 (19)	4	362	27 (56)	15	366	52 (20)

Figure 6: Six-Minute Walk Distance Median Change from Baseline by Original Randomization



The 1 and 2 year survival rates for the open label study population were 97% and 93%, respectively which is comparable to the results of other PAH medications.



Weeks	0	13	26	39	52	65	78	91	104	117	130	143	156	169	182	195
# Events	0	2	4	5	5	5	9	9	11	12	12	12	12	12	12	12
# Censored	1	13	31	37	42	53	77	106	125	142	154	164	176	186	191	194
# Pts Remaining	205	191	171	164	159	148	120	91	70	52	40	30	18	8	3	0

Compared to baseline values, there was an improvement in the functional class as shown in the following table.

Time (months)	NYHA Classification I/II/III/IV								
	Original Randomization								
	Active			Placebo			Overall		
	n	Baseline	Follow-up	n	Baseline	Follow-up	n	Baseline	Follow-up
12	79	0/0/76/3	2/28/48/1	79	0/16/63/0	4/35/40/0	158	0/16/139/3	6/63/88/1
24	38	0/0/37/1	3/14/20/1	32	0/9/23/0	0/14/17/1	69	0/9/60/1	3/28/37/2
36	11	0/0/10/1	0/6/4/1	4	0/2/2/0	0/1/3/0	15	0/2/12/1	0/7/7/1

The results though positive are difficult to interpret considering the main efficacy issues raised with the initial double-blind placebo-controlled study. Long term open label studies are usually more supportive to the safety analysis.

Supportive studies for Treprostinil Inhalation. The applicant submitted two investigator-initiated studies in support of the long term efficacy of treprostinil inhalation.
Channik et al., 2006[2] was an open-label study in 12 PAH patients administered treprostinil inhalation for 12 weeks on top of bosentan. The reported results of the 6-MWT were better than those reported with other PAH agents used as monotherapy. These results serve to emphasize the variability of the 6-MWT and the possible placebo effect associated with such open-label studies. The recruited number of patients (n=12) is another drawback. The haemodynamic results are in line with those reported and discussed above under dose response studies (Voswinckel et al., 2006). However, the PK data are somewhat different where the dose of 30 µg treprostinil resulted in a Cmax of 0.33 ng/ml in the Channik study and almost double of 0.65 ng/ml in the Voswinckel study. The administered dose of 45 µg was observed to achieve better haemodynamic and 6-MWT results compared to the 30 µg treprostinil.
The open-label long-term follow-up study by **Voswinckel et al., 2008** (not published yet) reports on the assessment of 27 PAH patients who were either treatment naïve or on stable doses of bosentan or sildenafil and have an add-on therapy of treprostinil inhalation ranging from 15 µg to 60 µg, QID. Again the open-label non-controlled study design and the few patients studied limit the usefulness of such a study. Generally, the 6-MWT showed slow deterioration in the first 2 years, followed by stabilization in the next 2 years. Survival after 1, 2, 3 and 4 years was 92%, 84%, 76% and 72% which compares to those reported for ambrisentan.
No firm conclusions can be drawn from such non-controlled data except to offer some reassurance regarding the long term safety of treprostinil inhalation compared to historical data.

Supportive data from Remodulin SC. As Remodulin SC is already registered in many EU countries following an MRP procedure FR/H/278/01, it was considered relevant to include some clinical data from that dossier. The applicant also referred to data pertaining to treprostinil IV and oral administration. As these routes are not registered in EU the data was not considered relevant and was not included in the current report. A type II variation to introduce the IV route of administration in Europe received a negative opinion in March 2008 due to safety issues relating to central venous catheter-related blood stream infections. Studies P01:04 and P01:05 were the pivotal studies submitted for the registration of Remodulin SC in EU. Their study design was in line with other pivotal PAH studies. These were 12-week, international, double-blind, randomized, parallel, placebo-controlled trials with a primary endpoint of change in the 6-MWT from baseline to 12 weeks. The starting dose was selected based on the results of a pilot study which showed that AEs occurred more frequently with initiation of doses at 2.5 or 5 ng/kg/min. The main difference with TRIUMPH study is the recruitment of only PAH treatment naïve patients.
The pooled studies P01:04 and 01:05 enrolled 470 patients making this one of the largest studies in PAH. In the pooled studies, the majority of the recruited patients were functional class WHO III mainly diagnosed with primary pulmonary hypertension PPH. Around a quarter of the patients were diagnosed as pulmonary hypertension associated with congenital systemic to pulmonary shunts which is also a high percentage and could have affected the results, see later.
The administered treprostinil dose in these trials was 9.3±0.38 ng/kg/min SC infusion and accordingly, this was the recommended dose in the approved SPC through the MRP. Still, as mentioned by the applicant, long term experience with Remodulin shows that this may not be the most efficacious dose (see below).

