PASS INFORMATION

Title	A National, Multicenter, Prospective, Single-arm Registry PASS of Pulmonary Hypertension Patients Treated with Riociguat (Adempas®) in China (EXPERT China)
Version identifier and date of the final study report	Version 1.010-MAR-2021
Study type / Study phase	PASS / Phase IV
EU PAS register number	EUPAS39007
Active substance	Riociguat (ATC code C02KX05)
Medicinal product	Adempas®
Product reference	MK-4836 (BAY 63-2521)
Procedure number	NA
Research question and objectives	The aim of the study was the assessment of the long-term safety profile of riociguat (Adempas®) in real-life clinical practice. In addition, it was to prospectively collect data on clinical effectiveness, resource use, and how Adempas® was used by pulmonary hypertension (PH) experts under real-life conditions.
Country of study	China
Author	PPD , MSD R&D (China) Co., Ltd. T PPD PPD 1-13F, Building 21 Rongda Road, Wangjing R&D Base, Zhongguancun Electronic Zone West Zone, Chaoyang District, Beijing, China 100012
Merck Final Repository (RCAM) Date	10-MAR-2021

MARKETING AUTHORIZATION HOLDER

Marketing authorization holder (MAH)	Bayer AG 51368 Leverkusen, Germany
MAH contact person	PPD, Bayer Healthcare Co. Ltd.

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1 ABSTRACT

Abbreviated Title	**EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension in **China (EXPERT China)**
Report version and date	Version 1.0, 10-MAR-2021
Key words	Pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, utilization, safety
Author	PPD MSD R&D (China) Co., Ltd.
Rationale and background	Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) are rare and life-threatening diseases. Riociguat (Adempas®) is the first member of a new class of drugs, the soluble guanylate cyclase-stimulators and the first drug ever having shown efficacy in CTEPH. Riociguat has shown to be effective and well tolerated in patients with PAH and CTEPH in randomized controlled trials. It is approved in China to treat patients with CTEPH that is persistent/recurrent after surgical treatment or inoperable and in patients with PAH. In accordance with the regulatory requirements, this registry has been designed to collect information about the long-term safety of Adempas® in real-life clinical practice outside the regulated environment of a controlled clinical study.
Research questions and objectives	The primary objective was to assess the long-term safety of Adempas® in real-life clinical practice. The secondary objectives were: • Long-term safety of Adempas® in the different Pulmonary Hypertension (PH) indications (PAH, CTEPH) • Effectiveness of Adempas® (including clinical worsening) in the long-term follow-up of PH patients • Information on resource use • Information on how Adempas® was used (eg, indication and indication subgroups, dose).
Study design	The EXPERT China registry was a national, multicenter, prospective, single-arm study collecting observational data from patients with PAH and CTEPH treated with Adempas®, within the approved indication.
Setting	9 investigational sites in China
Patients and study size, including dropouts	80 evaluable patients with PH/PAH including: • 23 newly starting Adempas® treatment within 3 months before enrollment • 57 patients who had already been treated with Adempas® more than 3 months before enrollment, of which 50 patients were transitioned from Adempas® long-term extension clinical trials (PATENT-2 and CHEST-2).
Variables and data sources	The patient's clinical information was documented at time of the initial visit and approximately every 3 to 6 months according to local clinical practice thereafter. Data collection continued for approximately 1 year

	or until 30 days after the end of Adempas® therapy. The primary endpoints were: • Incidence of adverse events (AEs)/serious adverse events (SAEs) • Incidence of all-cause mortality The secondary endpoints were: For safety • Incidence of AE and SAE in the different PH indications (PAH, CTEPH) • Incidence of AE of interest overall and in the different PH indications (PAH, CTEPH) For effectiveness • Clinical effect in the follow-up of PH patients, if both baseline and postbaseline measurements were available o 6-minute walk distance (6MWD) o World Health Organization Functional Class (WHO FC) o Borg Dyspnea Index o Biomarkers (Brain Natriuretic Peptide [BNP], N-terminal pro BNP) o EuroQoL 5 dimensions questionnaire - Visual Analogue Scale o Haemodynamic parameters from right heart catheterization measurement For resource use • Hospitalization/outpatient visits • Administration and any change in drug treatment for PAH or CTEPH
Results	All of the 80 enrolled patients (100.0%) were evaluable for the safety analysis. Of the 80 evaluable patients, 51 patients (63.75%) had PAH and 29 (36.25%) had CTEPH. Mean (±Standard Deviation [SD]) disease duration since the initial PH/PAH diagnosis was 6.7 (±3.7) years. The majority of patients had known PAH/CTEPH disease (n=74; 92.5%). Six patients (7.5%) had newly diagnosed PAH/CTEPH. There were 57 (71.3%) Adempas® pre-treated patients (ie, receiving Adempas® for ≥3 months before enrollment) and 23 (28.8%) Adempas® newly treated patients. At baseline, the mean (±SD) age was 49.0 (±13.8) years, with a range from 22.0 to 74.0 years. Most (69 patients, 86.3%) of the patients were female. The majority of patients were in New York Heart Association/WHO FC II (68.8%) or III (23.8%). Mean (±SD) 6MWD was 437.5 (±93.5) meters. Mean (±SD) Borg Dyspnea Index was 2.02 (±2.03). At baseline, 44 patients (55.0%) had Adempas® monotherapy while 36 patients (45.0%) received Adempas® and at least 1 other PH medication. The mean (±SD) daily dose was 6.9 (±1.4) mg (median

	7.5 mg, range 2.0 to 7.5 mg). The median Adempas® dose remained stable during the study course. No patient was administered Adempas® at a daily dose above 7.5 mg. In the total population of 80 patients, 58 patients (72.5%) experienced at least 1 treatment-emergent adverse event (TEAE). Drug-related TEAEs were documented in 13 patients (16.3%). No TEAE leading to drug discontinuation occurred. A TEAE-related death was documented in 1 patient (1.3%). Serious AEs were reported in 12 patients (15.0%). No SAEs led to drug discontinuation or were considered drug-related. The most frequently reported TEAEs by system organ class were infections and infestations (27.5%), followed by gastrointestinal disorders (25.0%), respiratory, thoracic and mediastinal disorders (23.8%), followed by nervous system disorders (17.5%), general disorders and administration site conditions and injury, poisoning and procedural complications (both 16.3%), and blood and lymphatic system disorders (13.8%). The most frequently reported TEAEs by preferred term were accidental overdose (without associated AEs, 15.0%), upper respiratory tract infection (13.8%), dizziness and headache (both 8.8%), anaemia and cough (both 7.5%), oedema peripheral, haemoptysis, pulmonary hypertension (all 6.3%), vertigo, gastroesophageal reflux disease, and hypotension (all 5.0%). In the total population, 4 patients (5.0%) experienced treatment-emergent hypotension: 3 (5.9%) from the PAH population and 1 (3.4%) from the CTEPH population. Treatment-emergent haemoptysis or pulmonary haemorrhage occurred in 5 patients (6.3%), 1 (1.3%) of which was assessed as drug-related and 1 (1.3%) was assessed as serious. Results for indicators of efficacy (6MWD, Borg Dyspnea Index, hemodynamic measurements, and biomarkers) had many missing data points and varied greatly between patients. No additional outpatient visit was noted at Follow-up visits 1, 3, and 6. One patient (1.4%) had an additional outpatient visit reported at Follow-up visit 2. Three patients each had additional outpatient visits reported at Follow-up visits 4 and 5 (5.3% and 4.3%, respectively). No patient had home care or nursing care during the study. One patient each had stayed at a pulmonary rehabilitation facility / hospital since the last visit at Follow-up visits 1 and 4. Compared with Adempas® pre-treated patients (n=57), Adempas® newly treated patients (n=23) had a shorter mean (±SD) disease duration (2.8 [±2.5] versus 8.3 [±2.8] years), a lower proportion of Adempas® monotherapy at baseline (30.4% versus 64.9%), a higher proportion of prior PH-targeted therapy (82.6% versus 7.0%), a higher

	proportion of concomitant PH-targeted therapy (69.6% versus 35.1%), and a higher mean value of Borg Dyspnea Index (2.75 versus 1.68 at baseline and 2.84 versus 1.59 at the last available visit). There was only 1 patient who was taking Adempas® at a daily dose of 4.5 mg (1.5 mg 3 times a day [tid]), and 67 patients were at a daily dose of 7.5 mg (2.5 mg tid). The dose-response effect comparative analysis and benefit-risk assessment between maintenance single doses (titrated up to) 1.5 mg tid and 2.5 mg tid was not feasible in the EXPERT China study given the very small number of patients (less than 5) per category.
Discussion	The results of PASS EXPERT China revealed no new safety signals in relation to treatment with Adempas® in the approved indications of PAH and CTEPH in patients in China. Incidence of TEAEs and treatment-emergent haemoptysis and hypotension was low and in line with the known safety profile. The observed safety profile in EXPERT China is consistent with the information from Core Company Data Sheet and package insert of Adempas®. Benefit-risk balance of Adempas® in the approved indications remains positive.
Marketing Authorization Holder	Bayer AG 51368 Leverkusen, Germany
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators and sites participating in the study are listed in Section 16.1.4.

2 LIST OF ABBREVIATIONS

6MWD	6-Minute Walk Distance
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
ARO	Academic Research Organization
BCRP	Breast Cancer Resistance Protein
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BPA	Balloon Pulmonary Angioplasty
cGMP	Cyclic Guanosine Monophosphate
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CYP	Cytochrome P450
DLCO	Diffusing Capacity for Carbon Monoxide
DMP	Data Management Plan
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EQ-5D	EuroQoL 5 Dimensions Questionnaire
ERA	Endothelin Receptor Antagonist
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INR	International Normalized Ratio
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
mPAP	Mean Pulmonary Arterial Pressure
NMPA	National Medical Products Administration
NO	Nitric Oxide
NT-pro BNP	N-terminal pro Brain Natriuretic Peptide
NYHA	New York Heart Association
P-gp	P-glycoprotein
$PaCO_2$	Partial Pressure of CO_2
PAH	Pulmonary Arterial Hypertension
PaO_2	Partial Pressure of O_2
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study

PCWP	Pulmonary Capillary Wedge Pressure
PDE-5	Phosphodiesterase Type 5
PEA	Pulmonary Endarterectomy
PH	Pulmonary Hypertension
PT	Preferred Term
PVR	Pulmonary Vascular Resistance
Qp	Pulmonary Blood Flow Index
Qs	Systemic Blood Flow Index
RAP	Right Atrial Pressure
Rp	Pulmonary Vascular Resistance Index
Rs	Systemic Vascular Resistance Index
RHC	Right Heart Catheterization
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
sGC	Soluble Guanylate Cyclase
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
sTfR	Soluble Transferrin Receptor
TEAE	Treatment-Emergent Adverse Event
tid	3 Times a Day
TLC	Total Lung Capacity
VAS	Visual Analogue Scale
VKA	Vitamin K Antagonists
WHO FC	World Health Organization Functional Class

3 ETHICS, INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

3.1 Ethics

3.1.1 Independent Ethics Committee or Institutional Review Board

The protocol and protocol amendment were reviewed and approved by each study site's Independent Ethics Committee (IEC) before the start of the study. A list of IECs consulted can be found in Section 16.1.3.

3.1.2 Ethical Conduct of the Study

The study was carried out within an approved indication in accordance with guidelines and regulations of China National Medical Products Administration (NMPA) and applicable local law(s) and regulation(s). International Council for Harmonisation guideline E6: Good Clinical Practice (GCP) guidelines and China GCP were followed whenever possible.

3.1.3 Patient Information and Consent

An informed consent form (ICF) explaining the procedures of the study including the potential hazards was reviewed and approved by the IECs before its use. Only after the patient signed the ICF was he/she able to enter the study. If the patient was not capable of providing a signature, an oral statement of consent could be given in the presence of a witness. Each patient or representative received a signed and dated copy of the ICF.

A sample ICF and written information given to the patients are provided in Section 16.1.3.

3.2 Investigators and Study Administrative Structure

The study operations were outsourced to a contract research organization (CRO) (Covance, Inc.) including the preparation and finalization of the clinical study report (CSR). Data management and statistical analysis were outsourced to an academic research organization (ARO) (GWT-TUD GmbH).

The study was conducted at 9 study sites in China. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug. At each center, the coordinating investigator was responsible for the study. Contact details of the principal and/or coordinating investigators for each site participating in the study are listed in Section 16.1.4. The signatures of the principal investigators are located in Section 16.1.5.

3.3 Competent Authorities

As applicable according to local regulations, the protocol and protocol amendment were reviewed and approved by NMPA.

4 OTHER RESPONSIBLE PARTIES

Shared responsibilities	
1. Merck/MSD Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. 2000 Galloping Hill Road, Kenilworth, NJ 07033, USA	Clinical director Clinical scientist Clinical operation lead Study epidemiologist Study statistician Study data manager
2. Bayer AG 51368 Leverkusen, Germany	Regulatory strategist Study safety lead Qualified person responsible for pharmacovigilance
3. ARO: GWT-TUD GmbH Clinical Research/Epidemiological Center Freiberger Straße 33 D-01067 Dresden, Germany	Data manager Study statistician
4. CRO: Covance, Inc. Building No.9, 338 Jialilue Road Zhangjiang Hi-Teck Park, Pudong New Area, Shanghai, 201203, China	Project director Project manager Medical monitor Clinical team lead Patient safety solutions Global regulatory submission Clinical ancillary supply service Medical writer

5 MILESTONES

Milestone	Actual date	Comments
Start of data collection	27-MAR-2019	The date that first site was ready to transition a patient from PATENT-2 study or CHEST-2 study or enroll a new patient
End of data collection	26-NOV-2020	Date of database lock
Registration in the European Union Post-Authorization Study register	12-FEB-2021	NA
Registration in China Center for Drug Evaluation register	29-DEC-2018	NA
Final report of study results	10-MAR-2021	NA

6 RATIONALE AND BACKGROUND

Pulmonary Arterial Hypertension (PAH) is a rare, progressive, and life-threatening disease. It

is characterized by a chronic increase in pulmonary vascular resistance (PVR), due to progressive vascular remodeling that can ultimately lead to right heart failure and death [1,2]. Symptoms of PAH are related to right heart failure and include exercise-induced dyspnea, exhaustion, leg edema, and decreased quality of life. The survival rates of Chinese patients with idiopathic PAH and familial PAH on conventional therapy at 1 and 3 years were 68.0% and 38.9%, respectively [3]. With the targeted therapy, the survival rates at 1 and 3 years increased to 84.1% and 70.6%, respectively [4]. According to another retrospective cohort study from China, 1- and 3-year survival estimates were 92.1% and 75.1%, respectively, in patients with idiopathic PAH, and 85.4% and 53.6%, respectively, in patients with connective tissue disease-associated PAH. Though survival improved, PAH still imposes enormous burden in Chinese patients [5]. Available PAH-specific treatments include prostacyclin analogues, endothelin receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE-5)-inhibitors. The available drugs predominantly act as vasodilators and improve exercise capacity [6]. Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a different progressive and life-threatening type of pulmonary hypertension (PH). Whereas symptoms, as well as epidemiology, of CTEPH are similar compared with PAH, there are significant differences regarding etiology, diagnosis, and treatment [7,8]. In CTEPH, the increase in PVR is a result of a pulmonary artery obstruction by residual organized thrombi [9]. A ventilation perfusion scan is important for differential diagnosis as a normal scan excludes CTEPH [1]. The standard and potentially curative treatment for CTEPH is pulmonary endarterectomy (PEA). However, 20% to 40% of patients are not eligible for surgery and, in 10% to 15% of patients, PH may persist or reoccur after surgery [10-13]. Specific PAH drugs had failed in the past to show efficacy in inoperable CTEPH and, before Adempas®, no drug treatment had been approved for these patients [14].Adempas® is the first member of a new class of drugs, the soluble guanylate cyclase (sGC)-stimulators. It restores the nitric oxide (NO)-sGC-cyclic guanosine monophosphate (cGMP) pathway and leads to increased generation of cGMP which plays an important role in regulating vascular tone, proliferation, fibrosis, and inflammation. Adempas® directly stimulates sGC independently of NO, while also increasing the sensitivity of sGC to NO. This appears to be of importance as PH is associated with pulmonary endothelial dysfunction and can be related to low levels of NO [15-19].Adempas® is the first drug that could demonstrate robust efficacy in 2 placebo-controlled, multicenter trials in 2 different indications of PH. In the CHEST-1 study, Adempas® showed, for the first time, robust clinical efficacy in patients with inoperable chronic thromboembolic PH, in patients with persistent CTEPH after surgery [20]. Adempas® significantly improved exercise capacity as well as relevant secondary endpoints such as hemodynamics and World Health Organization Functional Class (WHO FC). In the PATENT-1 study in PAH patients, Adempas® showed significant improvement in exercise capacity in treatment-naïve patients as well as in patients pre-treated with ERAs or nonintravenous prostacyclin analogues [21]. At the same time, a consistent significant improvement across the secondary endpoints including hemodynamics, WHO FC, and time to clinical worsening could be demonstrated. In both studies, Adempas® was well tolerated with a good safety profile [22**Error! Reference source not found.**].

Adempas® was approved in China in SEP-2017. It is approved to treat the patients with the following indications:

Chronic thromboembolic pulmonary hypertension (CTEPH)

For the treatment of adult patients with WHO FC II to III with persistent/recurrent CTEPH after surgical treatment, or inoperable CTEPH, to improve exercise capacity.

Pulmonary arterial hypertension (PAH) As monotherapy, or used in combination with ERAs or prostanoid, Adempas® is indicated for the treatment of adult patients with PAH with WHO FC II to III to improve exercise capacity. The confirmatory trial enrolled the PAH population including etiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease with WHO FC II to III.

In agreement with European Medicine Agency, EXPERT, a global, multicenter, prospective, uncontrolled, noninterventional cohort registry of patients treated with commercial riociguat, designed to collect information about the long-term safety of Adempas® in real clinical practice outside the regulated environment of a controlled clinical study, was implemented after European Union registration. During review of the Adempas® marketing application in China, NMPA requested a safety registry study in China. The proposed China registry was based on the global EXPERT study with consideration for local regulatory requirements. Also considering the difficulty of local patients' ability to afford the drug, the Sponsor provided Adempas® at no charge. However, the noninterventional nature of the study was not changed, and all data collected were based on real-life clinical practice.

The registry was a multicenter prospective study of patients treated with Adempas® in accordance with the local label. It was to capture data from patients with Adempas® treatment in a real-life clinical setting and outside the regulated environment of a controlled clinical study.

The objective of the registry was to describe the safety profile of Adempas® under clinical practice conditions. In addition, the registry offered a structured prospective collection of data on the clinical effect, and resource use, and could be used to gather information on how Adempas® was used by PH experts.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 Primary Objective

The primary objective was the assessment of long-term safety of Adempas® in real-life clinical practice.

