Title Page

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Performing Laboratory:
28 countries in the regions Europe, Canada, Asia Pacific, and Latin America.

Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	**EXPERT**, **EXP**osur**E** Registry RiociguaT in patients with pulmonary hypertension
Report version and date	Version 1.0 26 JUL 2019
Study type / Study phase	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS6115
Active substance	Riociguat (ATC code C02KX05)
Medicinal product	Adempas
Product reference	BAY 63-2521
Procedure number	NA
Study Initiator and Funder	Bayer AG
Research question and objectives	Assessment of the long-term safety profile of riociguat (Adempas) in real life clinical practice
Countries of study	28 countries in the regions Europe, Canada, Asia Pacific, and Latin America.
Author	PPD

Marketing authorization holder	Bayer AG
MAH contact person	PPD

Confidentiality statement:

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1. Abstract

Acronym/Title	**EXPERT**, **EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension
Report version and date **Author**	Version 1.0, 26 JUL 2019 PPD
Keywords	Pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, observational, utilization, safety
Rationale and background	PAH and CTEPH are rare and life-threatening diseases. Adempas has shown to be effective and well tolerated in both indications in two randomized controlled trials. Adempas is the first member of a new class of drugs, the sGC-stimulators (soluble guanylate cyclase-stimulators), and the first drug ever having shown efficacy in CTEPH. The study was designed to collect information about the long-term safety of Adempas in real clinical practice outside the regulated environment of a controlled clinical study.
Research question and objectives	The primary objective was the assessment of long-term safety of Adempas in real life clinical practice. Further, the study aimed to collect data on clinical effectiveness, resource use, and on the use of Adempas by PH experts under real-life conditions.
Study design	Global, multicenter, prospective, uncontrolled, non-interventional cohort study documenting data from patients with PH treated with Adempas.
Setting	28 countries in the regions Europe, Asia Pacific, Latin America.
Subjects and study size, including dropouts	1348 enrolled, 1330 evaluable patients with PH/PAH
Variables and data sources	Patient's clinical information was documented at time of the initial visit and approximately every three to six months according to local clinical practice thereafter. Data collection continued until 30 days after the end of Adempas therapy. The primary endpoints were: • Incidence of adverse events/serious adverse events • 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 for resource use • Hospitalization/outpatient visits • Administration and any change in drug treatment for PH
Results	Of the 1348 enrolled patients, 1330 (100.0%) were evaluable for analysis. Of these, 326 (24.5%) had PAH, 956 had CTEPH (71.9%), and 48 (3.6%, manually calculated) other forms of PH. Mean disease duration since the initial PH/PAH diagnosis was 3.8 (SD 4.5) years, with mean age at initial diagnosis being 59.3 (SD 16.4) years. The majority (993 patients, 74.7%) were prevalent patients (disease duration ≥6 months), 274 (20.6%) were incident (newly diagnosed), and in 63 patients (4.7%) the status was unknown. There were 733 (55.1%) riociguat pre-treated patients (i.e., receiving riociguat for ≥3 months before entry), and 597 (44.9%) riociguat newly treated patients. Mean age was 63.3 (SD 15.3) years, with a range from PPD to PPD years. More women than men were enrolled (62.4% versus 37.6%). The majority of patients were in NYHA/WHO functional class II (36.2%) or III (49.7%). Mean 6-minute walk distance was 367.4 (SD 130.7) meters. 846 patients (63.6%) had Adempas monotherapy and 484 patients (36.4%) received Adempas and in addition at least one other PH medication. At baseline, the mean Adempas dose was 6.8 (SD 1.3) mg (median 7.5 mg, range 1.5 – 7.5 mg). The median Adempas dose remained stable during the study course. No patient received a dose higher than 7.5 mg daily at any visit. Of the 846 patients who were on Adempas monotherapy at baseline, 128 received any other PH drug during the course of follow-up. In the approved indications (PAH/CTEPH combined), 844 patients (65.8%) experienced any treatment-emergent AE. Drug-related treatment-emergent AE were documented in 197 patients (15.4%) and treatment-emergent AE leading to study drug discontinuation occurred in 79 patients (6.2%). Treatment-emergent AE-related deaths occurred in 133 patients (10.4%). In PAH/CTEPH combined, any treatment-emergent SAE was reported in 517 patients (40.3%), any drug-related treatment-emergent SAE in 57 patients (4.4%), and SAE leading to drug discontinuation in 59 patients (4.6%). At SOC level, the most frequent TEAEs were Respiratory, Thoracic and Mediastinal disorders (24.6%), followed by Infections and Infestations (23.5%), General Disorders and Administration Site Conditions (23.0%), Gastrointestinal Disorders (19.0%), Cardiac

	Disorders (18.8%) and Nervous System Disorders (17.4%). The most frequently named PTs were dizziness (8.6%), dyspnea (8.3%), peripheral edema (7.4%), right ventricular failure (6.7%), pneumonia (5.5%), and cough (5.3%) With respect to adverse events of special interest, any treatment-emergent hypotension occurred in 54 CTEPH/PAH patients (4.2%); it was drug related in 35 patients (2.7%), any serious hypotension in 9 patients (0.7%), and drug-related serious hypotension in 7 patients (0.5%). Any treatment-emergent hemoptysis/pulmonary hemorrhage occurred in 34 CTEPH/PAH patients (2.7%), drug related in 6 patients (0.5%) any serious hemoptysis in 22 patients (1.7%), serious drug-related in 5 patients (0.4%). Results for indicators of efficacy (6-MWD, Borg Dyspnea Index, EQ5D VAS, hemodynamic measurements, and biomarkers) had many missing data points and varied greatly between patients. Data on 6-MWD and WHO FC from patients with at least one baseline and follow-up indicated stabilization or slight improvement. An annualized rate of 0.48 (SD 2.73) additional outpatient visits at the PH center were reported, 0.30 (SD 3.06) days per week in home care, 1.09 (SD 7.41) days at a pulmonary rehabilitation facility/hospital, and 1.09 (SD 10.74) hospitalizations.
Discussion	AEs and SAEs reported in EXPERT are consistent with the known safety profile of Adempas. The drug was generally well tolerated and no new safety signals were identified. Rates of hemoptysis and symptomatic hypotension remain low and comparable to previous data. The study supports the known benefit-risk balance of Adempas in the approved indications.
Marketing Authorization Holder	Bayer AG
Names and affiliations of principal investigators	Contact details of the principal and/or coordinating investigators for each country and site participating in the study are listed in a stand-alone document: Annex 1: List of stand-alone documents which is available upon request.

2. List of abbreviations

6 MWD	6-minute walking distance
AE	Adverse Event
AG	Aktiengesellschaft
ATC	Anatomical Therapeutic Chemical (Classification System)
BPA	Balloon pulmonary angioplasty
CI	Confidence interval
CRF	Case Report Form
COMPERA	Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CRO	Contract Research Organization
CTEPH	Chronic thromboembolic pulmonary hypertension
DMP	Data Management Plan
EC	European Commission
EDC	Electronic Data Capture
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
ERA	Endothelin receptor antagonist
EQ-5	EurQuol 5 dimensions (questionnaire)
EU	European Union
FC	Functional Class
HEOR	Health Economics and Outcomes Research
ID	Identifier
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
Nmiss	Number of missing values
NYHA	New York Heart Association
OS	Observational Study
PAH	Pulmonary Arterial Hypertension
PEA	Pulmonary endarterectomy
PDE	Phosphodiesterase
PH	Pulmonary Hypertension
PASS	Post-Authorization Safety Study
PT	Preferred Term

QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Events
VAS	Visual analogue scale
WHO	World Health Organization

3. Investigators

Contact details of the principal and/or coordinating investigators, co-investigators and other site personnel for each country and site participating in the study are listed in a stand-alone document see Annex 1: List of stand-alone documents which is available upon request.

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5. Milestones

Table 5–1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection / observation	30 MAY 2014	31 MAY 2014	
End of data collection / observation	31 MAR 2018	31 MAR 2018	1 year after completed enrolment according to plan
Registration in the EU PAS register	n.a.	21 MAR 2014	
IEC or IRB approval Study protocol version 1.0*	24 NOV 2013	First approval: 02 MAY 2014 Last approval: 30 NOV 2016	
IEC or IRB approval 1st Study amendment	n.a.	First approval: n.a. Last approval: n.a.	Denmark
IEC or IRB approval 2nd Study amendment	n.a.	First approval: 04 MAR 2016 Last approval: 08 AUG 2016	Turkey
IEC or IRB approval 3rd Study amendment	n.a.	First approval: 15 DEC 2016 Last approval: 14 FEB 2017	Germany
Database Clean	30 JUN 2018	29 JUN 2018	
Final report of study results	30 APR 2019	26 JUL 2019	

* Complete list of IEC or IRB approvals is provided as a stand-alone document (see Annex 1: List of stand-alone documents) which is available upon request.

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. In untreated patients with idiopathic PAH the life expectancy is reduced to 2.8 years after diagnosis, whereas in contemporary registries in the era of modern PAH-specific treatments the survival rates have increased to 83% and 58% at 1 and 3 years respectively [3, 4]. The incidence is currently estimated as 2.4 cases per million adult inhabitants per year with a prevalence of 15 cases per million adult inhabitants [5]. Available PAH-specific treatments include prostacyclin analogues, endothelin receptor antagonists, and PDE-5 inhibitors. The available drugs predominantly act as vasodilators and improve exercise capacity [6]. Despite advances in the clinical management based on these available therapies for PAH, there is still significant unmet medical need for improvement as the mortality of patients with PAH remains high (15% at 1 year and 32% at 3 years) [7].

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a different progressive and life-threatening type of pulmonary hypertension. Whereas symptoms as well as epidemiology of CTEPH are similar compared with PAH, there are significant differences regarding etiology, diagnosis and treatment [8, 9]. In CTEPH the increase in pulmonary vascular resistance is a result of a pulmonary artery obstruction by residual organized thrombi [10]. A ventilation-perfusion-scan is important for differential diagnosis as a normal scan excludes CTEPH [11]. 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 10-15% of patients PH may persist or reoccur after surgery [12-15]. Specific PAH drugs had failed in the past to show efficacy in inoperable CTEPH and before Adempas no drug treatment has been approved for these patients [16].

Adempas is the first member of a new class of drugs, the sGC-stimulators (soluble guanylate cyclase-stimulators). It restores the NO-sGC-cGMP pathway and leads to increased generation of cyclic guanosine monophosphate (cGMP) which plays an important role in regulating vascular tone, proliferation, fibrosis, and inflammation. Adempas directly stimulates sGC independently of nitric oxide (NO), while also increasing the sensitivity of sGC to NO. This appears to be of importance as pulmonary hypertension (PH) is associated with pulmonary endothelial dysfunction and can be related to low levels of NO [17-21].

Adempas is the first drug that could demonstrate robust efficacy in two placebo-controlled, multicenter trials in two different indications of pulmonary hypertension (PH). In the CHEST-1 study Adempas showed for the first time robust clinical efficacy in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) and in patients with persistent CTEPH after surgery by significantly improving exercise capacity as well as relevant secondary endpoints such as hemodynamics and WHO functional class. In the PATENT-1 study in pulmonary arterial hypertension (PAH) Adempas could for the first time show significant improvement in exercise capacity in treatment-naïve patients as well as in patients pre-treated with endothelin receptor antagonists (ERAs) or non-intravenous prostacyclin analogues. At the same time a consistent significant improvement across the secondary endpoints including hemodynamics, WHO functional class and time to clinical worsening could be demonstrated. In both studies Adempas was well tolerated with a good safety profile [22, 23].

The Adempas registry EXPERT is a global, multicenter, prospective, uncontrolled, non-interventional study documenting data from patients with PH treated with Adempas. The objective of the registry is to monitor the long-term safety of Adempas under clinical practice conditions outside the regulated environment of a controlled clinical study. In addition, the registry offers a structured prospective collection of data on the clinical effect, resource use, and how Adempas is used by PH experts. The study was a non-imposed post approval safety study (PASS) and was proposed by the MAH on the voluntary basis during marketing authorization process in EU.

In accordance with guidance from the 5th World Symposium on Pulmonary Hypertension and the European Union Committee of Experts on Rare Diseases on the future setup of registries, EXPERT was linked with the Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), a global academic PH registry, instead of creating another drug registry in this rare disease area.

With currently more than 9000 PH patients, COMPERA is the largest global academic databases in PH, characterized by high data quality and low loss to follow up (Clintrials.gov identifier: NCT01347216). COMPERA captures relevant demographics, information on diagnostics and treatment, and patients' outcomes. Results of the registry have been described in a number of publications [24-29]. Although COMPERA is predominantly present in Europe, there are no geographical restrictions.

COMPERA was the technical and data platform for EXPERT. Data were captured according to the COMPERA core CRF and Adempas-specific data and more detailed safety documentation were added.

EXPERT was an Adempas safety registry and participating investigators had contracts with Bayer separate from COMPERA. The specific reporting requirements of a post-approval safety study were specified in the contract. Bayer has exclusive access to the data captured specifically for Adempas. The requirements for safety data reporting were fulfilled. Data documented for EXPERT according to the information in the COMPERA standard CRF were available and accessible in the COMPERA registry. A center participating in EXPERT could object to have the data documented in COMPERA (opt-out option).

Alignment of data documentation and format was discussed that could enable an exchange and comparability of data on Adempas use from other academic national registry e.g. with the French National Registry, however, this concept was not further pursued.

7. Research question and objectives

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

The secondary objectives in this study were:

- Long-term safety of Adempas in the different PH indications (PAH, CTEPH)
- Effectiveness of Adempas in the long-term follow-up of PH patients
- Information on resource use
- Information on how Adempas is used (e.g. indication and indication subgroups, dose)

8. Amendments and updates

Table 8–1: Amendments

Amendment Number	Reason for Amendment	New version number	Effective Date
AM01	The Danish Health and Medicines Authority required a change of the protocol due to their assessment (in accordance with Section 92d(1) of the Danish Medicines Act) that the description of Adempas® in the protocol was not objective and without subjective claims and that conducting of the study also promoted the use of Adempas®.	V 1.1 Denmark	18 MAR 2015
AM02	The applicable guideline for observational studies in Turkey stated that the plan/protocol of the studies should use the name of active ingredient instead of the brand name. For this reason, the brand name was changed with the active ingredient within the whole protocol.	V 1.2 Turkey	06 JUL 2015
AM03	The letter from BfArM dated 09 Aug 2016 (reference no. 73-3815/27415/16) stated that the legally valid definition of a non-interventional study according to AMG § 4 sec. 23 allows treatment of patients within the specifications of the Summary of Product Characteristics only. The advice was to follow the local regulations (AMG § 4 sec. 23) within the non-interventional study EXPERT.	V 1.3 Germany	12 OCT 2016

9. Research methods

9.1 Study design

EXPERT is a global, multicenter, prospective, uncontrolled, non-interventional cohort study documenting data from patients with PH treated with Adempas. It is linked with the existing global COMPERA registry, a global academic multicenter prospective registry, which documents consecutive patients with the different forms of pulmonary hypertension (PH) treated with specific PAH drugs. For EXPERT the documentation in COMPERA was extended to include additional Adempas-specific safety data.

All patients prescribed with Adempas for a medically appropriate use, consent to participate, and fulfilled the selection criteria were eligible for enrolment into the study. Patients were followed up for an observation period of 1 up to 4 years (recruitment period 3 years). Patient's clinical information was documented at time of the initial visit and approximately every three to six months according to local clinical practice thereafter. Data collection continued until 30 days after the end of Adempas therapy. The study was conducted in accordance with good pharmacovigilance practices.

The decision on clinical management of the patient including the actual treatment duration was determined solely by the physician.

The study ended 12 months after enrolment of the last patient.

Serious adverse events were followed up until resolution.

The primary endpoints were:

- Incidence of adverse events/serious adverse events
- 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

for resource use

- Hospitalization/outpatient visits
- Administration and any change in drug treatment for PH

9.2 Setting

The study included 28 countries in the regions Europe, Asia Pacific, and Latin America. Centers in the following participated: Argentina, Australia, Austria, Belgium, Canada, Colombia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Russia, Saudi Arabia, Slovakia, Spain, Sweden, Switzerland, Taiwan, Turkey, and the United Kingdom.

A list of recruited patients per country is in the Annex 1: List of stand-alone documents.

The study started after Adempas was authorized and made commercially available in the countries involved in the study.

EXPERT was conducted from May 2014 (first patient, first visit) to March 2018 (last patient, last visit).

9.3 Subjects

9.3.1 Eligibility

Patients who were prescribed Adempas for a medically appropriate use were eligible to be included into this registry. Indications and contraindications according to the local market authorization were carefully considered.

Inclusion criterion/criteria

- Female and male patients who start or are on treatment with Adempas
- Written informed consent

Exclusion criterion/criteria

- Patients currently participating in an interventional clinical trial

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. The investigator documented the study-relevant data for each patient in the case report form (CRF). The CRF is listed in Annex 1: List of stand-alone documents.

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	X	X	X
Smoking history/status	X	X	X
Systemic blood pressure before start of Adempas	X		
6 Minute Walking Test	X	X	X
NYHA/ WHO FC	X	X	X
Borg Dyspnoea Index	X	X	X
EQ5D VAS	X	X	X
Hemodynamic measurements, lung function, cardiac rhythm	X	X	X
Biomarkers	X	X	X
Laboratory tests	X	X	X
Treatment and concomitant medication	X	X	X
Resource use in hospital and outpatient care		X	X

Data were only collected on assessments that are performed routinely.
* Serious Adverse Events were to be reported to the sponsor within 24 hours.

Variables to determine the primary endpoint(s)

The variables for primary objective were:

- Number of adverse events (AE) and serious adverse events (SAE)
- Incidence of all-cause mortality

The outcome variables for secondary objectives were:

- Number of AE and SAE in the different PH indications (PAH, CTEPH)
- Adverse events 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 lab values and outcome to be documented in a specific CRF section in case AE/SAE of interest occurred

  AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

- Measurements of clinical effect

  6-minutes Walking Test

  NYHA/ WHO FC

  Borg Dyspnoea Index

  EQ5D VAS

Haemodynamic parameters from right heart catheter 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)

  Rehabilitation/nursery home (days)

  Drug use, including switch or interruption or discontinuation of Adempas and associated reason

- Demographics

  Year of birth

  Sex

  Height, weight, body mass index

Co-morbidities (medical history, concomitant diseases): for any co-morbidity, the diagnosis, the start and the stop date (or ongoing status) had to be documented.

Co-morbidities were any medical findings, whether or not they pertained to the study indication, that were present before start of therapy with Adempas, independent on whether or not they were still present.

