Non-interventional study information

Acronym / Title	**EXPERT**, **EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not registered
Active substance	Riociguat
Medicinal product	Adempas®
Product reference	BAY 63-2521
Procedure number	NA
Marketing authorization holder(s)	Bayer Pharma AG
Research question and objectives	The aim of the study is the assessment of the long-term safety profile of Adempas® in real life clinical practice.
Country(-ies) of study	Approx. 35 countries in the region Europe, Asia Pacific, Latin America. The countries have not been identified yet. An updated list is available as stand-alone document listed in Annex 1).
Author	Christian Meier, MD PhD
NIS Template-Protocol Version	v2.0, March 2013

Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG,
MAH contact person	Contact Dr. Laila Narouz-Ott

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

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2 List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical (Classification System)
BNP	Brain Natriuretic Peptide
CCB	Calcium Channel Blockers
cGMP	Cyclic Guanosine Monophosphate
CFR	Code of Federal Regulations
CRF	Case Report Form
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
EQ5D	EuroQoL questionnaire
ERA	Endothelin receptor antagonist
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMA	Global medical affairs
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
HEOR	Health Economics and Outcomes Research
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IRB	Institutional Review Board
IT	Information Technology

MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NIS	Non-Interventional Study
NNH	Number Needed to Harm
NO	Nitric oxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA functional class	New York Heart Association functional class
OM	Operating manual
PAH	Pulmonary arterial hypertension
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible For Pharmacovigilance
QRP	Quality Review Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO DD	World Health Organization Drug Dictionary
WHO FC	World Health Organization Functional Class
6-MWT	Six minute walk test

3 Responsible parties

3.1 Sponsor / MAH

Function:	Qualified person responsible for pharmacovigilance (QPPV)
Name:	Michael Kayser
Title:	European Qualified Person for Pharmacovigilance
Address:	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

Function:	Study medical expert
Name:	Christian Meier
Title:	Global Medical Affairs Physician General Medicine PH
Address:	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

Function:	Study conduct responsible
Name:	Monika Brunn
Title:	Global Project Manager NIS
Address:	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

Function:	Study statistician
Name:	Annette Böckenhoff
Title:	Global Integrated Analysis Statistician
Address:	Bayer Pharma AG, Elberfeld 0470, 42117 Wuppertal, Germany

Function:	Study data manager
Name:	Anja Laske
Title:	Global Data Manager Non-Interventional Studies
Address:	Bayer Vital GmbH, 51366 Leverkusen, Germany

Function:	Study epidemiologist
Name:	Alexander Michel
Title:	Director, Global Epidemiology
Address:	Bayer Pharma AG, 13342 Berlin, Germany

Function:	Study health economics and outcomes research (HEOR) responsible
Name:	Margarita de la Orden Abad
Title:	Head GHEOR Cardio-Pulmonary
Address:	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

3.2 Collaborators / Committees

See list of stand-alone documents section Annex1

4 Abstract

Acronym / Title	**EXPERT**, **EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒NO
Author	Christian Meier, MD PhD
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. In accordance with the regulatory requirements this registry has been 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 is the assessment of long-term safety of Adempas® in real life clinical practice. In addition it is going to prospectively collect data on clinical effectiveness, resource use, and how Adempas® is used by PH experts under real-life conditions.
Study design	The EXPERT registry is a global, multicenter, prospective, uncontrolled, non-interventional cohort study documenting data from patients with PH treated with Adempas®.
Population	Patients who have been prescribed Adempas® for a medically appropriate use will be eligible to be included into this registry. Indications and contraindications according to the local market authorization should be considered.

Variables	Adverse and serious adverse events will be captured as well as all-cause mortality. Extra space will be provided for the documentation of symptomatic hypotension, hemoptysis and pulmonary haemorrhage as events of special interest. In addition relevant information on medical history, concomitant conditions and medication, resource use and clinical effectiveness will be captured.
Data sources	The investigator is requested to collect historic data (demographic and clinical characteristics) from medical records, and to collect treatment related data during visits that take place in routine clinical practice.
Study size	It is planned to enroll 900 patients with the aim to include a significant proportion of patients newly starting Adempas® treatment. This sample size allows detecting at least three "uncommon" AEs (with a probability of 83%) with an incidence of 0.5% (5/1000) or more.
Data analysis	All background variables and outcome parameters will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by summary statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable. All analyses will be performed for the total study population (overall analysis) and separately for PH subtype, patients who newly started or have already been on Adempas® , countries or regions if applicable and if patient numbers are sufficient, and in patients receiving at least one dose of Adempas®. All statistical details will be described in the Statistical Analysis Plan (SAP). It is planned to have yearly interim analyses on primary and secondary endpoints for the purpose of the PSUR and a final analysis after end of the study.
Milestones	Start of data collection will be in April 2014 after official EMA approval with inclusion of the first patient (FPFV). With a recruitment period of 3 years and an observation period of 1-4 years LPLV is planned for April 2018.