7.2 Secondary Objectives

The secondary objectives in this study were:

- Long-term safety of Adempas® in the different PH indications (PAH, CTEPH)
- Effectiveness of Adempas® (including clinical worsening) in the long-term follow-up of PH patients

- Information on resource use
- Information on how Adempas® was used (eg, indication and indication subgroups, dose)

8 AMENDMENTS AND UPDATES

Amendment Number	Main Reason for Amendment	New version number	Effective Date
AM01	To clarify the patient eligibility criteria, prior and concomitant medications, statistical considerations and update responsible parties, MAH and define sponsorship.	MK-4836-001-01	27-MAR-2019

9 RESEARCH METHODS

9.1 Study Design

EXPERT China was a national, multicenter, prospective, single-arm study documenting data from patients with PH treated with commercial riociguat (Adempas®) for the locally approved indications of PH. The China registry was based on the global EXPERT study with consideration for local regulatory requirements. Also considering the difficulty of local patients' ability to afford the drug, the Sponsor provided Adempas® at no charge. However, the noninterventional nature of the study was not changed, and all data collected were based on real-life clinical practice.

All patients prescribed with Adempas® for a medically appropriate use, who consented to participate, and fulfilled the selection criteria were eligible for enrollment into the study. Patients were followed up for an observation period of at least 1 year or until 30 days after the end of Adempas® therapy. The enrollment period to obtain the required 80 patients was 4 months (27-MAR-2019 to 29-JUL-2019). The patient's clinical information was documented at time of the initial visit and approximately every 3 to 6 months according to routine clinical practice thereafter. Data collection continued until 30 days after the end of Adempas® therapy. Serious adverse events (SAEs) were followed up until resolution. The study was conducted in accordance with good pharmacovigilance practices. The decisions on clinical management of the patient, including the actual treatment duration, were determined solely by the Investigator.

9.2 Setting

This China only Post-Authorization Safety Study (PASS) started after Adempas® was authorized and made commercially available in China. A total of 80 patients were enrolled under the responsibility of the investigators. At the time of the final clinical database lock (26-NOV-2020), 80 patients were enrolled across 9 sites in China.

EXPERT China was conducted from 27-MAR-2019 (first patient, first visit) to 27-SEP-2020 (last patient, last visit).

9.3 Patients

9.3.1 Eligibility

Patients who had been prescribed Adempas® for a medically appropriate use were eligible to be included into this registry. Indications and contraindications according to the local Chinese label for Adempas® should have been carefully considered.

Inclusion Criteria:

- Patients who have been diagnosed with PAH or CTEPH
- Female and male patients who started or were on treatment with Adempas®
- WHO FC II to III for patients newly treated with Adempas®
- Written informed consent

Exclusion Criteria:

- Patients participating in an interventional clinical trial (if a patient was currently in the CHEST or PATENT [riociguat] long-term extension trials, the patient could be considered for transition into EXPERT China study after the last dosing of riociguat)
- Female patient who was pregnant
- Patients with severe hepatic impairment (Child-Pugh grade C)
- Patients with systolic blood pressure (BP) <95 mmHg and who were newly treated with Adempas®
- Patients who had been diagnosed with idiopathic interstitial pneumonia
- Coadministration with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE-5 inhibitors (such as dipyridamole or theophylline)
- Coadministration with nitrates or NO donors (such as amyl nitrite) in any form
- Any condition which, in the opinion of the investigator, may have confounded the results or resulted in unwarranted risk in administering Adempas® to the patient

9.4 Variables

The investigator collected historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator

collected treatment-related data during initial visit and follow-up visits based on assessments that were performed routinely. The investigator documented the study-relevant data for each patient in the case report form (CRF). The sample CRF is listed in Section 16.1.2. A tabulated overview on variables collected during the study is displayed in Table 9-1.

Table 9-1: Tabulated Overview on Variables Collected During the Study

Variables	**Initial visit**	**Follow-up visit(s)**	**Final visit**
Demographics	X	X	X
Medical history	X		
Concomitant disease	X	X	X
Adverse Events**	X	X	X
PH etiology	X		
Pregnancy status	X	X	X
Smoking history/status	X	X	X
Systemic BP before start of Adempas®	X		
6-minute walk test*	X	X	X
WHO FC*	X	X	X
Borg dyspnea index*	X	X	X
EQ-5D VAS*	X	X	X
Hemodynamic measurements, lung function, cardiac rhythm*	X	X	X
Biomarkers*	X	X	X
Laboratory tests*	X	X	X
Treatment medication	X	X	X
Concomitant medication	X	X	X
Resource use in hospital and outpatient care	X	X	X

Abbreviations: BP = blood pressure; EQ-5D = EuroQoL 5 dimensions questionnaire; PH = pulmonary hypertension; VAS = visual analogue scale; WHO FC = World Health Organization Functional Class.
* If data were available and done as per standard of care
**Serious adverse events had to be reported to Bayer within 24 hours.

The variables for the primary objective were:

- Incidence of adverse events (AEs) and SAEs
- Incidence of all-cause mortality

The outcome variables for the secondary objectives were:

- AE and SAE in different PH indications (PAH, CTEPH)
- AEs of interest
    - Symptomatic hypotension (date BP measurement, symptoms)
    - Haemoptysis and pulmonary haemorrhage (serious and non-serious).

Specific information regarding relevant history, current condition, diagnostics, treatment, specific laboratory values, and outcome to be documented in a specific CRF section in case AE/SAE of interest occurred

- Measurements of clinical effect
    - 6-minute walk distance (6MWD)
    - WHO FC
    - Borg Dyspnea Index
    - EuroQoL 5 dimensions questionnaire (EQ-5D) visual analogue scale (VAS)
    - Haemodynamic parameters from right heart catheterization (RHC) measurement
    - Biomarkers
- Resource use
    - Hospitalization (due to PH or other reason, emergency admission, intensive care unit, number of days)
    - Outpatient visits at PH center
    - Home care (nurse, days per week, hours per day)
    - Drug use, including switch or interruption or discontinuation of Adempas® and associated reason
- Clinical Worsening

As an additional effectiveness outcome, rates of clinical worsening events and time to clinical worsening (the latter for Adempas® newly treated patients only) were reported descriptively (no combined measures were used). This report includes a statement on limitations around these endpoints.

The following conditions were listed as indicators for clinical worsening:

In patients with PAH:

- All-cause death
- Heart/lung transplantation
- Atrial septostomy
- Hospitalization due to PH

- Start of new PH-specific treatment
- Decrease of more than 15% from baseline or more than 30% compared to the last study-related measurement in 6MWD due to worsening PH (based on medical note)
- Worsening of functional class due to worsening PH (based on medical note)

In patients with CTEPH:

- All-cause death
- Heart/lung transplantation
- PEA
- Hospitalization due to PH
- Start of new PH-specific treatment
- Decrease of more than 15% from baseline or more than 30% compared to the last study-related measurement in 6MWD due to worsening PH (based on medical note)
- Worsening of functional class due to worsening PH (based on medical note)

- Demographics

For demographic/socio-demographic assessment, the following data were recorded:Year of birth

- Sex
- Height and weight

Comorbidities were any medical findings, whether they pertained to the study indication, that were present before start of therapy with Adempas®, independent of whether they were still present.

Findings meeting the criteria listed below were relevant to the study indication and should have been documented if collected as part of routine clinical practice:

- Date of first PH diagnosis (month/year)
- Etiology of PH according to Nice Classification 2013, subgroups of CTEPH (inoperable, postsurgery), subgroups of PAH (monotherapy, combination therapy)
- Relevant concomitant diseases (eg, vascular disease, diabetes, cancer)

  - Date of diagnosis

- History of haemoptysis (date frequency, severity, bronchial arterial embolization, other pulmonary disease, trauma)

- Hepatic impairment (no/yes)

  - Child-Pugh classification

- Renal impairment (no/yes)

  - Severity

  - Estimated glomerular filtration rate (eGFR) by Cockroft-Gault formula

For any comorbidity, the specific diagnosis as well as start and stop dates/ongoing had to be documented.

- Pregnancy

- Smoking (history, current status)

- 6MWD (date and distance in meters)

- WHO FC with date

- Borg Dyspnea Index with date

- EQ-5D VAS score with date

- Haemodynamic measurements

  - Date

  - Mean pulmonary arterial pressure (mPAP, mmHg)

  - PVR (dyn*sec*cm^{-5})

  - Pulmonary capillary wedge pressure (PCWP, mmHg)

  - Right atrial pressure (RAP, mmHg)

  - Cardiac index (L/min/m^2)

- Cardiac rhythm with date (categories: normal sinus rhythm, atrial fibrillation, atrial flutter, or other arrhythmia)

- Lung function with date

- Total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), diffusing capacity for carbon monoxide (DLCO), partial pressure of O_2 (PaO_2), partial pressure of CO_2 ($PaCO_2$), oxygen supply during blood gas analysis

- Biomarkers with date
  - Brain Natriuretic Peptide (BNP; pg/mg or pmol/L)
  - N-terminal pro Brain Natriuretic Peptide (NT-pro BNP, pg/mg or pmol/L)
- Laboratory tests
  - Date
  - Hemoglobin
  - Hematocrit
  - International normalized ratio (INR) (if on Vitamin K Antagonists [VKA] treatment)
  - Creatinine
  - Transaminases (alanine transaminase [ALT]/aspartate transaminase [AST])
- Additional laboratory tests for patients with congenital heart disease only
  - Date
  - Uric acid
  - Sodium
  - Iron, ferritin, transferrin, soluble transferrin receptor (sTfR), sTfR-ferritin index
  - C-reactive protein
  - Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)
  - Homocysteine
- Prior and concomitant medications (according to the criteria listed in Section 6.3.16 of the protocol, Section 16.1.1)
  - Trade name and International Nonproprietary Name

- Start and stop date
- Date of dose change, switch or addition of a specific drug/Adempas®
- Reason for change (lack of efficacy or tolerability, patient's request, administrative)
- Dose
- Unit
- Frequency
- Administration mode
- Indication

- Additional information on Adempas® :
  - Individual dose after initial dose adjustment period
  - BP before the first administration

9.5 Data Sources and Measurement

The investigators collected current and historic patient data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collected treatment-related data during visits that took place in routine practice. Each patient was identified by a unique central patient identification code, which was only used for study purposes. For the duration of the study and afterwards, only the patient's investigator was able to identify the patient based on the patient identification code. The investigator documented the study-relevant data for each patient in the CRF. The sample CRF is included in Section 16.1.2.

9.6 Bias

Several sources for bias may exist (ie, selection biases in patient recruitment, information bias due to missing values as well as recall bias if the information was not in the medical chart and the investigator needed to ask the patient for medical history). To reduce patient selection bias, physicians documented consecutive patients who received Adempas® and provided informed consent. Missing data are a common methodological problem in registries due to the observational nature of this study type, recognizing specific clinical tests cannot be mandated. To decrease information bias, 100% source data verification was performed in all the study sites to check for completeness, accuracy, plausibility, and validity of the documented data. The distribution of missing values is reported for each variable in the analyses. No missing values were imputed.

9.7 Study Size

Sample size was determined by feasibility, and was set to 80 patients at study initiation.

9.8 Data Transformation

Patient data consistency checks, derived variables, coding of medical terms, and concomitant medication were described in detail in the Data Management Plan (DMP).

Statistical transformations including calculated variables and proposed format and content of tables were detailed in the Statistical Analysis Plan (SAP).

9.8.1 Data Management

An ARO was selected and assigned for electronic data capture (EDC) system development. The CRF was part of the EDC system which allowed documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system will be available upon request. Detailed information on data management, including procedures for data collection, retrieval, and preparation, is provided in the DMP, which will be available upon request.

One hundred percent source document verification was conducted on all study data. The purpose was to review the documented data for completeness and plausibility, adherence to the study protocol, and verification with source documents. To accomplish this, monitors accessed medical records on site for data verification. Detailed measures for quality reviews were described in the Site Monitoring Plan.

9.9 Statistical Methods

Statistical analyses were conducted by using the software package SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). All collected variables and outcome parameters were analyzed descriptively with appropriate statistical methods.

9.9.1 Main Summary Measures

Categorical variables were reported in frequency tables including information about absolute and relative frequencies and the number of missing values.

Continuous variables were analyzed by showing the (i) sample mean and its standard deviation (SD) and (ii) the median (50^{th} percentile), minimum, and maximum.

Categorical and continuous variables were described by absolute value and as change from baseline per analysis time point, if applicable.

The 95% confidence intervals (CIs) for incidence proportions were calculated by the Pearson-Clopper method and by Poisson rate CIs for incidence rates for AEs of interest.

The incidence rate was the number of AEs divided by the cumulative person time on treatment (person-years). The incidence rate was reported as number of AEs per 100 total person-years of drug exposure.

Time-to-events endpoint was described by Kaplan-Meier curve.

All statistical analyses were conducted in the total population and separately for PH subtype (PAH, CTEPH).

9.9.2 Main Statistical Methods

9.9.2.1 Population Characteristics

The number of patients enrolled and included in the safety population was tabulated. The reasons for patients being excluded from analyses were also analyzed.

All background data such as patient demographics (Table 9-2) and clinical characteristics (Table 9-3) at baseline were described by presenting absolute and relative frequencies and the number of missing values or summary statistics (mean, SD, median, minimum, and maximum), if appropriate.

Table 9-2: Categorized Demographic Characteristics

Characteristics	**Category**
Sex	male, female
Age (years)	<65, ≥65
Body mass index (kg/m²)	<18.5, ≥18.5 to <25, ≥25 to <30, ≥30
Weight (kg)	≤60, >60 to <90, ≥90
Smoking status	never, former, current
Pregnancy	yes, no

Table 9-3: Primary Diagnosis and Clinical Characteristics at Baseline

Characteristics	**Category**
NYHA / WHO functional class	I, II, III, IV, unknown
Newly diagnosed patient	Yes (inclusion within 6 months of diagnosis), no, unknown
PAH/ PH subtype	PAH, CTEPH
Type of PAH (PAH patients only)	Idiopathic PAH/heritable PAH, PAH associated with connective tissue disease, PAH associated with congenital heart disease, other
Patient status with respect to surgery (CTEPH patients only)	Surgically accessible, inoperable due to peripheral localization of the thrombus, persistent PH following PEA, persistent PH following balloon pulmonary angioplasty, inoperable due to comorbidities, operability under investigation (not yet decided), PEA or surgical assessment declined by the patient
Patient status with respect to surgery, categories	Inoperable (inoperable due to peripheral

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

(CTEPH patients only)	localization of the thrombus, inoperable due to comorbidities) Postsurgery (persistent PH following PEA, persistent PH following balloon pulmonary angioplasty) Other (surgically accessible, operability under investigation [not yet decided], PEA or surgical assessment declined by the patient)
Comorbidities (coronary heart disease, arterial hypertension, venous thromboembolism, diabetes mellitus, thyroid disease, obstructive sleep apnea, cancer, history of hemoptysis/ lung bleeding, hepatic impairment, renal impairment, any other comorbidities)	No, yes, unknown
6-minute walk distance in meters	(i) <320, ≥320 (ii) <380, ≥380
Systolic blood pressure (mmHg)	(i) <95, ≥95 (ii) <110, ≥110
Invasive hemodynamics	No invasive measurements were performed to date, Right Heart Catheterization
Cardiac rhythm	Sinus rhythm, atrial fibrillation, atrial flutter, other, unknown
Creatinine clearance/eGFR (mL/min)	(i) <30, ≥30 to <50, ≥50 to <80, ≥80 [a] (ii) <30, ≥30 to <60, ≥60 to <90, ≥90 [b]

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PEA = pulmonary endarterectomy; PH = pulmonary hypertension; WHO = World Health Organization.
[a] According to FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function (1998)
[b] According to FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function (Draft 2010).

9.9.2.2 Adempas® Treatment Data

For each patient, the duration of Adempas® treatment in the observational period (date of study enrollment or Adempas® start in the observational period until last observation) was derived in days and months. Treatment interruptions (ie, no treatment for at least one day) were ignored. Descriptive characteristics of treatment duration in days and months were presented in summary tables. Reasons for treatment discontinuation were presented in a frequency table.

Descriptive statistics were used for analyzing the initial daily dose of Adempas®, daily doses used at any time in the study, the number of patients with at least one dose change, the total number of dose changes, and the reason for dose changes.

The number of patients with at least one interruption, the total number of interruptions, the duration of interruptions, and reasons for interruptions were tabulated by visit.

These analyses were also provided for Adempas® newly treated patients and Adempas® pre-treated patients (Adempas® newly treated patients are defined as patients who started

Adempas® within 3 months prior to or on the date of enrollment. Adempas® pre-treated patients had already been treated with Adempas® more than 3 months before enrollment into the study).

9.9.2.3 Pre- and Concomitant Medication

General summary tables of concomitant medications by Anatomical Therapeutic Chemical (ATC) class and subclass were prepared and present the frequencies of patients with medications that were ongoing at or began after the start of Adempas®.

Prior and current PH-targeted therapies (Table 9-4) were reported separately.

Table 9-4: Categorized Prior and Current PH-targeted Therapy

Characteristics	**Category**
ERA	no, yes (bosentan, ambrisentan, macitentan)
PDE-5 Inhibitors	no, yes (sildenafil, tadalafil)
PCA	no, yes (epoprostenol, treprostinil, iloprost, beraprost)
Other PH/PAH-targeted therapy	no, yes (calcium channel blocker, other)
Anticoagulation including platelet inhibitors	no, yes (vitamin K antagonists, others)
Reasons for discontinuation of Adempas® (patients with discontinued therapy only)	unknown, lack of efficacy or tolerability, patient's request, administrative, other
Monotherapy of Adempas® at baseline	no, yes (treatment with Adempas® without use of ERA, PDE-5 inhibitor, PCA, other PH/PAH-targeted therapy)
Combination therapy of Adempas® at baseline	no, yes (treatment with Adempas® in combination with ERA, or PDE-5 inhibitor, or PCA, or other PH/PAH-targeted therapy)

Abbreviations: ERA = endothelin receptor antagonist; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; PDE-5 = phosphodiesterase type 5; PH = pulmonary hypertension.

9.9.2.4 Primary Outcome Variables

The main study aim was to estimate the incidence of AEs, SAEs, and all-cause mortality under Adempas® in a real-life setting. All AEs and SAEs reported in this study were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0). Tables which show the incidence proportion of AEs overall and by MedDRA preferred term (PT) within the primary system organ class (SOC) were also presented.

The incidence proportions were presented as well as incidence rates per person-time under Adempas® treatment.

The incidence proportion was the number of patients with at least one AE divided by the number of treated patients. The incidence rate was the number of AEs divided by the cumulative person time on treatment (person-years). The incidence rate was reported as number of AEs per 100 total person-years of drug exposure.

The incidence proportion and incidence rates of AEs, SAEs, and all-cause mortality were calculated separately for Adempas® newly or pre-treated patients.

The statistics were calculated for all patients and stratified for medically relevant **subgroups (if approximately 5 or more patients per category were present)**. Medically relevant subgroups were defined by characteristics at baseline as specified in Table 9-2 and Table 9-3.