Based on the primary planned analysis, the median treatment effect as compared to placebo was +10 meters (p = 0.0064). Several analyses were submitted trying to account for this small improvement in the 6-MWT. Analysis based on aetiology showed that the subgroup with PPH had a significant increase of +19.1 meters [IC 95% 7.0; 35.0; p=0.0433] compared to the non-significant increase in patients with PH associated to connective disease (CTD) of +25.0 [IC 95% -1.0; 52.9] (p=0.0551).

[2] Channik et al., 2006: Safety and Efficacy of Inhaled Treprostinil as Add-On Therapy to Bosentan in Pulmonary Arterial Hypertension. J Am Coll Cardiol 2006;48:1433–7

Also better results were shown in the subgroup of FC WHO III. This may indicate that severe cases may have better response. This is further supported by the analysis in the published study by Simonneau et al., 2002[3] which stated that severely ill patients who walked less than 150 m at baseline had an estimated treatment effect of +51±16 m (p=0.002), while less sick patients who walked more than 351 m at baseline had no substantial estimated treatment effect (-2±12 m, p=0.869). Another issue that may explain this limited improvement is the administered dose. When patients were grouped by quartile of the dose achieved at Week 12, the highest quartile dose (>13.8 ng/kg/min, n=53) had the greatest improvement in 6-MWT, and the first and second quartile dose had small improvements.

Regarding the secondary endpoints, no difference in time-to-event (death, transplantation, or discontinuation due to clinical deterioration) was observed between the treatment groups which could have been expected considering the short duration of the study. Patients treated with treprostinil SC infusion had a significant improvement in some of the haemodynamic profiles while patients treated with placebo slightly worsened.

Considering that treprostinil is the same active constituent in both the SC preparation and the inhalation, several issues need to be addressed. Following the registration of Remodulin SC and through actual clinical experience, it appeared that the effective dose lies above that used in the pivotal clinical study which was approximately 10 ng/kg/min. The typical range of Remodulin doses in current clinical practice is estimated to be approximately 20-100 ng/kg/min, with a mean of 53 ng/kg/min. According to the applicant, this need for continuous dose escalation with chronic use is only seen with continuous infusion. One explanation for this difference may be the functionality of the prostacyclin receptors in the face of continuous versus intermittent drug exposure, where tolerance is more seen with the former method. This explanation appears plausible; however, considering that the long term extension study was not actively controlled, the need for dose escalation can not be excluded. In the long term open-label extension TRIUMPH study doses up to 72 µg q.i.d. have already been utilized. The possibility of using even higher doses as is currently practiced with Remodulin can not be excluded. However, as relevant safety data are lacking, an adequate warning should be added.

In **conclusion**, the efficacy of treprostinil inhalation is based on the results of one pivotal trial which showed a statistically significant increase in the 6-MWD in patients administered treprostinil inhalation on top of bosentan or sildenafil. The combination may fulfil an unmet medical need for a combination therapy but the target group should be defined as clinically stable patients. According to EMA inspections, TRIUMPH was considered non-GCP compliant. This questions the credibility of the data and precludes any final assessment of the results (see MO1).
Results of the long term extension support the maintenance of such effect though are not conclusive. Clinical experience with treprostinil SC administration supports the modest efficacy of the inhalation route.

Clinical safety

Clinical safety data considers the available safety information related to inhaled treprostinil based on the clinical studies together with the available body of safety data that has previously been generated for Remodulin Solution for SC Infusion. This approach is acceptable considering that systemic exposure of the inhalation route is expected to be less than that following the SC infusion. However, specific issues pertaining to the mode of administration can only be assessed through the Treprostinil inhalation studies.
The database for Tyvaso is considered very limited with only 105 patients administered Tyvaso for the whole 12 weeks in the placebo-controlled study (table S1). In the double-blind phase, the majority of patients in the active group (78%) achieved nine breaths during the study, with 72% receiving nine breaths at Week 12. On average, the maximum dose was achieved by Week 3.

[3] Simonneau, et al., Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension. A Double-blind, Randomized, Placebo-controlled TrialAm J Respir Crit Care Med Vol 165. pp 800–804, 2002

Table S1: Exposure to Study Drug Among Patients in the Active Treatment- Group of the Double-Blind Phase of TRIUMPH I

Period	Total Daily Dose	Number of Subjects (%)
Week 1-3		(n = 115 patients)
	1-72 mcg	13 (11%)
	72-144 mcg	61 (53%)
	144-216 mcg	40 (35%)
	216-288 mcg	1 (<1%)
Week 4-6		(n=111 patients)
	1-72 mcg	5 (5%)
	72-144 mcg	26 (23%)
	144-216 mcg	78 (70%)
	216-288 mcg	2 (2%)
Week 7-9		(n=108 patients)
	1-72 mcg	6 (6%)
	72-144 mcg	16 (15%)
	144-216 mcg	83 (77%)
	216-288 mcg	3 (3%)
Week 10-12		(n=105 patients)
	1-72 mcg	6 (6%)
	72-144 mcg	16 (15%)
	144-216 mcg	81 (77%)
	216-288 mcg	2 (2%)

Safety data from the long term extension study were submitted using a cut-off date of 1 January, 2009.