Findings meeting the criteria listed below were considered to be relevant to the study indication and had to be documented:

- Date of first PH diagnosis (month/year)
- Etiology of PH according to Dana Point Classification 2008, subgroups of CTEPH (inoperable, post-surgery), subgroups of PAH (monotherapy, combination therapy)
- Relevant concomitant diseases (e.g. vascular disease, diabetes, cancer)
- History of hemoptysis (date frequency, severity, bronchial arterial embolization (BAE), other pulmonary disease, trauma)
- Hepatic impairment (no/yes), by Child-Pugh Classification
- Renal impairment (no/yes)
  - Severity
  - Estimated Glomerular Filtration Rate by Cockcroft Gault formula
- Pregnancy
- Smoking (history, current status)
- 6-Minute Walking Test (date, distance in meters)
- Functional class (WHO, NYHA) with date
- Borg dyspnoea index with date
- EQ5D visual analogue scale score with date

- Haemodynamic measurements with date
    - Mean pulmonary arterial pressure (mPAP, mmHg)
    - Pulmonary arterial resistance (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: sinus rhythm, atrial fibrillation, atrial flutter or other arrhythmia)
- Lung function with date
    - TLC, FVC, FEV1, DLCO, paO2, paCO2, O2 BGA
- Biomarkers:
    - Brain Natriuretic Peptide (BNP; pg/mg or pmol/l)
    - NT-pro BNP (pg/mg or pmol/l)
- Laboratory tests: haemoglobin, haematocrit, INR (if on VKA treatment), creatinine, transaminases (ALT/AST)
- Additional laboratory tests for CHD patients only: uric acid, sodium, iron, ferritin, transferrin, soluble Transferrin receptor, sTfR-ferritin index, C-reactive protein, MCV, MCH, MCHC, homocysteine
- Prior and concomitant medication

  All medication taken before study start (initiated and stopped before study start) is termed prior medication. All medication taken in addition (either initiated before study start or during the study) is termed concomitant medication.

  Prior and concomitant medication meeting the criteria listed below were considered to be relevant and had to be documented:
- PH/PAH-specific therapy
    - Adempas (with individual dose after initial dose adjustment period; blood pressure after first administration)
    - ERA: bosentan, sitaxsentan, ambrisentan, macitentan
    - PDE-5 inhibitors: sildenafil, tadalafil
    - Prostacyclins: epoprostenol (Flolan), treprostinil, iloprost, beraprost
    - tyrosine kinase inhibitor: imatinib
    - other specific targeted therapy: calcium channel blocker, other
- oral anticoagulation
    - vitamin K antagonists
    - other
- other medications (only CHD: other cardiovascular drugs, antiplatelets)

Information on medication included: trade name and INN, Start and stop date; dose/unit/ frequency/administration mode; date of switch or addition of a specific drug/Adempas; reason for change (lack of efficacy or tolerability, patient's request, administrative); indication.

9.5 Data sources and measurement

The investigator collected current and anamnestic 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.

9.6 Bias

Several sources for bias may exist, i.e. reporting as well as selection biases in patient recruitment and du to missing values. To decrease the reporting bias source data verification was performed in at least 10% of the centers in countries where legally permitted. To reduce patient selection bias physicians must document consecutive patients who receive Adempas and provide informed consent. Furthermore, subgroup analyses are performed in Adempas newly treated and pretreated patients and in PH incident and prevalent patients to compare the patients characteristics with the COMPERA dataset for representativeness.

Missing data are a common methodological problem in registries due to the observational character of this study type, and specific clinical tests cannot be mandated. The distribution of missing values is reported for each variable in the analyses. No missing values were imputed.

9.7 Study size

It was planned to enroll 900 patients in specialized centers with the expectation to include a significant proportion of patients newly starting Adempas monotherapy. This sample size allowed detecting at least three "uncommon" AEs (with a probability of 83%) with an incidence of 0.5% (5/1000) or more. This is in the range of "uncommon" AE (0.1%=1/1000 to 1%=1/100).

If the sample size increased to 1130, at least three "uncommon" AEs with incidence of 0.4% or more can be detected with the same probability.

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 Report.

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

9.9 Statistical methods

Statistical analyses were conducted by using the software package SAS version 9.3 (SAS Institute Inc, Cary, NC, USA) or higher. 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 as well as the number of missing values. Continuously distributed variables were analyzed by showing (i) the sample mean and its standard deviation and (ii) the

median (50th percentile), and minimum and maximum. If it is appropriate, continuous variables were classified in clinically meaningful categories.

The incidence rate is the number of adverse events divided by the cumulative person time on treatment (person-years). The incidence rate was reported as number of adverse events per 100 total years of drug exposure. The Poisson rate confidence interval was calculated for incidence rates. The incidence proportion was also calculated for adverse events. 95% confidence intervals for incidence proportions were calculated by Pearson-Clopper and by Poisson rate confidence intervals for incidence rates for AEs of interest.

In addition, for the adverse events of special interest the incidence proportions was presented as well as incidence rates per person-time under Adempas treatment along with the corresponding exact 95% confidence interval. Furthermore, Kaplan Meier table and plots describe 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.

9.9.2 Main statistical methods

All analyses were considered as purely explorative. No confirmatory hypothesis tests were performed. Confidence intervals were reported at the 95% level. Given the explorative analysis character, no adjustments to significance levels were made to account for multiple comparisons on the same data or for subgroups. The 95% confidence interval was interpreted as a metric for uncertainty.

The primary objective of the study was to comprehensively and systematically assess the long-term safety profile of Adempas. A further aspect was to evaluate the effectiveness of Adempas in real life use (clinical effect in the follow-up) and the resource use during treatment of PH patients (hospitalization, outpatient visits and administration, any change in drug treatment for PH).

All safety data were analyzed with respect to their observed time since start of enrollment into the study and the last available study visit in case of ongoing treatment with Adempas or the date of discontinuation in case of stopping Adempas irrespective of the study visits.

All analyses were performed for the total population and the PH subtype (PAH, CTEPH and other PH). In addition, the following subgroups were considered for the analyses of the primary and secondary outcome variables. Medically relevant subgroups are defined by characteristics at baseline, e.g.

- age groups (<65, ≥65 to <75, ≥75 years)
- sex
- geographic region
- hepatic impairment
- renal impairment
- WHO functional class/NYHA group (I/II versus III/IV)
- according to 6 MWD thresholds ≥ 380 m versus < 380 m
- systolic blood pressure (< 110 mmHg, ≥110 mmHg)
- total German population, as well as German patients who have been prescribed Adempas for a medically appropriate use

- Adempas newly treated and Adempas pre-treated patients. Adempas newly treated patients started Adempas within 3 months prior to enrollment.
- Adempas monotherapy or combination therapy at enrolment
- transitioned patients (newly treated patients with <=10 days between stop of previous therapy and commencing riociguat, i.e. switched patients)
- non-transitioned patients (non-switched)
- patients simultaneously starting Adempas and ERA
- patients starting Adempas within 3 months after start of ERA

9.9.3 Missing values

The frequency of missing values was assessed in detail. Percentages were calculated as proportion of 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 adverse events, and date of initial PH/PAH diagnosis. The details are described in the Statistical analysis plan.

9.9.4 Sensitivity analyses

No sensitivity analyses were performed.

9.9.5 Amendments to the statistical analysis plan

The statistical analysis plan was amended to cover additional safety topics. The amended version included

- important identified risks (upper gastrointestinal motility disorders)
- other significant events (adverse events with fatal outcome, patients with uncontrolled hypertension at baseline, patients who underwent a procedure of PEA or BPA in follow-up, patients with hepatic or renal impairment at baseline

9.10 Quality control

All participating sites including physicians and study nurses were trained on the principles of the study and on the handling of the electronic data capture (EDC) tool before they were allowed to enroll patients. Therefore, the physicians as well as study nurses had to complete the online training module, which was integrated in the EDC system. It consisted of a mandatory presentation of the study principles followed by a test, which had to be passed before patient enrollment and documentation was allowed. Questions arising from the training could be addressed to the local project manager at any time via telephone or email.

The CRF data for this study were collected with an EDC system which was provided by the CRO. It combined data capture, automated plausibility checks, manual query processes, and remote data review. The relevant study variables were recorded in a standardized eCRF. After data entry, missing or implausible data were queried. All checks for completeness, accuracy, plausibility and validity of the documented data were specified within the data management plan (DMP) which is available on request (see Annex 1: List of stand-alone documents). The

final data management report (DMR) is also part of Annex 1: List of stand-alone documents and is available on request.

As specified in the quality review plan, quality reviews were performed. Data verification at the sites was performed in at least 10% of the centers in countries where legally permitted.

10. Results

10.1 Participants

10.1.1 Patient disposition

A total of 1348 patients were enrolled into the study, of whom 9 withdrew consent and 9 had no riociguat dosing information according to the data validity report . Thus, a total of 1330 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 cohort, a total of 453 patients (33.6%) prematurely discontinued the study with the primary reason (as reported by the physician) being patient death in 148 patients (11.0%), no final visit documented in 101 patients (7.5%), patient lost to follow-up in 63 patients (4.7%), other reasons in 84 patients (6.2%), and missing reason in 48 patients (3.6%). Nine patients (0.7%) withdrew consent during the study.

Table 10–1: Patient disposition

	PAH N=331 (100%)		CTEPH N=969 (100%)		Other N=48 (100%)		PAH/CTEPH N=1300 (100%)		Total N=1348 (100%)	
	N	%	N	%	N	%	N	%	N	%
Completed (Regular end of observation as per protocol)	226	68.3	649	67.0	20	41.7	875	67.3	895	66.4
Not completed (per protocol)	105	31.7	320	33.0	28	58.3	425	32.7	453	33.6
Primary reason										
Patient withdrew consent	4	1.2	5	0.5	0	0.0	9	0.7	9	0.7
Patient lost to follow-up	15	4.5	46	4.7	2	4.2	61	4.7	63	4.7
Patient died	43	13.0	99	10.2	6	12.5	142	10.9	148	11.0
Other	17	5.1	48	5.0	19	39.6	65	5.0	84	6.2
Missing	8	2.4	40	4.1	0	0.0	48	3.7	48	3.6
No final visit documented	18	5.4	82	8.5	1	2.1	100	7.7	101	7.5

* Physicians reported death as primary reason for study discontinuation for 148 patients. Source: post-text Table 1.3
For information on adverse events with fatal outcome, see Table 10–21.

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 total evaluable population (n=1330), 326 patients (24.5%) had PAH (Group 1) and 956 CTEPH (71.9%, Group 4). A small proportion of patients (n=48; 3.6%) (manually calculated) had other forms of PH (Groups 2, 3, 5), outside the labelling of Adempas.

Table 10–2: PAH/PH etiology according to Dana Point classification 2008

		Total N=1330 (100%) N	%
1.	**PAH**	**326**	**24.5**
1.1.	**Idiopathic PAH**	**226**	**17.0**
1.2	**Heritable PAH**	**9**	**0.7**
	1.2.1. BMPR2	3	0.2
	1.2.2. ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)	1	0.1
	1.2.3. Unknown	5	0.4
1.3.	**Drug- and toxin-induced**	**4**	**0.3**
1.4.	**Associated PAH**	**87**	**6.5**
	1.4.1.1. Systemic sclerosis	32	2.4
	1.4.1.2. Systemic Lupus Erythematodes (SLE)	6	0.5
	1.4.1.3. Mixed connective tissue disease (MCTD), anti-U1-RNP positive	3	0.2
	1.4.1.4. Undifferentiated connective tissue diseases (not fulfilling any classification criteria, but evidence for autoimmune rheumatic disease)	3	0.2
	1.4.1.5. Overlap (fulfilling two classification criteria)	1	0.1
	1.4.1.6. Other autoimmune rheumatic diseases	3	0.2
	1.4.2. HIV infection	2	0.2
	1.4.3. Portal hypertension	9	0.7
	1.4.4. Congenital heart diseases[a]	28	2.2
	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**
2.	**PH due to left heart disease**	**17**	**1.3**
	2.1. Systolic dysfunction	2	0.2
	2.2. Diastolic dysfunction	14	1.1
	2.3. Valvular disease	1	0.1
3.	**PH owing to lung diseases and/or hypoxia**	**24**	**1.8**
	3.1. Chronic obstructive pulmonary disease	13	1.0
	3.2. Interstitial lung disease	7	0.5
	3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern	3	0.2
	3.4. Sleep-disordered breathing	0	0.0
	3.5. Alveolar hypoventilation disorders	1	0.1
	3.6. Chronic exposure to high altitude	0	0.0
	3.7. Developmental abnormalities	0	0.0
4.	**Chronic thromboembolic pulmonary hypertension (CTEPH)**	**956**	**71.9**

Table 10–2: PAH/PH etiology according to Dana Point classification 2008

			Total N=1330 (100%) N	%
5.	**PH with unclear multifactorial mechanism**		**7**	**0.5**
	5.1.	Hematologic disorders: myeloproliferative disorders, splenectomy	0	0.0
	5.2.	Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis	6	0.5
	5.3.	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders	0	0.0
	5.4.	Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis	1	0.1

[a] Manually calculated from 'Congenital heart diseases' and 'Congenital heart diseases (extended CRF including Eisenmenger)'
Source: post-text Table 1.1

Among the 326 patients with PAH, 226 (17.0% of total had idiopathic PAH, 9 (0.7%) heritable PAH, 48 (3.6%) (manually calculated) PAH associated with connective tissue disease, 28 (2.2%) PAH associated with congenital heart disease, and 15 (1.1%) (manually calculated) other conditions within this class (Table 10–2).

10.1.3 CTEPH subgroups

Among the 956 patients with CTEPH, 54 (5.6% of Group 4) were surgically accessible, 304 (31.8%) inoperable due to peripheral localization of the thrombus, 207 (21.7%) had persistent PH following pulmonary endarterectomy (PEA), 26 (2.7%) had persistent PH following pulmonary angioplasty (BPA), 129 (13.5%) were inoperable due to comorbidities, for 90 (9.4%), operability was under investigation, 87 (9.1%) PEA or surgical assessment has been declined by the patient, and in 59 (6.2%) the status was missing (post-text Table 1.1.2).

10.1.4 Patients with prevalent disease versus newly diagnosed

The majority of patients had known PH/PAH disease (n= 993; 74.7%). Newly diagnosed patients had PH/PAH diagnosed less than six months before baseline (n=274; 20.6%). The date of diagnosis was unknown in 63 (4.7%) of patients. Details are presented in Table 10–3.

Table 10–3: Patient status regarding PH disease duration

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Prevalent patient	254	77.9	713	74.6	26	54.2	967	75.4	993	74.7
Newly diagnosed patients	61	18.7	197	20.6	16	33.3	258	20.1	274	20.6
Unknown	11	3.4	46	4.8	6	12.5	57	4.4	63	4.7

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Newly diagnosed patients: Disease duration of less than 6 months.
Source: post-text Table 1.4

10.1.5 Study region

In the total cohort, 938 patients (70.5%) were from Western Europe, 155 (11.7%) from Eastern Europe. 107 (8.0%) from North America (Canada only), 81 (6.1%) from Asia/Pacific, 32 (2.4%) from Latin America and 17 (1.3%) from Middle East. Details on the study region are shown in post-text Table 1.5.1.

10.2 Descriptive data

10.2.1 Demographic characteristics

In the total cohort, mean age was 63.3 (SD 15.3) years, with a range from PPD to PPD years. More women than men were enrolled (62.4% versus 37.6%). There were no pregnancies at baseline. Mean body mass index was 28.2 (SD 14.2) kg/m^2. The majority of patients had never smoked (63.5%) or were former smokers (32.0%), while few were current smokers (4.4%). Patient characteristics are shown in detail in .

Table 10–4: Age, sex, BMI and smoking status at baseline

Characteristic		PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
		N	%	N	%	N	%	N	%	N	%
Age (years)											
	N	326		956		48		1282		1330	
	Nmiss	0		0		0		0		0	
	Min	15.0		21.0		36.0		15.0		15.0	
	Mean	PP		PP		PP		PP		PP	
	SD	16.5		13.7		12.1		15.4		15.3	
	Median	PP		PP		PP		PP		PP	
	Max	PP		PP		PP		PP		PP	
	<65	236	72.4	366	38.3	16	33.3	602	47.0	618	46.5
	65 - <75	51	15.6	260	27.2	13	27.1	311	24.3	324	24.4
	>=75	39	12.0	330	34.5	19	39.6	369	28.8	388	29.2
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sex											
	Male	92	28.2	386	40.4	22	45.8	478	37.3	500	37.6
	Female	234	71.8	570	59.6	26	54.2	804	62.7	830	62.4
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Body Mass Index (in kg/m²)											
	N	326		956		48		1282		1330	
	Nmiss	0		0		0		0		0	
	Min	15.6		2.7		14.8		2.7		2.7	
	Mean	27.0		28.6		27.0		28.2		28.2	
	SD	11.8		15.2		6.2		14.4		14.2	
	Median	25.6		27.1		26.3		26.7		26.7	
	Max	212.0		402.0		48.1		402.0		402.0	

Table 10–4: Age, sex, BMI and smoking status at baseline

Characteristic		PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
		N	%	N	%	N	%	N	%	N	%
BMI, category (kg/m²)	<18.5	13	4.0	24	2.5	2	4.2	37	2.9	39	2.9
	18.5 - <25	137	42.0	290	30.3	16	33.3	427	33.3	443	33.3
	25 - <30	96	29.4	348	36.4	18	37.5	444	34.6	462	34.7
	>=30	80	24.5	294	30.8	12	25.0	374	29.2	386	29.0
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Smoking status											
	never	218	66.9	602	63.0	25	52.1	820	64.0	845	63.5
	former	91	27.9	314	32.8	21	43.8	405	31.6	426	32.0
	current	17	5.2	40	4.2	2	4.2	57	4.4	59	4.4
	Missing	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: post-text Tables 1.5.1 and 1.5.2

10.2.2 PH/PAH disease characteristics

A summary of disease history and disease characteristics at baseline in the total cohort and in the various subgroups is provided in Table 10–5.

In the total cohort, the majority of patients were in NYHA/WHO functional class II (36.2%) or III (49.7%). Mean 6-minute walk distance was 367.4 (SD 130.7) meters, and 29.0% of patients had a walk distance < 320 meters. Mean Borg dyspnea index was 3.93 (SD 2.29). Mean EQ-5D on the 100-point visual analogue scale, as reported by 345 patients, was 61.5 (SD 21.1) points.

Mean disease duration since the initial PH/PAH diagnosis was 3.8 (SD 4.5) years, with mean age at initial diagnosis 59.3 (SD 16.4) years.