The subgroup 'type of PH pre-treatment' included the categories:

- therapy-naïve (eg, newly treated with Adempas®)
- pre-treated with any single PH-specific drug
  - pre-treated with ERA (bosentan, ambrisentan, macitentan)
  - pre-treated with PDE-5 inhibitor (sildenafil, tadalafil)
  - pre-treated with prostacyclin analogues (epoprostenol, iloprost, other prostacyclin analogues)
  - pre-treated with concomitant other drugs used for PH (calcium channel blockers)
  - pre-treated with Adempas®
- pre-treated with a combination of PH-specific drugs

9.9.2.5 Secondary Outcome Variables

Secondary outcome variables were defined in Section 9.4.

For the AEs of special interest, the incidence proportions, incidence rates per person-time under Adempas® treatment, and exact 95% CI were presented (see Section 9.9.1).

Furthermore, a Kaplan-Meier table and plot described the time course until the first event of special interest. Patients who did not experience the event until end of Adempas® therapy plus 2 days were right-censored.

Effectiveness analyses were based on the variables: 6MWD, New York Heart Association (NYHA)/WHO FC, Borg Dyspnea Index, EQ-5D VAS, hemodynamic measurements, and biomarkers. The change from baseline in each variable under Adempas® treatment were calculated and reported in summary tables for the total population and medically relevant subgroups where sample size was adequate.

As an additional effectiveness outcome, rates of clinical worsening events and time to clinical worsening (the latter for Adempas® newly treated patients only) were reported descriptively (no combined measures were used). The report included a statement on limitations around these endpoints.

The following conditions were listed as indicators for clinical worsening:

In patients with PAH:

- All-cause death
- Heart/lung transplantation

- Atrial septostomy
- Hospitalization due to PH
- Start of new PH-specific treatment
- Decrease of more than 15% from baseline or more than 30% compared to the last study-related measurement in 6MWD due to worsening PH (based on medical note)
- Worsening of functional class due to worsening PH (based on medical note)

In patients with CTEPH:

- All-cause death
- Heart/lung transplantation
- PEA
- Hospitalization due to PH
- Start of new PH-specific treatment
- Decrease of more than 15% from baseline or more than 30% compared to the last study-related measurement in 6MWD due to worsening PH (based on medical note)
- Worsening of functional class due to worsening PH (based on medical note)

Information on resource use and information on how Adempas® was used (eg, indication and indication subgroups, dose) were analyzed in frequency tables. The analyses include the following variables:

- Hospitalization (due to PH or other reason, emergency admission, intensive care unit, number of days)
- Outpatient visits at PH center
- Home care (nurse, days per week, hours per day), home rehabilitation/nursery (days)
- Drug use, including switch or interruption or discontinuation of Adempas® and associated reason

9.9.2.6 Therapy

The number and proportion of patients on monotherapy and combination therapy of Adempas® were reported at each visit by frequency tables. Changes in therapy of Adempas® after baseline (monotherapy at baseline to combination therapy, combination at baseline to monotherapy at each visit, and no change in therapy) were reported by number and proportion at each visit.
For patients with CTEPH, the frequency of patients with surgery (PEA) or balloon pulmonary angioplasty (BPA) since last visit were presented at each visit.

9.9.2.7 Adverse Events

In addition to the analysis of the primary and secondary outcome variables, which were also safety variables, the following other safety analyses were performed.
The incidence proportion overall and by MedDRA PT within the primary SOC were shown for the following events:

- any treatment-emergent adverse event (TEAE, defined as events that started or worsened during treatment and up to 2 days after the last Adempas® dose)
- any treatment-emergent SAE (defined as SAEs that occurred during treatment and up to 2 days after the last Adempas® dose)
- any drug-related TEAE
- any serious drug-related TEAE
- any AE leading to discontinuation

The incidence rates (incidence per 100 person-years) were shown for the following events:

- any TEAE
- any treatment-emergent SAE
- any drug-related TEAE
- any serious drug-related TEAE
- any AE of special interest
- any AE of hypotension
- any AE of hemoptysis

In addition, the incidence rate for TEAEs and treatment-emergent SAEs were presented by MedDRA PT within the primary SOC.

The SOC and the PTs within the SOC were displayed alphabetically.

Patients who died were listed with indication, last dose, and duration of Adempas® treatment, as well as details from all reported AEs with fatal outcome.

For patients with lung bleedings data listings were prepared which present all information from the bleeding questionnaire. In the listing for TEAEs, lung bleedings concomitant medications were shown.

For AEs related to change of systemic BP, the BP and heart rate were documented.

Adverse event tables were produced for current smokers at baseline.

9.9.2.8 Important Potential Risks

Additional AE tables/listings were produced for patients with the following:

- Bleeding (defined by MedDRA Standardised MedDRA Queries [SMQ] "haemorrhages")
- Embryo-fetal toxicity (defined by MedDRA SMQ "pregnancy and neonatal topics")
- Renal failure (defined by MedDRA SMQ "acute renal failure")
- Pre-existing atrial fibrillation (concomitant condition defined by MedDRA PT "atrial fibrillation" or "atrial flutter")
- Listing of patients with treatment-emergent atrial fibrillation or atrial flutter (included medical history for these patients and other TEAEs)
- Bone changes and fractures (defined by MedDRA high-level group term "fractures")

9.9.2.9 Important Identified Risks

Additional AE tables/listings were produced for patients with the following:

- Haemoptysis or pulmonary haemorrhages (defined by MedDRA PT "haemoptysis" or PT "pulmonary haemorrhage") including serious and non-serious events
- Hypotension (defined by Project Bayer MedDRA Query "hypotension [Riociguat]"), also considering specific drug-drug interactions, see below
- Upper gastrointestinal motility disorders
- Smokers
- Patients under 18 years

For hypotension, the concomitant use of the following drug groups was considered:

- Patients concomitantly treated with PDE-5 inhibitors at baseline as indicated by Standardised Drug Grouping "Phosphodiesterase type 5 inhibitors", narrow scope
- Patients concomitantly treated with organic nitrates (ATC codes "C01DA", "C02DD") and molsidomin and linsidomin (from ATC code "C01DX")
- Strong multipathway cytochrome P450 (CYP) and P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) inhibitors
    - CYP inhibitors: Bayer World Health Organization drug dictionary groupings "P_Code 6" and ATC codes "CYP2C8", "CYP3A4"
    - P-gp inhibitors: Bayer World Health Organization drug dictionary groupings "B_Code 1055"
    - BCRP inhibitors: Bayer World Health Organization drug dictionary groupings "B_Code 1123"
- Strong CYP1A1 inhibitors including ketoconazole, itraconazole, posaconazole, nilotinib, lapatinib, imatinib, crizotinib, erlotinib, dasatinib, and pazopanib (ATC code "CYP1A1")

Listings were prepared if there were any patients with medical history and/or AE that included any of the following PTs: interstitial lung disease / idiopathic interstitial pneumonia / idiopathic pulmonary fibrosis / pulmonary fibrosis.

A table was presented for patients who presented with syncope (defined by MedDRA PT "Syncope", "Pre-syncope", and "Loss of consciousness").

9.9.2.10 Lung Function

The last available value for the following lung function parameters was recorded at each visit:

- % predicted TLC
- % predicted FVC
- % predicted FEV1
- % predicted DLCO
- PaO_2 (mmHg)
- $PaCO_2$ (mmHg)
- Oxygen supply during blood gas analysis (O_2 Blood Gas Analyzer, L/min)

Lung function values were presented by mean value, SD, median, minimum, and maximum. The change in lung function parameters from baseline to the specific time point was reported by mean value, SD, median, minimum, and maximum.

9.9.2.11 Right Heart Catheterization

The last available result of the RHC was used for analysis at baseline and at each follow-up. Because in many patients an RHC was only performed to establish the PAH diagnosis and not repeated thereafter, a high rate of missing values could be expected at the follow-up visits. Due to the fact that the Sponsor could not influence if and when RHC was performed, the prospect of receiving meaningful RHC data was unclear.

The following invasive hemodynamic parameters were evaluated, if available:

- Saturated venous oxygen (%)
- Saturated arterial oxygen (%)
- mPAP (mmHg)
- Transpulmonary gradient (difference between mPAP and PCWP, mmHg)
- Pulmonary blood flow index (Qp, L*min-1*m^{-2})
- Systemic blood flow index (Qs, L*min-1*m^{-2})
- Quotient of Qp and Qs (Qp/Qs, %)

- PVR (dyn*sec*cm^{-5})
- PVR index (Rp, dyn*sec*cm^{-5}*m^2)
- Systemic vascular resistance index (Rs, dyn*sec*cm^{-5}*m^2)
- Quotient of Rp and Rs (Rp/Rs, %)
- PCWP (mmHg)
- Mean RAP (mmHg)
- RAP (mmHg)
- Cardiac index (L/min/m^2)

The last available result of the RHC was presented by mean value, SD, median, minimum, and maximum.

9.9.2.12 Cardiac Rhythm

The cardiac rhythm at baseline and follow-up was presented in frequency tables. Cardiac rhythm included the categories of sinus rhythm, atrial fibrillation, atrial flutter, other, and unknown. Changes in cardiac rhythm from baseline were reported by number and proportion at each visit.

9.9.2.13 Biomarkers

In this noninterventional study, the last available value for the following laboratory parameters was intended to be recorded at each visit if clinically indicated:

- BNP (pg/mL)
- NT-pro BNP (pg/mL)
- Homocysteine (µmol/L)

Biomarkers were presented by summary statistics (mean value, SD, median, minimum, and maximum) at each visit and change from baseline.

9.9.2.14 Laboratory Data

In this noninterventional study, the last available value for the following laboratory parameters was recorded at each visit if clinically indicated:

- Hemoglobin (g/dL)
- Hematocrit (%)
- INR (if on VKA treatment)
- Creatinine (mg/dL)
- Transaminases (ALT/AST, U/L)

- Bilirubin (mg/dL)

Additional laboratory tests for patients in the Dana Point group 1.4.4 (congenital heart disease patients only):

- Uric acid (mg/dL)
- Sodium (mmol/L)
- Iron (mg/dL), ferritin (mcg/mL), transferrin (g/L), sTfR (nmol/L), sTfR-Ferritin-Index
- C-reactive protein (mg/dL)
- MCV (fl), MCH (pg), MCHC (g/dL)

Values for creatinine clearance/eGFR in mL/min were calculated at baseline and at each follow-up visit.

Laboratory data were presented by summary statistics (mean value, SD, median, minimum, and maximum) at each visit and change from baseline.

9.9.3 Missing Values

Sites were reminded to document all the available follow-up visits and take measures to achieve low dropout rates during the study. As the analyses were based on all patients who received Adempas® for at least one dose, patients who stopped the study prematurely were also part of the safety analysis population. Consequently, those patients were censored at date of last contact. Reasons for discontinuation were shown in a frequency table.

The frequency of missing values was assessed in detail. Percentages were calculated as the proportion in each category including the category of missing values. The frequency of missing values was also calculated for continuously distributed variables.

No missing values were imputed except for incomplete calendar dates such as start and discontinuation dates and dates for dose changes of Adempas®, start and stop dates of AEs, and date of initial PH/PAH diagnosis.

Start and discontinuation dates as well as dates for dose changes of Adempas® that were missing completely were not imputed for the analysis. In cases where the start or stop date of Adempas® treatment or the start date of an AE was incomplete but at least some information (such as month or year) was available, the date was imputed based on the following rules:

Partially missing dates for start of Adempas® treatment were set to the earliest logically possible date:

- In case only the day was missing, the date was imputed as the maximum of (date of initial visit, day of incomplete date replaced by first day of the month).

- In case the day and the month were missing (ie, only the year was available), the date was imputed as the maximum of (date of initial visit, day and month of incomplete date replaced by January 1st).

In the cases where the start date was missing completely and parts of the stop date were available, the start date was replaced with the date of initial visit, since information was available that the patient took Adempas®.

Partially missing dates for stop of Adempas® treatment were set to the latest logically possible date:

- In case only the day was missing, the date was imputed as the minimum of (date of death, date of visit at which Adempas® discontinuation was reported, date of last contact, day of incomplete date replaced by last day of the month).
- In case the day and the month were missing (ie, only the year was available), the date was imputed as the minimum of (date of death, date of visit at which Adempas® discontinuation was reported, day and month of incomplete date replaced by December 31st).

Date of last contact was considered as the maximum of (date of end of observation, latest AE start date, latest date for follow-up visits).

Dates of AEs:

- In case that only the day was missing, the date was imputed as the maximum of (date of start of Adempas® treatment, day of incomplete date replaced by first day of the month).
- In case that the day and the month were missing (ie, only the year was available), the date was imputed as the maximum of (date of start of Adempas® treatment, day and month of incomplete date replaced by January 1st).

Date of initial PH/PAH diagnosis:

- In case only the day was missing, the day was imputed by the first of the month.
- In case the day and month were missing, the day was imputed by the first of the month and the month was imputed by the sixth month of the year.

9.9.4 Data Rules

Baseline was generally defined as documentation at enrollment into the study.

Post-treatment values were considered to be on treatment if measured within the time window of the 2 calendar days after the day study drug administration stopped.

An AE was considered as emergent under Adempas® treatment when it had started or worsened after first application of study medication up to 2 days after end of treatment with study medication.

The follow-up visits were performed at 3- to 6-month intervals (according to the management of the individual patient) starting with the baseline assessment.

- Follow-up visit 1 included the follow-up documentation 1.5 to <4.5 months after baseline
- Follow-up visit 2 (month 4.5 - <7.5 months)
- Follow-up visit 3 (month 7.5 - <10 months)
- Follow-up visit 4 (month 10.5 - <13.5 months)
- Follow-up visit 5 (month 13.5 - <16.5 months)
- Follow-up visit 6 (month 16.5 - <19.5 months).

In case that for a patient in any time window more than one value was available, then the following rule was applied: the last available values were taken into account in summary statistics in the applicable time interval (and assigned to Follow-up visit 1, 2, 3, 4, 5, or 6).

Final visit (last observation) was performed within 30 days after discontinuation or end of study Adempas® treatment. If the date of last observation preceded the date of Adempas® start in the observational period, the treatment duration was set to be 1 day.

9.9.5 Sensitivity Analyses

No sensitivity analysis was done in this study.

9.10 Changes in the Conduct of the Study or Planned Analyses

9.10.1 Changes in the Conduct of the Study

Part of this study was conducted during the Coronavirus Disease 2019 (COVID-19) pandemic. All the clinical investigator study sites were located in China. Deviations regarding telephone visits and COVID-19 are listed in Section 16.2.2.

9.10.2 Amendments to the Planned Analyses

The first version SAP was issued on 02-JUL-2020 and was updated once on 05-NOV-2020. Section 6 was updated to indicate that 95% CIs for incidence proportions were to be calculated by the Pearson-Clopper method and by Poisson rate CIs for incidence rates for AEs of interest.

9.11 Quality Control

The Sponsor was responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures to ensure that studies were conducted and data were generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and

Pharmacoepidemiology Practice, and all applicable local laws, and rules and regulations relating to the conduct of the study.

Before the study started at the sites, all investigators were sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators had the chance to discuss and develop a common understanding of the study protocol and the CRF.

An ARO was selected and assigned for EDC system development, quality control, verification of the data collection, data analysis, and data transfer to the Sponsor.

All outcome variables and covariates were recorded in a standardized CRF. After data entry, missing or implausible data were queried, and the data were validated. A check for multiple documented patients was done.

Detailed information on checks for completeness, accuracy, plausibility, and validity were given in the DMP. The plan specified measures for handling of missing data and permissible clarifications. The DMP is available upon request.

Electronic records used for capturing patient documentation (electronic CRF, eCRF) was validated. The documentation is available upon request.

A CRO was assigned for study operation and project management. All patient data relating to the study were recorded on eCRFs. Clinical Reaserch Associates performed ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel were accurate, complete, and verifiable from source documents and that the study was being conducted in accordance with the protocol and any other study agreements, International Conference of Harmonisation GCP, and all applicable regulatory requirements.

10 RESULTS

10.1 Participants

A total of 80 patients with PH/PAH were enrolled into the study, including 23 patients (28.8%) newly starting Adempas® treatment and 57 patients (71.3%) who had already been on Adempas® for more than 3 months before enrollment, of whom 50 were transitioned from Adempas® long-term extension of clinical trials (PATENT-2 and CHEST-2)[23,24].

10.1.1 Patient Disposition

A total of 80 patients were enrolled into the study, of whom 73 completed the study. All enrolled patients took at least 1 dose of Adempas® during the observation period. Thus, 80 patients (100.0%) were evaluable for the safety analysis. No other patient set was analyzed.

The patient disposition including the number of completed observations, premature discontinuation, and the respective primary reason are given in Table 10-1. In the total

population, 7 patients (8.8%) prematurely discontinued the study with the primary reason (as reported by the physician) being lost to follow-up in 1 patient (1.3%), death in 1 patient (1.3%), and other reasons in 5 patients (6.3%).

Table 10-1: Patient Disposition

	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Completed (Regular end of observation as per protocol)	46	90.2	27	93.1	73	91.3
Not completed (per protocol)	5	9.8	2	6.9	7	8.8
Patient withdrew consent	0	0.0	0	0.0	0	0.0
Patient lost to follow-up	0	0.0	1	3.4	1	1.3
Patient died	1	2.0	0	0.0	1	1.3
Other	4	7.8	1	3.4	5	6.3

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.
Source: Table 1.1

10.1.2 Dana Point Subgroups

The breakdown of the total population according to the Dana Point classification for PAH/PH is given in Table 10-2.

Of the 80 evaluable patients, 51 patients (63.75%) had PAH and 29 (36.25%) had CTEPH. Among the 51 patients with PAH, 33 (41.3%) had idiopathic PAH, 18 (35.3%) had PAH associated with connective tissue disease, of whom 13 (16.3%) were associated with systemic lupus erythematosus, 3 (3.8%) associated with congenital heart diseases, 1 (1.3%) associated with portal hypertension, and 1 (1.3%) associated with other autoimmune rheumatic diseases.

Table 10-2: PAH / PH Etiology According to Dana Point Classification 2008

	Total N=80 (100%)	
	N	%
1. PAH	51	63.8
1.1. Idiopathic PAH	33	41.3
1.2 Heritable PAH	0	0.0
1.2.1 BMPR2	0	0.0
1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)	0	0.0
1.2.3. Unknown	0	0.0
1.3. Drug- and toxin-induced	0	0.0

	Total N=80 (100%)	
	N	**%**
1.4 Associated PAH	18	22.5
1.4.1.1. Systemic sclerosis	0	0.0
1.4.1.2. Systemic Lupus Erythematodes (SLE)	13	16.3
1.4.1.3. Mixed connective tissue disease (MCTD), anti-U1-RNP positive	0	0.0
1.4.1.4. Undifferentiated connective tissue diseases (not fulfilling any classification criteria, but evidence for autoimmune rheumatic disease)	0	0.0
1.4.1.5. Overlap (fulfilling two classification criteria)	0	0.0
1.4.1.6. Other autoimmune rheumatic diseases	1	1.3
1.4.2. HIV infection	0	0.0
1.4.3. Portal hypertension	1	1.3
1.4.4. Congenital heart diseases	3	3.8
1.4.4. Congenital heart diseases (extended CRF including Eisenmenger)	0	0.0
1.4.5. Schistosomiasis	0	0.0
1.4.6. Chronic hemolytic anemia	0	0.0
1.5 Persistent pulmonary hypertension of the newborn	0	0.0
1.6. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)	0	0.0
4. Chronic thromboembolic pulmonary hypertension (CTEPH)	29	36.3

Abbreviations: CRF = case report form; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.
Source: Table 1.3

10.1.3 CTEPH Subgroups

Among the 29 patients with CTEPH, 12 (41.4%) were inoperable due to peripheral localization of the thrombus, 6 (20.7%) had persistent PH following BPA, 6 (20.7%) were inoperable due to comorbidities, 1 (3.4%) had persistent PH following PEA, and in 4 (13.8%) the status was missing (Table 10-3).