5 Amendments and updates

NA

6 Milestones

Definitions:

- Start of study: first center initiated
- Start of data collection: date of first data entry in database (prospective studies usually: FPFV; retrospective studies: start of data entry)
- End of data collection: date of last data entry in database (usually after LPLV)
- End of study: database close
- Observation period: time-window for data collection (usually FPFV to LPLV)
- Final report: Final report of study results 12 months after database close

Table 1 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol.

Table 1: Milestones

Milestone	**Planned date**
Registration in the EU PAS register	Mar 2014
Start of data collection	Apr 2014
End of data collection	Apr 2018
Final report of study results	Aug 2018

7 Introduction: Background and Rationale

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 PDE5-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 aetiology, 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] [13] [14] [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] [18] [19] [20] [21].

Adempas® is the first drug that could demonstrate robust efficacy in two placebo-controlled, multicentre 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].

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.

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 will be linked with COMPERA, one of the largest global academic PH registries, instead of creating another drug registry in this rare disease area.

With currently more than 4800 PH patients, COMPERA is the largest global academic databases in PH, characterised by high data quality and low loss to follow up [24] COMPERA captures the relevant

demographic and clinical data on PH. Although COMPERA is predominantly present in Europe, there are no geographical restrictions.

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

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

Alignment of data documentation and format will be 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.

8 Research questions and objectives

8.1 Primary objective

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

8.2 Secondary objective(s)

The secondary objective(s) in this study is/are:

- 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)

9 Research methods

9.1 Study design

The EXPERT registry 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 will be extended to include additional Adempas®-specific data.

It is planned to include around 35 countries in the region Europe, Asia Pacific, Latin America.

The study will start after Adempas® has been authorized and made commercially available in the countries involved in the study.

All patients prescribed with Adempas® for a medically appropriate use, consent to participate, and fulfil the selection criteria are eligible for enrolment into the study. Patients will be followed up for an observation period of 1 up to 4 years (recruitment period 3 years). Patient's clinical information will be documented at time of the initial visit and approximately every three to six months according to local clinical practice thereafter. Data collection will continue until 30 days after the end of Adempas® therapy.

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

The study ends 12 months after enrolment of the last patient

Serious adverse events will be followed up until resolution.

9.1.1 Primary endpoint(s)

The primary endpoints are:

- Incidence of adverse events/ serious adverse events
- Incidence of all-cause mortality

9.1.2 Secondary endpoint(s)

The secondary endpoints are:

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)

Effectiveness

- Clinical effect in the follow-up of PH patients

Resource use

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

9.1.3 Strengths of study design

In this rare disease area a multinational exposure registry provides the ideal setting to monitor long-term drug safety and clinical effect in real clinical practice. This setting with a larger patient number than in regulated controlled clinical studies allows for a structured prospective documentation of long-term data on safety, clinical effect, and information on how Adempas® is used by PH experts. As Adempas® is the first sGC-stimulator in clinical use and all available clinical data derive from well-defined clinical studies, this registry may collect additional data on important potential safety risks, drug interactions and missing information.

The link with an existing, large and well established pulmonary hypertension registry is expected to enhance acceptance and facilitate patient recruitment for the study.

9.2 Setting

9.2.1 Eligibility

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

9.2.2 Inclusion criterion/criteria

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

9.2.3 Exclusion criterion/criteria

- Patients currently participating in an interventional clinical trial

9.2.4 Withdrawal

Each patient has the right to refuse further participation in the study at any time and without providing any reasons. A patient's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this on the Case Report Form (CRF).

In this non-interventional study, withdrawal from the study is independent of the underlying therapy. On the other hand, the follow-up documentation will continue until 30 days after end of therapy.

9.2.5 Replacement

Patients will not be replaced after drop out.

9.2.6 Representativeness

Source population of the present study are patients with pulmonary hypertension, primarily PAH and CTEPH. Patients with this rare condition are mostly diagnosed and managed in specialized centers. This includes the initiation and any change of specific drug therapy. The participation of these specialized centers into the registry, the consecutive recruiting of patients and the broad definition of selection criteria is going to ensure the representativeness of the study population.

9.2.7 Visits

Due to the observational trial design, the study protocol does not define exact dates of the follow-up visits. Data are only collected on assessments that are performed by the site routinely as per local standards of care.