Hepatic impairment at baseline was reported in 32 patients (2.4%): 15 patients were in Child-Pugh class A, 8 in class B, and 1 in class C (missing information on class in 8 patients).

Renal impairment at baseline was reported in 224 patients (16.8%). Of these, 85 patients had mild impairment, 99 patients moderate impairment, and 28 patients severe impairment (missing information on severity in 12 patients).

Table 10–5: Disease characteristics at baseline

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
NYHA/WHO functional class										
I	13	4.0	38	4.0	0	0.0	51	4.0	51	3.8
II	109	33.4	365	38.2	8	16.7	474	37.0	482	36.2
III	161	49.4	479	50.1	21	43.8	640	49.9	661	49.7
IV	22	6.7	29	3.0	9	18.8	51	4.0	60	4.5
unknown	21	6.4	45	4.7	10	20.8	66	5.1	76	5.7

Table 10–5: Disease characteristics at baseline

		PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
		N	%	N	%	N	%	N	%	N	%
6-minute walk test in meters											
	N	282		811		31		1093		1124	
	Nmiss	44		145		17		189		206	
	Min	0.0		0.0		45.0		0.0		0.0	
	Mean	386.3		364.7		267.2		370.3		367.4	
	SD	131.8		128.2		139.6		129.4		130.7	
	Median	394.5		372.0		244.0		380.0		376.5	
	Max	720.0		756.0		528.0		756.0		756.0	
	<320	76	23.3	290	30.3	20	41.7	366	28.5	386	29.0
	>=320	206	63.2	521	54.5	11	22.9	727	56.7	738	55.5
	Missing	44	13.5	145	15.2	17	35.4	189	14.7	206	15.5
	<380	122	37.4	421	44.0	25	52.1	543	42.4	568	42.7
	>=380	160	49.1	390	40.8	6	12.5	550	42.9	556	41.8
	Missing	44	13.5	145	15.2	17	35.4	189	14.7	206	15.5
Borg Dyspnea Index											
	N	252		701		24		953		977	
	Nmiss	74		255		24		329		353	
	Min	0.00		0.00		2.00		0.00		0.00	
	Mean	4.13		3.80		5.50		3.89		3.93	
	SD	2.35		2.24		2.27		2.27		2.29	
	Median	4.00		4.00		5.50		4.00		4.00	
	Max	10.00		10.00		10.00		10.00		10.00	
EQ-5D, VAS score											
	N	113		229		3		342		345	
	Nmiss	213		727		45		940		985	
	Min	0.0		0.0		50.0		0.0		0.0	
	Mean	60.0		62.3		60.0		61.6		61.5	
	SD	22.4		20.6		10.0		21.2		21.1	
	Median	60.0		65.0		60.0		60.0		60.0	
	Max	100.0		95.0		70.0		100.0		100.0	
Systolic blood pressure, mmHg											
	N	294		878		44		1172		1216	
	Nmiss	32		78		4		110		114	
	Min	86.0		80.0		90.0		80.0		80.0	
	Mean	114.6		123.8		118.6		121.5		121.4	
	SD	15.0		17.8		17.0		17.6		17.5	
	Median	111.5		121.0		118.0		120.0		120.0	
	Max	170.0		202.0		150.0		202.0		202.0	
	<95 mmHg	16	4.9	21	2.2	4	8.3	37	2.9	41	3.1
	>=95 mmHg	278	85.3	857	89.6	40	83.3	1135	88.5	1175	88.3
	Missing	32	9.8	78	8.2	4	8.3	110	8.6	114	8.6
	<110 mmHg	105	32.2	159	16.6	12	25.0	264	20.6	276	20.8

Table 10–5: Disease characteristics at baseline

		PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
		N	%	N	%	N	%	N	%	N	%
	>=110 mmHg	189	58.0	719	75.2	32	66.7	908	70.8	940	70.7
	Missing	32	9.8	78	8.2	4	8.3	110	8.6	114	8.6
Diastolic blood pressure, mmHg											
	N	294		877		44		1171		1215	
	Nmiss	32		79		4		111		115	
	Min	46.0		43.0		47.0		43.0		43.0	
	Mean	70.9		74.3		71.0		73.4		73.3	
	SD	10.0		11.4		12.6		11.1		11.2	
	Median	70.0		74.0		70.0		72.0		72.0	
	Max	100.0		111.0		95.0		111.0		111.0	
Disease duration of initial PH/PAH diagnosis, years											
	N	316		912		43		1228		1271	
	Nmiss	10		44		5		54		59	
	Min	0.0		0.0		0.0		0.0		0.0	
	Mean	4.8		3.5		3.1		3.8		3.8	
	SD	5.4		4.0		5.0		4.5		4.5	
	Median	3.4		2.1		0.8		2.4		2.4	
	Max	49.6		39.7		20.7		49.6		49.6	
Age at onset of initial PH/PAH diagnosis, years											
	N	316		912		43		1228		1271	
	Nmiss	10		44		5		54		59	
	Min	1.3		18.2		26.5		1.3		1.3	
	Mean	48.9		62.7		64.4		59.2		59.3	
	SD	17.2		14.5		15.3		16.4		16.4	
	Median	48.8		65.7		69.7		61.9		62.3	
	Max	85.0		91.8		82.4		91.8		91.8	
Hepatic impairment at baseline											
	no	286	87.7	910	95.2	47	97.9	1196	93.3	1243	93.5
	yes	15	4.6	16	1.7	1	2.1	31	2.4	32	2.4
	unknown	7	2.1	5	0.5	0	0.0	12	0.9	12	0.9
	Missing	18	5.5	25	2.6	0	0.0	43	3.4	43	3.2
Child-Pugh classification for hepatic impairment											
	A	10	66.7	4	25.0	1	100.0	14	45.2	15	46.9
	B	3	20.0	5	31.3	0	0.0	8	25.8	8	25.0
	C	0	0.0	1	6.3	0	0.0	1	3.2	1	3.1
	D	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Missing	2	13.3	6	37.5	0	0.0	8	25.8	8	25.0
Renal impairment at baseline											
	no	259	79.4	765	80.0	31	64.6	1024	79.9	1055	79.3
	yes	45	13.8	163	17.1	16	33.3	208	16.2	224	16.8
	unknown	3	0.9	7	0.7	0	0.0	10	0.8	10	0.8
	Missing	19	5.8	21	2.2	1	2.1	40	3.1	41	3.1

Table 10–5: Disease characteristics at baseline

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Severity of renal impairment (by Cockcroft Gault formula)										
mild (creatinine clearance 50-80 ml/min)	17	37.8	63	38.7	5	31.3	80	38.5	85	37.9
moderate (creatinine clearance 30-49 ml/min)	23	51.1	68	41.7	8	50.0	91	43.8	99	44.2
severe (creatinine clearance <30 ml/min)	3	6.7	23	14.1	2	12.5	26	12.5	28	12.5
Missing	2	4.4	9	5.5	1	6.3	11	5.3	12	5.4

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: post-text Table 1.5.3

10.2.3 Medical history and concomitant diseases

In the total cohort, information on one medical history finding at baseline was reported in 1241 patients (93.3%).

Using a list of pre-specified list of conditions in the baseline CRF, the following rates were reported: coronary heart disease in 183 patients (13.8%), arterial hypertension in 587 patients (44.1%), venous thromboembolism in 465 patients (35.0%), diabetes mellitus in 184 patients (13.8%), thyroid disease in 274 patients (20.6%), obstructive sleep apnea in 138 patients (10.4%), cancer in 147 patients (11.1%) and history of hemoptysis/lung bleeding in 46 patients (3.5%). Other comorbidities (in free text) were reported in 1053 patients (79.2%). A summary is provided in post-text Table 1.7.

10.2.4 PH-targeted therapy in patient history

In the total cohort, 355 patients (26.7%) had at least one prior medication and 316 (23.8%) had at least one prior PH-targeted medication.

In 68 patients (5.1%) prior therapy with endothelin receptor antagonists, in 268 patients (20.2%) prior therapy with PDE-5 inhibitors, in 34 patients (2.6%) prior therapy with prostanoids, and in 25 patients (1.9%) prior therapy with other PH-targeted medication was reported. Prior oxygen use was reported in 23 patients (1.7%).

Prior anticoagulation including platelet inhibitors was reported in 52 patients (3.9%). A summary of prior PH-targeted medication at baseline in the total cohort and in the various subgroups is provided in post-text Table 1.9.1.

10.2.5 Concomitant PH-targeted therapy at baseline

In the total cohort, at baseline 484 patients (36.4%) had at least one concomitant PH-targeted medication.

In 425 patients (32.0%) concomitant therapy with endothelin receptor antagonists was reported, mostly with bosentan (172 patients, 12.9%), followed by ambrisentan (86 patients, 6.5%), or macitentan (167 patients, 12.6%), respectively.

No patient (0.0%) received concomitant therapy with PDE-5 inhibitors.

In 88 patients (6.6%), concomitant therapy with prostanoids was reported, mostly with iloprost (59 patients, 4.4%) or treprostinil (24 patients, 1.8%).

In 44 patients (3.3%), concomitant calcium channel blocker therapy was reported. Concomitant oxygen use was reported in 431 patients (32.4%).

Concomitant anticoagulation including platelet inhibitors was reported in 1055 patients (79.3%), antiplatelets in 95 patients (7.1%), and other anticoagulants in 76 patients (5.7%).

A summary of concomitant PH-targeted medication at baseline in the total cohort and in the various subgroups is provided in Table 10–6.

Table 10–6: Concomitant PH-targeted medication at baseline

		PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
		N	%	N	%	N	%	N	%	N	%
Number of patients (%) with at least one current PAH targeted concomitant medication		247	75.8	226	23.6	11	22.9	473	36.9	484	36.4
Endothelin receptor antagonists		226	69.3	189	19.8	10	20.8	415	32.4	425	32.0
	Bosentan	93	28.5	75	7.8	4	8.3	168	13.1	172	12.9
	Ambrisentan	40	12.3	44	4.6	2	4.2	84	6.6	86	6.5
	Macitentan	93	28.5	70	7.3	4	8.3	163	12.7	167	12.6
PDE-5 inhibitors		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Sildenafil	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Tadalafil	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Prostanoids		55	16.9	28	2.9	5	10.4	83	6.5	88	6.6
	Epoprostenol (Flolan®)	4	1.2	0	0.0	0	0.0	4	0.3	4	0.3
	Epoprostenol (Veletri®)	2	0.6	2	0.2	0	0.0	4	0.3	4	0.3
	Treprostinil	16	4.9	6	0.6	2	4.2	22	1.7	24	1.8
	Iloprost	36	11.0	20	2.1	3	6.3	56	4.4	59	4.4
	Beraprost	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Other PH/PAH-targeted therapy (including calcium channel blockers)		34	10.4	42	4.4	1	2.1	76	5.9	77	5.8
	Calcium channel blocker	22	6.7	22	2.3	0	0.0	44	3.4	44	3.3
	Other	12	3.7	20	2.1	1	2.1	32	2.5	33	2.5
Oxygen		92	28.2	308	32.2	31	64.6	400	31.2	431	32.4
Anticoagulation including platelet inhibitors											
	Oral anticoagulation	161	49.4	861	90.1	33	68.8	1022	79.7	1055	79.3
	Antiplatelets	41	12.6	44	4.6	10	20.8	85	6.6	95	7.1
	Other anticoagulant	7	2.1	66	6.9	3	6.3	73	5.7	76	5.7

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: Post-text Table 1.9.2.

10.2.6 Duration of observation

In the total cohort, the mean duration of observation was 544.3 (SD 311.7) days (median 488.5, maximum 1381.0; post-text Table 1.10.2).

Investigators were free to select visit dates, and thus the time pattern of visits showed substantial variation. Information on the time to visit (median days) from the initial (baseline) visit is provided in Table 10–7. The median time between baseline and follow-up visit 1 was 101 days, to follow-up visit 2 210 days, to follow-up visit 3 315 days, and to follow-up visit 4 406 days.

Table 10–7: Time to follow-up visit from initial (baseline) visit

		PAH	CTEPH	Other	PAH/CTEPH	Total
Follow-up visit 1	N	324	944	47	1268	1315
	Days (median)	102.0	104.0	65.0	103.0	101.0
Follow-up visit 2	N	289	852	32	1141	1173
	Days (median)	205.0	217.0	167.5	214.0	210.0
Follow-up visit 3	N	248	717	22	965	987
	Days (median)	301.5	326.0	246.0	316.0	315.0
Follow-up visit 4	N	210	584	17	794	811
	Days (median)	393.5	413.5	330.0	407.0	406.0
Follow-up visit 5	N	161	438	14	599	613
	Days (median)	497.0	490.0	435.0	491.0	490.0
Follow-up visit 6	N	127	348	9	475	484
	Days (median)	560.0	588.5	533.0	581.0	578.0
Follow-up visit 7	N	99	240	8	339	347
	Days (median)	655.0	683.0	566.5	679.0	671.0
Follow-up visit 8	N	68	150	6	218	224
	Days (median)	729.0	710.5	623.0	720.5	716.0
Follow-up visit 9	N	50	94	3	144	147
	Days (median)	819.0	740.5	738.0	764.0	758.0
Follow-up visit 10	N	38	66	3	104	107
	Days (median)	854.5	737.5	836.0	803.5	810.0
Follow-up visit 11	N	28	53	0	81	81
	Days (median)	864.5	749.0	-	785.0	785.0
Follow-up visit 12	N	18	38	0	56	56
	Days (median)	874.0	784.0	-	816.0	816.0
Follow-up visit 13	N	11	21	0	32	32
	Days (median)	889.0	589.0	-	702.0	702.0
Follow-up visit 14	N	8	16	0	24	24
	Days (median)	935.5	576.5	-	773.5	773.5
Follow-up visit 15	N	3	14	0	17	17
	Days (median)	413.0	490.5	-	426.0	426.0

Visits with less than 10 patients in the total cohort not shown. N = number of patients.
Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: Post-text Table 1.10.3

10.2.7 Adempas pre-treatment

There were 733 (55.1%) riociguat pre-treated patients (i.e., receiving riociguat for ≥3 months before entry), and 597 (44.9%) riociguat newly treated patients. Details are shown in Table 10–8.

Table 10–8: Type of riociguat pre-treatment

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Adempas pre-treated patients	182	55.8	537	56.2	14	29.2	719	56.1	733	55.1
Adempas newly treated patients	144	44.2	419	43.8	34	70.8	563	43.9	597	44.9

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Adempas newly treated patients: Patients started Adempas within 3 months prior to enrolment.
Source: Post-text Table 1.6

10.2.8 Adempas monotherapy and combination therapy

Table 10–9 and post-text Tables 1.9.3, 30.15.2 and 30.15.3 provide an overview on patients on Adempas monotherapy at baseline and combination therapy (Adempas and any other PH-specific drug) at baseline and during the study. In the total cohort, at baseline, 846 patients (63.6%) had Adempas monotherapy while 484 patients (36.4%) received Adempas and in addition at least one other PH medication.

Of the 846 patients who were on Adempas monotherapy at baseline, 128 started to receive another PH drug during the course of follow-up (post-text Table 30.15.3).

Table 10–9: Adempas monotherapy and combination therapy at baseline and during follow-up

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Monotherapy of Adempas at baseline	79	24.2	730	76.4	37	77.1	809	63.1	846	63.6
Combination therapy of Adempas at baseline	247	75.8	226	23.6	11	22.9	473	36.9	484	36.4
Monotherapy of Adempas in all study visits	55	16.9	630	65.9	33	68.8	685	53.4	718	54.0
Combination therapy of Adempas in at least one study visit including baseline	271	83.1	326	34.1	15	31.3	597	46.6	612	46.0
Change from Monotherapy to Combination therapy of Adempas during follow-up	24	7.4	100	10.5	4	8.3	124	9.7	128	9.6

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: Post-text Tables 1.9.3 and 30.15.2

Post-text Table 1.10.5 summarizes information on Adempas therapy continuation, change and discontinuation at all FU visits.

10.2.9 Adempas daily dose over time

In the total cohort, at baseline, the mean dose was 6.8 (SD 1.3) mg (median 7.5 mg, range 1.5 – 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. Post-text Table 1.10.4 provides an overview on the Adempas daily dose at baseline and during the study.

10.2.10 PH medications and anticoagulation over time

Post-text Table 1.9.3 shows the rate of patients with Adempas monotherapy and combination therapy over time. The rate of patients on combination therapy increased steadily over time (from baseline 36.4%, follow-up visit 1 37.3%, follow-up visit 2 38.6%, follow-up visit 3 40.2%, follow-up visit 4 42.2%).

10.2.11 Lung function

In the total cohort, mean % predicted total lung capacity, available for 792 patients, was 93.86 (SD 17.08). Post-text Table 1.12.1 summarizes summary statistics and change from baseline for % pred TLC.

Mean % predicted forced vital capacity, available for 958 patients, was 87.38 (SD 20.94). Post-text Table 1.12.2 summarizes summary statistics and change from baseline for % pred FVC.

Mean % predicted forced expiratory volume in 1 second, available for 981 patients, was 79.04 (SD 20.77). Post-text Table 1.12.3 summarizes summary statistics and change from baseline for % pred FEV1.

Mean % predicted diffusing capacity for carbon monoxide (DLCO) available for 741 patients, was 59.46 (SD 23.86). Post-text Table 1.12.4 summarizes summary statistics and change from baseline % pred DL_{CO}.

Mean partial pressure of O2, available for 627 patients, was 66.36 (SD 26.50) mmHg. Post-text Table 1.12.5 summarizes summary statistics and change from baseline for paO_2.

Mean partial pressure of CO_2, available for 621 patients, was 35.05 (SD 6.62) mmHg. Post-text Table 1.12.6 summarizes summary statistics and change from baseline for pa CO_2.

Mean Oxygen supply during blood gas analysis (O_2 BGA), available for 431 patients, was 2.58 (SD 11.99) liters/min. Post-text Table 1.12.7 summarizes summary statistics and change from baseline for O_2 BGA.

10.2.12 Cardiac rhythm

In the total cohort, at baseline, 970 patients (72.9%) were in sinus rhythm, 112 (8.4%) had atrial fibrillation, 9 (0.7%) had atrial flutter, 55 (4.1%) other rhythm, and 184 (13.8%) an unknown rhythm. Post-text Table 1.13.8 provides a summary on cardiac rhythm at baseline and follow-up visits.