Table 10-3: Patient Status With Respect to Surgery (CTEPH Patients Only)

	CTEPH N=29 (100%)	
	N	**%**
Inoperable due to peripheral localization of the thrombus	12	41.4
Persistent PH following pulmonary endarterectomy (PEA)	1	3.4
Persistent PH following balloon pulmonary angioplasty (BPA)	6	20.7
Inoperable due to comorbidities	6	20.7
Missing	4	13.8

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension.
Source: Table 1.3.1

10.1.4 Patients With Prevalent Disease versus Newly Diagnosed

The majority of patients had known PAH/CTEPH disease (n=74; 92.5%). Six patients (7.5%) had newly diagnosed PAH/CTEPH, defined as diagnosis less than 6 months before baseline (Table 10-4).

Table 10-4: Patient Status Regarding Disease Duration

	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Prevalent patient	47	92.2	27	93.1	74	92.5
Newly diagnosed patients	4	7.8	2	6.9	6	7.5

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension.
Newly diagnosed patients: Disease duration of less than 6 months
Source: Table 1.4

10.2 Descriptive Data

10.2.1 Demographic Characteristics

In the total population, mean (±SD) age was 49.0 (±13.8) years, with a range from 22.0 to 74.0 years. Most (69 patients, 86.3%) of the patients were female. Mean (±SD) body mass index was 22.8 (±3.4) kg/m^2. The majority of patients had never smoked (88.8%) or were former smokers (10.0%). Only 1 patient (1.3%) was a current smoker. Patient characteristics are shown in detail in Table 10-5.

No meaningful differences were observed in demographic characteristics between the 2 observational PH subgroups.

Table 10-5: Age, Sex, Body Mass Index and Smoking Status at Baseline

		PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
		N	%	N	%	N	%
Age (in years)							
	N	51		29		80	
	Nmiss	0		0		0	
	Min	22.0		45.0		22.0	
	Mean	43.4		58.8		49.0	
	SD	13.2		8.4		13.8	
	Median	40.0		58.0		48.0	
	Max	73.0		74.0		74.0	
	<65	45	88.2	22	75.9	67	83.8
	65 - <75	6	11.8	7	24.1	13	16.3
	>=75	0	0.0	0	0.0	0	0.0

		PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
		N	%	N	%	N	%
	Missing	0	0.0	0	0.0	0	0.0
Sex							
	Male	3	5.9	8	27.6	11	13.8
	Female	48	94.1	21	72.4	69	86.3
	Missing	0	0.0	0	0.0	0	0.0
Body Mass Index (in kg/m²)							
	N	51		29		80	
	Nmiss	0		0		0	
	Min	17.6		17.2		17.2	
	Mean	22.3		23.8		22.8	
	SD	3.2		3.5		3.4	
	Median	22.2		23.2		22.6	
	Max	32.0		30.8		32.0	
	<18.5	6	11.8	2	6.9	8	10.0
	18.5 - <25	37	72.5	17	58.6	54	67.5
	25 - <30	6	11.8	7	24.1	13	16.3
	>=30	2	3.9	3	10.3	5	6.3
	Missing	0	0.0	0	0.0	0	0.0
Smoking status							
	never	47	92.2	24	82.8	71	88.8
	former	3	5.9	5	17.2	8	10.0
	current	1	2.0	0	0.0	1	1.3
	Missing	0	0.0	0	0.0	0	0.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; SD = standard deviation.
Source: Tables 1.5.1 and 1.5.2

10.2.2 PH/PAH Disease Characteristics

Disease history and disease characteristics at baseline in the total population and in the various subgroups are summarized in Table 10-6.

Overall, the majority of patients were in NYHA/WHO FC II (68.8%) or III (23.8%). Mean (±SD) 6MWD was 437.5 (±93.5) meters; 5 patients (6.3%) had a walk distance <320 meters. Mean (±SD) Borg Dyspnea Index was 2.02 (±2.03).

No data were provided for EQ-5D VAS as no data was available for any patient (Table 1.11.3).

Mean (±SD) disease duration since the initial PH/PAH diagnosis was 6.7 (±3.7) years, with the mean (±SD) age at initial diagnosis of 42.3 (±13.6) years.

Hepatic impairment at baseline was reported in only 1 patient (1.3%), but Child-Pugh classification was not reported. Renal impairment at baseline was reported in 3 patients (3.8%). Of these, 2 patients had mild impairment and 1 patient had moderate impairment.

Table 10-6: Disease Characteristics at Baseline

		PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
		N	%	N	%	N	%
NYHA/ WHO functional class							
	I	1	2.0	4	13.8	5	6.3
	II	37	72.5	18	62.1	55	68.8
	III	13	25.5	6	20.7	19	23.8
	IV	0	0.0	1	3.4	1	1.3
	unknown	0	0.0	0	0.0	0	0.0
6-minute walk test in meters							
	N	44		24		68	
	Nmiss	7		5		12	
	Min	144.0		250.0		144.0	
	Mean	441.1		430.7		437.5	
	SD	98.6		84.9		93.5	
	Median	420.0		445.5		423.0	
	Max	618.0		633.0		633.0	
	<320	3	5.9	2	6.9	5	6.3
	>=320	41	80.4	22	75.9	63	78.8
	Missing	7	13.7	5	17.2	12	15.0
	<380	10	19.6	6	20.7	16	20.0
	>=380	34	66.7	18	62.1	52	65.0
	Missing	7	13.7	5	17.2	12	15.0
Borg Dyspnea Index							
	N	29		21		50	
	Nmiss	22		8		30	
	Min	0.00		0.00		0.00	
	Mean	1.78		2.36		2.02	
	SD	1.75		2.36		2.03	
	Median	1.00		2.00		1.00	
	Max	8.00		8.00		8.00	
EQ-5D VAS scores	No data available						
Systolic blood pressure in mmHg							
	N	51		29		80	
	Nmiss	0		0		0	
	Min	93.0		87.0		87.0	

		PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
		N	%	N	%	N	%
	Mean	108.6		109.0		108.7	
	SD	10.0		10.0		10.0	
	Median	107.0		111.0		110.0	
	Max	134.0		127.0		134.0	
	<95 mmHg	1	2.0	1	3.4	2	2.5
	>=95 mmHg	50	98.0	28	96.6	78	97.5
	Missing	0	0.0	0	0.0	0	0.0
	<110 mmHg	28	54.9	11	37.9	39	48.8
	>=110 mmHg	23	45.1	18	62.1	41	51.3
	Missing	0	0.0	0	0.0	0	0.0
Diastolic blood pressure in mmHg							
	N	51		29		80	
	Nmiss	0		0		0	
	Min	52.0		45.0		45.0	
	Mean	70.6		68.6		69.8	
	SD	8.4		9.7		8.9	
	Median	70.0		69.0		70.0	
	Max	90.0		88.0		90.0	
Disease duration of initial PH/PAH diagnosis in years							
	N	51		29		80	
	Nmiss	0		0		0	
	Min	0.0		0.0		0.0	
	Mean	6.8		6.6		6.7	
	SD	3.9		3.5		3.7	
	Median	8.1		8.1		8.1	
	Max	14.1		11.1		14.1	
Age at onset of initial PH/PAH diagnosis in years							
	N	51		29		80	
	Nmiss	0		0		0	
	Min	17.7		36.9		17.7	
	Mean	36.6		52.2		42.3	
	SD	12.7		8.7		13.6	
	Median	33.2		52.9		41.4	
	Max	70.1		68.1		70.1	
Hepatic impairment at baseline							
	no	50	98.0	29	100.0	79	98.8
	yes	1	2.0	0	0.0	1	1.3
	unknown	0	0.0	0	0.0	0	0.0
	Missing	0	0.0	0	0.0	0	0.0
Child-Pugh classification for hepatic impairment							

(EU GUIDANCE: 23 JANUARY 2013 EMA/738724/2012)

		PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
		N	%	N	%	N	%
	A	0	0.0	0	.	0	0.0
	B	0	0.0	0	.	0	0.0
	C	0	0.0	0	.	0	0.0
	D	0	0.0	0	.	0	0.0
	Missing	1	100.0	0	.	1	100.0
Renal impairment at baseline							
	no	48	94.1	29	100.0	77	96.3
	yes	3	5.9	0	0.0	3	3.8
	unknown	0	0.0	0	0.0	0	0.0
	Missing	0	0.0	0	0.0	0	0
Severity of renal impairment (by Cockroft Gault formula)							
	mild (creatinine clearance 50-80 mL/min)	2	66.7	0	.	2	66.7
	moderate (creatinine clearance 30-49 mL/min)	1	33.3	0	.	1	33.3
	severe (creatinine clearance <30 mL/min)	0	0.0	0	.	0	0.0
	Missing	0	0.0	0	.	0	0.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; EQ-5D = EuroQoL 5 dimensions questionnaire; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; SD = standard deviation; VAS = visual analogue scale; WHO = World Health Organization.
No data were provided for EQ-5D as no data matched the selected criteria.
Source: Table 1.5.3

10.2.3 Medical History and Concomitant Diseases

In total, 63 patients (78.8%) had reported at least 1 medical history finding at baseline.

Using a pre-specified list of conditions in the baseline CRF, the following rates were reported: coronary heart disease in 3 patients (3.8%), arterial hypertension in 8 patients (10.0%), venous thromboembolism in 2 patients (2.5%), diabetes mellitus in 2 patients (2.5%), thyroid disease in 5 patients (6.3%), obstructive sleep apnea in 2 patients (2.5%), history of hemoptysis/lung bleeding in 6 patients (7.5%), hepatic impairment in 1 patient (1.3%), and renal impairment in 3 patients (3.8%). Other comorbidities (in free text) were reported in 59 patients (73.8%). A summary is provided in Table 1.7.

10.2.4 PH-targeted Therapy in Patient History

In the total population, 31 patients (38.8%) had at least 1 prior medication and 23 patients (28.8%) had at least 1 prior PH-targeted medication.

Prior PH-targeted medication was reported as follows: 21 patients (26.3%) with PDE-5 inhibitors, 5 patients (6.3%) with prostanoids, and 1 patient (1.3%) with ERAs (bosentan). Prior anticoagulation including platelet inhibitors was reported in 10 patients (12.5%). A

summary of prior PH-targeted therapy at baseline in the total population and in the 2 subgroups is provided in Table 1.9.1.

10.2.5 Concomitant PH-targeted Therapy at Baseline

In the total population, at baseline, 76 patients (95.0%) had at least 1 concomitant medication and 36 patients (45.0%) had at least 1 concomitant PH-targeted medication.

In 27 patients (33.8%), concomitant therapy with ERAs was reported, mostly with ambrisentan (15 patients, 18.8%), followed by bosentan (10 patients, 12.5%).

Because of the contraindication for use of Adempas® with PDE-5 inhibitors, if patients were taking PDE-5 inhibitor, it was discontinued at the time of enrollment in this study. No patient (0.0%) received concomitant therapy with PDE-5 inhibitors at baseline.

In 5 patients (6.3%), concomitant therapy with prostanoids was reported, mostly with iloprost (3 patients, 3.8%).

In 6 patients (7.5%), concomitant therapy with other PH-targeted medications including calcium channel blockers was reported.

Concomitant anticoagulation therapy was reported in 49 patients (61.3%) including 47 patients (58.8%) with platelet inhibitors and 2 patients (2.5%) with antiplatelet.

A summary of concomitant PH-targeted therapy at baseline in the total population and in the 2 subgroups is provided in Table 10-7.

Table 10-7: Concomitant PH-targeted Therapy at Baseline

		PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
		N	%	N	%	N	%
Number of patients (%) with at least one medication		47	92.2	29	100.0	76	95.0
Number of patients (%) with at least one PH-targeted medication		28	54.9	8	27.6	36	45.0
Endothelin receptor antagonists		25	49.0	2	6.9	27	33.8
	Bosentan	9	17.6	1	3.4	10	12.5
	Ambrisentan	14	27.5	1	3.4	15	18.8
	Macitentan	2	3.9	0	0.0	2	2.5
Prostanoids		2	3.9	3	10.3	5	6.3
	Iloprost	0	0.0	3	10.3	3	3.8
	Beraprost	1	2.0	0	0.0	1	1.3
	Treprostinil	1	2.0	0	0.0	1	1.3
PDE-5 inhibitors		0	0.0	0	0.0	0	0.0
	Sildenafil	0	0.0	0	0.0	0	0.0
	Tadalafil	0	0.0	0	0.0	0	0.0
Other PH/PAH-targeted therapy (including calcium channel blockers)		2	3.9	4	13.8	6	7.5
Number of patients (%) with at least one Anticoagulation therapy		20	39.2	29	100.0	49	61.3
	Direct oral anticoagulants	0	0.0	10	34.5	10	12.5
	Vitamin k antagonist	18	35.3	22	75.9	40	50.0
	Antiplatelet	2	3.9	0	0.0	2	2.5
	Heparins	0	0.0	3	10.3	3	3.8

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PDE-5 = Phosphodiesterase Type 5; PH = pulmonary hypertension.
Because of the contraindication for use of Adempas® with PDE-5 inhibitors, if patients were taking PDE-5 inhibitor, it was discontinued at the time of enrollment in this study.
Source: Table 1.9.2

10.2.6 Duration of Observation

In the total population, the mean (±SD) duration of observation was 422.4 (±83.9) days (median 431.5, maximum 513.0; Table 1.10.2).

The follow-up visits were performed at 3- to 6-month intervals according to the management of the individual patient starting with the baseline assessment and the site standard of care. Thus, the time pattern of visits showed substantial variation. Visit numbers were based on a date range since baseline so a patient could have a visit 4 based on the date of their visit even if he/she did not have a visit 2 or 3. Information on the time to visit (median days) from the initial (baseline) visit is provided in Table 10-8. The median time between baseline and

Follow-up visit 1 was 91.0 days, to Follow-up visit 2 was 182.0 days, to Follow-up visit 3 was 283.5 days, to Follow-up visit 4 was 391.0 days, to Follow-up visit 5 was 441.0 days, and to Follow-up visit 6 was 512.0 days.

Table 10-8: Time to Follow-up Visit from Initial Visit

		PAH N	CTEPH N	Total N
Follow-up Visit 1	N	49	27	76
	Median (days)	91.0	85.0	91.0
Follow-up Visit 2	N	43	26	69
	Median (days)	184.0	176.5	182.0
Follow-up Visit 3	N	25	7	32
	Median (days)	284.0	277.0	283.5
Follow-up Visit 4	N	35	22	57
	Median (days)	391.0	391.0	391.0
Follow-up Visit 5	N	44	26	70
	Median (days)	448.5	435.0	441.0
Follow-up Visit 6	N	8	0	8
	Median (days)	512.0	.	512.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Source: Table 1.10.3

10.2.7 Adempas® Pre-treatment

There were 57 (71.3%) Adempas® pre-treated patients (ie, receiving Adempas® for ≥3 months before enrollment) and 23 (28.8%) Adempas® newly treated patients. Details are shown in Table 10-9.

Table 10-9: Type of PH Pre-treatment

	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Adempas® pre-treated patients	32	62.7	25	86.2	57	71.3
Adempas® newly treated patients	19	37.3	4	13.8	23	28.8

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Adempas® newly treated patients: Patients started Adempas® within 3 months prior to enrolment.
Source: Table 1.6

10.2.8 Adempas® Monotherapy and Combination Therapy

Table 10-10 provides an overview of patients on Adempas® monotherapy and combination therapy (Adempas® and any other PH-specific drug) at baseline and during the study. In the total population, at baseline, 44 patients (55.0%) had Adempas® monotherapy while 36 patients (45.0%) received Adempas® and at least 1 other PH medication.

Of the 44 patients who were on Adempas® monotherapy at baseline, 31 patients (79.5%) were on Adempas® monotherapy and 8 patients (20.5%) were on Adempas® combination therapy at Follow-up visit 5 (Month 13.5 - <16.5 months) (Table 14.8.3). Table 1.10.5 summarizes information on Adempas® therapy continuation, change, and discontinuation at all follow-up visits.

Table 10-10: Number of Patients on Adempas® Monotherapy and Combination Therapy at Baseline and During Follow-up

		PAH		CTEPH		Total	
		N	%	N	%	N	%
Baseline		51	100.0	29	100.0	80	100.0
	Monotherapy	23	45.1	21	72.4	44	55.0
	Combination therapy	28	54.9	8	27.6	36	45.0
Follow-up Visit 1		49	100.0	27	100.0	76	100.0
	Monotherapy	21	42.9	20	74.1	41	53.9
	Combination therapy	28	57.1	7	25.9	35	46.1
Follow-up Visit 2		43	100.0	26	100.0	69	100.0
	Monotherapy	19	44.2	20	76.9	39	56.5
	Combination therapy	24	55.8	6	23.1	30	43.5
Follow-up Visit 3		25	100.0	7	100.0	32	100.0
	Monotherapy	10	40.0	7	100.0	17	53.1
	Combination therapy	15	60.0	0	0.0	15	46.9
Follow-up Visit 4		35	100.0	22	100.0	57	100.0
	Monotherapy	15	42.9	16	72.7	31	54.4
	Combination therapy	20	57.1	6	27.3	26	45.6

		PAH		CTEPH		Total	
		N	%	N	%	N	%
Follow-up Visit 5		44	100.0	26	100.0	70	100.0
	Monotherapy	16	36.4	17	65.4	33	47.1
	Combination therapy	28	63.6	9	34.6	37	52.9
Follow-up Visit 6		8	100.0	0	100.0	8	100.0
	Monotherapy	0	0.0	0	0	0	0.0
	Combination therapy	8	100.0	0	0	8	100.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Combination therapy refers to Adempas® and in addition at least 1 other PH medication.
Source: Table 1.9.3

10.2.9 Adempas® Daily Dose Over Time

In the total population, at baseline, the mean (±SD) daily dose was 6.9 (±1.4) mg (median 7.5 mg, range 2.0 to 7.5 mg). The median Adempas® dose remained stable during the study course. No patient was administered Adempas® at a daily dose above 7.5 mg. Table 10-11 provides an overview on the Adempas® daily dose at baseline and during the study.