Safety data from investigator-initiated studies (n=9) will also be considered when relevant. Three different studies were conducted on a total of 123 patients (Voswinckel et al. JACC 2006). Reference will also be made to safety of Remodulin SC infusion in a later section.

Adverse Events. Over the 12-week placebo-controlled period in TRIUMPH, slightly more adverse events were reported in patients who received treprostinil (n=101/115; 88%) compared to patients on placebo (n=100/120; 83%). However, AEs probably or possibly related to study drug were more frequently reported with treprostinil (77% vs 54%). The most frequent of these AEs reported with inhaled treprostinil were cough (51% vs 23%), headache (34% vs 18%), dizziness (16% vs 11%), nausea (15% vs 5%) and flushing (15% vs <1%) compared to placebo respectively (table S2). These adverse events relate to the pharmacologic actions of treprostinil or the method of administration and are in line with those reported with other prostanoids e.g. iloprost.

Table S2: Adverse Events Probably or Possibly Related to Study Drug Occurring in at Least 3% of Treprostinil Patients and More Frequently than in Placebo Patients

Adverse Event	Treatment n (%)	
	Inhaled Treprostinil n = 115	Placebo n = 120
Any Event	88 (77)	65 (54)
Cough	59 (51)	28 (23)
Headache	39 (34)	22 (18)
Dizziness	18 (16)	13 (11)
Nausea	17 (15)	6 (5)
Flushing	17 (15)	1 (<1)
Throat Irritation	16 (14)	9 (8)
Pharyngolaryngeal pain	13 (11)	5 (4)
Diarrhoea	8 (7)	3 (3)
Chest Discomfort	7 (6)	2 (2)
Fatigue	6 (5)	4 (3)
Jaw Pain	6 (5)	5 (4)
Chest Pain	3 (3)	1 (<1)
Chills	3 (3)	0
Wheezing	3 (3)	0

Likewise, the most frequently reported AEs in the open-label extension study were: cough (34%), headache (22%), dyspnoea (16%), nausea (15%) and pulmonary hypertension (13%).
According to the applicant, tolerance to these adverse events seems to develop with chronic dosing, allowing higher doses with chronic administration. It is agreed that there is a decline in the frequency of the AE which were probably or possibly related to drug administration from the pivotal study to the long term extension (e.g., headache, dizziness and nausea). During the first 3 weeks of the treatment period there were 10 events that occurred at a frequency of at least 5% in the treprostinil treatment group (cough 46%; headache 32%; nausea 16%; throat irritation 13%; dizziness 11%; flushing 11%; pharyngolaryngeal pain 10%; diarrhoea 6%; fatigue 5%; dyspnoea 5%). The frequencies of onset of all these events in the treprostinil treatment group were substantially reduced during the subsequent 3 week intervals to rates comparable to that of placebo. Dose-response analysis of prostanoid-related AEs could be complicated because of tolerance. The results show lack of dose response, with most of the frequently reported AEs reported with the lowest administered doses.

Other common adverse events that were noted in TRIUMPH I were related to the route of administration. These included cough, throat irritation, and pharyngolaryngeal pain, which were reported with frequencies of 51%, 14%, and 11%, respectively in the double-blind phase. In the open label phase, these adverse events still persisted but were reported less frequently: 34%, 9% and 10% respectively. These local effects are in line with the labelling of iloprost. During the double-blind phase of the TRIUMPH I study, there was a trend towards a higher rate of lower respiratory tract infections in the treprostinil group [5 cases (4%)] compared with placebo (1 case (0.8%). The incidence of pneumonia was 8% in the open-label phase of TRIUMPH (4% reported as serious). The possibility that treprostinil may be associated with a significant increase in respiratory infections and that the severity of these infections may be associated with treatment duration can not be excluded. Further analysis of the study did not reveal any conclusive data. In order to address the long term safety issues with Tyvaso, an observational study was agreed with the FDA. This observational study should also be part of a FUM, in case Tyvaso is registered.