10.2.13 Laboratory data

Laboratory data are summarized in post-text Table 1.15.1 (haemoglobin), post-text Table 1.15.2 (haematocrit), post-text Table 1.15.3 (INR), post-text Table 1.15.4 (ALT), post-text Table 1.15.5 (AST), post-text Table 1.15.6 (bilirubin), post-text Table 1.15.7 (uric acid), post-text Table 1.15.8 (sodium), post-text Table 1.15.9 (C-reactive protein), post-text Table 1.15.10 (MCV), post-text Table 1.15.11 (MCH), post-text Table 1.15.12 (MCHC), post-text

Table 1.15.13 (iron), post-text Table 1.15.14 (transferrin), post-text Table 1.15.15 (ferritin), post-text Table 1.15.16 (sTfR), post-text Tables 1.15.17 ff (creatinine, creatinine clearance/eGFR (Cockcroft and Gault).

10.3 Outcome data

The numbers of subjects across categories of main outcomes are presented in section 10.5.1 (incidence of adverse events/serious adverse events) and section 10.5.5 (incidence of all-cause mortality).

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 the different PH indication (PAH, CTEPH)" are presented in section 10.5 Adverse Events.

10.4.2 Effectiveness of Adempas in the long-term

10.4.2.1 6-minute walking distance

From the baseline mean value of 367.4 meters in the total cohort, at the first 7 visits small improvements were noted. Details are presented in Table 10–10. There was a considerable rate of missing values at baseline, even higher with increasing observation time, which makes the interpretation of findings difficult.

Table 10–10: Six-minute walking distance (total cohort)

	Value at visit							Change from baseline at visit						
	N	Nmiss	Min	Mean	SD	Median	Max	N	Nmiss	Min	Mean	SD	Median	Max
Baseline	1124	206	0.0	367.4	130.7	376.5	756.0	-	-	-	-	-	-	-
Follow-up visit 1	713	602	17.0	384.1	129.3	390.0	827.0	665	650	-300.0	7.3	68.9	3.0	512.0
Follow-up visit 2	650	523	0.0	385.5	127.7	395.5	763.0	597	576	-258.0	6.1	70.3	3.0	375.0
Follow-up visit 3	535	452	5.0	393.0	124.1	400.0	750.0	498	489	-325.0	7.0	78.1	0.0	500.0
Follow-up visit 4	439	372	19.0	391.0	117.8	400.0	720.0	411	400	-203.0	9.1	75.4	1.0	440.0
Follow-up visit 5	304	309	0.0	394.1	125.4	394.0	750.0	278	335	-370.0	0.0	83.4	-3.5	456.0
Follow-up visit 6	250	234	42.0	396.3	123.9	403.5	750.0	229	255	-406.0	-0.8	75.2	0.0	285.0
Follow-up visit 7	170	177	75.0	406.0	118.1	401.5	794.0	153	194	-180.0	-2.7	68.0	-9.0	280.0
Follow-up visit 8	101	123	60.0	387.7	121.9	397.0	657.0	91	133	-317.0	-19.8	81.3	-9.0	216.0
Follow-up visit 9	71	76	96.0	401.6	127.2	418.0	846.0	64	83	-318.0	-7.3	84.3	0.0	192.0
Follow-up visit 10	54	53	35.0	399.3	125.1	434.5	632.0	52	55	-258.0	-13.4	77.8	-18.0	155.0
Follow-up visit 11	32	49	234.0	392.9	104.2	409.0	568.0	30	51	-164.0	8.1	105.4	-22.0	440.0
Follow-up visit 12	24	32	175.0	367.8	129.7	393.0	696.0	23	33	-300.0	-25.3	95.0	-27.0	245.0
Follow-up visit 13	10	22	204.0	384.1	115.1	383.5	552.0	10	22	-146.0	-1.3	64.1	28.0	69.0

Visits with less than 10 6-min walk distance values not shown.
Nmiss= number of patients with missing values
Source: Post-text Table 1.11.1.2

Further, post-text Table 1.11.1.1 contains the number of patients with 6-min walking test by distance category (< 320m, ≥ 320m), post-text Table 1.11.1.2 by subgroup (PAH, CTEPH, PAH/CTEPH combined, other).

10.4.2.2 NYHA/WHO FC

Post-text Table 1.11.4 contains the number of patients and values of NYHA/WHO functional class including the change from baseline at the various visits. Rates of missing data were very high.

10.4.2.3 Borg Dyspnea Index

Table 10–11 contains the number of patients and values of the Borg Dyspnea Index including the change from baseline at the various visits. There appeared slight mean changes over time. There was a high rate of missing values at baseline, even higher with increasing observation time, which makes the interpretation of findings difficult.

Table 10–11: Summary statistics and change from Baseline for Borg Dyspnea Index (total cohort)

	Value at visit							Change from baseline at visit						
	N	Nmiss	Min	Mean	SD	Median	Max	N	Nmiss	Min	Mean	SD	Median	Max
Baseline	977	353	0.00	3.93	2.29	4.00	10.00	-	-	-	-	-	-	-
Follow-up visit 1	611	704	0.00	3.91	2.25	4.00	10.00	553	762	-8.00	-0.05	2.03	0.00	10.00
Follow-up visit 2	548	625	0.00	3.94	2.16	4.00	10.00	490	683	-8.00	-0.07	2.00	0.00	10.00
Follow-up visit 3	456	531	0.00	4.13	2.27	4.00	10.00	412	575	-8.00	-0.15	2.09	0.00	10.00
Follow-up visit 4	359	452	0.00	4.04	2.26	4.00	10.00	321	490	-7.00	-0.23	2.12	0.00	10.00
Follow-up visit 5	246	367	0.00	4.08	2.17	4.00	10.00	212	401	-7.00	-0.14	2.19	0.00	10.00
Follow-up visit 6	209	275	0.00	4.11	2.19	4.00	10.00	186	298	-6.00	-0.11	2.07	0.00	10.00
Follow-up visit 7	141	206	0.00	4.35	2.36	4.00	10.00	122	225	-5.00	-0.03	1.84	0.00	5.00
Follow-up visit 8	86	138	0.00	4.22	2.22	4.00	10.00	74	150	-4.00	-0.09	1.87	0.00	5.00
Follow-up visit 9	63	84	0.00	4.19	2.30	5.00	9.00	55	92	-5.00	-0.07	2.25	0.00	7.00
Follow-up visit 10	48	59	0.00	4.04	2.20	4.00	10.00	45	62	-5.00	0.00	2.50	0.00	8.00
Follow-up visit 11	30	51	0.00	4.17	2.13	4.00	8.00	27	54	-5.00	0.07	2.23	0.00	5.00
Follow-up visit 12	20	36	1.00	4.70	2.49	5.00	9.00	19	37	-2.00	0.42	2.22	0.00	6.00

Follow-up visits with less than 10 Borg Dyspnea index values not shown.
Nmiss= number of patients with missing values
Source: Post-text Table 1.11.2

10.4.2.4 EQ-5D VAS

Table 10–12 contains the number of patients and values of EQ-5D VAS including the change from baseline at the various visits. Rates of missing data were very high.

Table 10–12: Summary statistics and change from Baseline for EQ-5D VAS (total cohort)

	Value at visit							Change from baseline at visit						
	N	Nmiss	Min	Mean	SD	Median	Max	N	Nmiss	Min	Mean	SD	Median	Max
Baseline	345	985	0.0	61.5	21.1	60.0	100.0	-	-	-	-	-	-	-
Follow-up visit 1	268	1047	0.0	64.0	19.8	65.0	100.0	219	1096	-85.0	3.2	17.4	0.0	68.0
Follow-up visit 2	235	938	0.0	64.3	20.5	65.0	100.0	197	976	-70.0	3.4	16.5	0.0	68.0
Follow-up visit 3	198	789	15.0	64.4	18.6	65.0	100.0	165	822	-50.0	3.6	17.1	0.0	71.0
Follow-up visit 4	167	644	6.0	65.4	20.3	70.0	100.0	132	679	-44.0	2.8	16.1	1.0	66.0
Follow-up visit 5	115	498	15.0	65.5	19.7	63.0	100.0	93	520	-60.0	2.4	14.5	1.0	40.0
Follow-up visit 6	102	382	29.0	67.2	17.2	70.0	95.0	85	399	-35.0	2.9	14.4	0.0	40.0
Follow-up visit 7	69	278	10.0	65.8	20.5	70.0	95.0	58	289	-35.0	2.2	13.4	0.0	40.0
Follow-up visit 8	48	176	5.0	67.2	20.6	70.0	100.0	42	182	-34.0	2.5	13.4	0.0	40.0
Follow-up visit 9	34	113	25.0	64.3	19.1	62.5	100.0	29	118	-14.0	6.8	15.1	0.0	52.0
Follow-up visit 10	30	77	0.0	59.3	21.1	60.0	94.0	27	80	-15.0	1.3	11.2	0.0	35.0
Follow-up visit 11	20	61	38.0	65.4	16.3	65.0	90.0	18	63	-20.0	0.2	9.0	0.0	20.0
Follow-up visit 12	15	41	50.0	74.1	12.4	80.0	90.0	12	44	-20.0	-1.0	11.4	-0.5	25.0

Follow-up visits with less than 10 EQ-5D VAS values not shown.
Nmiss= number of patients with missing values.
Source: Post-text Table 1.11.3

10.4.2.5 Invasive hemodynamics

Post-text Table 1.13.1. provides an overview on the number of patients with invasive hemodynamics (right heart catheter, RHC) at baseline and the follow-up visits.

In the total cohort, at baseline 1199 patients (90.2%) had RHC results, while 131 patients (9.8%) had not.

In the total population, at baseline, mean saturated venous oxygen (SvO2, %), available in 853 patients was 63.70 (SD 9.89). Mean pulmonary arterial pressure (PaPm), available in 1172 patients, was 45.06 (SD 12.82) mmHg. Mean pulmonary vascular resistance (PVR), available in 1062 patients, was 690.73 (SD 508.37) dyn*sec*cm^{-5}. Mean pulmocapillary wedge pressure (PCWP), available in 1115 patients, was 10.99 (SD 5.16) mmHg. Mean right atrial pressure (RAP), available in 947 patients, was 9.02 (SD 5.78) mmHg. Mean cardiac index (CI), available in 1037 patients was 2.71 (SD 3.81) l/min/m^2.

Post-text Table 1.13.2 to post-text Table 1.13.7 show statistics for various RHC variables.

10.4.2.6 Biomarkers BNP and NT-pro BNP

Post-text Table 1.14.1 to post-text Table 1.14.3 provide an overview on the biomarkers Brain Natriuretic Peptide (BNP) and N-Terminal pro BNP (NT-pro BNP), and homocysteine at baseline and the follow-up visits.

In the total cohort, at baseline, mean BNP, available in 217 patients, was 346.12 (SD 647.97) pg/mL, NT-pro BNP, available in 684 patients was 1759.0 (SD 7928.1) pg/mL, and homocysteine, available in 43 patients was 15.37 (SD 5.60) mcmol/L.

10.4.3 Resource use

The number of additional outpatient visits at the PH center is shown by visit in post-text Table 1.17.1, the days in home care or the nursing home in post-text Table 1.17.2, the number of days at a pulmonary rehabilitation facility/hospital in post-text Table 1.17.3, and hospitalizations in post-text Table 1.18.2. Summary statistics (annualized rates) are shown in Table 10–13 for these variables: a mean of 0.48 (SD 2.73) additional outpatient visits at the

PH center per year were reported, 0.30 (SD 3.06) days per week in home care, 1.09 (SD 7.41) days at a pulmonary rehabilitation facility/hospital, and 1.09 (10.74) hospitalizations.

Table 10–13: Resource use: annualized rates of outpatient visits, days in home care, days in rehabilitation care and number of hospitalizations

		PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
		N	%	N	%	N	%	N	%	N	%
Number of additional outpatient visits at PH center			.		.		.		.		.
	N	323	.	948	.	47	.	1271	.	1318	.
	Nmiss	3	.	8	.	1	.	11	.	12	.
	Min	0.00	.	0.00	.	0.00	.	0.00	.	0.00	.
	Mean	0.31	.	0.52	.	0.70	.	0.47	.	0.48	.
	SD	1.52	.	3.05	.	2.31	.	2.74	.	2.73	.
	Median	0.00	.	0.00	.	0.00	.	0.00	.	0.00	.
	Max	14.05	.	52.18	.	13.04	.	52.18	.	52.18	.
			.		.		.		.		.
Number of days per week by home care			.		.		.		.		.
	N	323	.	948	.	47	.	1271	.	1318	.
	Nmiss	3	.	8	.	1	.	11	.	12	.
	Min	0.00	.	0.00	.	0.00	.	0.00	.	0.00	.
	Mean	0.71	.	0.10	.	1.59	.	0.25	.	0.30	.
	SD	4.60	.	1.33	.	8.91	.	2.60	.	3.06	.
	Median	0.00	.	0.00	.	0.00	.	0.00	.	0.00	.
	Max	60.88	.	33.06	.	59.46	.	60.88	.	60.88	.
			.		.		.		.		.
Number of days at a pulmonary rehabilitation facility/hospital			.		.		.		.		.
	N	323	.	948	.	47	.	1271	.	1318	.
	Nmiss	3	.	8	.	1	.	11	.	12	.
	Min	0.00	.	0.00	.	0.00	.	0.00	.	0.00	.
	Mean	1.57	.	0.84	.	2.76	.	1.02	.	1.09	.
	SD	11.86	.	4.63	.	11.75	.	7.20	.	7.41	.
	Median	0.00	.	0.00	.	0.00	.	0.00	.	0.00	.
	Max	179.48	.	72.09	.	76.45	.	179.48	.	179.48	.
			.		.		.		.		.
Number of hospitalizations			.		.		.		.		.
	N	323	.	948	.	47	.	1271	.	1318	.
	Nmiss	3	.	8	.	1	.	11	.	12	.
	Min	0.00	.	0.00	.	0.00	.	0.00	.	0.00	.
	Mean	1.00	.	0.52	.	13.23	.	0.64	.	1.09	.
	SD	2.05	.	1.45	.	55.42	.	1.64	.	10.74	.
	Median	0.00	.	0.00	.	1.31	.	0.00	.	0.00	.
	Max	15.88	.	20.29	.	365.25	.	20.29	.	365.25	.
			.		.		.		.		.

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: Post-text Table 30.15.1

10.5 Adverse Events

A summary of the overall treatment-emergent adverse events (TEAEs) is presented in Table 10–14.

TEAEs in patients treated with Adempas in the approved indications (PAH and CTEPH) are shown individually and combined (PAH/CTEPH). For the sake of completeness, TEAEs are shown in the small group of patients ("other", n=48) who received Adempas outside the approved indications, i.e. in Dana Point groups 2, 3 and 5 (please also see Section 10.6.2 "Use of riociguat outside the approved indications"). The patients in the PAH, CTEPH and Other groups add up to the total of 1330 patients.

Table 10–14: Number of patients with treatment-emergent Adverse Events

	PAH N=326 (100%)			CTEPH N=956 (100%)			Other N=48 (100%)			PAH/CTEPH N=1282 (100%)			Total N=1330 (100%)		
	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI
Any AE	229	70.2	65.0 - 75.2	615	64.3	61.2 - 67.4	41	85.4	72.2 - 93.9	844	65.8	63.2 - 68.4	885	66.5	63.9 - 69.1
AE-related death	40	12.3	8.9 - 16.3	93	9.7	7.9 - 11.8	5	10.4	3.5 - 22.7	133	10.4	8.8 - 12.2	138	10.4	8.8 - 12.1
Any Drug Related AE	**49**	**15.0**	**11.3 - 19.4**	**148**	**15.5**	**13.2 - 17.9**	**23**	**47.9**	**33.3 - 62.8**	**197**	**15.4**	**13.4 - 17.5**	**220**	**16.5**	**14.6 - 18.6**
Discontinuation of study drug due to AE	24	7.4	4.8 - 10.8	55	5.8	4.4 - 7.4	14	29.2	17.0 - 44.1	79	6.2	4.9 - 7.6	93	7.0	5.7 - 8.5
Any SAE	152	46.6	41.1 - 52.2	365	38.2	35.1 - 41.3	34	70.8	55.9 - 83.0	517	40.3	37.6 - 43.1	551	41.4	38.8 - 44.1
Any Drug Related SAE	23	7.1	4.5 - 10.4	34	3.6	2.5 - 4.9	14	29.2	17.0 - 44.1	57	4.4	3.4 - 5.7	71	5.3	4.2 - 6.7
Discontinuation of study drug due to SAE	21	6.4	4.0 - 9.7	38	4.0	2.8 - 5.4	12	25.0	13.6 - 39.6	59	4.6	3.5 - 5.9	71	5.3	4.2 - 6.7

PAH = pulmonary arterial hypertension, CTEPH = chronic thromboembolic pulmonary hypertension, AE = adverse event, SAE = serious adverse event.
Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: Post-text Table 1.16.1.

In the total cohort of 1330 patients, 885 patients (66.5%) experienced any TEAE. Drug-related TEAE were documented in 220 patients (16.5%). TEAE leading to drug discontinuation occurred in 93 patients (7.0%). TEAE-related deaths were documented in 138 patients (10.4%).

Any SAE was reported in 551 patients (41.4%), any drug-related SAE in 71 patients (5.3%), and SAE leading to drug discontinuation in 71 patients (5.3%) (post-text Table 1.16.1).

The total number of AEs was 4014, of SAE 1360, of drug-related AE 453, of drug related SAE 97 (post-text Table 1.16.2).

Use in approved indications. In the approved indications (PAH/CTEPH combined), 844 patients (65.8%) experienced any TEAE. Drug-related TEAE were documented in 197 patients (15.4%). AE leading to drug discontinuation occurred in 79 patients (6.2%). AE-related deaths occurred in 133 patients (10.4%). Any SAE was reported in 517 patients (40.3%), any drug-related SAE in 57 patients (4.4%), and SAE leading to drug discontinuation in 59 patients (4.6%).

Outcomes of TEAE in total, in the approved indications, and in patients in other indications are summarized in Table 10–15. The outcome of TEAEs was reported as "recovered/resolved" in the majority of the cases.