Table 10-11: Adempas® Daily Dose in mg

		PAH		CTEPH		Total	
		N	%	N	%	N	%
Pre-treated patients only (titration completed at baseline)		32	100.0	25	100.0	57	100.0
	2 mg	0	0.0	1	4.0	1	1.8
	3 mg	1	3.1	2	8.0	3	5.3
	4 mg	0	0.0	1	4.0	1	1.8
	4.5 mg	1	3.1	0	0.0	1	1.8
	6 mg	2	6.3	2	8.0	4	7.0
	7.5 mg	28	87.5	19	76.0	47	82.5
	Min	3.0		2.0		2.0	
	Mean	7.2		6.7		6.9	
	SD	1.0		1.7		1.4	
	Median	7.5		7.5		7.5	
	Max	7.5		7.5		7.5	
Newly treated patients only (titration completed after baseline)		19	100.0	4	100.0	23	100.0
	6 mg	3	15.8	0	0.0	3	13.0
	7.5 mg	16	84.2	4	100.0	20	87.0
	Min	6.0		7.5		6.0	
	Mean	7.3		7.5		7.3	
	SD	0.6		0.0		0.5	
	Median	7.5		7.5		7.5	

	PAH		CTEPH		Total	
	N	%	N	%	N	%
Max	7.5		7.5		7.5	

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension; SD = standard deviation.
Daily dose was taken from the most recent visit CRF for newly-treated patients.
Source: Table 1.10.4

10.2.10 Lung Function

Rates of missing data for lung function were very high (>90.0%).

In the total population, mean (±SD) % predicted TLC, available for 5 patients at baseline, was 78.92 (±4.75). Table 1.12.1 summarizes summary statistics and change from baseline at Follow-up visits 1 and 4 for % predicted TLC.

Mean (±SD) % predicted FVC, available for 3 patients at baseline, was 75.67 (±6.66). Table 1.12.2 summarizes summary statistics and change from baseline at Follow-up visits 1 and 4 for % predicted FVC.

Mean (±SD) % predicted FEV1, available for 5 patients at baseline, was 76.00 (±11.90). Table 1.12.3 summarizes summary statistics and change from baseline at Follow-up visits 1 and 4 for % predicted FEV1.

Mean (±SD) % predicted DLCO, available for 3 patients at baseline, was 56.00 (±10.54). Table 1.12.4 summarizes summary statistics and change from baseline at Follow-up visits 1 and 4 for % predicted DLCO.

Data for PaO_2 and $PaCO_2$ were not available in any patient (Tables 1.12.5 and 1.12.6).

10.2.11 Cardiac Rhythm

In the total population, at baseline, 19 patients (23.8%) were in sinus rhythm, 3 (3.8%) had atrial fibrillation, 1 (1.3%) had atrial flutter, and 57 (71.3%) had unknown rhythm. Table 1.13.8 provides a summary on cardiac rhythm at baseline and follow-up visits.

10.2.12 Laboratory Data

Overall, only a limited number of patients had postbaseline assessments for laboratory tests at the individual visits. These parameters may not be frequently assessed under routine clinical practice conditions. Laboratory data are summarized in Table 1.15.1 (hemoglobin), Table 1.15.2 (hematocrit), Table 1.15.3 (INR), Table 1.15.4 (ALT), Table 1.15.5 (AST), Tables 1.15.16.1 to 1.15.16.5 (creatinine, creatinine clearance/eGFR [Cockcroft and Gault], and creatinine clearance/eGFR [Modification of Diet in Renal Disease]). No data were reported for uric acid, sodium, C-reactive protein, MCV, MCH, MCHC, iron, transferrin, ferritin, or sTfR. Considering the high rate of missing values at baseline, and increasing missing data with increasing observation time for laboratory data, the interpretation of findings was difficult.

10.3 Outcome Data

The numbers of patients across categories of the main outcomes are presented in Section 10.5 (Adverse Events).

10.4 Main Results

10.4.1 Long-term Safety of Adempas®

Analyses/results for the primary objective "assessment of long-term safety of Adempas® in real-life clinical practice" and the secondary objective "long-term safety of Adempas® in different PH indications (PAH, CTEPH)" are presented in Section 10.5 (Adverse Events).

10.4.2 Effectiveness of Adempas® in the Long-term

10.4.2.1 Six-minute Walk Distance

At baseline, the mean 6MWD value was 437.5 meters in the total population. Details of statistics and change from baseline in 6MWD in the total population and by subgroup (PAH, CTEPH) are presented in Table 10-12. The mean (±SD) 6MWD from the last available visit was 435.7 (±92.9) meters, which was similar to the mean value at baseline. The 6MWD was not available for some patients at baseline, and the number of patients with missing 6MWD increased at follow-up visits of the study, which makes the interpretation of these findings difficult.

The number of patients with 6MWD category (<320 m, ≥320 m) is presented in Table 1.11.1.1.

Table 10-12: Six-minute Walk Distance in Meters (Total Population)

		Value at visit							Change from baseline at visit						
		N	**Nmiss**	**Min**	**Mean**	**SD**	**Median**	**Max**	**N**	**Nmiss**	**Min**	**Mean**	**SD**	**Median**	**Max**
PAH	Baseline	44	7	144.0	441.1	98.6	420.0	618.0	.	.	.	.	.	.	.
	Follow-up Visit 1	24	25	192.0	438.2	108.0	446.0	615.0	23	26	-111.0	-14.3	48.0	-3.0	66.0
	Follow-up Visit 2	21	22	268.0	448.9	102.2	411.0	642.0	20	23	-130.0	2.9	76.2	3.0	267.0
	Follow-up Visit 3	8	17	354.0	519.9	104.3	523.5	669.0	8	17	-178.0	4.5	139.2	-4.0	297.0
	Follow-up Visit 4	24	11	201.0	420.2	93.0	409.0	636.0	23	12	-111.0	-2.0	57.3	-4.0	119.0
	Follow-up Visit 5	8	36	397.0	521.6	104.2	541.0	652.0	8	36	-125.0	6.3	115.8	-5.0	256.0
	Follow-up Visit 6	0	8	.	.	.	.	.	0	8	.	.	.	.	.
	Last available visit	38	13	268.0	439.8	90.5	416.5	652.0	36	15	-125.0	-0.6	68.1	-3.5	256.0
CTEPH	Baseline	24	5	250.0	430.7	84.9	445.5	633.0	.	.	.	.	.	.	.
	Follow-up Visit 1	17	10	270.0	426.6	75.7	402.0	579.0	16	11	-63.0	-7.1	33.1	3.0	65.0
	Follow-up Visit 2	14	12	252.0	441.7	81.6	443.0	588.0	13	13	-114.0	-0.7	49.5	12.0	68.0
	Follow-up Visit 3	0	7	.	.	.	.	.	0	7	.	.	.	.	.
	Follow-up Visit 4	12	10	263.0	428.6	97.6	441.5	606.0	11	11	-100.0	1.3	61.3	-12.0	125.0
	Follow-up Visit 5	1	25	525.0	525.0	.	525.0	525.0	1	25	-7.0	-7.0	.	-7.0	-7.0
	Last available visit	25	4	252.0	429.6	97.9	433.0	606.0	22	7	-114.0	-2.3	54.8	-1.5	125.0
Total	Baseline	68	12	144.0	437.5	93.5	423.0	633.0	.	.	.	.	.	.	.
	Follow-up Visit 1	41	35	192.0	433.4	95.1	436.0	615.0	39	37	-111.0	-11.4	42.2	0.0	66.0
	Follow-up Visit 2	35	34	252.0	446.0	93.3	426.0	642.0	33	36	-130.0	1.5	66.1	6.0	267.0
	Follow-up Visit 3	8	24	354.0	519.9	104.3	523.5	669.0	8	24	-178.0	4.5	139.2	-4.0	297.0
	Follow-up Visit 4	36	21	201.0	423.0	93.2	418.5	636.0	34	23	-111.0	-1.0	57.7	-8.0	125.0
	Follow-up Visit 5	9	61	397.0	522.0	97.5	525.0	652.0	9	61	-125.0	4.8	108.4	-7.0	256.0
	Follow-up Visit 6	0	8	.	.	.	.	.	0	8	.	.	.	.	.
	Last available visit	63	17	252.0	435.7	92.9	426.0	652.0	58	22	-125.0	-1.2	62.9	-3.5	256.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; max = maximum; min = minimum; PAH = pulmonary arterial hypertension; SD = standard deviation.
Source: Table 1.11.1.2

10.4.2.2 NYHA/WHO Functional Class

The distribution of NYHA/WHO FC and change from baseline at the various visits are included in Table 1.11.4. At Follow-up visit 4, improvement by 1 functional class was observed in 12 patients (21.1%) and the NYHA/WHO FC remained unchanged in 34 patients (59.6%). There were 3 patients (5.3%) whose NYHA/WHO FC worsened by 1 class. Rates of missing data were very high.

10.4.2.3 Borg Dyspnea Index

The number of patients and values of the Borg Dyspnea Index including the change from baseline at the various visits are included in Table 10-13. There appeared slight fluctuations over time. Considering the high rate of missing values at baseline and increasing missing data at follow-up visits, the interpretation of findings is difficult.

Table 10-13: Summary Statistics and Change From Baseline for Borg Dyspnea Index (Total Population)

		Value at visit							Change from baseline at visit						
		N	**Nmiss**	**Min**	**Mean**	**SD**	**Median**	**Max**	**N**	**Nmiss**	**Min**	**Mean**	**SD**	**Median**	**Max**
PAH	Baseline	29	22	0.00	1.78	1.75	1.00	8.00	.	.	.	.	.	.	.
	Follow-up Visit 1	22	27	0.00	1.45	1.81	1.00	7.00	19	30	-2.50	-0.05	1.03	0.00	2.00
	Follow-up Visit 2	21	22	0.00	2.10	2.22	1.00	8.00	17	26	-2.00	0.21	0.87	0.50	1.00
	Follow-up Visit 3	8	17	2.00	2.75	1.39	2.00	6.00	8	17	-1.00	0.50	1.07	1.00	2.00
	Follow-up Visit 4	23	12	0.00	1.65	1.56	1.00	5.00	13	22	-1.00	0.04	0.69	0.00	1.50
	Follow-up Visit 5	8	36	1.00	2.63	1.19	2.50	5.00	8	36	0.00	0.38	0.74	0.00	2.00
	Follow-up Visit 6	0	8	.	.	.	.	.	0	8	.	.	.	.	.
	Last available visit	36	15	0.00	2.01	1.93	1.50	8.00	24	27	-2.00	0.27	0.92	0.00	2.00
CTEPH	Baseline	21	8	0.00	2.36	2.36	2.00	8.00	.	.	.	.	.	.	.
	Follow-up Visit 1	17	10	0.00	2.00	2.93	1.00	8.00	16	11	-1.00	-0.06	1.01	0.00	3.00
	Follow-up Visit 2	14	12	0.00	2.29	3.18	0.50	8.00	13	13	-3.00	-0.27	1.58	0.00	3.00
	Follow-up Visit 3	0	7	.	.	.	.	.	0	7	.	.	.	.	.
	Follow-up Visit 4	12	10	0.00	1.04	0.99	0.75	3.00	9	13	-2.00	-0.33	1.00	-0.50	1.50
	Follow-up Visit 5	1	25	1.00	1.00	.	1.00	1.00	0	26	.	.	.	.	.
	Last available visit	25	4	0.00	1.78	2.50	1.00	8.00	19	10	-3.00	-0.24	1.45	0.00	3.00
Total	Baseline	50	30	0.00	2.02	2.03	1.00	8.00	.	.	.	.	.	.	.
	Follow-up Visit 1	39	37	0.00	1.69	2.34	1.00	8.00	35	41	-2.50	-0.06	1.01	0.00	3.00
	Follow-up Visit 2	35	34	0.00	2.17	2.60	1.00	8.00	30	39	-3.00	0.00	1.22	0.00	3.00
	Follow-up Visit 3	8	24	2.00	2.75	1.39	2.00	6.00	8	24	-1.00	0.50	1.07	1.00	2.00
	Follow-up Visit 4	35	22	0.00	1.44	1.40	1.00	5.00	22	35	-2.00	-0.11	0.83	0.00	1.50
	Follow-up Visit 5	9	61	1.00	2.44	1.24	2.00	5.00	8	62	0.00	0.38	0.74	0.00	2.00
	Follow-up Visit 6	0	8	.	.	.	.	.	0	8	.	.	.	.	.
	Last available visit	61	19	0.00	1.92	2.16	1.00	8.00	43	37	-3.00	0.05	1.19	0.00	3.00

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; max = maximum; min = minimum; PAH=pulmonary arterial hypertension; SD = standard deviation.
Source: Table 1.11.2

10.4.2.4 EQ-5D VAS

EQ-5D VAS data were not available for this study as no data were reported (Table 1.11.3).

10.4.2.5 Invasive Hemodynamics

Table 1.13.1 provides an overview on the number of patients with invasive hemodynamics (RHC) at baseline and the follow-up visits. In the total population, at baseline, 39 patients (48.8%) had RHC results, while 41 patients (51.3%) did not.

Table 1.13.2 to Table 1.13.7 show statistics for various RHC variables. In the total population, at baseline, mean (±SD) saturated venous oxygen (%), available in 26 patients, was 66.23 (±17.85) (Table 1.13.2). Rates of missing data were very high for mPAP (Table 1.13.3), which makes the data interpretation difficult. Mean (±SD) PVR, available in 34 patients, was 979.09 (±615.80) dyn*sec*cm-5 at baseline (Table 1.13.4). Mean (±SD) PCWP, available in 31 patients, was 10.26 (±9.18) mmHg at baseline (Table 1.13.5). Mean (±SD) RAP, available in 28 patients, was 8.32 (±5.26) mmHg at baseline (Table 1.13.6). Mean (±SD) cardiac index, available in 29 patients, was 2.62 (±0.85) L/min/m^2 at baseline (Table 1.13.7).

10.4.2.6 Biomarkers BNP and NT-pro BNP

Table 1.14.1 to Table 1.14.3 provide an overview on the biomarkers BNP and NT-pro BNP, and homocysteine at baseline and the follow-up visits.

In the total population, at baseline, mean (±SD) NT-pro BNP, available in 44 patients, was 1559.5 (±2330.0) pg/mL. At the last available visit, mean (±SD) NT-pro BNP, available in 46 patients, was 1083.8 (±1954.2) pg/mL (Table 10-14). Rates of missing data were very high for BNP. Homocysteine data were not available for this study as no data were reported.

Table 10-14: Summary Statistics and Change From Baseline for NT-pro BNP in pg/mL

		Value at visit							Change from baseline at visit						
		N	**Nmiss**	**Min**	**Mean**	**SD**	**Median**	**Max**	**N**	**Nmiss**	**Min**	**Mean**	**SD**	**Median**	**Max**
PAH	Baseline	26	25	57.00	1600.8	2333.5	321.50	8333.0	.	.	.	.	.	.	.
	Follow-up Visit 1	15	34	57.00	775.14	1201.0	451.00	4631.0	12	37	-2143	-166.1	637.18	-2.00	211.00
	Follow-up Visit 2	16	27	15.00	1804.8	2927.5	469.00	11562	14	29	-2397	168.12	1206.0	-11.50	3229.0
	Follow-up Visit 3	10	15	21.00	804.91	1282.6	460.00	4373.0	9	16	-200.0	458.89	1215.7	31.00	3673.0
	Follow-up Visit 4	15	20	6.70	774.59	1147.6	424.00	4255.0	11	24	-4368	-472.7	1325.0	-136.0	530.00
	Follow-up Visit 5	8	36	36.00	333.63	498.46	134.00	1537.0	8	36	-298.0	17.13	351.43	-53.00	837.00
	Follow-up Visit 6	0	8	.	.	.	.	.	0	8	.	.	.	.	.
	Last available visit	28	23	6.70	1182.9	2301.7	319.50	11562	21	30	-4368	-79.86	1242.7	-83.00	3229.0
CTEPH	Baseline	18	11	60.00	1499.7	2391.2	428.50	7774.0	.	.	.	.	.	.	.
	Follow-up Visit 1	11	16	90.00	1675.7	2145.6	1199.0	6096.0	9	18	-1629	-193.4	876.18	-106.0	1545.0
	Follow-up Visit 2	9	17	35.00	583.87	822.47	293.80	2536.0	9	17	-738.2	-133.8	251.65	-43.00	81.00
	Follow-up Visit 3	0	7	.	.	.	.	.	0	7	.	.	.	.	.
	Follow-up Visit 4	11	11	29.00	1160.9	1796.0	156.00	5027.0	8	14	-388.0	242.88	1094.4	-69.50	2923.0
	Follow-up Visit 5	3	23	111.00	1197.7	1019.8	1348.0	2134.0	3	23	-5591	-1862	3229.2	-14.00	18.00
	Last available visit	18	11	29.00	929.64	1285.8	320.40	5027.0	14	15	-5591	-524.2	1475.1	-65.50	81.00
Total	Baseline	44	36	57.00	1559.5	2330.0	373.00	8333.0	.	.	.	.	.	.	.
	Follow-up Visit 1	26	50	57.00	1156.2	1689.7	463.50	6096.0	21	55	-2143	-177.8	728.40	-14.00	1545.0
	Follow-up Visit 2	25	44	15.00	1365.3	2437.2	402.00	11562	23	46	-2397	49.98	951.37	-25.00	3229.0
	Follow-up Visit 3	10	22	21.00	804.91	1282.6	460.00	4373.0	9	23	-200.0	458.89	1215.7	31.00	3673.0
	Follow-up Visit 4	26	31	6.70	938.03	1437.3	308.00	5027.0	19	38	-4368	-171.4	1254.2	-130.0	2923.0
	Follow-up Visit 5	11	59	36.00	569.27	738.13	146.00	2134.0	11	59	-5591	-495.5	1715.4	-21.00	837.00
	Follow-up Visit 6	0	8	.	.	.	.	.	0	8	.	.	.	.	.
	Last available visit	46	34	6.70	1083.8	1954.2	320.40	11562	35	45	-5591	-257.6	1337.6	-83.00	3229.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; max = maximum; min = minimum; PAH=pulmonary arterial hypertension; SD = standard deviation.
Source: Table 1.14.2

10.4.2.7 Clinical Worsening

Table 10-15 presents the details of clinical worsening in the total population and in PAH and CTEPH groups.

A total of 11 patients (13.8%) had clinical worsening during the study: 9 patients (17.6%) from the PAH group and 2 patients (6.9%) from the CTEPH group. The reasons for clinical worsening in PAH patients were clinical worsening requiring therapy escalation (6 patients, 11.8%), hospitalization due to PH (3 patients, 5.9%), worsening of functional class due to worsening PH (3 patients, 5.9%), all-cause death (1 patient, 2.0%), and decrease in 6MWD of more than 15% from baseline or more than 30% compared to the last study-related measurement (1 patient, 2.0%). The reason for clinical worsening for both CTEPH patients was hospitalization due to PH.