The investigator documents an initial visit, follow-up visits and a final visit for each patient in the case report form (CRF). Follow-up visits in clinical routine usually take place every 3 to 6 months. The CRF will allow for the documentation of visits as performed according to the management of the individual patient.

The final visit is meant to document the end of observation.

Patients will be followed up for an observation period of 1 up to 4 years (recruitment period 3 years) or until 30 days after end of Adempas® treatment.

Enrollment / Initial visit

Once a patient is found eligible for inclusion, the investigator will inform the patient about the study. Where applicable, this will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent.

- Following information will be collected (details in section 9.3) Patient Demographics
- Medical history
- Comorbidity
- Adverse events
- PH etiology according to Dana Point Classification 2008 and disease history
- Pregnancy
- History of smoking
- 6-minute walking distance
- NYHA/ WHO FC
- Borg dyspnoea index
- EQ5D VAS,
- Lung Function, Cardiac rhythm,
- Haemodynamic parameters from right heart catheter measurement
- Biomarkers (NTproBNP, BNP)
- Laboratory tests
- Treatment:
    - Relevant prior and concomitant medication
    - PAH-specific drugs or Adempas®
    - Systemic BP before start of Adempas®
- Resource use

Follow-up visits during treatment

Follow-up examinations in clinical routine usually take place every 3 to 6 months. The CRF will allow for visits to be documented according to the management of the individual patient. At each of these visits the following will be documented:

- Adverse events
- Changes of treatment
- Changes regarding demographics, pregnancy, smoking
- 6-minute walking distance
- NYHA/ WHO FC
- Borg dyspnoea index

- EQ5D VAS,
- Lung Function, Cardiac rhythm,
- Haemodynamic parameters from right heart catheter measurement
- Biomarkers (NTproBNP, BNP)
- Laboratory tests
- Resource use

Final visit and end of observation period

The final data collection (last visit) is 30 days after discontinuation of therapy or at end of study (whatever is earlier). At this final observation point, the patient's condition and a treatment assessment will be documented as at the follow-up visit with the additional information on:

- regular end of observation, or
- discontinuation of therapy
- reason for discontinuation, i.e.: patient failed to follow up, patient decision, investigator decision, pregnancy, insufficient / no treatment effect, unexpected strong treatment effect, (suspected) drug interaction, SAE (must be reported immediately!), death (date and relation to disease or treatment), therapy change (which therapy and reason for switch), centre closed, study termination

9.3 Variables

The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during initial visit and follow-up visits. The investigator documents the study-relevant data for each patient in the case report form (CRF). The CRF is available upon request. The respective document, <3>, is listed in Annex 1.

Table 2: 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 BP 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	X

* Data are only collected on assessments that are performed routinely.

**Serious Adverse Events must be reported to the sponsor within 24 hours.

9.3.1 Variables to determine the primary endpoint(s)

The variables for primary objective are:

- Adverse events (AE) and serious adverse events (SAE)
- All-cause mortality

9.3.2 Variables to determine the secondary endpoint(s)

The outcome variable(s) for secondary objective(s) is/are:

- 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
- 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

9.3.3 Demographics

For demographic / socio-demographic assessment, the following data will be recorded:

- Year of birth
- Sex
- Height, Weight, BMI

9.3.4 Co-morbidities (medical history, concomitant diseases)

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

Findings meeting the criteria listed below are considered to be relevant to the study indication and have 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)
    - Child-Pugh Classification
- Renal impairment (no/yes)
    - Severity
    - Estimated Glomerular Filtration Rate by Cockroft Gault formula

For any co-morbidity, the diagnosis, the start and the stop date/ongoing have to be documented.

9.3.5 Pregnancy

- Pregnancy Monitoring Form

9.3.6 Smoking

- Smoking history
- Current status

9.3.7 6-Minute Walking Test

- Date
- Distance

9.3.8 Functional class (WHO, NYHA)

- Date
- Result

9.3.9 Borg dyspnoea index

- Date
- Result

9.3.10 EQ5D visual analog scale,

- Date
- Score

9.3.11 Haemodynamic measurements

- Date

- Mean pulmonary arterial pressure (mPAP, mmHg)
- Pulmonary vascular resistance (dyn*sec*cm-5)
- Pulmonary capillary wedge pressure (PCWP, mmHg)
- Right Atrial Pressure (RAP, mmHg)
- Cardiac index (L/min/m2)

9.3.12 Cardiac Rhythm

- Date
- Normal sinus rhythm, atrial fibrillation, atrial flutter or other arrhythmia