Table 10–15: Overall summary of treatment-emergent adverse events

	PAH		CTEPH		Other		PAH/CTEPH		Total	
	N	%	N	%	N	%	N	%	N	%
Any AE	1231	100.0	2496	100.0	287	100.0	3727	100.0	4014	100.0
AE-related death	44	3.6	110	4.4	5	1.7	154	4.1	159	4.0
Any Drug Related AE	122	9.9	280	11.2	51	17.8	402	10.8	453	11.3
Outcome										
Recovered/resolved	695	56.5	1318	52.8	176	61.3	2013	54.0	2189	54.5
Recovering/resolving	134	10.9	226	9.1	26	9.1	360	9.7	386	9.6
Recovered/resolved with sequelae	20	1.6	51	2.0	19	6.6	71	1.9	90	2.2
Not recovered/not resolved	244	19.8	521	20.9	43	15.0	765	20.5	808	20.1
Fatal	44	3.6	110	4.4	5	1.7	154	4.1	159	4.0
Unknown	94	7.6	270	10.8	18	6.3	364	9.8	382	9.5
Any SAE	395	32.1	855	34.3	110	38.3	1250	33.5	1360	33.9
Any Drug Related SAE	32	2.6	45	1.8	20	7.0	77	2.1	97	2.4
Outcome										
Recovered/resolved	269	21.9	555	22.2	74	25.8	824	22.1	898	22.4
Recovering/resolving	33	2.7	64	2.6	10	3.5	97	2.6	107	2.7
Recovered/resolved with sequelae	16	1.3	35	1.4	14	4.9	51	1.4	65	1.6
Not recovered/not resolved	21	1.7	68	2.7	6	2.1	89	2.4	95	2.4
Fatal	44	3.6	110	4.4	5	1.7	154	4.1	159	4.0
Unknown	12	1.0	23	0.9	1	0.3	35	0.9	36	0.9

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: Post-text Table 1.16.2

10.5.1 Incidence of treatment-emergent Adverse Events (primary outcome)

Table 10–16 provides a breakdown of the 885 of 1330 patients of the total cohort with any treatment-emergent event (defined as events that occurred during treatment and up to 2 days after the last Adempas dose) by System Organ Class.

The SOC most frequently affected were Respiratory, Thoracic and Mediastinal disorders (25.6%), followed by General Disorders and Administration Site Conditions (23.5%), Infections and Infestations (23.8%), Cardiac Disorders (19.4%), Gastrointestinal Disorders (19.3%), and Nervous System Disorders (17.9%).

The most frequently named PTs were dyspnea (8.9%), dizziness (8.7%), peripheral edema (7.8%), right ventricular failure (6.6%), pneumonia (5.8%), and cough (5.3%). (post-text Table 1.16.6). All other PTs had an incidence of less than 5.0%.

Table 10–16: Number of patients with treatment-emergent adverse events by primary system organ class (incidence ≥ 5.0% in total population)

System Organ Class	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	**229**	**70.2**	**615**	**64.3**	**41**	**85.4**	**844**	**65.8**	**885**	**66.5**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	27	8.3	64	6.7	9	18.8	91	7.1	100	7.5
CARDIAC DISORDERS	78	23.9	163	17.1	17	35.4	241	18.8	258	19.4
GASTROINTESTINAL DISORDERS	81	24.8	162	16.9	14	29.2	243	19.0	257	19.3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	98	30.1	197	20.6	18	37.5	295	23.0	313	23.5
INFECTIONS AND INFESTATIONS	104	31.9	197	20.6	15	31.3	301	23.5	316	23.8
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	19	5.8	72	7.5	3	6.3	91	7.1	94	7.1
INVESTIGATIONS	30	9.2	53	5.5	9	18.8	83	6.5	92	6.9
METABOLISM AND NUTRITION DISORDERS	40	12.3	78	8.2	11	22.9	118	9.2	129	9.7
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	33	10.1	74	7.7	1	2.1	107	8.3	108	8.1
NERVOUS SYSTEM DISORDERS	69	21.2	154	16.1	15	31.3	223	17.4	238	17.9
RENAL AND URINARY DISORDERS	19	5.8	47	4.9	7	14.6	66	5.1	73	5.5
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	88	27.0	228	23.8	25	52.1	316	24.6	341	25.6
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	16	4.9	29	3.0	6	12.5	45	3.5	51	3.8
SURGICAL AND MEDICAL PROCEDURES	24	7.4	42	4.4	5	10.4	66	5.1	71	5.3
VASCULAR DISORDERS	22	6.7	63	6.6	12	25.0	85	6.6	97	7.3

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: Post-text Table 1.16.6

Use in approved indications (PAH/CTEPH): The SOC most frequently affected were Respiratory, Thoracic and Mediastinal disorders (24.6%), followed by Infections and Infestations (23.5%), General Disorders and Administration Site Conditions (23.0%), Gastro-intestinal Disorders (19.0%), Cardiac Disorders (18.8%), and Nervous System Disorders (17.4%).

The most frequently named PTs were dizziness (8.6%), dyspnea (8.3%), peripheral edema (7.4%), right ventricular failure (6.7%), pneumonia (5.5%), and cough (5.3%) (post-text Table 1.16.6). All other PTs had an incidence of 5.0% or less.

Table 10–17 provides an overview of the incidence of adverse events per 100 person years. In the total cohort, the incidence was 207.5 events per 100 person years (95% confidence interval 201.2 to 214.0 events) for any adverse event, and 70.3 per 100 person years (95 % confidence interval 66.6 to 74.1) for any Serious Adverse Event.

Table 10–17: Incidence of adverse events per 100 person years

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	95% CI	N	95% CI	N	95% CI	N	95% CI	N	95% CI
Any adverse event (rate per 100 person years)	1231 (259.2)	244.9 - 273.9	2496 (175.4)	168.6 - 182.4	287 (820.0)	728.8 - 918.6	3727 (196.4)	190.1 - 202.7	4014 (207.5)	201.2 - 214.0
Any SAE	395 (83.2)	75.2 - 91.6	855 (60.1)	56.1 - 64.2	110 (314.3)	259.2 - 376.7	1250 (65.9)	62.3 - 69.6	1360 (70.3)	66.6 - 74.1

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Adverse events are sorted in alphabetical order by primary SOC and preferred term; N in the header is the number of subjects. The total number of events is presented in the body of the table; a subject may have more than one event. Rate per 100 subject years is the number of events divided by (total drug exposure in years / 100). CI = confidence interval.
Source: post-text Table 1.16.12

10.5.2 Incidence of treatment-emergent serious adverse events

Table 10–18 provides a breakdown of the 551 patients of the total cohort with any treatment-emergent serious adverse event (defined as serious events that occurred during treatment and up to 2 days after the last Adempas dose) by System Organ Class.

The SOC most frequently affected were Cardiac Disorders (14.5%), followed by Respiratory, Thoracic and Mediastinal disorders (12.6%), Infections and Infestations (11.4%), General Disorders and Administration Site Conditions (6.1%), Gastrointestinal Disorders (5.5%), and Nervous System Disorders (4.9%).

The most frequently named PTs were right ventricular failure (6.5%), pneumonia (5.0%), dyspnea (4.3%), and syncope (3.0%) (post-text Table 1.16.7). All other PTs had an incidence of 2.0% or less.

Use in approved indications (PAH/CTEPH): The SOC most frequently affected were Cardiac Disorders (14.0%), Respiratory, Thoracic and Mediastinal disorders (11.6%), followed by Infections and Infestations (11.1%), General Disorders and Administration Site Conditions (5.9%),Gastrointestinal Disorders (5.4%), and Nervous System Disorders (4.5%).

The most frequently named PT were right ventricular failure (6.6%), pneumonia (4.6%), dyspnea (3.7%), and syncope (2.7%) (post-text Table 1.16.7). All other PTs had an incidence of < 2.0%.

Table 10–18: Number of patients with treatment-emergent serious adverse events by primary system organ class (≥2% in total population)

System Organ Class	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	**152**	**46.6**	**365**	**38.2**	**34**	**70.8**	**517**	**40.3**	**551**	**41.4**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	11	3.4	13	1.4	3	6.3	24	1.9	27	2.0
CARDIAC DISORDERS	62	19.0	118	12.3	13	27.1	180	14.0	193	14.5
GASTROINTESTINAL DISORDERS	19	5.8	50	5.2	4	8.3	69	5.4	73	5.5
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	27	8.3	48	5.0	6	12.5	75	5.9	81	6.1
INFECTIONS AND INFESTATIONS	44	13.5	98	10.3	10	20.8	142	11.1	152	11.4
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6	1.8	33	3.5	1	2.1	39	3.0	40	3.0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	7	2.1	23	2.4	2	4.2	30	2.3	32	2.4
NERVOUS SYSTEM DISORDERS	17	5.2	41	4.3	7	14.6	58	4.5	65	4.9
RENAL AND URINARY DISORDERS	11	3.4	26	2.7	6	12.5	37	2.9	43	3.2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	44	13.5	105	11.0	19	39.6	149	11.6	168	12.6
SURGICAL AND MEDICAL PROCEDURES	19	5.8	34	3.6	4	8.3	53	4.1	57	4.3

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: Post-text Table 1.16.7

10.5.3 Drug-related TEAEs

In total, 220 of 1330 patients in the total cohort (16.5%), and 197 of the 1282 PAH/CTEPH patients (15.4%) experienced TEAEs that were assessed as drug-related by the investigator. These cases are presented and discussed in details in Section 10.7 (Adverse events/adverse reactions).

10.5.4 Adverse Events of special interest

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

Hypotension

An overview on the number of patients with treatment-emergent hypotension is given in post-text Table 29.3.1 and in Table 10–19.

Table 10–19: Overall summary of number of patients with treatment-emergent hypotension

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Any Event of Hypotension	13	4.0	41	4.3	9	18.8	54	4.2	63	4.7
Any Drug Related Event of Hypotension	9	2.8	26	2.7	8	16.7	35	2.7	43	3.2
Discontinuation of study drug due Event of Hypotension	3	0.9	4	0.4	3	6.3	7	0.5	10	0.8
Any Serious Event of Hypotension	5	1.5	4	0.4	2	4.2	9	0.7	11	0.8
AE-related Death	0	.	0	.	0	.	0	.	0	.
Any Drug Related Serious Event of Hypotension	4	1.2	3	0.3	2	4.2	7	0.5	9	0.7
Discontinuation of study drug due to Serious Event of Hypotension	1	0.3	1	0.1	2	4.2	2	0.2	4	0.3

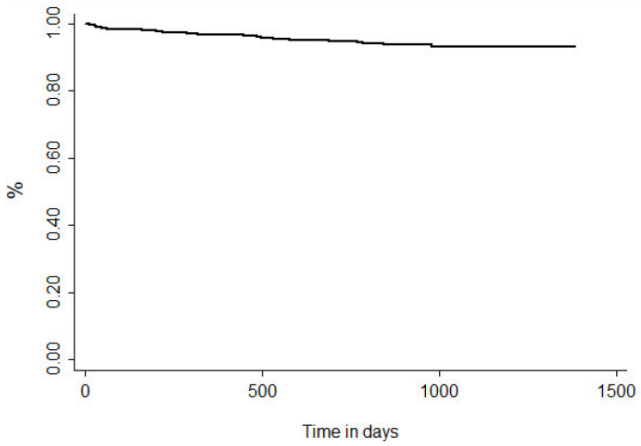
Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Events were identified by Project Bayer MedDRA Query 'Hypotension (Riociguat)'
Source: Post-text Table 29.3.1

In the total population, 63 cases of treatment-emergent hypotension (4.7%) were reported.

In the pooled CTEPH/PAH population, treatment-emergent hypotension was reported in 54 patients (4.2% of the pooled PAH and CTEPH population), of which 35 (2.7%) were assessed as drug-related by the reporting investigators, while serious treatment-emergent hypotension was reported in 9 out of 1282 patients (0.7% of the pooled PAH and CTEPH population), the majority (7 patients, 0.5%) of these cases were assessed as related to riociguat by the reporting investigators.

shows the onset of hypotension (identified as PT Hypotension) in the total cohort.

Figure 10–1: Kaplan-Meier curve on the onset of hypotension (total cohort)



Source: Post-text Figure 1.19.3

There were no differences in the time course between PAH and CTEPH patients (post-text Figure 1.19.4).

Hemoptysis/pulmonary hemorrhage:

An overview on the number of patients with treatment-emergent hemoptysis is given in Table 10–20. In the total population any such events occurred in 36 patients (2.7%), drug related in 8 patients (0.6%), fatal in 4 patients (0.3%), any serious hemoptysis in 24 patients (1.8%), serious drug-related in 7 patients (0.5%).

In the pooled CTEPH/PAH population, any treatment-emergent hemoptysis occurred in 34 patients (2.7%), drug related in 6 patients (0.5%), any serious hemoptysis in 22 patients (1.7%), serious drug-related in 5 patients (0.4%). Pulmonary haemorrhage occurred in 2 patients (0.2%). The outcome of haemoptysis was fatal in 4 cases (0.3%) cases, in the majority of the serious cases the outcome was recovered/resolved (21 of 26 events, manually calculated) and in 1 case the outcome was reported as recovered/resolved with sequelae. The outcome of the two cases of pulmonary haemorrhage was reported as recovered/resolved with sequelae (post-text Tables 29.1.1)

Among the 4 cases with fatal outcome, 3 occurred in patients with CTEPH and 1 occurred in a patient with PAH. In all 4 cases, the fatal events occurred with a long latency after initiation of Adempas. Confounding factors in the 3 CTEPH patients included concomitant use of anticoagulants, medical history of bronchial artery embolization, and/or history of haemoptysis. The patient with PAH had confounding factors of concurrent pneumonia and hereditary haemorrhagic telangiectasia.

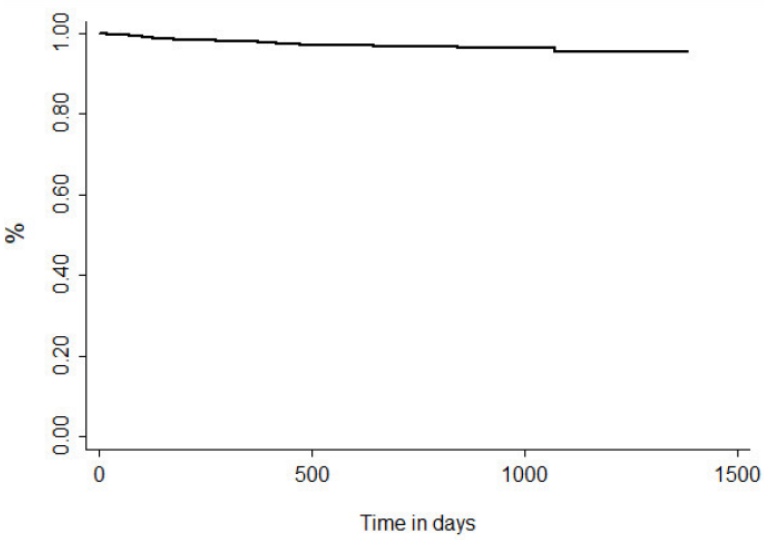
Notably, the majority of patients in the EXPERT study received concomitant oral anticoagulation at baseline (49.4% of PAH, 90.1% for CTEPH) (post-text Table 1.9.2).

Table 10–20: Overall summary of number of patients with treatment-emergent hemoptysis

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Any Event of hemoptysis/pulmonary haemorrhage	8	2.5	26	2.7	2	4.2	34	2.7	36	2.7
Any Drug Related Event of hemoptysis/ pulmonary haemorrhage	3	0.9	3	0.3	2	4.2	6	0.5	8	0.6
Discontinuation of study drug due Event of hemoptysis/pulmonary haemorrhage	2	0.6	2	0.2	0	0.0	4	0.3	4	0.3
Any Serious Event of hemoptysis/ pulmonary haemorrhage	6	1.8	16	1.7	2	4.2	22	1.7	24	1.8
Any Fatal Event of hemoptysis/pulmonary haemorrhage	1	0.3	3	0.3	0	0.0	4	0.3	4	0.3
Any Drug Related Serious Event of hemoptysis/pulmonary haemorrhage	3	0.9	2	0.2	2	4.2	5	0.4	7	0.5
Discontinuation of study drug due Serious Event of hemoptysis/pulmonary haemorrhage	2	0.6	2	0.2	0	0.0	4	0.3	4	0.3

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Adverse events of hemoptysis are defined by MedDRA PT 'haemoptysis' and 'pulmonary haemorrhage'
Source: post-text Table 29.1.1.

Figure 10–2: Kaplan-Meier curve on the onset of hemoptysis (total cohort)



Source: Post-text Figure 1.19.5

10.5.5 Deaths

In the total cohort,

151/1330 (11.4%) patients died during the study (manually calculated):

- 138 patients (10.4%) resulting from TEAEs (AE onset within 2 days of the last dose of riociguat),
- 13 patients from post-treatment AEs (i.e. onset of the events was > 2 days following the last dose of riociguat and before 30 days safety follow up period).

In addition, there were 3 further fatal AE which occurred > 30 days after Adempas discontinuation which were recorded in the study database and are noted for completeness.

Details are shown in Table 10–21.

Table 10–21: Overall number of patients with adverse events with fatal outcome

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Any adverse event with fatal outcome during the treatment phase (AE onset <=2 days)	40	12.3	93	9.7	5	10.4	133	10.4	138	10.4
Any Drug Related adverse event with fatal outcome during the treatment phase (AE onset <=2 days)	1	0.3	2	0.2	0	0.0	3	0.2	3	0.2
Any adverse event with fatal outcome during the 30-day safety follow-up	4	1.2	8	0.8	1	2.1	12	0.9	13	1.0
Any Drug Related adverse event with fatal outcome during the 30-day safety follow-up	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Any adverse event with fatal outcome that occurred > 30-day after Adempas discontinuation	1	0.3	2	0.2	0	0.0	3	0.2	3	0.2

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: post-text Table 30.5.1.

Treatment-emergent adverse events with fatal outcome:

The 138 deaths resulting from TEAEs occurred in 40 PAH patients, 93 CTEPH patients and 5 patients in which riociguat was used outside approved indications. The TEAE with fatal outcomes are presented by System Organ Class and by Preferred Term in Table 10–22.

In the total cohort, the SOCs most frequently noted were Cardiac Disorders (50 deaths, 3.8% of all patients), General Disorders and Administrative Site Conditions (33 deaths, 2.5%), Respiratory, Thoracic and Mediastinal disorders (23 deaths, 1.7%), Infections and infestations (12 deaths, 0.9%), Neoplasms (9 deaths, 0.7%). The most frequently named preferred terms were right ventricular failure (32 deaths, 2.4%), and (unspecified) death (26 cases, 2.0%).

In the pooled CTEPH/PAH population, the SOCs most frequently noted were Cardiac Disorders (48 deaths, 3.7% of all patients), General Disorders and Administrative Site Conditions (32 deaths, 2.5%), Respiratory, Thoracic and Mediastinal disorders (21 deaths, 1.6%), Infections and infestations (12 deaths, 0.9%), Neoplasms (9 deaths, 0.7%), The most frequently named preferred terms in this group were right ventricular failure (32 deaths, 2.5%), and (unspecified) death (25 cases, 2.0%).

A listing of patients with treatment-emergent fatal SAEs is shown in post-text Table 30.5.5.