Table 10-15: Clinical Worsening (Total Population)

	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Clinical Worsening	9	17.6	2	6.9	11	13.8
All-cause death	1	2.0	0	0.0	1	1.3
Heart/lung transplantation	0	0.0	0	0.0	0	0.0
Atrial septostomy	0	0.0	0	0.0	0	0.0
Pulmonary endarterectomy (PEA)	0	0.0	0	0.0	0	0.0
Hospitalization due to Pulmonary Hypertension	3	5.9	2	6.9	5	6.3
Clinical worsening requiring therapy escalation	6	11.8	0	0.0	6	7.5
Decrease in 6MWD of more than 15% from baseline or more than 30% compared to the last study related measurement	1	2.0	0	0.0	1	1.3
Worsening of functional class due to worsening pulmonary hypertension	3	5.9	0	0.0	3	3.8

Abbreviations: 6MWD=6-minute walk distance; CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Source: Table 1.20.1

In the total population (n=80), clinical worsening rate was 6.3% (95% CI: 2.7%, 14.5%) and 12.7% (95% CI: 7.1%, 22.3%) at Month 6 and Month 12, respectively (Table 1.20.2).

In newly treated patients (n=23), clinical worsening rate was 18.1% (95% CI: 7.2%, 41.2%) and 31.7% (95% CI: 16.5%, 55.2%) at Month 6 and Month 12, respectively (Table 2.15.2).

In pre-treated patients (n=57), clinical worsening rate was 1.8% (95% CI: 0.3%, 11.8%) and 5.3% (95% CI: 1.7%, 15.5%) at Month 6 and Month 12, respectively (Table 3.15.2).

As shown in Table 10-16, newly treated patients appeared to have a higher rate of clinical worsening including hospitalization due to PH, clinical worsening requiring therapy escalation, decrease in 6MWD of more than 15% from baseline or more than 30% compared

to the last study-related measurement, all-cause death, and worsening of functional class due to worsening PH.

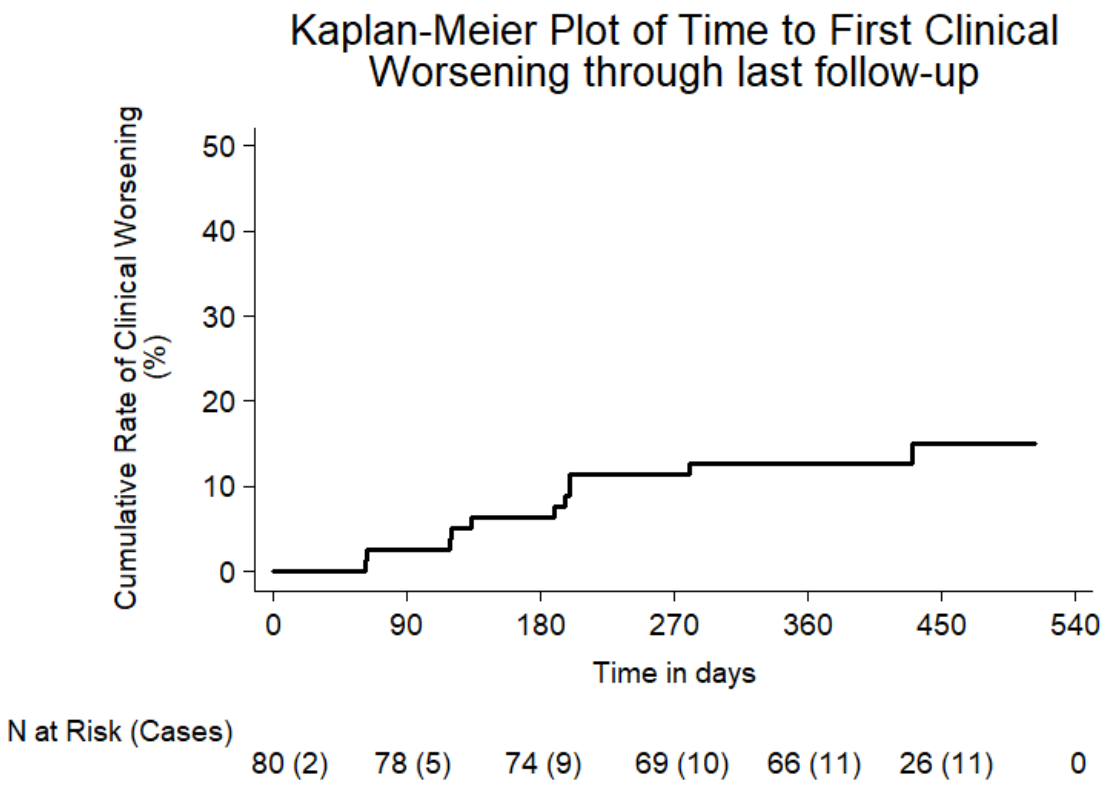
Table 10-16: Clinical Worsening for Newly Treated and Pre-treated Patients

	Newly treated N=23 (100%)		Pre-treated N=57 (100%)		Total N=80 (100%)	
	N	**%**	**N**	**%**	**N**	**%**
Clinical Worsening	7	30.4	4	7.0	11	13.8
All-cause death	1	4.3	0	0.0	1	1.3
Heart/lung transplantation	0	0.0	0	0.0	0	0.0
Atrial septostomy	0	0.0	0	0.0	0	0.0
Pulmonary endarterectomy (PEA)	0	0.0	0	0.0	0	0.0
Hospitalization due to Pulmonary Hypertension	3	13.0	2	3.5	5	6.3
Clinical worsening requiring therapy escalation	5	21.7	1	1.8	6	7.5
Decrease in 6MWD of more than 15% from baseline or more than 30% compared to the last study related measurement	1	4.3	0	0.0	1	1.3
Worsening of functional class due to worsening pulmonary hypertension	2	8.7	1	1.8	3	3.8

Abbreviations: 6MWD = 6-minute walk distance; CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Source: Tables 1.20.1, 2.15.1, and 3.15.1

Figure 10-1 shows the Kaplan-Meier estimate of time to first clinical worsening in the total population.

Figure 10-1: Kaplan-Meier Curve for Time to First Clinical Worsening (Total Population)



Source: Figure 1.20.3

10.4.3 Resource Use

The number of additional outpatient visits (not counting study visits) at the PH center is shown by visit in Table 1.17.1, the number of patients in home care or the nursing home in Table 1.17.2, the number of days at a pulmonary rehabilitation facility/hospital in Table 1.17.3, and hospitalizations in Table 1.18.2.

No additional outpatient visit was noted at Follow-up visits 1, 3, and 6. One of the 69 patients (1.4%) had an additional outpatient visit reported at Follow-up visit 2. Three patients each had additional outpatient visits reported at Follow-up visits 4 and 5 (3/57 [5.3%] and 3/70 [4.3%], respectively). No patient had home care or nursing care during the study. One patient each had stayed at a pulmonary rehabilitation facility/hospital since the last visit at Follow-up visits 1 and 4.

10.5 Adverse Events

A summary of the overall TEAEs is presented in Table 10-17. TEAEs in patients treated with Adempas® in the total population and in the PAH and CTEPH groups are presented.

In the total population of 80 patients, 58 patients (72.5%) experienced at least 1 TEAE. Drug-related TEAEs were documented in 13 patients (16.3%). No TEAE leading to drug discontinuation occurred. A TEAE-related death was documented in 1 patient (1.3%).

Serious AEs were reported in 12 patients (15.0%). No SAEs led to drug discontinuation or were considered drug-related.

Table 10-17: Overall Summary of Patients With Treatment-emergent Adverse Events

	PAH N=51 (100%)			CTEPH N=29 (100%)			Total N=80 (100%)		
	N	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
Any AE	37	72.5	58.3 – 84.1	21	72.4	52.8 – 87.3	58	72.5	61.4 – 81.9
AE-related death	1	2.0	0.1 – 10.5	0	0.0	0.0 – 11.9	1	1.3	0.0 – 6.8
Any Drug Related AE	12	23.5	12.8 – 37.5	1	3.4	0.1 – 17.8	13	16.3	9.0 – 26.2
Discontinuation of study drug due to AE	0	0.0	0.0 – 7.0	0	0.0	0.0 – 11.9	0	0.0	0.0 – 4.5
Any SAE	7	13.7	5.7 – 26.3	5	17.2	5.9 – 35.8	12	15.0	8.0 – 24.7
Any Drug Related SAE	0	0.0	0.0 – 7.0	0	0.0	0.0 – 11.9	0	0.0	0.0 – 4.5
Discontinuation of study drug due to SAE	0	0.0	0.0 – 7.0	0	0.0	0.0 – 11.9	0	0.0	0.0 – 4.5

Abbreviations: AE = adverse event; CI=confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension; SAE = serious adverse event.
Source: Table 1.16.2

During the study there were 233 AEs, 16 SAEs, and 29 drug-related AEs (Table 10-18). Outcomes of TEAE in total and in the subgroups are also summarized in Table 10-18. The outcome of TEAEs was reported as “recovered/resolved” in the majority of the cases (174 AEs, 74.7%).

Table 10-18: Overall Summary of Treatment-emergent Adverse Events

	PAH 131 AE (100%)		CTEPH 102 AE (100%)		Total 233 AE (100%)	
	AE	**%**	**AE**	**%**	**AE**	**%**
Any AE	131	100.0	102	100.0	233	100.0
AE-related death	1	0.8	0	0.0	1	0.4
Any Drug Related AE	24	18.3	5	4.9	29	12.4
Outcome						
Recovered/resolved	102	77.9	72	70.6	174	74.7
Recovering/resolving	11	8.4	5	4.9	16	6.9
Recovered/resolved with sequelae	2	1.5	0	0.0	2	0.9
Not recovered/not resolved	11	8.4	24	23.5	35	15.0
Fatal*	2	1.5	0	0.0	2	0.9

	PAH 131 AE (100%)		CTEPH 102 AE (100%)		Total 233 AE (100%)	
	AE	%	AE	%	AE	%
Unknown	3	2.3	1	1.0	4	1.7
Any SAE	8	6.1	8	7.8	16	6.9
Any Drug Related SAE	0	0.0	0	0.0	0	0.0
Outcome						
Recovered/resolved	4	3.1	6	5.9	10	4.3
Recovering/resolving	2	1.5	2	2.0	4	1.7
Recovered/resolved with sequelae	1	0.8	0	0.0	1	0.4
Not recovered/not resolved	0	0.0	0	0.0	0	0.0
Fatal	1	0.8	0	0.0	1	0.4
Unknown	0	0.0	0	0.0	0	0.0

Abbreviations: AE = adverse event; CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension; SAE = serious adverse event.
* A non-serious AE of 'aggravation of pulmonary hypertension' (started on 06-DEC-2019, ended on 20-APR-2020) was reported for patient 01-001-0001. This patient died on 20-APR-2020 from 'acute exacerbation of pulmonary hypertension' (SAE started on 08-MAR-2020, ended on 20-APR-2020). The outcome of the prior non-serious AE was entered as 'fatal' by mistake, the actual outcome was 'not recovered'. In this study, only one all-cause death was documented for this identical patient.
Source: Table 1.16.3

10.5.1 Incidence of Treatment-emergent Adverse Events (Primary Outcome)

Table 10-19 provides a breakdown of the 58 of 80 patients of the total population with any TEAE by SOC.

The most frequently reported TEAEs by SOC were infections and infestations (27.5%, 22 patients), followed by gastrointestinal disorders (25.0%, 20 patients), respiratory, thoracic and mediastinal disorders (23.8%, 19 patients), followed by nervous system disorders (17.5%, 14 patients), general disorders and administration site conditions and injury, poisoning and procedural complications (both 16.3%, 13 patients), and blood and lymphatic system disorders (13.8%, 11 patients).

The most frequently reported TEAEs by PT were accidental overdose (without associated AEs, 15.0%, 12 patients), upper respiratory tract infection (13.8%, 11 patients), dizziness and headache (both 8.8%, 7 patients), anaemia and cough (both 7.5%, 6 patients), oedema peripheral, haemoptysis, pulmonary hypertension (all 6.3%, 5 patients), vertigo, gastrooesophageal reflux disease, and hypotension (all 5.0%, 4 patients) (Table 1.16.7). All other PTs had an incidence of less than 5.0%.

PAH

For PAH patients, the most frequently reported TEAEs by SOC were infections and infestations (29.4%, 15 patients), respiratory, thoracic and mediastinal disorders (25.5%, 13 patients), gastrointestinal disorders and nervous system disorders (both 23.5%,

12 patients), blood and lymphatic system disorders (13.7%, 7 patients), general disorders and administration site conditions (11.8%, 6 patients), followed by cardiac disorders, injury, poisoning and procedural complications, metabolism and nutrition disorders (all 7.8%, 4 patients), and musculoskeletal and connective tissue disorders, and reproductive system and breast disorders, and vascular disorders (all 5.9%, 3 patients).

The most frequently reported TEAEs by PT were headache (13.7%, 7 patients), upper respiratory tract infection, dizziness, cough (all 11.8%, 6 patients), pulmonary hypertension (9.8%, 5 patients), gastrooesophageal reflux disease and accidental overdose (without associated AEs, both 7.8%, 4 patients), iron deficiency anaemia, influenza, haemoptysis, diarrhea, pyrexia, and hypotension (all 5.9%, 3 patients) (Table 1.16.7). All other PTs had an incidence of less than 5.0%.

CTEPH

For CTEPH patients, the most frequently reported TEAEs by SOC were injury, poisoning and procedural complications (31.0%, 9 patients), gastrointestinal disorders (27.6%, 8 patients), general disorders and administration site conditions and infections and infestations (both 24.1%, 7 patients), respiratory, thoracic and mediastinal disorders (20.7%, 6 patients), blood and lymphatic system disorders and cardiac disorders (both 13.8%, 4 patients), endocrine disorders and vascular disorders (both 10.3%, 3 patients), hepatobiliary disorders, metabolism and nutrition disorders, ear and labyrinth disorders, and nervous system disorders (all 6.9%, 2 patients).

The most frequently reported TEAEs by PT were accidental overdose (without associated AEs, 27.6%, 8 patients), upper respiratory tract infection (17.2%, 5 patients), anaemia and oedema peripheral (both 13.8%, 4 patients), cyanosis, palpitations, vertigo, gingival swelling, haemoptysis, hepatic cyst, and hypoxia (all 6.9%, 2 patients) (Table 1.16.7). All other PTs had an incidence of less than 5.0%.

Table 10-19: Number of Patients With Treatment-emergent Adverse Events by Primary System Organ Class

System Organ Class	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	37	72.5	21	72.4	58	72.5
Blood and lymphatic system disorders	7	13.7	4	13.8	11	13.8
Cardiac disorders	4	7.8	4	13.8	8	10.0
Congenital, familial and genetic disorders	1	2.0	0	0.0	1	1.3
Ear and labyrinth disorders	2	3.9	2	6.9	4	5.0
Endocrine disorders	1	2.0	3	10.3	4	5.0
Eye disorders	2	3.9	1	3.4	3	3.8
Gastrointestinal disorders	12	23.5	8	27.6	20	25.0
General disorders and administration site conditions	6	11.8	7	24.1	13	16.3
Hepatobiliary disorders	2	3.9	2	6.9	4	5.0
Immune system disorders	0	0.0	1	3.4	1	1.3
Infections and infestations	15	29.4	7	24.1	22	27.5
Injury, poisoning and procedural complications	4	7.8	9	31.0	13	16.3
Investigations	2	3.9	0	0.0	2	2.5
Metabolism and nutrition disorders	4	7.8	2	6.9	6	7.5
Musculoskeletal and connective tissue disorders	3	5.9	1	3.4	4	5.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2.0	0	0.0	1	1.3
Nervous system disorders	12	23.5	2	6.9	14	17.5
Psychiatric disorders	1	2.0	1	3.4	2	2.5
Renal and urinary disorders	0	0.0	1	3.4	1	1.3
Reproductive system and breast disorders	3	5.9	0	0.0	3	3.8
Respiratory, thoracic and mediastinal disorders	13	25.5	6	20.7	19	23.8
Skin and subcutaneous tissue disorders	2	3.9	1	3.4	3	3.8
Surgical and medical procedures	1	2.0	1	3.4	2	2.5
Vascular disorders	3	5.9	3	10.3	6	7.5

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Source: Table 1.16.7

Table 10-20 provides an overview of the incidence of TEAEs per 100 person-years. In the total population, the incidence was 267.8 events per 100 person-years (95% CI: 234.9 to 303.7 events) for any AE, and 18.4 per 100 person-years (95% CI: 10.8 to 28.9 events) for any SAE. The incidence appeared higher in the CTEPH group compared with that in the PAH group for any AE per 100 person-years. The incidence for the AEs of hypotension, symptomatic hypotension, and hemoptysis were low in the total population and in the PAH and CTEPH groups.

Table 10-20: Incidence of Treatment-emergent Adverse Events per 100 Person-years

	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	AE	**95% CI**	**AE**	**95% CI**	**AE**	**95% CI**
Any adverse event (rate per 100 person-years)	131 (233.9)	196.1 – 276.3	102 (329.0)	269.2 – 397.1	233 (267.8)	234.9 – 303.7
Any Drug Related AE	24 (42.9)	27.9 – 62.4	5 (16.1)	5.8 – 34.7	29 (33.3)	22.6 – 47.0
Any SAE	8 (14.3)	6.5 – 26.6	8 (25.8)	11.8 – 48.0	16 (18.4)	10.8 – 28.9
Any Event of hypotension	3 (5.4)	1.3 – 13.9	1 (3.2)	0.2 – 14.2	4 (4.6)	1.4 – 10.7
Any Event of symptomatic hypotension	1 (1.8)	0.1 – 7.9	1 (3.2)	0.2 – 14.2	2 (2.3)	0.4 – 7.1
Any Event of hemoptysis	3 (5.4)	1.3 – 13.9	5 (16.1)	5.8 – 34.7	8 (9.2)	4.2 – 17.1

Abbreviations: AE = adverse event; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension; SAE = serious adverse event.
N in the header is the number of patients. The total number of events are presented in the body of the table, a patient may have had more than one event; Rate per 100 patient years is the number of events divided by (total drug exposure in years / 100)
Events of symptomatic hypotension were identified by MedDRA Preferred Terms 'blood pressure ambulatory decreased', 'blood pressure decreased', 'blood pressure diastolic decreased', 'blood pressure orthostatic decreased', 'blood pressure systolic decreased', 'blood pressure systolic inspiratory decreased', 'diastolic hypotension', 'hypotension', 'orthostatic hypotension'
Source: Table 1.16.13

10.5.2 Incidence of Treatment-emergent Serious Adverse Events (Primary Outcome)

Table 10-21 provides a breakdown of the 12 patients with any treatment-emergent SAE by SOC.

For the total population, the most frequently reported TEAEs by SOC were respiratory, thoracic and mediastinal disorders (5.0%, 4 patients), cardiac disorders (2.5%, 2 patients). The only PT that had an incidence of more than 2.0% was pulmonary hypertension (2.5%, 2 patients).