Serious adverse events
Serious adverse events were more common in the placebo group (11%) than in the active treatment group (8%) during the double-blind phase of TRIUMPH I. The reported number of events is generally too low to allow conclusions. The most common serious adverse events occurring in the treprostinil group included worsening pulmonary hypertension (3% vs 2% in placebo), syncope (2% vs <1% in placebo), and one event of each of the following: anaemia, abdominal pain, diabetes mellitus, diarrhoea, gastric ulcer, and right ventricular failure. Numerically more cases of the SAE "worsening pulmonary hypertension" was reported with the active treatment group (3% vs 2%). Again, pulmonary hypertension is the most commonly reported SAE in the open phase (7%) which could be explained by the progressive nature of the disease. Chest pain was also reported as a serious AE in 2% of the cases and should be included in section 4.8. Myocardial ischemia is excluded as a cause.

Deaths
There were no deaths reported in patients in the treprostinil inhalation treatment arm in the placebo-controlled phase. Nine patients died during the open label phase of the study and three additional patients died within 15 days of study discontinuation. Nine patients were recorded as discontinued from study due to death, however one patient was recorded as discontinued due to an AE and two patients were recorded as discontinued due to disease progression prior to death.
For completeness, all twelve of these deaths are summarised in table S3. None of the fatal events were considered to be probably or possibly related to inhaled treprostinil. However, further data are requested regarding the reported death due to gastrointestinal bleeding.

Table S3: Deaths that Occurred during the Open Label Phase (up to 1 January 2009)

Patient number	Cause of Death	Study Day Drug Stopped	Study Day of Death	Relationship to Study Drug
10015	Septic shock	495	498	Unrelated
11006	Pneumonia	657	658	Unrelated
13015	Oesophageal tumour	437	457	Unrelated
14011	Gastrointestinal bleed	718	718	Unrelated
15003	Right heart failure	195	199	Unrelated
17001	Left heart failure	757	757	Unrelated
19009	Worsening pulmonary hypertension	68	68	Unrelated
25001	Post anoxic encephalopathy	116	121	Unlikely
36001	Small cell lung cancer*	74	75	Unrelated
36008	Drowning	520	521	Unrelated
44001	Pulmonary embolism	119	119	Unlikely
47004	Worsening pulmonary hypertension	463	475	Unrelated

* Small cell lung cancer was confirmed prior to treatment with treprostinil

Seven deaths were reported in the long-term study conducted by independent investigators in which the 27 patients were treated with open-label treprostinil at doses of ranging from 15 µg to 60 µg QID for a mean follow-up time of 159 weeks (range 125 to 211 weeks)(the submitted manuscript Voswinckel et al. 2008). All 7 deaths were judged not related to treprostinil. However, one death was reported as "sudden death after exercise". No conclusion can be drawn over the actual cause of this death as no autopsy was conducted.
The 1-year and 2- year survival rates in the study were approximately 97% and 92%, respectively which appears comparable to those reported with other PAH medications although historical comparisons are difficult to interpret specially with the additive treatment management employed in this study.

Other Significant Adverse Events
The applicant addressed 3 adverse events that could be of special importance to treprostinil inhalation: syncope, adverse events related to pharyngolaryngeal irritation and bronchospasm.

Syncope is a common symptom of the disease itself, but can also occur under therapy. The increased occurrence of syncope can denote disease deterioration or insufficient efficiency of the drug. Syncope is specifically reported with iloprost use in trough intervals and patients using iloprost who experience syncope are accordingly advised to avoid any exceptional straining, to inhale before physical exertion and consider therapy adaptation or change in case of exertional or nocturnal syncope.
The current results show a higher frequency of syncope in the active controlled study [7 events (6%) vs 1 in placebo group (<1%)]. Two severe cases were considered to be possibly/probably related to the study drug. In the long-term extension study with a cut-off of 1 July, 2008, 15 events of syncope were reported in 13 patients; five events were serious adverse events; only one event was judged probably attributable to treprostinil inhalation. Further analysis of the data showed that syncope is mostly related to severe PAH and in most cases the patients were eventually administered parenteral prostanoid. The reported cases in the open label phase were even administered higher than the currently recommended doses, probably indicating inadequate control by Tyvaso in these cases. One case was probably related to under treatment and the other associated with cough.
It can be agreed with the applicant that the pathogenesis of syncope with PAH is complex. The nature of the disease, the mechanism of action of the PAH drugs and the co-administered drugs all complicate the causal relationship with syncope.
The currently proposed text by the applicant in sections 4.4 and 4.8 is considered sufficient to address this issue. The text is also in line with that accepted for Ventavis.
Adverse events related to ***oesophageal /throat irritation*** were more frequently reported with treprostinil inhalation (n=16; 14%) than the placebo group (n=10; 8%), although it is acknowledged that these events were mostly mild in severity and self limiting. Events related to possible irritation were still reported in the open-label extension study (10 patients). The two 13-week inhalation toxicology studies that were performed in rats and dogs raised the possibility that inhalation of treprostinil sodium might result in local irritation of the respiratory tract. According to the applicant these pre-clinical findings may have been a consequence of the relatively long period of exposure needed in order to deliver the desired dose levels of treprostinil to the study animals. However, the current results do not conclusively support such an explanation. This point should be further investigated in the planned observational study which is currently requested as a FUM.
The applicant explored the incidence of ***bronchospasm*** using the terms: wheezing, pleuritic pain, dyspnoea, and dyspnoea exacerbated. In the placebo-controlled trial, wheezing was reported more frequently in the treprostinil group (3 and in one case leading to discontinuation) than the placebo controlled group (0), pleuritic pain was not reported in either group, dyspnoea was reported equally in both groups (6) and dyspnoea exacerbated reported more in the placebo group (5) than the treprostinil group (3). All 17 patients with a past medical history of asthma were examined (8 in the active group and 9 in the placebo group). All these patients completed the 12-week double-blind phase of the study. The incidence of adverse events suggestive of bronchospasm was comparable between the 2 groups. Such adverse events were still reported during the open label study.
Adverse events denoting bronchospasm were also reported in single dose studies, using 30-120 µg doses. In the applicant-sponsored studies, 2 events of chest pain and discomfort were reported among 6 healthy volunteers. In another study, a case of severe cough leading to discontinuation, two cases of bronchoconstriction (one mild and one moderate) occurred following administration of 50, 30 and 120 µg respectively. In the last study a formulation containing metacresol was used, making it difficult to conclude on the causative factor. It should be noted that the currently proposed inhalation packaging is metacresol-free. This could add to other safety issues as indicated in the Quality section, where the possible overgrowth of micro-organisms can not be excluded when using a preservative-free formulation. The present results are not conclusive regarding the potential of treprostinil to induce bronchospasm. A warning is already included in the labelling of iloprost against the possibility of bronchospasm and related events in susceptible patients. Monitoring is recommended in cases of severe asthma.