Table 10–22: Number of patients with treatment-emergent adverse events during the treatment phase (AE onset ≤2 days after Adempas discontinuation) with fatal outcome by primary system organ class, preferred term

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
System Organ Class Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Number of patients (%) with at least one such adverse event	**40**	**12.3**	**93**	**9.7**	**5**	**10.4**	**133**	**10.4**	**138**	**10.4**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
DISSEMINATED INTRAVASCULAR COAGULATION	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
CARDIAC DISORDERS	12	3.7	36	3.8	2	4.2	48	3.7	50	3.8
CARDIAC ARREST	1	0.3	3	0.3	0	0.0	4	0.3	4	0.3
CARDIAC FAILURE	1	0.3	4	0.4	2	4.2	5	0.4	7	0.5
CARDIAC FAILURE ACUTE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CARDIAC FAILURE CHRONIC	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CARDIAC FAILURE CONGESTIVE	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
CARDIOGENIC SHOCK	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CARDIOPULMONARY FAILURE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CARDIORENAL SYNDROME	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CARDIOVASCULAR INSUFFICIENCY	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
RIGHT VENTRICULAR FAILURE	8	2.5	24	2.5	0	0.0	32	2.5	32	2.4
GASTROINTESTINAL DISORDERS	1	0.3	4	0.4	0	0.0	5	0.4	5	0.4
ABDOMINAL PAIN	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
DIARRHOEA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTROINTESTINAL HAEMORRHAGE	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
PANCREATITIS ACUTE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14	4.3	18	1.9	1	2.1	32	2.5	33	2.5
DEATH	9	2.8	16	1.7	1	2.1	25	2.0	26	2.0
MULTIPLE ORGAN DYSFUNCTION SYNDROME	3	0.9	1	0.1	0	0.0	4	0.3	4	0.3
SUDDEN CARDIAC DEATH	2	0.6	0	0.0	0	0.0	2	0.2	2	0.2
SUDDEN DEATH	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INFECTIONS AND INFESTATIONS	3	0.9	9	0.9	0	0.0	12	0.9	12	0.9
CELLULITIS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
LUNG INFECTION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PNEUMONIA	1	0.3	3	0.3	0	0.0	4	0.3	4	0.3
PNEUMONIA VIRAL	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
RESPIRATORY TRACT INFECTION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
SEPSIS	1	0.3	3	0.3	0	0.0	4	0.3	4	0.3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	0.3	6	0.6	0	0.0	7	0.5	7	0.5
ACCIDENT	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
ACCIDENT AT HOME	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CHEST INJURY	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
FALL	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
FEMUR FRACTURE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
HIP FRACTURE	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
RIB FRACTURE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
SUBDURAL HAEMATOMA	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
SUBDURAL HAEMORRHAGE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INVESTIGATIONS	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
OCCULT BLOOD POSITIVE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
METABOLISM AND NUTRITION DISORDERS	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
DECREASED APPETITE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
FLUID OVERLOAD	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1

Table 10–22: Number of patients with treatment-emergent adverse events during the treatment phase (AE onset ≤2 days after Adempas discontinuation) with fatal outcome by primary system organ class, preferred term

	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
System Organ Class Preferred Term	N	%	N	%	N	%	N	%	N	%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2	0.6	7	0.7	0	0.0	9	0.7	9	0.7
ADENOCARCINOMA	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
GASTRIC CANCER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
LUNG NEOPLASM MALIGNANT	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
MALIGNANT ASCITES	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
METASTASES TO LIVER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
METASTASES TO LUNG	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
METASTATIC NEOPLASM	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
MYELODYSPLASTIC SYNDROME	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
NEOPLASM MALIGNANT	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
OVARIAN CANCER METASTATIC	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
NERVOUS SYSTEM DISORDERS	0	0.0	4	0.4	0	0.0	4	0.3	4	0.3
BRAIN INJURY	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CEREBELLAR INFARCTION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CEREBRAL HAEMORRHAGE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
HAEMORRHAGE INTRACRANIAL	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PSYCHIATRIC DISORDERS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
COMPLETED SUICIDE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
RENAL AND URINARY DISORDERS	1	0.3	2	0.2	0	0.0	3	0.2	3	0.2
ACUTE KIDNEY INJURY	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
RENAL FAILURE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
URINARY BLADDER HAEMORRHAGE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8	2.5	13	1.4	2	4.2	21	1.6	23	1.7
ACUTE PULMONARY OEDEMA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
ACUTE RESPIRATORY FAILURE	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
DYSPNOEA	2	0.6	1	0.1	0	0.0	3	0.2	3	0.2
HAEMOPTYSIS	1	0.3	3	0.3	0	0.0	4	0.3	4	0.3
HYPOXIA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PNEUMONIA ASPIRATION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PULMONARY ARTERIAL HYPERTENSION	2	0.6	0	0.0	0	0.0	2	0.2	2	0.2
PULMONARY EMBOLISM	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
PULMONARY FIBROSIS	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
PULMONARY HYPERTENSION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
RESPIRATORY FAILURE	2	0.6	2	0.2	1	2.1	4	0.3	5	0.4
SURGICAL AND MEDICAL PROCEDURES	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
LUNG TRANSPLANT	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
VASCULAR DISORDERS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
SHOCK HAEMORRHAGIC	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1

Shaded column PAH/CTEPH highlights the approved indications for Adempas
Source: post-text Table 30.5.2

In 3 cases (0.2% of total population, manually calculated) the events with fatal outcome were assessed as related to riociguat by the reporting investigators:

PPD

Post-treatment adverse events with fatal outcome:

In the post-treatment period during the 30-day safety follow-up after Adempas discontinuation with fatal outcome, in the total cohort 13 patients (1.0%) died (Table 10–23). As SOC, most frequently Cardiac Disorders (5 deaths, 0.4%) and General Disorders and administration site conditions (7 deaths, 0.5%) were noted. As PT, most frequently cardiac failure (2 deaths, 0.2%) and death (5 cases, 0.4%) were noted.

In the CTEPH/PAH group, in the 30-day safety follow-up 12 patients (0.9%) died. As SOC, most frequently Cardiac Disorders (5 deaths, 0.4%) and General Disorders and administration site conditions (6 deaths, 0.5%) were noted. As PT, most frequently cardiac failure (2 deaths, 0.2%) and death (4 cases, 0.3%) were noted.

Table 10–23: Number of patients with post treatment adverse events during the 30-day safety follow-up after Adempas discontinuation with fatal outcome by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	**4**	**1.2**	**8**	**0.8**	**1**	**2.1**	**12**	**0.9**	**13**	**1.0**
CARDIAC DISORDERS	2	0.6	3	0.3	0	0.0	5	0.4	5	0.4
CARDIAC FAILURE	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
CARDIAC FAILURE CONGESTIVE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
RIGHT VENTRICULAR FAILURE	2	0.6	0	0.0	0	0.0	2	0.2	2	0.2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	0.3	5	0.5	1	2.1	6	0.5	7	0.5
DEATH	1	0.3	3	0.3	1	2.1	4	0.3	5	0.4
MULTIPLE ORGAN DYSFUNCTION SYNDROME	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
SUDDEN DEATH	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INFECTIONS AND INFESTATIONS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PULMONARY SEPSIS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
NERVOUS SYSTEM DISORDERS	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
HAEMORRHAGE INTRACRANIAL	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: post-text Table 30.5.3

A listing of patients with treatment-emergent fatal SAEs is shown in post-text Table 30.5.6. All of the events were assessed as unrelated to riociguat by the reporting investigators.

Serious adverse events with fatal outcome with onset date after the end of the study:

For completeness, also the 3 deaths (0.2%) that occurred more than 30 days after Adempas discontinuation are presented. All of them occurred in the CTEPH/PAH subgroup. There was one case of right ventricular failure, one subdural hematoma, and one renal failure, all of which were assessed as not related to riociguat by the reporting investigators. Table 10–24 summarizes these cases. Details of TEAEs with fatal outcome are shown in post-text Table 1.16.15 and post-text Table 30.5.7.

Table 10–24: Number of patients with adverse events with fatal outcome that occurred > 30-day after Adempas discontinuation by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	**1**	**0.3**	**2**	**0.2**	**0**	**0.0**	**3**	**0.2**	**3**	**0.2**
CARDIAC DISORDERS	1	0.3	0	0.0	.	.	1	0.1	1	0.1
RIGHT VENTRICULAR FAILURE	1	0.3	0	0.0	.	.	1	0.1	1	0.1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0.0	1	0.1	.	.	1	0.1	1	0.1
SUBDURAL HAEMATOMA	0	0.0	1	0.1	.	.	1	0.1	1	0.1
RENAL AND URINARY DISORDERS	0	0.0	1	0.1	.	.	1	0.1	1	0.1
RENAL FAILURE	0	0.0	1	0.1	.	.	1	0.1	1	0.1

Shaded column PAH/CTEPH highlights the approved indications for Adempas
Source post-text Table 30.5.4

10.6 Other analyses

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 post-text Tables 22.ff and Tables 23.ff.

PAH. In PAH, riociguat newly treated patients (n=144) compared with riociguat-pretreated patients (n=182) had a shorter mean disease duration (3.8 (SD 4.8) versus 5.6 (SD 5.8) years), post-text Tables 22.5.3 and 23.5.3); shorter mean 6-MWD 365.5 (SD 132.3) versus 401.9 (SD 129.6) meters, post-text Tables 22.5.3 and 23.5.3); a higher proportion of WHO FC III/IV disease (56.9%/8.3% versus 43.4%/5.5%, post-text Tables 22.5.3 and 23.5.3); and a greater proportion of newly diagnosed disease (36.8% versus 4.4%, post-text Tables 22.4 and 23.4).

AEs were reported in 107 riociguat newly treated patients (74.3%) and 122 riociguat-pretreated patients (67.0%) (post-text Tables 22.14 and 23.14). SAEs were reported in 78 patients (54.2%) and 74 patients (40.7%), respectively (post-text Tables 22.14 and 23.14). AEs and SAEs in riociguat newly treated patients were more often considered drug-related, and more often lead to drug discontinuation, than in riociguat-pretreated patients (post-text Tables 22.14 and 23.14).For the respective AEs and SAEs, differences between riociguat newly treated and riociguat-pretreated patients were small, with some events more often detected in one and others in the other group.

CTEPH. In CTEPH, baseline demographics and disease characteristics were generally similar between riociguat newly treated and riociguat-pretreated patients (post-text Tables 22.5.3 and 23.5.3). However, pretreated patients had a higher proportion of prevalent disease than newly treated patients (89.6% versus 55.4%, post-text Tables 22.4 and 23.4). Pretreated patients had a longer mean 6-minute walk distance than newly treated patients: 381.6 (SD 121.9) versus 340.7 (SD 133.3) meters (post-text Tables 22.5.3 and 23.5.3). Pretreated patients had a more favorable distribution of WHO FC: 50.7% versus 31.3% (manually calculated) of patients were in class I/II (post-text Tables 22.5.3 and 23.5.3). Riociguat newly treated patients reported similar frequencies as riociguat-pretreated patients of AEs and SAEs (post-text Tables 22.14 and 23.14). Compared with riociguat-pretreated patients, AEs or SAEs in riociguat newly treated patients were more often considered drug-related, and more often led to discontinuation of the drug (post-text Tables 22.14 and 23.14).

Table 10–25 presents an overview on the treatment-emergent adverse events that occurred in Adempas newly treated patients (i.e. those who started Adempas within 3 months prior to enrollment), and Table 10–26 in pretreated patients.

Table 10–25: Overall summary of number of patients with treatment-emergent adverse events for Adempas newly treated patients

	PAH N=144 (100%)				CTEPH N=419 (100%)				Other N=34 (100%)				PAH/CTEPH N=563 (100%)				Total N=597 (100%)			
	N	%	95% CI		N	%	95% CI		N	%	95% CI		N	%	95% CI		N	%	95% CI	
Any AE	107	74.3	66.4	- 81.2	270	64.4	59.6	- 69.0	30	88.2	72.5	- 96.7	377	67.0	62.9	- 70.8	407	68.2	64.3	- 71.9
AE-related death	19	13.2	8.1	- 19.8	38	9.1	6.5	- 12.2	4	11.8	3.3	- 27.5	57	10.1	7.8	- 12.9	61	10.2	7.9	- 12.9
Any Drug Related AE	36	25.0	18.2	- 32.9	95	22.7	18.7	- 27.0	20	58.8	40.7	- 75.4	131	23.3	19.8	- 27.0	151	25.3	21.9	- 29.0
Discontinuation of study drug due AE	20	13.9	8.7	- 20.6	34	8.1	5.7	- 11.2	12	35.3	19.7	- 53.5	54	9.6	7.3	- 12.3	66	11.1	8.7	- 13.8
Any SAE	78	54.2	45.7	- 62.5	166	39.6	34.9	- 44.5	25	73.5	55.6	- 87.1	244	43.3	39.2	- 47.5	269	45.1	41.0	- 49.1
Any Drug Related SAE	18	12.5	7.6	- 19.0	21	5.0	3.1	- 7.6	13	38.2	22.2	- 56.4	39	6.9	5.0	- 9.3	52	8.7	6.6	- 11.3
Discontinuation of study drug due SAE	17	11.8	7.0	- 18.2	21	5.0	3.1	- 7.6	10	29.4	15.1	- 47.5	38	6.7	4.8	- 9.1	48	8.0	6.0	- 10.5

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: post text Table 22.14.1

Table 10–26: Overall summary of number of patients with treatment-emergent adverse events for Adempas pretreated patients

	PAH N=182 (100%)				CTEPH N=537 (100%)				Other N=14 (100%)				PAH/CTEPH N=719 (100%)				Total N=733 (100%)			
	N	%	95% CI		N	%	95% CI		N	%	95% CI		N	%	95% CI		N	%	95% CI	
Any AE	122	67.0	59.7	- 73.8	345	64.2	60.0	- 68.3	11	78.6	49.2	- 95.3	467	65.0	61.3	- 68.4	478	65.2	61.6	- 68.7
AE-related death	21	11.5	7.3	- 17.1	55	10.2	7.8	- 13.1	1	7.1	0.2	- 33.9	76	10.6	8.4	- 13.1	77	10.5	8.4	- 13.0
Any Drug Related AE	13	7.1	3.9	- 11.9	53	9.9	7.5	- 12.7	3	21.4	4.7	- 50.8	66	9.2	7.2	- 11.5	69	9.4	7.4	- 11.8
Discontinuation of study drug due AE	4	2.2	0.6	- 5.5	21	3.9	2.4	- 5.9	2	14.3	1.8	- 42.8	25	3.5	2.3	- 5.1	27	3.7	2.4	- 5.3
Any SAE	74	40.7	33.5	- 48.2	199	37.1	33.0	- 41.3	9	64.3	35.1	- 87.2	273	38.0	34.4	- 41.6	282	38.5	34.9	- 42.1
Any Drug Related SAE	5	2.7	0.9	- 6.3	13	2.4	1.3	- 4.1	1	7.1	0.2	- 33.9	18	2.5	1.5	- 3.9	19	2.6	1.6	- 4.0
Discontinuation of study drug due SAE	4	2.2	0.6	- 5.5	17	3.2	1.9	- 5.0	2	14.3	1.8	- 42.8	21	2.9	1.8	- 4.4	23	3.1	2.0	- 4.7

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: post text Table 23.14.1

10.6.2 Use of Adempas outside the approved indications

Collection of information on how Adempas is used (e.g. indication and indication subgroups, dose) was listed amongst secondary objectives of the study.

Notably, in January 2017 upon request by German regulatory authority and following implementation of a local protocol amendment 1.3, all investigators in Germany were contacted regarding their patients treated for unapproved indications, to inform that the documentation of off-label patients in EXPERT was no longer allowed and request to complete an end of study visit.

Adempas was used in patients with PH groups other than PAH and CTEPH in 48 patients (3.6%).

In these patients, a total of 41 AEs (23 drug related) and 34 SAEs (14 drug-related) occurred. Five deaths were AE-related (manually calculated from Table 10–27).

Table 10–27 provides an overview on treatment-emergent adverse events in the Dana Point groups 2, 3 and 5 (i.e. outside the Adempas indications).

Table 10–27: Treatment-emergent adverse events in the Dana Point groups 2, 3 and 5

	Group 2 PH due to left heart diseases N=17 (100%)		Group 3 PH due to lung diseases and/or hypoxia N=24 (100%)		Group 5 PH with unclear multifactorial mechanism N=7 (100%)	
AE Type	**N**	**%**	**N**	**%**	**N**	**%**
Any AE	15	88.2	19	79.2	7	100.0
AE-related death	3	17.6	2	8.3	0	0.0
Any Drug Related AE	7	41.2	15	62.5	1	14.3
Discontinuation of study drug due AE	3	17.6	9	37.5	2	28.6
Any SAE	12	70.6	15	62.5	7	100.0
Any Drug Related SAE	5	29.4	8	33.3	1	14.3
Discontinuation of study drug due SAE	3	17.6	7	29.2	2	28.6

Source: post-text Tables 30.7.1ff

The number of patients with treatment-emergent adverse events by primary system organ class, preferred term in PH group 2 (PH due to left heart disease) is shown in post-text Table 30.7.13, group 3 in post-text Table 30.7.17, and group 5 in post-text Table 30.7.22. The number of patients with serious treatment-emergent adverse events by primary system organ class, preferred term in PH group 2 is shown in post-text Table 30.7.25, group 3 in post-text Table 30.7.29, group 5 in post-text Table 30.7.34.

10.6.3 Use of riociguat in other medical relevant subgroups

A number of exploratory subgroup analyses were performed and presented in the post-text Tables as follows: age group <65 years (post-text Tables 2.1ff), age group 65 to < 75 (post-text Tables 3.1ff), age group 75 years and older (post-text Tables 4.1ff), male patients (post-text Tables 5.1ff), female patients (post-text Tables 6.1ff), patients in various geographic regions and countries (post-text Tables 7.1ff to 12.1ff, 21.1ff), patients with hepatic impairment at Baseline (post-text Tables 13.1ff), patients with renal impairment at Baseline (post-text Tables 14.1ff), patients in WHO Functional Class (NYHA) I or II, or III or IV at baseline (tables 15.1ff and 16.1ff), patients with 6-Minute Walk Distance < 380 m, or ≥ 380 m at baseline (post-text Tables 17.1ff and 18.1ff), patients with Systolic Blood Pressure < 110, or ≥ 110 mmHg at baseline (post-text Tables 19.1ff and 20.1ff), transient patients (newly treated patients with ≤10 days between stop of previous therapy and commencing riociguat), and non-transient patients (post-text Tables 24.1ff and 25.1ff), patients simultaneously starting Adempas and endothelin receptor antagonists (post-text Tables 26.1ff), patients starting Adempas within 3 months after start of endothelin receptor antagonists (post-text Tables 27.1ff).