In PAH patients, the most frequently reported treatment-emergent SAEs by SOC were respiratory, thoracic and mediastinal disorders (3.9%, 2 patients), cardiac disorders, hepatobiliary disorders, infections and infestations, neoplasms benign, malignant and unspecified (incl cysts and polyps), nervous system disorders, surgical and medical procedures (all 2.0%, 1 patient each). The reported PTs included pulmonary hypertension (3.9%, 2 patients), cardiac dysfunction, cholecystitis acute, pneumonia, endometrial cancer, dizziness, and coronary artery bypass (all 2.0%, 1 patient each).

In CTEPH patients, the most frequently reported treatment-emergent SAEs by SOC were respiratory, thoracic and mediastinal disorders (6.9%, 2 patients), cardiac disorders, general disorders and administration site conditions, injury, poisoning and procedural complications, musculoskeletal and connective tissue disorders (all 3.4%, 1 patient each). The reported PTs included cardiac failure congestive, polyp, crush injury, synovitis, haemoptysis, and pulmonary embolism (all 3.4%, 1 patient each).

Table 10-21: Number of Patients With Treatment-emergent Serious Adverse Events by Primary System Organ Class, Preferred Term

System Organ Class Preferred Term	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	7	13.7	5	17.2	12	15.0
Cardiac disorders	1	2.0	1	3.4	2	2.5
Cardiac dysfunction	1	2.0	0	0.0	1	1.3
Cardiac failure congestive	0	0.0	1	3.4	1	1.3
General disorders and administration site conditions	0	0.0	1	3.4	1	1.3
Polyp	0	0.0	1	3.4	1	1.3
Hepatobiliary disorders	1	2.0	0	0.0	1	1.3
Cholecystitis acute	1	2.0	0	0.0	1	1.3
Infections and infestations	1	2.0	0	0.0	1	1.3
Pneumonia	1	2.0	0	0.0	1	1.3
Injury, poisoning and procedural complications	0	0.0	1	3.4	1	1.3
Crush injury	0	0.0	1	3.4	1	1.3
Musculoskeletal and connective tissue disorders	0	0.0	1	3.4	1	1.3
Synovitis	0	0.0	1	3.4	1	1.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	2.0	0	0.0	1	1.3
Endometrial cancer	1	2.0	0	0.0	1	1.3
Nervous system disorders	1	2.0	0	0.0	1	1.3
Dizziness	1	2.0	0	0.0	1	1.3
Respiratory, thoracic and mediastinal disorders	2	3.9	2	6.9	4	5.0
Haemoptysis	0	0.0	1	3.4	1	1.3
Pulmonary embolism	0	0.0	1	3.4	1	1.3
Pulmonary hypertension	2	3.9	0	0.0	2	2.5
Surgical and medical procedures	1	2.0	0	0.0	1	1.3
Coronary artery bypass	1	2.0	0	0.0	1	1.3

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Source: Table 1.16.8

10.5.3 Drug-related TEAEs

Table 10-22 provides a breakdown of treatment-emergent study drug-related AEs. In total, 13 of the 80 patients (16.3%) in the total population experienced TEAEs that were assessed as drug-related by the investigator. Twelve of these patients were from the PAH group.

The affected SOCs included nervous system disorders (8.8%, 7 patients), vascular disorders (5.0%, 4 patients), gastrointestinal disorders (3.8%, 3 patients), general disorders and administration site conditions, musculoskeletal and connective tissue disorders, and respiratory, thoracic and mediastinal disorders (all 1.3%, 1 patient each).

The affected PTs were headache (6.3%, 5 patients), hypotension (5.0%, 4 patients), dizziness (3.8%, 3 patients), abdominal distension, dysphagia, gastrooesophageal reflux disease,

nausea, oedema peripheral, myalgia, and haemoptysis (all 1.3%, 1 patient each). No patients experienced treatment-emergent study drug-related (assessed by the investigator) SAEs (Table 1.16.10).

Table 10-22: Number of Patients With Treatment-emergent Study Drug-related (Assessed by the Investigator) Adverse Events by Primary System Organ Class, Preferred Term

System Organ Class Preferred Term	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	12	23.5	1	3.4	13	16.3
Gastrointestinal disorders	2	3.9	1	3.4	3	3.8
Abdominal distension	0	0.0	1	3.4	1	1.3
Dysphagia	0	0.0	1	3.4	1	1.3
Gastrooesophageal reflux disease	1	2.0	0	0.0	1	1.3
Nausea	1	2.0	0	0.0	1	1.3
General disorders and administration site conditions	0	0.0	1	3.4	1	1.3
Oedema peripheral	0	0.0	1	3.4	1	1.3
Musculoskeletal and connective tissue disorders	1	2.0	0	0.0	1	1.3
Myalgia	1	2.0	0	0.0	1	1.3
Nervous system disorders	7	13.7	0	0.0	7	8.8
Dizziness	3	5.9	0	0.0	3	3.8
Headache	5	9.8	0	0.0	5	6.3
Respiratory, thoracic and mediastinal disorders	1	2.0	0	0.0	1	1.3
Haemoptysis	1	2.0	0	0.0	1	1.3
Vascular disorders	3	5.9	1	3.4	4	5.0
Hypotension	3	5.9	1	3.4	4	5.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Source: Table 1.16.9

10.5.4 Adverse Events of Special Interest

Adverse events of special interest were treatment-emergent symptomatic hypotension and hemoptysis.

10.5.4.1 Hypotension

An overview of the number of patients with treatment-emergent hypotension is given in Table 10-23.

Table 10-23: Overall Summary of Number of Patients With Treatment-emergent Hypotension

	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Any Event of Hypotension	3	5.9	1	3.4	4	5.0
Any Drug-related Event of Hypotension	3	5.9	1	3.4	4	5.0
Discontinuation of study drug due to Event of Hypotension	0	0.0	0	0.0	0	0.0
Any Serious Event of Hypotension	0	0.0	0	0.0	0	0.0
AE-related Death	0	0.0	0	0.0	0	0.0
Any Drug-related Serious Event of Hypotension	0	0.0	0	0.0	0	0.0
Discontinuation of study drug due to Serious Event of Hypotension	0	0.0	0	0.0	0	0.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Events of hypotension were identified by MedDRA Preferred Terms 'blood Pressure Ambulatory Decreased', 'Blood Pressure Decreased', 'Blood Pressure Diastolic Decreased', 'Blood Pressure Orthostatic Decreased', 'Blood Pressure Systolic Decreased', 'Blood Pressure Systolic Inspiratory Decreased', 'Diastolic Hypotension', 'Hypotension', 'Orthostatic Hypotension'
Source: Tables 1.16.5 and 1.22.4.1

In the total population, 4 patients (5.0%) experienced treatment-emergent hypotension: 3 (5.9%) from the PAH population and 1 (3.4%) from the CTEPH population. Three of the 4 patients who experienced hypotension were Adempas® newly treated. All the reported treatment-emergent hypotension were assessed as drug-related by the reporting investigators, but none of them were serious or led to discontinuation of study drug (Table 1.16.5). Symptomatic hypotension was reported in 2 patients (2.5%): 1 each from the PAH and CTEPH populations.

Figure 1.19.2 shows the onset of symptomatic hypotension (identified as PT hypotension accompanied by patient reported signs and symptoms such as: dizziness or lightheadedness, fainting, blurred or fading vision) in the total population.

10.5.4.2 Haemoptysis / Pulmonary Haemorrhage

An overview on the number of patients with treatment-emergent haemoptysis or pulmonary haemorrhage is given in Table 10-24. Treatment-emergent haemoptysis or pulmonary haemorrhage occurred in 5 patients (6.3%), 1 (1.3%) of which was assessed as drug-related and 1 (1.3%) was assessed as serious. The serious haemoptysis was considered not related to study drug by the reporting investigator. There were no cases with fatal outcome. No serious drug-related haemoptysis or pulmonary haemorrhage was reported. No treatment-emergent haemoptysis or pulmonary haemorrhage led to study drug discontinuation.

One non-serious AE of haemoptysis was reported as drug-related in 1 PAH patient (2.0%) with a long latency after initiation of Adempas® and concomitant use of warfarin. Three

serious episodes of haemoptysis in 1 patient (1.3%) were assessed as not drug-related (Table 1.16.13).

Eight AEs of haemoptysis were reported in 5 patients (6.3%) (Table 1.16.6). The majority (6 out of 8) of cases occurred with a long latency after initiation of Adempas® for 4 out of the 5 patients. The other patient reported bloody sputum within 7 days after initiation of heparin and 2 days after initiation of direct oral anticoagulant, respectively. Confounding factors in the 2 CTEPH patients included concomitant use of anticoagulants and concurrent bronchiectasis.

The 3 patients with PAH had confounding factors of medical history of haemoptysis, concurrent acute respiratory infection and pneumonia, and concomitant use of anticoagulants.

Notably, the majority of patients in the EXPERT China study received concomitant anticoagulation therapy at baseline (39.2% for PAH, 100.0% for CTEPH) (Table 1.9.2).

Figure 1.19.3 shows the first onset of haemoptysis in the total population.

Table 10-24: Overall Summary of Number of Patients With Treatment-emergent Haemoptysis or Pulmonary Haemorrhage (Including Non-Serious Events)

	PAH N=51 (100%)		CTEPH N=29 (100%)		Total N=80 (100%)	
	N	%	N	%	N	%
Any Event of hemoptysis/ pulmonary haemorrhage	3	5.9	2	6.9	5	6.3
Any Drug Related Event of hemoptysis/ pulmonary haemorrhage	1	2.0	0	0.0	1	1.3
Discontinuation of study drug due Event of hemoptysis/ pulmonary haemorrhage	0	0.0	0	0.0	0	0.0
Any Serious Event of hemoptysis/ pulmonary haemorrhage	0	0.0	1	3.4	1	1.3
Any Fatal Event of hemoptysis/ pulmonary haemorrhage	0	0.0	0	0.0	0	0.0
Any Drug Related Serious Event of hemoptysis/ pulmonary haemorrhage	0	0.0	0	0.0	0	0.0
Discontinuation of study drug due Serious Event of hemoptysis/ pulmonary haemorrhage	0	0.0	0	0.0	0	0.0

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension.
Source: Table 1.22.5.1

10.5.5 Death

In the total population, 1 patient (1.3%) from the PAH group died during the study. The onset of the SAE resulting in death occurred within 2 days of the last dose of Adempas®. The death was due to the SAE of pulmonary hypertension (verbatim term: acute exacerbation of pulmonary hypertension) (Table 1.16.1).

Patient [PPD] was a [PPD] who was diagnosed with idiopathic PAH since DEC-2017 and was treated with Adempas® from 30-MAY-2019. The patient's medical history included heart failure NYHA class II with concurrent condition of hypertension pulmonary aggravated since [PPD]. The patient experienced acute exacerbation of pulmonary hypertension since [PPD], approximately 9 months of Adempas® treatment, with increased NT-pro BNP of 13599.00 pg/mL on [PPD]. [PPD] was hospitalized in a local hospital on [PPD] and received concomitant medications including dopamine hydrochloride and recombinant human natriuretic peptide. The patient was discharged from local hospital 4 days later and was readmitted in the investigational site on [PPD] following treatment of norepinephrine, dobutamine, vasoactive drugs, and furfuramide. Meanwhile, the dose of Adempas® was reduced to 1.25 mg 3 times a day (tid) in response to the SAE of pulmonary hypertension since [PPD] (attempting to increase dose to 1.66 mg tid on [PPD] led to intolerability) until death.

The patient died on [PPD], 43 days after the onset of the SAE of pulmonary hypertension aggravated and right heart failure. The investigator considered the event to be unrelated to Adempas®. Based on the available information, the MAH agreed with the investigator and assessed the event as unrelated to Adempas® therapy and related to the natural course/progression of the underlying pulmonary hypertension.

Details of the treatment-emergent fatal SAE are shown in Section 16.2.7.

10.5.6 Important Potential Risks

10.5.6.1 Haemorrhages

The number of patients with treatment-emergent haemorrhages are summarized in Table 1.21.1.1. A total of 8 patients experienced haemorrhages. One patient from the PAH group experienced drug-related haemorrhage. One patient (CTEPH group) reported the SAE of haemoptysis (Table 1.21.1.4). The most reported AE for treatment-emergent haemorrhage by PT was haemoptysis (5 patients, 6.3%) (Table 1.21.1.2). The incidence of treatment-emergent haemorrhages per 100 person-years for the total population was 13.8 events (Table 1.21.1.3). The incidence of treatment-emergent serious haemorrhages per 100 person-years for the total population was 3.4 events (Table 1.21.1.5).

10.5.6.2 Embryo-fetal Toxicity

There was no pregnancy reported during the time under observation (Table 1.21.2).

10.5.6.3 Renal Failure

The number of patients with treatment-emergent renal AEs is summarized in Table 1.21.3.1. Only 1 patient (1.3%) from the CTEPH group experienced a treatment-emergent renal AE of renal impairment (Table 1.21.3.2). No patients reported drug-related or serious renal AEs.

10.5.6.4 Pre-existing Atrial Fibrillation

Of the 4 patients with atrial fibrillation or atrial flutter at baseline, all (100.0%) experienced at least 1 AE during the study, 1 of whom (25.0%) experienced an SAE of synovitis (Table 1.21.4.1). Treatment-emergent AEs by primary SOC and PT in patients with atrial fibrillation or atrial flutter at baseline are presented in Table 1.21.4.2. The most commonly reported AE was accidental overdose (3 patients, 75.0%). The other AEs were only reported in 1 patient (25.0%). No patients reported treatment-emergent events of atrial fibrillations or atrial flutter during the time under observation (Table 1.21.4.3).

10.5.6.5 Bone Changes and Fractures

No patients reported bone changes or fractures during the time under observation (Table 1.21.5).

10.5.7 Important Identified Risks

10.5.7.1 Concomitant Smoking

At baseline, there was 1 current smoker in the total population (Table 1.5.2). This patient experienced TEAEs of diarrhea, upper respiratory tract infection, and insomnia during the observation period (Table 1.22.1.1 and Table 1.22.1.2).

10.5.7.2 Off-label Use in Patients Aged <18 Years

No patient was aged <18 years at baseline (Table 1.22.2).

10.5.7.3 Upper Gastrointestinal Motility Disorders

The number of patients with treatment-emergent upper gastrointestinal motility disorders are summarized in Table 1.22.3.1. A total of 5 patients (6.3%) experienced upper gastrointestinal motility disorders. Two patients (2.5%) experienced drug-related upper gastrointestinal motility disorders. No patients reported SAEs of upper gastrointestinal motility disorders.

Four (5.0%) of the 5 patients reported upper gastrointestinal motility disorders of gastrooesophageal reflux disease and the other patient (1.3%) reported dysphagia (Table 1.22.3.2).

10.5.7.4 Hypotension

Details for patients with hypotension are presented in Section 10.5.4.1. For patients with a TEAE of hypotension, no concomitant use of PDE-5 inhibitors, organic nitrates, strong multi-pathway CYP, P-gp/BCRP inhibitors, or strong CYP1A1 inhibitors was reported (Table 1.22.4.3).

10.5.7.5 Serious Haemoptysis or Pulmonary Haemorrhage

Details for patients with haemoptysis or pulmonary haemorrhage are presented in Section 10.5.4.2.

10.6 Other Analyses

All tables for the analyses not described in the main body of the CSR but defined in the SAP will be provided in Section 14.

10.6.1 Adempas® Newly Treated versus Pre-treated Patients by Subtype

Detailed information on Adempas® newly treated versus pre-treated patients is provided in Section 2 and Section 3 of the tables.

In Adempas® newly treated patients, a higher percentage of patients were in the PAH group compared with Adempas® pre-treated patients (82.6% versus 56.1%). Adempas® newly treated patients (n=23) compared with Adempas® pre-treated patients (n=57) had a shorter mean (±SD) disease duration (2.8 [±2.5] versus 8.3 [±2.8] years) (Tables 2.4.3 and 3.4.3), a lower proportion of Adempas® monotherapy at baseline (30.4% versus 64.9%, Tables 2.7 and 3.7), a higher proportion of prior PH-targeted therapy (82.6% versus 7.0%, Tables 2.8.1 and 3.8.1), a higher proportion of concomitant PH-targeted therapy (69.6% versus 35.1%, Tables 2.8.2 and 3.8.2), and a higher mean value of Borg Dyspnea Index (2.75 versus 1.68 at baseline and 2.84 versus 1.59 at the last available visit, Tables 2.10.2 and 3.10.2).

Adverse events were reported in 23 Adempas® newly treated patients (100.0%) and 35 Adempas® pre-treated patients (61.4%). Serious AEs were reported in 4 Adempas® newly treated patients (17.4%) and 8 Adempas® pre-treated patients (14.0%), respectively. Adverse events in Adempas® newly treated patients were more often considered drug-related than in Adempas® pre-treated patients (Tables 2.13.2 and 3.13.2).

Table 10-25 presents an overview on the TEAEs that occurred in Adempas® newly treated patients (ie, those who started Adempas® within 3 months prior to enrollment), and Table 10-26 in pre-treated patients.

Table 10-25: Overall Summary of Number of Newly Treated Patients With Treatment-emergent Adverse Events

	PAH N=19 (100%)			CTEPH N=4 (100%)			Total N=23 (100%)		
	N	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
Any AE	19	100.0	82.4 - 100.0	4	100.0	39.8 - 100.0	23	100.0	85.2 - 100.0
AE-related death	1	5.3	0.1 - 26.0	0	0.0	0.0 - 60.2	1	4.3	0.1 - 22.0
Any Drug Related AE	11	57.9	33.5 - 79.8	1	25.0	0.6 - 80.6	12	52.2	30.6 - 73.2
Discontinuation of study drug due to AE	0	0.0	0.0 - 17.7	0	0.0	0.0 - 60.2	0	0.0	0.0 - 14.8
Any SAE	3	15.8	3.4 - 39.6	1	25.0	0.6 - 80.6	4	17.4	5.0 - 38.8
Any Drug Related SAE	0	0.0	0.0 - 17.7	0	0.0	0.0 - 60.2	0	0.0	0.0 - 14.8
Discontinuation of study drug due to SAE	0	0.0	0.0 - 17.7	0	0.0	0.0 - 60.2	0	0.0	0.0 - 14.8

Abbreviations: AE = adverse event; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension; SAE = serious adverse event.
Source: Table 2.13.2

Table 10-26: Overall Summary of Number of Pre-treated Patients With Treatment-emergent Adverse Events

	PAH N=32 (100%)			CTEPH N=25 (100%)			Total N=57 (100%)		
	N	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
Any AE	18	56.3	37.7 - 73.6	17	68.0	46.5 - 85.1	35	61.4	47.6 - 74.0
AE-related death	0	0.0	0.0 - 10.9	0	0.0	0.0 - 13.7	0	0.0	0.0 - 6.3
Any Drug Related AE	1	3.1	0.1 - 16.2	0	0.0	0.0 - 13.7	1	1.8	0.0 - 9.4
Discontinuation of study drug due to AE	0	0.0	0.0 - 10.9	0	0.0	0.0 - 13.7	0	0.0	0.0 - 6.3
Any SAE	4	12.5	3.5 - 29.0	4	16.0	4.5 - 36.1	8	14.0	6.3 - 25.8
Any Drug Related SAE	0	0.0	0.0 - 10.9	0	0.0	0.0 - 13.7	0	0.0	0.0 - 6.3
Discontinuation of study drug due to SAE	0	0.0	0.0 - 10.9	0	0.0	0.0 - 13.7	0	0.0	0.0 - 6.3

Abbreviations: AE = adverse event; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension; SAE = serious adverse event.
Source: Table 3.13.2

10.6.2 Dose-response Effect Comparative Analysis and Benefit-risk Assessment Between Maintenance Doses (titrated up to) of 1.5 mg tid and 2.5 mg tid

The number of patients at a different daily dose is summarized in Table 1.10.4. For newly initiated patients, the daily dose of Adempas® was documented at the most recent follow-up visit after titration was completed. For pre-treated patients with Adempas®, the daily dose

was documented at baseline. The daily doses of 2 mg and 4 mg at baseline were verified by clinical research associates with investigators' confirmation on reduced dosing frequency to twice daily due to unaffordability.