Laboratory findings
Clinical laboratory evaluations did not reveal clinically significant trends or consistent changes. In the open-label phase of TRIUMPH I 12 patients with abnormal ALT (SGPT) or AST (SGOT) values classified by investigators to be clinically significant were reported. Nine of these cases were already administered bosentan (6.3%) which is known to be associated with elevation in hepatic enzymes

(reported rate in the SPC of 5.9%). It is agreed that the identified cases of hepatic impairment could not be considered related to treprostinil.
Epistaxis and **haemoptysis** were reported with higher frequencies of 5% and 3% in the treprostinil group versus 2% and 0% in the placebo group. According to the applicant, the reported epistaxis is probably a consequence of the systemic effect rather than local irritation, considering that the incidence of epistaxis with treprostinil SC infusion (4.2%) is comparable to that of Tyvaso (5%) in the controlled clinical trials. Accepting this argument also motivates the need to contraindicate Tyvaso in susceptible patients. A contraindication for these groups is already implemented in both Remodulin and Ventavis. In the absence of direct comparative PK data for systemic exposure between the inhalation and SC infusions routes, the current clinical data substantiate implementing the same contraindication. Regarding interaction with other anticoagulants, the warning is considered sufficient, but should also include a warning with "other inhibitors of platelet aggregation", as the possibility of PD interaction can not be excluded as well.
Ancillary data show that hypokalaemia is a frequent adverse event associated to inhaled treprostinil versus placebo (4% vs. 2% in the TRIUMPH study) but also with parenteral treprostinil versus placebo (2% vs. 0% in studies P01:04/05), whereas hyperkalaemia has been infrequently reported with treprostinil. This should be stated in the SPC.

The presented analysis regarding the incidence of hyperglycaemia in relation to Tyvaso administration identified few cases, of which one is serious, but was assessed as unlikely related. Placebo-controlled data of parenteral treprostinil did not reveal more data. In the long term un-controlled data of treprostinil, few cases were also identified, but it is agreed with the applicant that with lack of controlled data, no conclusions can be made. Pre-clinical data on treprostinil also do not support a causal relation with hyperglycaemia either.

There is a biological plausibility of a prostanoid to increase sweat production, and results from either subcutaneous (4 vs. 2), intravenous (1 vs. 0) or inhalation (2 vs. 0) routes consistently indicates a higher rate of events of hyperhidrosis associated to treprostinil compared to placebo (1.7% vs. 0.5%). Therefore, "hyperhidrosis" may be considered a frequent adverse event associated to treprostinil (rate 1.7%) and should be included in section 4.8 of the SPC.

Vital Signs and Other Observations Related to Safety
No clinically significant findings related to vital signs or lung function were observed during the placebo-controlled or the open-label extension studies. No adverse events of hypotension were reported either which were already reported as frequent adverse event with treprostinil SC infusion. This data is reassuring. The submitted results do not indicate a significant hypotensive effect for treprostinil when administered on top on bosentan or sildenafil compared to placebo. A tendency for more frequent reductions in SBP $\geq$ 15 mm Hg is observed in the sildenafil group. However, the numbers are too few precluding any conclusions.