In the safety review of these analyses, no new safety signals were detected.

10.6.4 Use of riociguat in patients under 18 years

One PPD PAH patient (N=1) was enrolled in EXPERT. After 2 years on treatment PPD experienced a treatment-emergent SAE chest pain, which was assessed as unrelated to riociguat by the reporting investigator and resolved while riociguat was ongoing (post-text Listing 28.6).

10.6.5 Use of riociguat during pregnancy

Two PPD became pregnant during Adempas treatment (post-text Listings 28.2.2):

PPD

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PPD

10.7 Adverse events/adverse reactions

Table 10–28 provides an overview on the patients with treatment-emergent study **drug-related** adverse events by primary system organ class and preferred term.

In total, 220 of 1330 patients in total (16.5%), and 197 of the 1282 PAH/CTEPH patients (15.4%) experienced TEAEs that were assessed as drug-related by the investigator.

The SOC most frequently affected in PAH/CTEPH patients were Gastrointestinal Disorders (6.6%), Nervous System Disorders (5.7%), Respiratory, Thoracic and Mediastinal disorders (2.8%), and Vascular Disorders (3.1%), General disorders and administration site conditions (2.5%).

The Preferred Terms most frequently listed in the pooled PAH/CTEPH population were dyspepsia (2.3%), dizziness (3.6%) and hypotension (2.7%).

Table 10–28: Number of patients with treatment-emergent study drug-related adverse events by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	**49**	**15.0**	**148**	**15.5**	**23**	**47.9**	**197**	**15.4**	**220**	**16.5**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	0.3	2	0.2	0	0.0	3	0.2	3	0.2
ANAEMIA	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
THROMBOCYTOPENIA	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
CARDIAC DISORDERS	9	2.8	10	1.0	5	10.4	19	1.5	24	1.8
ARRHYTHMIA	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
ATRIAL FIBRILLATION	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
ATRIAL FLUTTER	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
CARDIAC FAILURE HIGH OUTPUT	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CARDIOVASCULAR DISORDER	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
PALPITATIONS	3	0.9	2	0.2	1	2.1	5	0.4	6	0.5
PERICARDIAL EFFUSION	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2

Table 10–28: Number of patients with treatment-emergent study drug-related adverse events by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
RIGHT VENTRICULAR FAILURE	1	0.3	3	0.3	1	2.1	4	0.3	5	0.4
SINUS TACHYCARDIA	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
TACHYCARDIA	3	0.9	3	0.3	2	4.2	6	0.5	8	0.6
EAR AND LABYRINTH DISORDERS	2	0.6	0	0.0	2	4.2	2	0.2	4	0.3
AUDITORY DISORDER	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
VERTIGO	1	0.3	0	0.0	1	2.1	1	0.1	2	0.2
VERTIGO POSITIONAL	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
EYE DISORDERS	2	0.6	2	0.2	0	0.0	4	0.3	4	0.3
BLEPHARITIS	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
BLINDNESS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PHOTOPSIA	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
VISUAL IMPAIRMENT	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTROINTESTINAL DISORDERS	17	5.2	68	7.1	5	10.4	85	6.6	90	6.8
ABDOMINAL DISCOMFORT	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
ABDOMINAL DISTENSION	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
ABDOMINAL PAIN	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
ABDOMINAL PAIN UPPER	2	0.6	8	0.8	0	0.0	10	0.8	10	0.8
BOWEL MOVEMENT IRREGULARITY	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
CHRONIC GASTRITIS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
CONSTIPATION	1	0.3	2	0.2	0	0.0	3	0.2	3	0.2
DIARRHOEA	3	0.9	4	0.4	0	0.0	7	0.5	7	0.5
DUODENAL ULCER	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
DYSPEPSIA	4	1.2	26	2.7	1	2.1	30	2.3	31	2.3
DYSPHAGIA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
FLATULENCE	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
GASTRIC DISORDER	0	0.0	4	0.4	0	0.0	4	0.3	4	0.3
GASTRIC ULCER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTRITIS	3	0.9	3	0.3	1	2.1	6	0.5	7	0.5
GASTROINTESTINAL DISORDER	1	0.3	4	0.4	0	0.0	5	0.4	5	0.4
GASTROOESOPHAGEAL REFLUX DISEASE	4	1.2	8	0.8	1	2.1	12	0.9	13	1.0
HAEMATEMESIS	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
HAEMORRHOIDAL HAEMORRHAGE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
NAUSEA	1	0.3	13	1.4	1	2.1	14	1.1	15	1.1
OESOPHAGEAL MOTILITY DISORDER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
OESOPHAGEAL ULCER	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
OESOPHAGITIS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
REGURGITATION	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
VOMITING	2	0.6	6	0.6	0	0.0	8	0.6	8	0.6
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	13	4.0	19	2.0	4	8.3	32	2.5	36	2.7
ASTHENIA	0	0.0	4	0.4	1	2.1	4	0.3	5	0.4
CHEST DISCOMFORT	3	0.9	3	0.3	0	0.0	6	0.5	6	0.5
CHEST PAIN	2	0.6	2	0.2	0	0.0	4	0.3	4	0.3
DRUG INEFFECTIVE	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
EXERCISE TOLERANCE DECREASED	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
FATIGUE	3	0.9	2	0.2	0	0.0	5	0.4	5	0.4
GENERAL PHYSICAL HEALTH DETERIORATION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
MALAISE	3	0.9	3	0.3	2	4.2	6	0.5	8	0.6
OEDEMA	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
OEDEMA DUE TO CARDIAC DISEASE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
OEDEMA PERIPHERAL	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
PERFORMANCE STATUS DECREASED	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1

Table 10–28: Number of patients with treatment-emergent study drug-related adverse events by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
PERIPHERAL SWELLING	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
HEPATOBILIARY DISORDERS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
HEPATOMEGALY	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INFECTIONS AND INFESTATIONS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PNEUMONIA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
ANKLE FRACTURE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
INTENTIONAL PRODUCT MISUSE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INVESTIGATIONS	2	0.6	2	0.2	0	0.0	4	0.3	4	0.3
BRAIN NATRIURETIC PEPTIDE INCREASED	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
CARDIAC OUTPUT INCREASED	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
COMPUTERISED TOMOGRAM ABNORMAL	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
INTERNATIONAL NORMALISED RATIO INCREASED	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PULMONARY ARTERIAL WEDGE PRESSURE INCREASED	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
METABOLISM AND NUTRITION DISORDERS	2	0.6	5	0.5	1	2.1	7	0.5	8	0.6
ABNORMAL LOSS OF WEIGHT	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
DECREASED APPETITE	2	0.6	2	0.2	1	2.1	4	0.3	5	0.4
FLUID RETENTION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INCREASED APPETITE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0.0	3	0.3	0	0.0	3	0.2	3	0.2
ARTHRALGIA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
JOINT SWELLING	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
MYALGIA	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTRIC CANCER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
NERVOUS SYSTEM DISORDERS	22	6.7	51	5.3	6	12.5	73	5.7	79	5.9
DIZZINESS	14	4.3	32	3.3	4	8.3	46	3.6	50	3.8
DIZZINESS POSTURAL	1	0.3	3	0.3	0	0.0	4	0.3	4	0.3
EXERTIONAL HEADACHE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
HEADACHE	3	0.9	10	1.0	2	4.2	13	1.0	15	1.1
HYPOTONIA	1	0.3	4	0.4	0	0.0	5	0.4	5	0.4
ORTHOSTATIC INTOLERANCE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PARAESTHESIA	0	0.0	1	0.1	1	2.1	1	0.1	2	0.2
PRESYNCOPE	0	0.0	2	0.2	1	2.1	2	0.2	3	0.2
SOMNOLENCE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
SYNCOPE	5	1.5	7	0.7	2	4.2	12	0.9	14	1.1
TREMOR	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PSYCHIATRIC DISORDERS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
RESTLESSNESS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
RENAL AND URINARY DISORDERS	1	0.3	2	0.2	2	4.2	3	0.2	5	0.4
ACUTE KIDNEY INJURY	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
RENAL FAILURE	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
RENAL IMPAIRMENT	0	0.0	2	0.2	0	0.0	2	0.2	2	0.2
URINARY RETENTION	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	13	4.0	23	2.4	9	18.8	36	2.8	45	3.4
ACUTE RESPIRATORY FAILURE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
COUGH	2	0.6	3	0.3	0	0.0	5	0.4	5	0.4
DYSPNOEA	4	1.2	12	1.3	6	12.5	16	1.2	22	1.7
DYSPNOEA EXERTIONAL	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
EPISTAXIS	1	0.3	4	0.4	0	0.0	5	0.4	5	0.4
HAEMOPTYSIS	3	0.9	3	0.3	2	4.2	6	0.5	8	0.6

Table 10–28: Number of patients with treatment-emergent study drug-related adverse events by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
HYPERVENTILATION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
NASAL CONGESTION	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
NASAL OBSTRUCTION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
NASAL OEDEMA	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
OBSTRUCTIVE AIRWAYS DISORDER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PULMONARY HYPERTENSION	1	0.3	1	0.1	1	2.1	2	0.2	3	0.2
PULMONARY TOXICITY	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
SNEEZING	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3	0.9	4	0.4	0	0.0	7	0.5	7	0.5
PAIN OF SKIN	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PRURITUS	2	0.6	0	0.0	0	0.0	2	0.2	2	0.2
RASH	0	0.0	3	0.3	0	0.0	3	0.2	3	0.2
RASH PRURITIC	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
VASCULAR DISORDERS	11	3.4	29	3.0	8	16.7	40	3.1	48	3.6
CIRCULATORY COLLAPSE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
FLUSHING	1	0.3	2	0.2	0	0.0	3	0.2	3	0.2
HYPERTENSION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
HYPOTENSION	9	2.8	26	2.7	8	16.7	35	2.7	43	3.2

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: post-text Table 1.16.8

Table 10–29 provides an overview on the patients with treatment-emergent study drug-related serious adverse events (TE SAE) by primary system organ class and preferred term.

In total, 71 of 1330 patients (5.3%), and 57/1282 PAH/CTEPH patients (4.4%) experienced TE SAEs that were assessed as drug-related by the investigator.

The SOC most frequently affected in the pooled PAH/CTEPH population were Respiratory, Thoracic and Mediastinal disorders (1.9%), Gastrointestinal Disorders (0.8%), Nervous System Disorders (0.8%), and Vascular Disorders (0.7%).

The Preferred Terms most frequently listed in the pooled PAH/CTEPH population were dyspnea (1.0%), hypotension (0.5%), syncope (0.5%) and hemoptysis (0.4%).

Table 10–29: Number of patients with treatment-emergent study drug-related serious adverse events by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
Number of patients (%) with at least one such adverse event	**23**	**7.1**	**34**	**3.6**	**14**	**29.2**	**57**	**4.4**	**71**	**5.3**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
THROMBOCYTOPENIA	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
CARDIAC DISORDERS	5	1.5	3	0.3	2	4.2	8	0.6	10	0.8
ARRHYTHMIA	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
ATRIAL FLUTTER	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
RIGHT VENTRICULAR FAILURE	1	0.3	3	0.3	1	2.1	4	0.3	5	0.4

Table 10–29: Number of patients with treatment-emergent study drug-related serious adverse events by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
TACHYCARDIA	2	0.6	0	0.0	1	2.1	2	0.2	3	0.2
EYE DISORDERS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
BLINDNESS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTROINTESTINAL DISORDERS	2	0.6	8	0.8	0	0.0	10	0.8	10	0.8
ABDOMINAL DISCOMFORT	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
ABDOMINAL PAIN UPPER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
DYSPEPSIA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
DYSPHAGIA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTRIC ULCER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTRITIS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTROOESOPHAGEAL REFLUX DISEASE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
HAEMATEMESIS	1	0.3	1	0.1	0	0.0	2	0.2	2	0.2
OESOPHAGEAL MOTILITY DISORDER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
OESOPHAGEAL ULCER	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
VOMITING	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1	0.3	2	0.2	1	2.1	3	0.2	4	0.3
ASTHENIA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
DRUG INEFFECTIVE	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
GENERAL PHYSICAL HEALTH DETERIORATION	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
OEDEMA DUE TO CARDIAC DISEASE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
INFECTIONS AND INFESTATIONS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PNEUMONIA	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
ANKLE FRACTURE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
INVESTIGATIONS	2	0.6	0	0.0	0	0.0	2	0.2	2	0.2
COMPUTERISED TOMOGRAM ABNORMAL	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
PULMONARY ARTERIAL WEDGE PRESSURE INCREASED	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
GASTRIC CANCER	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
NERVOUS SYSTEM DISORDERS	4	1.2	6	0.6	4	8.3	10	0.8	14	1.1
DIZZIINESS	1	0.3	3	0.3	1	2.1	4	0.3	5	0.4
HEADACHE	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
PRESYNCOPE	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
SYNCOPE	3	0.9	3	0.3	2	4.2	6	0.5	8	0.6
RENAL AND URINARY DISORDERS	1	0.3	0	0.0	2	4.2	1	0.1	3	0.2
ACUTE KIDNEY INJURY	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
RENAL FAILURE	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
URINARY RETENTION	0	0.0	0	0.0	1	2.1	0	0.0	1	0.1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9	2.8	15	1.6	8	16.7	24	1.9	32	2.4
ACUTE RESPIRATORY FAILURE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
DYSPNOEA	4	1.2	9	0.9	5	10.4	13	1.0	18	1.4
DYSPNOEA EXERTIONAL	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
EPISTAXIS	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
HAEMOPTYSIS	3	0.9	2	0.2	2	4.2	5	0.4	7	0.5
PULMONARY HYPERTENSION	1	0.3	1	0.1	1	2.1	2	0.2	3	0.2
PULMONARY TOXICITY	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1

Table 10–29: Number of patients with treatment-emergent study drug-related serious adverse events by primary system organ class, preferred term

System Organ Class Preferred Term	PAH N=326 (100%)		CTEPH N=956 (100%)		Other N=48 (100%)		PAH/CTEPH N=1282 (100%)		Total N=1330 (100%)	
	N	%	N	%	N	%	N	%	N	%
VASCULAR DISORDERS	5	1.5	4	0.4	2	4.2	9	0.7	11	0.8
CIRCULATORY COLLAPSE	1	0.3	0	0.0	0	0.0	1	0.1	1	0.1
FLUSHING	0	0.0	1	0.1	0	0.0	1	0.1	1	0.1
HYPOTENSION	4	1.2	3	0.3	2	4.2	7	0.5	9	0.7

Shaded column PAH/CTEPH highlights the approved indications for Adempas.
Source: post-text Table 1.16.9

Hypotension is a labelled common ADR for riociguat. Dyspnea and syncope are known to be associated with the underlying pulmonary hypertension.

The sponsor has performed medical review of individual cases of syncope which were assessed as related to riociguat by the reporting investigators (source: post-text Listing 29.4.4 and company safety database ARGUS). The summary of 6 cases of treatment-emergent serious events reported in PAH/CTEPH patients which were assessed as related to riociguat by the reporting investigators is presented in Table 10–30.

Table 10–30: Treatment-emergent Serious Adverse Events of Syncope in PAH/CTEPH patients assessed as related to riociguat*

Patient ID Age at Baseline/ Gender	Latency start	MedDRA PT	Action taken	Outcome	Comment
PPD	4 months	Syncope	Dose not changed	Recovered/ resolved	No further episodes reporting during more than a year of therapy
PPD	6.5 months	Syncope	Withdrawn	Recovered/ resolved	Confounded by concurrent atrial fibrillation.
PPD	12 months	Syncope	Dose not changed	Recovered/ resolved	Exertional syncope Diagnosed with PAH worsening 3 weeks after the episode.

Table 10–30: Treatment-emergent Serious Adverse Events of Syncope in PAH/CTEPH patients assessed as related to riociguat*

Patient ID Age at Baseline/ Gender	Latency start	MedDRA PT	Action taken	Outcome	Comment
PPD	2.5 months	Syncope Syncope	Dose not changed Withdrawn	Recovered/ resolved Recovered / resolved with sequelae	2 episodes of syncope (circumstances and BP values were not provided). Further episodes on discontinuation (negative de-challenge).
PPD	5 days	Syncope	Interrupted	Recovered/ resolved	Started on 1.5 mg TID. Possible reflex-mediated syncope. Adempas was continued at 7.5 mg daily without further episodes.
PPD	3.5 months	Syncope	Withdrawn	Recovered/ resolved	Likely disease–related (patient died 6 weeks after the event due to PAH worsening).

BP= blood pressure, F= female, M = male, MedDRA= Medical Dictionary for Regulatory Activities;
PT= preferred term;
*Investigator's assessment of causality.
Source: post-text Listing 29.4.4.

The majority (5 out of 6) cases occurred after the end of the titration phase. Confounding factors included worsening of the underlying pulmonary hypertension (2 cases), arrhythmia (atrial fibrillation), physical excretion (1), vasovagal syncope (1) (post-text listing 29.4.4). In 1 out of 6 cases low blood pressure values were reported on the day of the event, however, in this case riociguat was started at a dose higher than the recommended dose in EU-SmPC and no episodes were reported in further course.

Overall, based on the available information, there was no compelling evidence of causal association between administration of riociguat and occurrence of syncope.

11. Discussion

11.1 Key results

The soluble guanylate cyclase stimulator riociguat is approved for the treatment of adult patients with pulmonary arterial hypertension (PAH) and inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension following Phase 3 randomized trials. EXPosurE Registry RiociguaT in patients with pulmonary hypertension (acronym EXPERT) was a prospective cohort study in patients with all forms of pulmonary hypertension. The study was designed to collect information about the long-term safety of Adempas in real

clinical practice outside the regulated environment of a controlled clinical study (post authorization safety study, PASS). The study was conducted in 28 countries in Europe, North America (Canada), South America, Asia, and Australia. No US-American centers were involved. The study was linked to COMPERA which is one of the world-wide largest registries in the indication. The COMPERA data platform was used, and its case report form was adopted and amended with Adempas-specific safety information. EXPERT ran from May 2014 (first patient, first visit) to March 2018 (last patient, last visit), and was conducted in accordance with good pharmacovigilance practices.

Patients were followed for at least 1 year and up to 4 years from enrolment, or until 30 days after stopping riociguat treatment. Primary safety outcomes were adverse events (AEs) and serious adverse events (SAEs) coded using Medical Dictionary for Regulatory Activities preferred terms and System Organ Classes version 21.0, collected during routine clinic visits (usually every 3–6 months) and collated via case report forms.