Per request from China Center of Drug Evaluation, dose-response effect comparative analysis and benefit-risk assessment should be conducted between maintenance single doses (titrated up to) 1.5 mg tid and 2.5 mg tid. However, there was only 1 patient who was administered Adempas® at a daily dose of 4.5 mg (1.5 mg tid), and 67 patients were at a daily dose of 7.5 mg (2.5 mg tid). This analysis was not feasible in the EXPERT China study given the very small number of patients (less than 5) per category.

Table 10-27: Adempas® Daily Dose in mg for Pre-treated Patients and Newly Treated Patients

		PAH		CTEPH		Total	
		N	**%**	**N**	**%**	**N**	**%**
Pre-treated patients only (titration completed at baseline)		32	100.0	25	100.0	57	100.0
	2 mg	0	0.0	1	4.0	1	1.8
	3 mg	1	3.1	2	8.0	3	5.3
	4 mg	0	0.0	1	4.0	1	1.8
	4.5 mg	1	3.1	0	0.0	1	1.8
	6 mg	2	6.3	2	8.0	4	7.0
	7.5 mg	28	87.5	19	76.0	47	82.5
	Min	3.0		2.0		2.0	
	Mean	7.2		6.7		6.9	
	SD	1.0		1.7		1.4	
	Median	7.5		7.5		7.5	
	Max	7.5		7.5		7.5	
Newly treated patients only (titration completed after baseline)		19	100.0	4	100.0	23	100.0
	6 mg	3	15.8	0	0.0	3	13.0
	7.5 mg	16	84.2	4	100.0	20	87.0
	Min	6.0		7.5		6.0	
	Mean	7.3		7.5		7.3	
	SD	0.6		0.0		0.5	
	Median	7.5		7.5		7.5	
	Max	7.5		7.5		7.5	

Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension; PAH=pulmonary arterial hypertension; Max = maximum; Min = minimum; N = number of patients; Nmiss = number of patients with data missing; SD = standard deviation.
Newly treated Patients: daily dose was taken from the most recent visit CRF
Source: Tables 2.9.4 and 3.9.4

10.6.3 Use of Adempas® Outside the Approved Indications or Dosages

No off-label indications other than PAH and CTEPH were observed in this study. Unapproved maintenance daily dosages of 2.0 mg, 3.8 mg, and 4.0 mg were reported.

Inadvertent overdosing with total daily doses of 8.5 to 10 mg Adempas® between 2 to 37 days was reported in 12 patients from Site 001. The site investigator indicated that some patients did not return extra doses of the drug that were dispensed. These were reported as protocol deviations.

Due to the COVID-19 pandemic and visit restriction from JAN-2020 until JUL-2020, 5 patients were unable to obtain needed doses of Adempas® from either investigational sites or from pharmacies. They had off-label dosages of 1.25 mg bid for 4 days, 1.875 mg tid for 6 days, 2.5 mg bid for 2 days and 1.25 mg bid for 6 days, 1.25 mg tid for 4 days, and 1.66 mg tid for 1 day, respectively. One of the 5 patients, who took the dose of 1.25 mg tid for 4 days and 1.66 mg tid for 1 day under the investigator's direction, went on to take 1.25 mg tid for another 26 days during hospitalization. These dosages were obtained by splitting the tablets of 2.5 mg into 2 or 4 servings. No specific pattern of TEAEs could be identified in association with this use.

One patient visited a local hospital for lower extremities edema aggravated due to PAH worsening. The doctor suggested patient to titrate the dose of Adempas® to 3.0 mg tid. The patient had taken 3.0 mg tid from PPD No TEAEs in association with overdose were reported.

11 DISCUSSION

11.1 Key Results

The EXPERT China study ran from MAR-2019 (first patient, first visit) to SEP-2020 (last patient, last visit) in accordance with Good Pharmacovigilance Practice. A total of 80 patients were enrolled from 9 investigational sites and all took at least 1 dose of Adempas® during the observation period. Thus, all of the 80 enrolled patients (100.0%) were evaluable for the safety analysis. No other datasets were defined. The number of visits was determined by the treating physician. Patients were followed for up to 513 days from enrolment, or until 30 days after stopping Adempas® treatment.

Characteristics

Of the 80 evaluable patients, 51 patients (63.75%) had PAH and 29 (36.25%) had CTEPH. The majority of patients (74 patients, 92.5%) were prevalent patients with disease duration ≥6 months before baseline, and 6 patients (7.5%) were newly diagnosed.

Fifty-seven (71.3%) patients were pre-treated (ie, receiving Adempas® for ≥3 months before enrollment) and 23 patients (28.8%) were newly treated with Adempas®.

Mean (±SD) age was 49.0 (±13.8) years; most (69 patients, 86.3%) of the patients were female. Mean (±SD) body mass index was 22.8 (±3.4) kg/m^2.

The majority of patients were in NYHA/WHO FC II (68.8%) or III (23.8%). Mean (±SD) 6MWD was 437.5 (±93.5) meters, and 5 patients (6.3%) had a walk distance <320 meters. Mean (±SD) Borg Dyspnea Index was 2.02 (±2.03).

At baseline, mean (±SD) NT-pro BNP, available in 44 patients, was 1559.5 (±2330.0) pg/mL.

Mean (±SD) disease duration since the initial PH/PAH diagnosis was 6.7 (±3.7) years, with the mean (±SD) age at initial diagnosis of 42.3 (±13.6) years.

Concomitant diseases were frequent; 63 patients (78.8%) had at least 1 medical history finding at baseline.

A total of 31 patients (38.8%) had at least 1 prior medication: 23 patients (28.8%) had at least 1 prior PH-targeted medication, 10 patients (12.5%) had at least 1 prior anticoagulation therapy, and 11 patients (13.8%) had at least 1 other prior medication. Prior PH-targeted medication was reported in 21 patients (26.3%) with PDE-5 inhibitors, 5 patients (6.3%) with prostanoids, and 1 patient (1.3%) with ERAs.

Treatment

At baseline, 44 patients (55.0%) had Adempas® monotherapy while 36 patients (45.0%) received Adempas® and at least one other PH medication. Of the 44 patients who were on

Adempas® monotherapy at baseline, 31 patients (79.5%) were on Adempas® monotherapy and 8 patients (20.5%) were on Adempas® combination therapy at Follow-up visit 5 (Month 13.5 - <16.5 months).

At baseline, the mean (±SD) daily dose of Adempas® was 6.9 (±1.4) mg (median 7.5 mg, range 2.0 to 7.5 mg). The median Adempas® dose remained stable during the study course.

Adverse Events

In the total population of 80 patients, 58 patients (72.5%) experienced at least 1 TEAE. Drug-related TEAEs were documented in 13 patients (16.3%). No TEAE leading to drug discontinuation occurred. One TEAE-related death was documented (1.3%).

The most frequently reported TEAEs by SOC were infections and infestations (27.5%, 22 patients), gastrointestinal disorders (25.0%, 20 patients), respiratory, thoracic and mediastinal disorders (23.8%, 19 patients), followed by nervous system disorders (17.5%, 14 patients), general disorders and administration site conditions and injury, poisoning and procedural complications (both 16.3%, 13 patients), and blood and lymphatic system disorders (13.8%, 11 patients).

The most frequently reported TEAEs by PT were accidental overdose (without associated AEs, 15.0%, 12 patients), upper respiratory tract infection (13.8%, 11 patients), dizziness and headache (both 8.8%, 7 patients), anaemia and cough (both 7.5%, 6 patients), oedema peripheral, haemoptysis, pulmonary hypertension (all 6.3%, 5 patients), vertigo, gastrooesophageal reflux disease, and hypotension (all 5.0%, 4 patients). All other PTs had an incidence of less than 5.0%.

In the total population of 80 patients, 12 patients (15.0%) experienced at least 1 SAE. None of the SAEs led to drug discontinuation or were considered drug-related. The most frequently reported SOCs were respiratory, thoracic and mediastinal disorders (5.0%, 4 patients), cardiac disorders (2.5%, 2 patients). The only PT that had an incidence of more than 2.0% was pulmonary hypertension (2.5%, 2 patients). One SAE-related death was documented (1.3%).

With respect to AEs of special interest, TEAEs of hypotension occurred in 4 patients (5.0%), all of which were considered related to study drug, but none were serious or led to discontinuation of study drug. Symptomatic hypotension was reported in 2 patients (2.5%).

Treatment-emergent haemoptysis/pulmonary haemorrhage occurred in 5 patients (6.3%), 1 (1.3%) of which was assessed as drug-related by the investigator but confounded by concomitant use of anticoagulants. No TEAEs of haemoptysis/pulmonary haemorrhage led to discontinuation of study drug. An SAE of haemoptysis was reported in 1 patient (1.3%), which was considered unrelated to study drug by the reporting investigator.

In 1 of the 80 patients (1.3%), a post-treatment event with fatal outcome was reported, which was assessed as unrelated to Adempas® by the reporting investigator. Acute exacerbation of pulmonary hypertension was the reported cause of death.

No off-label indications other than PAH and CTEPH were observed in this study.

Effectiveness

6MWD from the last available visit did not show obvious difference with the value at baseline. At Follow-up visit 4, improvement by 1 functional class was observed in 12 patients (21.1%) and the NYHA/WHO FC remained unchanged in 34 patients (59.6%). No obvious changes were observed in Borg Dyspnea Index during the observation period compared with baseline. The mean (±SD) NT-pro BNP, available in 44 patients, was 1559.5 (±2330.0) pg/mL at baseline. At the last available visit, NT-pro BNP, available in 46 patients, was 1083.8 (±1954.2) pg/mL.

Clinical Worsening

A total of 11 patients (13.8%) had clinical worsening during the study: 9 (17.6%) from the PAH group and 2 (6.9%) from the CTEPH group. The top reason for clinical worsening in PAH patients (6 patients, 11.8%) was clinical worsening requiring therapy escalation while the reason for both CTEPH patients was hospitalization due to pulmonary hypertension.

Most clinical worsening events occurred in the newly treated patients. Among them (n=23), clinical worsening rate was 18.1% (95% CI: 7.2%, 41.2%) and 31.7% (95% CI: 16.5%, 55.2%) at Month 6 and Month 12, respectively.

Results for indicators of efficacy (6MWD, Borg Dyspnea Index, EQ-5D VAS, hemodynamic measurements, and biomarkers) had many missing data points and varied greatly between patients. These results are therefore not discussed here.

11.2 Interpretation

At the time this study was initiated, the main clinical knowledge about Adempas® was from the phase 3 registration studies CHEST-1 and PATENT-1, from the long-term extension studies CHEST-2 and PATENT-2. At the time the EXPERT China study was planned, the global EXPERT registry study was being conducted. The global EXPERT registry was a multicenter, prospective, uncontrolled, noninterventional cohort registry of patients treated with commercial riociguat, which was conducted in 28 countries in Europe, North America (Canada), South America, Asia, and Australia from MAY-2014 to MAR-2018. [25] The EXPERT China study was based on the global EXPERT study, designed to collect information about the long-term safety of Adempas® in real clinical practice outside the regulated environment of a controlled clinical study. This study provides valuable information on Chinese patients with PAH or inoperable/persistent/recurrent CTEPH that were continued or switched to Adempas®, including Adempas® dosing, prior and current PH treatments, as well as clinical parameters collected for monitoring of these patients.

The study did not collect information particularly about the dose adjustment phase in newly treated patients, as it is available from another observational study (CAPTURE).[26] In newly initiated patients, the daily dose of Adempas® was documented at the most recent follow-up visit after titration was completed, while in pre-treated patients with Adempas®, daily dose was documented at baseline. The median maintenance dose throughout the study

was 7.5 mg daily which is according to the Summary of Product Characteristics (SmPC) specifications. A small proportion of patients was administered lower doses, and few patients were maintained on a dose as low as or lower than 1.5 mg tid. Thus, dose-effect comparative analysis and benefit-risk assessment analyses between maintenance doses (titrated up to) 1.5 mg tid and 2.5 mg tid were not feasible in the EXPERT China study.

Of those patients who had received pre-treatment with other PH-targeted medication, almost all had received PDE-5 inhibitors (91.3%). None of the patients received PDE-5 inhibitors as post switch treatment combination. As the use of concomitant PDE-5 inhibitors is contraindicated, physicians adhered to the SmPC.

Regarding clinical parameters (6MWD, Borg Dyspnea Index, lung function parameters, NYHA/WHO FC, and biomarkers), data on standard assessments per routine clinical practice were evaluated. Overall, only a limited number of patients had postbaseline assessments for 6MWD, Borg Dyspnea Index, NYHA/WHO FC, and biomarkers at the individual visits, indicating that these parameters are not frequently assessed under routine clinical practice conditions or there was not a clinical indication to perform the test. This appeared similar between the global and China EXPERT studies. While information on these parameters, if available, may have been helpful in the evaluation of AEs, the evaluation of treatment effects in the full cohort or in subgroups is limited.

The focus of the study was on the systematic collection of safety information. Overall, during the mean observation time of 422 days, TEAEs were reported in 58 of 80 patients (72.5%). Drug-related TEAEs were documented in 13 patients (16.3%). No drug-related serious TEAEs occurred, and no permanent Adempas® discontinuation was due to TEAEs.

The incidences of TEAEs and drug-related TEAEs were similar to those reported in the global EXPERT study. The SAEs and drug-related TEAEs reported were generally consistent with the information from Core Company Data Sheet and package insert of Adempas®.

The most frequently reported TEAEs were accidental overdose (15.0%, 12 patients), upper respiratory tract infection (13.8%, 11 patients), dizziness and headache (both 8.8%, 7 patients), anaemia and cough (both 7.5%, 6 patients), oedema peripheral, haemoptysis, pulmonary hypertension (all 6.3%, 5 patients), vertigo, gastrooesophageal reflux disease, and hypotension (all 5.0%, 4 patients). All of the overdose AEs were reported for patients from Site 001. The site investigator indicated that some patients did not return extra doses of the drug that were dispensed. Patients insisted that the medications were taken and the investigator reported these cases as AEs of “accidental overdose”. There were no other AEs associated with the “accidental overdose”.

The most frequently reported events included known labeled adverse drug reactions for Adempas® (dizziness and headache, anemia, oedema peripheral, gastrooesophageal reflux disease, and hypotension) and signs/symptoms of worsening of the underlying PAH/CTEPH or conditions known to be associated with the PAH and CTEPH population (cough, haemoptysis, pulmonary hypertension, and dyspnea).

One TEAE of acute exacerbation of pulmonary hypertension with fatal outcome occurred with a long latency (283 days) after the initiation of Adempas®, which was assessed as unrelated to Adempas® by the reporting investigator. No evidence of causal relationship with Adempas® (in particular, with initiation of therapy) has been identified.

Subgroup analysis was done in Adempas® newly treated and pre-treated patients. The overall incidence of AEs in Adempas® newly treated patients appeared to be higher. A higher percentage of patients reported drug-related AEs than in newly treated patients. The patients transitioned from PATENT-2 and CHEST-2 studies who were still alive and on Adempas® after at least 7 years are patients who had more stable disease and had demonstrated that they were able to tolerate Adempas® so relatively few AEs are reported for the pre-treated patients. This observation may be biased by the small patient number, a possibility of enrollment of severely ill patients who have already failed on all other PH therapies.

Much less clinical worsening among the pre-treated patients was reported. This could be due to the same reasons for fewer drug-related AEs in pre-treated patients. The pre-treated patients were likely to have worsening events (hospitalizations, escalation of therapy, worsening of FC, or decrease in 6MWD) over the at least 7 years since they were enrolled in PATENT-1 or CHEST-1 studies, but are now in a stable period in their disease.

There was no use of Adempas® in pregnant patients or the pediatric population.

Overall, these findings were in line with the known safety profile of Adempas® in the approved indications. No new safety concern has been identified.

11.3 Limitations

Typical limitations inherent to the study design of registries include various types of bias and missing data.[27] The majority of the patients (92.5%) in this study were prevalent cases of PAH/CTEPH. Prevalent patients enrolled in a registry may be more likely to have relatively stable disease and/or better response to PAH management compared to patients not included.[28]

With regard to safety results, such as frequency and kind of adverse reactions, it was impossible to compare the results under Adempas® treatment with those on other therapies, as this study only included comprehensive AE/SAE information for Adempas® treated patients. Moreover, there is often increased awareness and AE reporting for new drugs compared to those already used for many years.

Typically for data collection under clinical practice conditions, sites showed considerable variance in terms of number of documented visits and visit time points, and in terms of completeness of data (each depending on their routine clinical schedule) including the documentation of functional capacity (6MWD), lung function, or laboratory tests. Results for indicators of efficacy (6MWD, Borg Dyspnea Index, hemodynamic measurements, NYHA/WHO FC, and biomarkers) had many missing data points and varied greatly between patients. While the 6MWD is typically used in PH registration studies, the EXPERT China study shows that it is not routinely used in clinical practice. Similarly, quality of life was not

documented.There might be a bias in terms of participating centers (who have a motivation to generate data) and patients willing to participate compared to those not taking part in studies.

11.4 Generalizability

In this study, patients were treated according to routine clinical practice conditions. The non-interventional nature of the study allowed collection of real-life data, without influencing the physicians' treatment decisions.

However, the generalizability might be limited to a certain extent by the study design, small sample size, and relatively small number of newly treated patients. The study was non-controlled with limited on-site monitoring and was performed during the COVID-19 pandemic. Therefore, it might be subject to missing, inaccurate, or incomplete data and physician/selection bias. The centers that participated in the study were all very experienced with PAH patients and most investigators had previous experience with the use of Adempas®.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

The results of PASS EXPERT China revealed no new safety signals in relation to treatment with Adempas® in the approved indications of PAH and CTEPH in patients in China.

Incidence of TEAEs and treatment-emergent haemoptysis and hypotension was low and in line with the known safety profile.

The observed safety profile in EXPERT China is consistent with the current labeling. Benefit-risk balance of Adempas® in the approved indications remains positive.

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