Special populations: In TRIUMPH I, adverse events were analysed in subgroups depending on gender, age, PAH aetiology, baseline 6MWD and background therapy. The low number of patients by subgroups is insufficient to draw valid conclusions on this matter.
Available data on safety outcomes in renal and hepatic impairment are extrapolated from the treprostinil parenteral solution (Remodulin). Of note is the influence of liver impairment on the plasma clearance of UT-15, where it is shown to be decreased by up to 80 % in nine patients with portopulmonary hypertension and stable, mild or moderate hepatic dysfunction compared to healthy adult volunteers. In line with the SPC of Remodulin, this is reflected as a contraindication to the use of Tyvaso in patients with severe hepatic impairment. The applicant should also implement dose recommendations for a lower starting dose for mild and moderate hepatic impairment in line with Remodulin SPC.

Safety related to drug-drug interactions
The frequency of adverse events with the combined administration of treprostinil with bosentan or sildenafil appears comparable in the pivotal study. No clear signals of better tolerability of the combination bosentan and treprostinil vs sildenafil and treprostinil can be observed. However, the frequencies of some AE are more frequently reported in one group than the other, in particular cough

and dizziness in the sildenafil group versus headache and syncope in the bosentan group. The applicant should try to explain this difference.

Discontinuation due to AES
During the double-blind phase of TRIUMPH I, the rate of discontinuation of patients due to AEs for treprostinil (7 patients: 6%) was double that recorded for patients on placebo (4 :3%). During the open-label phase, an additional 27 patients discontinued due to AEs. The results imply that the adverse event profile (headache, nausea) and the method of administration (cough, pharyngolaryngeal pain) have impact on patient compliance and accordingly possibly on their management. Generally, it is agreed that the mode of administration of Tyvaso could offer advantages over that of Ventavis due to lower frequency of administration. Compared to treprostinil SC infusion, a clear advantage is also foreseen. As the applicant mentions, the best measure to ensure good utilization of Tyvaso, is by providing proper information and training to the prescribers and patients. This is not currently addressed in the RMP. The RMP should be updated accordingly and the educational program discussed with the Rapporteur.

Withdrawal and Rebound
According to the applicant, no cases of rebound have been reported with treprostinil inhalation. The applicant excludes such a possibility based on the intermittent nature of administration. The same argument could apply to Ventavis and still a warning in section 4.4 is included. To be on the cautious side, a comparable warning should be implemented in Tyvaso SPC as well.

Safety of Treprostinil SC infusion
Two other forms of treprostinil are currently available on the market: treprostinil for SC infusion and treprostinil for IV infusion. However, only the SC form is currently approved in most EU countries through an MRP FR/H/278/01. This safety data is thus considered supportive to the current application. For the sake of brevity, reference is made to the currently approved SPC of treprostinil in EU. Since the MRP, the applicant has already submitted 5 PSURs, the last one submitted covering the period: 22 November 2007- 21 May 2008.
Based on data from clinical studies, adverse events in the EU SPC of Remodulin SC infusion were reported as very frequent (>10%) for headache, vasodilation, diarrhoea, nausea, rash, jaw pain, bleeding and adverse events related to the method of administration: pain and local reaction at the infusion site. Frequently reported AE (>1-10%) included: dizziness, hypotension, pruritis and oedema.
Special emphasis on bleeding tendencies is made, because of the inhibitory effect of treprostinil on platelet aggregation and the possibility of interaction with anti-coagulants which are frequently prescribed in these patients. The reported post-marketing AE events with treprostinil SC include: thrombophlebitis at the site of infusion, infection related to the central venous catheters, sepsis, bacteraemia, infection/ abscess at the infusion site, thrombocytopenia, bleeding related to the injection site, bone pain, skin eruptions (macular or popular) and cellulitis.
The frequency of the reported AE with Tyvaso appear to be generally in line with those previously reported in the SPC of Remodulin SC infusion (dizziness, headache, flushing, diarrhoea and nausea) with the main difference of AE related to the method of administration. The difference in the severity of these adverse events according to the method of administration is however not reported.
However, it is noticed that with the SC infusion, a variety of bleeding disorders are described (GIT bleeding, gum bleeding), while with the inhalation form, only epistaxis is reported as very common AE.
In summary, safety data of Tyvaso is based on one placebo-controlled trial and its open-label extension study (please refer to GCP section), building on previous data from the marketed Remodulin SC infusion. The reported AEs relating to the pharmacological action of treprostinil are in line with those reported with Remodulin; AEs such as headache, nausea, flushing and diarrhoea being the most frequently reported. Regarding the specific method of administration and in the recommended dose 54 µg QID, the placebo-controlled data is quite limited. AEs related to the method of inhalation such as cough and throat irritation/oropharyngeal pain were frequently reported, and the possibility of bronchospasm can not be excluded. The association of syncope to treprostinil administration is not clearly established due to the many factors involved, however, the current labelling is considered adequate. The planned observational study is important to identify long term local toxicities.