The primary objective was the assessment of long-term safety of Adempas in real life clinical practice. The primary endpoints were: incidence of adverse events/serious adverse events, 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, and for resource use hospitalization/outpatient visits, administration and any change in drug treatment for PH.

The study had three local amendments: in Denmark, the wording of the protocol was amended to make that the description of Adempas was objective; in Turkey, the brand name Adempas was replaced by the generic name riociguat, and in Germany, the eligibility criteria were restricted to patients with PAH and CTEPH, i.e. in-label use of Adempas.

No information is available on the number of screened patients for this study. A total of 1348 patients were enrolled, of whom 9 withdrew consent and for 9 no riociguat dosing information was available. Thus, a total of 1330 patients were evaluable at data cut-off (100.0%) who received at least 1 dose of Adempas and were valid for safety analysis. No other datasets were defined. The number of visits was determined by the treating physician. The mean duration of observation was 544.3 (SD 311.7) days (median 488.5, maximum 1381.0).

938 patients (70.5%) were from Western Europe, 155 (11.7%) from Eastern Europe. 107 (8.0%) from North America (Canada only), 81 (6.1%) from Asia/Pacific, 32 (2.4%) from Latin America and 17 (1.3%) from Middle East.

Characteristics

Of the 1330 evaluable patients, 326 (24.5%) had PAH, 956 had CTEPH (71.9%), and 48 (3.6%) other forms of PH. Among the 326 patients with PAH, 226 (69.3%) had idiopathic PAH/heritable PAH, 48 (14.7%) PAH associated with connective tissue disease, 28 (8.6%) PAH associated with congenital heart disease, and 24 (7.4%) other conditions within this class.

In the total cohort, 895 (66.4%) achieved the regular end of observation as per protocol (completers), while a total of 453 patients (33.6%) prematurely discontinued the study with the primary reason primarily being patient death in 148 patients (11.0%), no final visit documented in 101 patients (7.5%), patient lost to follow-up in 63 patients (4.7%), other

reasons in 84 patients (6.2%), and missing reason in 48 patients (3.6%). Nine (0.7%) patients withdrew consent during the study.

Patients with disease duration ≥6 months were defined as prevalent, and those with duration <6 months as newly diagnosed. 993 patients (74.7%) were prevalent patients, 274 (20.6%) were newly diagnosed (incident), and in 63 patients (4.7%) the status was unknown.

There were 733 (55.1%) riociguat pre-treated patients (i.e., receiving riociguat for ≥3 months before entry), and 597 (44.9%) riociguat newly treated patients.

In terms of demographics, mean age was 63.3 (SD 15.3) years, with a range from PPD to PPD years. More women than men were enrolled (62.4% versus 37.6%). Mean body mass index was 28.2 (SD 14.2) kg/m^2.

The majority of patients were in NYHA/WHO functional class II (36.2%) or III (49.7%). Mean 6-minute walk distance was 367.4 (SD 130.7) meters, and 29.0% of patients had walk distance <320 meters. Mean Borg dyspnea index was 3.93 (SD 2.29). Mean quality of life score (EQ-5D) on the 100-point visual analogue scale, as reported by 345 patients, was 61.5 (SD 21.1) points.

In terms of lung function, mean % predicted total lung capacity (% pred TLC), available for 792 patients, was 93.86 (SD 17.08), mean % predicted forced vital capacity (% pred FVC, available for 958 patients, 87.38 (SD 20.94), and mean % predicted forced expiratory volume (% pred FEV1), available for 981 patients, was 79.04 (SD 20.77), % predicted diffusing capacity for carbon monoxide (% pred DLCO), available for 741 patients, was 59.46 (SD 23.86).

At baseline, mean BNP, available in 217 patients, was 346.12 (SD 647.97) pg/mL, NT-pro BNP, available in 684 patients was 1759.0 (SD 7928.1) pg/mL, and homocysteine, available in 43 patients 15.37 (SD 5.60) mcmol/L.

Mean disease duration since the initial PH/PAH diagnosis was 3.8 (SD 4.5) years, with mean age at initial diagnosis being 59.3 (SD 16.4) years. Hepatic impairment at baseline was reported in 32 patients (2.4%), renal impairment at baseline in 224 patients (16.8%). Concomitant diseases were frequent (93.3% had at least 1 medical history finding), mostly coronary heart disease in 183 patients (13.8%), arterial hypertension in 587 patients (44.1%), venous thromboembolism in 465 patients (35.0%), diabetes mellitus in 184 patients (13.8%), thyroid disease in 274 patients (20.6%), obstructive sleep apnea in 138 patients (10.4%), cancer in 147 patients (11.1%) and history of hemoptysis/lung bleeding in 46 patients (3.5%). Other comorbidities (in free text) were reported in 1053 patients (79.2%).

A total of 355 patients (26.7%) had at least one prior medication, and 316 (23.8%) had at least 1 prior PH-targeted medication. In 68 patients (5.1%) prior therapy with endothelin receptor antagonists was reported, in 268 patients (20.2%) prior therapy with PDE-5 inhibitors, in 34 patients (2.6%) therapy with prostanoids, and in 25 patients (1.9%) therapy with other PH-targeted therapy (including calcium channel blockers). Prior oxygen use was reported in 23 patients (1.7%). Prior anticoagulation including platelet inhibitors was reported in 52 patients (3.9%).

Treatment

In the total cohort, at baseline, 846 patients (63.6%) had Adempas monotherapy and 484 patients (36.4%) received Adempas and in addition at least one other PH medication. In CTEPH patients, the rate of patients on Adempas monotherapy was higher than in the PAH

group.
In 425 patients (32.0%) concomitant therapy with endothelin receptor antagonists was reported, mostly with bosentan (172 patients, 12.9%), followed by ambrisentan (86 patients, 6.5%), or macitentan (167 patients, 12.6%), respectively. No patient (0.0%) received concomitant therapy with PDE-5 inhibitors. In 88 patients (6.6%), concomitant therapy with prostanoids was reported, mostly with iloprost (59 patients, 4.4%) or treprostinil (24 patients, 1.8%). In 77 patients (5.8%) concomitant therapy with other PH-targeted therapy (including calcium channel blockers) was reported. Concomitant oxygen use was reported in 431 patients (32.4%). Anticoagulation including platelet inhibitors was reported in 1055 patients (79.3%), antiplatelets in 95 patients (7.1%), and other anticoagulants in 76 patients (5.7%).

At baseline, the mean Adempas dose was 6.8 (SD 1.3) mg (median 7.5 mg, range 1.5 - 7.5 mg daily). The median Adempas dose remained stable during the study course. No patient received doses above 7.5 mg daily. Of the 846 patients who were on Adempas monotherapy at baseline, 128 received any other PH drug during the course of follow-up.

The rate of patients with Adempas combination therapy increased steadily during the study duration.

Adverse events

In the approved indications (pooled PAH/CTEPH population), 844 patients (65.8%) experienced any TEAE. Drug-related TEAE were documented in 197 patients (15.4%). TEAE leading to drug discontinuation occurred in 79 patients (6.2%). Any TE SAE was reported in 517 patients (40.3%), any drug-related TE SAE in 57 patients (4.4%), and SAE leading to drug discontinuation in 59 patients (4.6%).

In the pooled PAH/CTEPH population, the most frequently reported AEs by SOC were the Respiratory, Thoracic and Mediastinal Disorders (24.6%), followed by Infections and Infestations (23.5%), General Disorders and Administration Site Conditions (23.0%), Gastrointestinal Disorders (19.0%), Cardiac Disorders (18.8%), and Nervous System Disorders (17.4%).

The most frequently named PTs were dizziness (8.6%), dyspnea (8.3%), peripheral edema (7.4%), right ventricular failure (6.7%), pneumonia (5.5%), and cough (5.3%).

In review of TE SAEs in PAH/CTEPH patients, the SOC most frequently affected were Cardiac Disorders (14.0%), Respiratory, Thoracic and Mediastinal Disorders (11.6%), followed by Infections and Infestations (11.1%), General Disorders and Administration Site Conditions (5.9%), Gastrointestinal Disorders (5.4%), and Nervous System Disorders (4.5%). The most frequently reported SAEs by PT were right ventricular failure (6.6%), pneumonia (4.6%), dyspnea (3.7%), and syncope (2.7%), which are either signs/symptoms of worsening of the underlying PAH/CTEPH or conditions known to be associated with PAH and CTEPH population.

In the approved indications combined (PAH/CTEPH), the incidence of any TEAEs per 100 person years was 196.4 (95 % confidence interval 190.1 to 202.7), and the incidence of any serious TEAEs per 100 person years was 65.9 (95 % CI 62.3 to 69.9).

With respect to adverse events of special interest, any treatment-emergent hypotension occurred in 54 CTEPH/PAH patients (4.2%), drug related in 35 patients (2.7%), any serious hypotension in 9 patients (0.7%), drug-related serious hypotension in 7 patients (0.5%).

Any treatment-emergent hemoptysis/pulmonary hemorrhage occurred in 34 CTEPH/PAH patients (2.7%), drug related in 6 patients (0.5%) any serious hemoptysis in 22 patients (1.7%), serious drug-related in 5 patients (0.4%). The majority of the cases were confounded by concomitant use of anticoagulants.

Treatment-emergent adverse events with fatal outcome occurred in 133/1282 PAH/CTEPH patients (10.4%), the majority of which were assessed as unrelated to riociguat by the reporting investigators. Right ventricular failure was the most frequently reported cause of death. In 3 cases assessed as related to riociguat by the reporting investigators possible alternative explanations/confounding factors were present.

In 13 of the 1282 PAH/CTEPH patients (1.0%) post-treatment events with fatal outcome were reported, all were assessed ass unrelated to riociguat by the reporting investigators. The most frequently reported cause of death was cardiac failure (5 deaths, 0.5%) (manually calculated).

Overall, the results of PASS EXPERT revealed no new safety signals in relation to treatment with riociguat in the approved indications PAH and CTEPH. The observed safety profile in EXPERT is consistent with the current labelling.

The overall incidence of adverse events in patients treated in off-label indications other than PAH and CTEPH appears to be higher, but this observation may be biased by the small patient number, a possibility of off-label prescription to severely ill patients who have already failed on all other PH therapies and an closer follow-up. No specific pattern of TEAEs could be identified in association with this use.

Clinical events

In the follow-up visit CRF, a list was used to collect information on specific clinical events (lung transplantation, atrial septostomy, worsening of NYHA class, clinical worsening requiring therapy escalation, elevated hepatic transaminases, edema, and – in CTEPH patients only - pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA).

Results for indicators of efficacy (6-MWD, Borg Dyspnea Index, EQ5D VAS, hemodynamic measurements, and biomarkers) had many missing data and varied greatly between patients. Moreover, selection bias for repeat efficacy assessments during the study could confound the results. These results are therefore discussed here.

Resource use

Data on resource use (such outpatient visits etc.) were found not to be complete, as such information is primarily available at the patient's family physician, but not at the specialist PH center. Therefore, results are not discussed here either.

11.2 Limitations

Typical limitations inherent to the study design of registries have recently been summarized in a state of the art paper based on discussions at the 5th World Symposium on PH in Nice [26], with a focus on survival, various types of bias, and missing data.

The majority of patients were prevalent cases of PH. In the French PAH registry it could be shown that survival in PAH cohorts is not only strongly influenced by clinical baseline characteristics and associated conditions (e.g. systemic sclerosis, HIV infection) but also by the time-interval between diagnosis and recruitment into the registry (survivor bias). Patients

entering such a registry as prevalent case may be more likely to have relatively stable disease and/or better response to PAH management compared to patients not included [30].

With regard to safety results, such as frequency and kind of adverse reactions, it was impossible to compare the results under riociguat treatment with those on other therapies, as there were only comprehensive AE/SAE information available for riociguat treated patients. Planned documentation of safety for riociguat was more detailed and extensive than for other drugs in the existing COMPERA registry. Moreover, there is often increased awareness for new drugs compared to those already used for many years.

Typically for data collections 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 (6-minute walk distance), lung function, laboratory tests, or QoL reports. While the 6-minute walk distance is typically used in PH registration studies, EXPERT shows that is not routinely used in clinical practice. Similarly, quality of life was only sporadically 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.

11.3 Interpretation

At the time this study was initiated, the main clinical knowledge about Adempas was from the phase III registration studies CHEST and PATENT, and from the extension studies. EXPERT provides valuable information about on 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 [31]). In newly initiated patients, the first Adempas dose was documented at the first follow-up visit, in patients already treated with Adempas, at baseline. The median maintenance dose throughout the study was 7.5 mg daily which is according to the SmPC specifications. A small proportion of patients was administered lower doses, and few patients were maintained on a dose as low as 1.5 mg daily.

Of those patients who had received pretreatment with other PH-targeted medication, almost all had received PDE-5 inhibitors (94.9%). 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 [32].

Regarding clinical parameters (i.e. 6-MWD, Borg dyspnea index, lung function parameters, WHO/NYHA functional classification, biomarkers and), data on standard assessments were evaluated. Overall, only a limited number of patients had post-baseline assessments for the 6-MWD, Borg dyspnea index, WHO functional classification, and biomarkers at the individual visits, indicating that these parameters are not frequently assessed under routine clinical practice conditions. While information of these parameters, if available, may have been helpful in the evaluation of adverse events, 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 544 days, any TEAE in the PAH/CTEPH patients (approved indications) was reported in 844 of 1330 patients (63.2%). Drug-related TEAEs were documented in 197 patients (15.4%), and drug-related serious TEAEs occurred in 57 patients (4.4%) and 79 patients (6.2%) permanently discontinued Adempas due to TEAEs.

For comparison, the in the retrospective CAPTURE study in PAH and CTEPH patients whose data were analyzed in 125 patients over a 5-months period after Adempas initiation, AE incidence rates were in the same order [38]: overall, in CAPTURE any TEAE was reported in 71 of 125 patients (56.8%) and 56 of these experienced TEAEs during the titration period in the SAF (44.8% of overall patients). Drug-related TEAEs were documented in 39 patients (31.2%) and serious TEAEs were experienced by 15 patients (12.0%). Drug-related serious TEAEs occurred in 5 patients (4.0%) and 3 patients permanently discontinued Adempas due to TEAEs (2.4%).

At SOC level, the most frequent TEAEs were Respiratory, Thoracic and Mediastinal disorders (24.6%), followed by Infections and Infestations (23.5%), General Disorders and Administration Site Conditions (23.0%), Gastrointestinal Disorders (19.0%), Cardiac Disorders (18.8%) and Nervous System Disorders (17.4%).

At PT level, the most frequently named TEAE were dizziness (8.6%), dyspnea (8.3%), peripheral edema (7.4%), right ventricular failure (6.7%), pneumonia (5.5%) and cough (5.3%). The most frequently reported events included known labelled adverse drug reactions for riociguat (peripheral edema, dizziness) and signs/symptoms of worsening of the underlying PAH/CTEPH or conditions known to be associated with PAH and CTEPH population (dyspnea, right ventricular failure, pneumonia and cough).

TEAEs with fatal outcome were largely attributable to the progression of the underlying PAH/CTEPH or its complications. The majority of the events had long latency and were assessed as unrelated to riociguat by the reporting investigators. No specific pattern of the onset of AEs or evidence of causal relationship with riociguat (in particular, with initiation of therapy) has been identified.

In 3.6% of patients, Adempas was used in PH group 2, 3 and 5. The overall incidence of adverse events in patients treated in off-label indications other than PAH and CTEPH appears to be higher, but this observation may be biased by the small patient number and a closer follow-up, and a pattern of specific adverse events cannot be identified. Due to small numbers of patients from each of the PH subgroups the incidence of the TEAEs should be interpreted with caution.

There was very limited use in pregnant patients (2 cases) and pediatric population (1 case), which did not reveal any new safety concern.

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

11.4 Generalizability

The limited number of inclusion and exclusion criteria allowed the enrollment of a heterogeneous patient population with regard to demographic and disease characteristics and, thus, the patient population in this study is assumed to reflect the real-life situation in patients with PH who are maintained on, or newly treated with Adempas.

Patients were treated according to daily practice conditions. The non-interventional and retrospective nature of the study allowed to collect real-life data, without influencing the physicians' treatment decisions.

However, the generalizability might limited to a certain extent by the study design. The study was non-controlled and was not monitored on-site (with data verification). Therefore, it might be subject to missing, inaccurate or incomplete data and physician/selection bias. However, the sample size was large, as was the number of participating centers.

12. Other information

Not applicable.

13. Conclusion

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

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

The use of riociguat outside approved indications was very limited; no safety signal has been identified based on the available data.

The observed safety profile in EXPERT is consistent with the current labelling. Benefit-risk balance of riociguat in the approved indications remains positive.

14. References

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15. Annexes

Annex 1: List of stand-alone documents

Table 15–1: List of stand-alone documents

Document Name	Final version and date (if available)*
Investigator list	29 Jun 2018
Country & Site list	29 Jun 2018
CRF	29 Jun 2018
SAP	14 Jun 2018
DMR	21 May 2019

Annex 2: Additional information

Not applicable

Annex 3: Signature pages

Title	EXPERT, EXPosurE Registry RiociguaT in patients with pulmonary hypertension
Report version and date	Version 1.0 dated 26 JUL 2019
IMPACT study number	16657
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS6115
Medicinal product	Adempas
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD PPD

Date, Signature: 26.7.19

Title	EXPERT, EXPosurE Registry RiociguaT in patients with pulmonary hypertension
Report version and date	Version 1.0 dated 26 JUL 2019
IMPACT study number	16657
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS6115
Medicinal product	Adempas
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 26.07.2019, PPD

Title	EXPERT, EXPosurE Registry RiociguaT in patients with pulmonary hypertension
Report version and date	Version 1.0 dated 26 JUL 2019
IMPACT study number	16657
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS6115
Medicinal product	Adempas
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 05 Aug 2019 PPD

Title	EXPERT, EXPosurE Registry RiociguaT in patients with pulmonary hypertension
Report version and date	Version 1.0 dated 26 JUL 2019
IMPACT study number	16657
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS6115
Medicinal product	Adempas
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 05 Aug. 2019 PPD

Title	EXPERT, EXPosurE Registry RiociguaT in patients with pulmonary hypertension
Report version and date	Version 1.0 dated 26 JUL 2019
IMPACT study number	16657
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
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Print Name: PPD

Date, Signature: 26/7/2019 PPD

Title	EXPERT, EXPosurE Registry RiociguaT in patients with pulmonary hypertension
Report version and date	Version 1.0 dated 26 JUL 2019
IMPACT study number	16657
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS6115
Medicinal product	Adempas
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD Date, Signature: 26.07.09, PPD