The proposed indication as an add-on therapy to other vasodilators such as bosentan or sildenafil necessitates does not indicate a better safety better with either combination.

Pharmacovigilance system

The Applicant submitted a Pharmacovigilance System: Version: 2.0, Dated: 25-02-2009. The Rapporteur considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management plan

The local and systemic toxicity of treprostinil sodium administered by inhalation has been evaluated in rats and dogs. The most relevant findings regarding human usage are cardiac adverse events (minimal to slight myocardial degeneration/fibrosis observed at all dose levels), respiratory adverse events (respiratory tract irritation, squamous metaplasia in the larynx, slight haemorrhage and macrophage accumulation in the lungs. On the other hand, treprostinil inhalation administration may cause greater cardiac peak exposure than when it is administered intravenously or subcutaneously.

The overall safety database for inhaled treprostinil consists of approximately 600 subjects (115 exposed to treprostinil in the TRIUMPH double-blind phase study of 12 weeks duration, and 206 include in its open label phase). Populations underrepresented or not included in clinical studies were children, elderly, pregnant and lactating women, patients with renal or hepatic insufficiency, patients with pulmonary veno-occlusive disease, concurrent pulmonary venous hypertension, pulmonary capillary hemangiomatosis, severe chronic obstructive pulmonary disease, congenital pulmonary hypertension, chronic thromboembolic pulmonary hypertension, or any form of congenital heart disease or congenital heart defect, and patients with other severe pulmonary disease which could have interfered with the inhalation procedure.

The most frequent adverse event (AE) in TRIUMPH study was cough (41% with active treatment vs 23% with placebo). Other frequent AEs related to the inhaled route were throat irritation (14% vs 8%, respectively) and pharyngolaryngeal pain (11% vs 6%, respectively). Five events of bronchospasm were reported (4 after single doses above the maximum recommended dose and 3 in a study using a solution containing metacresol which is no longer used). Syncope was more frequently reported with treprostinil than with a placebo (6% vs <1%). All these AEs were considered important identified risks of inhaled treprostinil. Important potential risks considered by the MAH were its use in patients with asthma and bronchial hyperreactivity, and the potential off-label use in other types of pulmonary hypertension.

The pharmacovigilance plan for inhaled treprostinil mainly consists of routine pharmacovigilance practices (spontaneous reports and PSURs). Regarding important identified risks the MAH proposes routine pharmacovigilance. Additionally syncope and bronchospasm are considered ADRs of special interest and will be followed up using a template. Regarding important potential risks, the MAH plans a medical communication programme and routine pharmacovigilance for off label use and routine pharmacovigilance and long-term follow up of use in patients with asthma and bronchial hyperreactivity. The MAH does not justify that no action beyond routine pharmacovigilance is planned for important and potential risks. Regarding missing information the MAH submitted a Paediatric Investigation Plan and a carcinogenicity study is proposed.

The pharmacovigilance plan for inhaled treprostinil mainly consists of routine pharmacovigilance practices (spontaneous reports and PSURs). Regarding important identified risks the MAH only propose routine pharmacovigilance. Additionally syncope and bronchospasm are considered ADRs of special interest and will be followed up using a template. Regarding important potential risks, off label use and long-term follow up of use in patients with asthma and bronchial hyperactivity, the MAH plans a medical communication programme and routine pharmacovigilance. Outlines of the medical communication programme are present in the RMP and they are based on educational material aimed

at educating patients and specialists to assure appropriate use of inhaled treprostinil. Details of the educational program should be agreed with NCAs. Regarding missing information the MAH submitted a Paediatric Investigation Plan, a carcinogenicity study is proposed, as well as a pregnancy registry.
There are still few concerns not yet resolved by the MAH. Those are included in the list of questions.

IV. ORPHAN MEDICINAL PRODUCTS

Treprostinil sodium (inhalation) was designated as an Orphan Medicinal Product in the European Union on 14 April 2004 -EU/3/04/197. Advice has been sought from the SAWP on the chemical similarity of treprostinil to iloprost, which is already authorised with orphan drug status for the treatment of pulmonary arterial hypertension, to establish whether clinical superiority of treprostinil to iloprost would be required. The opinion of the CHMP, given in December 2005, was that these drugs were not chemically similar and clinical superiority does not need to be demonstrated. A similarity report is also prepared.

V. BENEFIT RISK ASSESSMENT

Treprostinil inhalation is developed as an add-on therapy for PAH patients on stable doses of bosentan or sildenafil, making this the first application for an add-on therapy in PAH. Considering the different mechanisms of action, synergistic or additive efficacy might be expected. Inhalation appears an attractive method of administration compared to SC/IV infusions, with limited systemic effects and ease of administration. Clinical data is mainly based on one placebo-controlled study TRIUMPH and its long-term extension, building on previous experience with treprostinil (Remodulin) SC infusion.

V.1 Benefits

The placebo-controlled phase of TRIUMPH showed that administration of Tyvaso on top of bosentan or sildenafil resulted in a significant median improvement of +21.6 meters in 6-MWD as compared to +3.0 meters in the placebo group. This was accompanied by improvement in the level of NT-Pro-BNP and in some scores of Quality of Life, but not in the functional class or time to clinical worsening. With study duration of 12 weeks, no significant effects in the latter endpoints were actually expected.
Long term data support the long term durability of the results, though are difficult to interpret considering the uncontrolled design.
Tyvaso is the first application for combination therapy in the management of PAH. The documented increase in the 6-MWT is in line with that shown with other combinations, in particular iloprost on existing bosentan therapy, sildenafil on top of epoprostenol, and tadalafil on top of bosentan. The current results can be considered of medical importance considering it will be the first authorized combination therapy, fulfilling such medical need. Also the pathogenesis of PAH is not fully understood and the rationale of a combination therapy targeting two different pathophyisiological pathways appears plausible especially in a fatal disease like PAH. The combination of Tyvaso with bosentan or sildenafil did not show relevant PK interactions, increasing the feasibility of such a combination where no dose adjustments are anticipated. This is contrast with the PK interactions seen when sildenafil and bosentan, or tadalafil and bosentan are co-administered. The clinical experience with other prostanoids in particular Remodulin (SC infusion) and Ventavis (inhalation) lends further support to the efficacy of treprostinil, though as a monotherapy. Tyvaso has an obvious advantage of easier application than Remodulin, and the applicant expects better compliance than with Ventavis because of lesser daily applications.
However, the target group of is combination therapy with Tyvaso should be adequately defined as clinically stable patients, to prevent using Tyvaso as a substitute for epoprostenol which is specifically indicated for unstable patients.
Following the EMA inspection of two investigator sites, several critical and major findings were identified with respect to trial management, quality of data, efficacy data and safety data. The inspectors concluded on the non-GCP compliance of the study. These deficiencies have a major

impact on the reporting of both efficacy and safety data and accordingly on further assessments. This is especially important considering that the application is based on one single pivotal study. In such cases, the trial design and performance are expected to be of compelling quality according to the relevant guidelines (CPMP/EWP/2330/99). This is not the current case.

V.2 Risks

The safety profile of treprostinil following systemic exposure is well characterized from previous experience with Remodulin SC infusion, with the most frequently reported AEs being headache, nausea, flushing and diarrhoea. Systemic exposure is also expected to be less with the inhalation method, which is reassuring. However, data on specific safety issues related to the inhalation method and in the recommended dose for long durations are considered quite limited and can not preclude chronic safety issues, especially with pre-clinical inconclusive data. AEs such as cough, throat irritation were frequently reported and the possibility of bronchospasm can not be excluded. Also as reported with iloprost, syncope is a possibly related AE. Bleeding and the possible interaction with administered anti-coagulants remains a concern even with the local administration.

V.3 Balance

Combination therapy is a new approach in the management of PAH, though none of the used combination is officially registered. Tyvaso is the first application for combination use on top of bosentan or sildenafil. The combination appears feasible as it targets two different pathophysiological pathways. No PK interactions are seen. The gain in the 6 MWT is moderate but in line with the other combinations. Efficacy of Tyvaso is also supported by the efficacy previously shown for Remodulin or Ventavis. It promises in addition easier and less frequent application. However, as with other prostanoids, tolerance to the effect and the need of higher doses with chronic administration can not be excluded. There is limited experience with higher doses, which should be reflected in the labelling.
No conclusions can be drawn regarding the superiority of Tyvaso when combined to bosentan compared to sildenafil due to study flaws. The combination of Tyvaso with either drugs is acceptable provided the target group is adequately defined as clinically stable patients and the expected treatment goals are clear. This is essential to avoid using Tyvaso as a substitute for epoprostenol.
Long term local toxicity data for the recommended dose are limited, but could be solved by the planned long term observational study as a follow-up measure. Other safety issues, in particular bleeding, syncope are currently addressed in the labelling.

The above data is mainly based on one single pivotal study TRIUMPH, which was considered non-GCP compliant following the EMA inspections. No decision can be currently made regarding the benefit/risk of the product without first ensuring the conduct of the study and the credibility of the data.

V.4 Conclusions

Based on the non-GCP compliance of the single pivotal study, the overall benefit/risk of treprostinil inhalation is considered negative.