9.3.13 Lung function

- Date
- TLC, FVC, FEV1, DLCO, paO2, paCO2, O2 BGA

9.3.14 Biomarkers

- Brain Natriuretic Peptide (BNP; pg/mg or pmol/l)
- NT-pro BNP (pg/mg or pmol/l)

9.3.15 Laboratory tests

- Hemoglobin
- Hematocrit
- 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 proteine
- MCV, MCH, MCHC
- Homocysteine

9.3.16 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 are considered to be relevant and have to be documented:

- PH/PAH-specific therapy
    - Adempas®
    - ERA: bosentan, sitaxsentan, ambrisentan, macitentan
    - PDE-5 inhibitors: sildenafil or tadalafil (physician will be alerted that the combination of PDE5 inhibitors with Adempas® is contraindicated)
    - 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 to be documented includes:

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

Additional information on Adempas® to be documented includes:

- Individual dose after initial dose adjustment period
- BP before the 1st administration

9.4 Data sources

The investigator collects current and anamnestic patient data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data during visits that take place in routine practice. Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and

afterwards, only the patient's investigator is able to identify the patient based on the patient identification code.

9.5 Study Size

It is planned to enrol 900 patients in specialized centers with the expectation to include a significant proportion of patients newly starting Adempas® monotherapy. This sample size allows 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 increases to 1130, at least three "uncommon" AEs with incidence of 0.4% or more can be detected with the same probability.

9.6 Data management

A Contract Research Organization (CRO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system is available upon request. The respective document, < 4>, is listed in Annex 1. Detailed information on data management, including procedures for data collection, retrieval and preparation are given in the Data Management Plan (DMP), which is available upon request. The respective document, <6>, is listed in Annex 1.

For information on quality control, refer to section 9.7.8.

9.7 Data analysis

9.7.1 Statistical considerations

Statistical analyses of this study will be of non-confirmative nature. This study is designed to support hypothesis generation.

All background variables and outcome parameters will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by summary statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will be described by absolute value and as change from baseline per analysis time point, if applicable.

All analyses will be performed for the total study population (overall analysis) and separately for PH subtype and subgroup, incident and prevalent patients, functional class at baseline, countries or regions if applicable and if patient numbers are sufficient. Prevalent patients is here defined as patients already on treatment, e.g. previously documented in the registry, whereas incident patients will be patients newly starting Adempas®.

Patients receiving at least one dose of Adempas® will be included in the analysis. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender).

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. The SAP is available upon request. The respective document, <7>, is listed in Annex 1.

It is planned to have at least yearly interim analysis/analyses e.g. for the purpose of the PSUR. The proportion of incident and prevalent subjects will be tracked. Analyses will refer to the primary and secondary objective. The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

All background data such as patient demographics, PH group and indication-specific characteristics and prior or concomitant medication of PH, and concomitant diseases will be described by presenting frequency distributions and/or basic summary statistics.

Sample size and disposition information by analysis time point will be displayed in a frequency table.

9.7.2 Analysis of treatment data

Duration and dose of the Adempas® treatment during the observation period will be calculated for each patient. The dose will be displayed at the different visits/time windows. The number of patients adding and removing various PH medications (including Adempas®) will be summarised using frequency tables.

9.7.3 Analysis of primary outcome(s)

The main goal of this global registry is to assess the long-term safety of Adempas® in real life clinical use. Incidences of treatment-emergent adverse events, serious adverse events and all-cause mortality will be calculated, including adverse events of interest. An adverse event is considered as treatment-emergent when it has started or worsened after first application of study medication up to 2 days after end of treatment with study medication.

For the events the ‘raw’ incidence proportion (regardless of the time each patient is treated), i.e. number of patients with events divided by the number of treated patients, will be presented as well as incidence rates, i.e. number of patients with events divided by the cumulative person-time on treatment (person-years) separately for incident and prevalent patients.

The statistics will be calculated for Adempas® and stratified for medically relevant subgroups, e.g.

- Age
- Gender
- Etiology (Dana Point Classification of PH)
- Hepatic impairment at baseline
- Renal impairment at baseline
- WHO functional class/NYHA group at baseline
- According to e.g. 6 MWD thresholds >= 380 m versus < 380m at baseline
- Type of PH pre-treatment
- Concomitant medication use
- Systolic blood pressure at baseline

The subgroup ‘Type of PH pre-treatment’ will include the categories ‘therapy-naïve’, ‘pre-treated with ERA’, ‘pre-treated with PDE5 inhibitors’, ‘pre-treated with prostacyclins’ and ‘pre-treated with Adempas®.

The ‘Concomitant medication use’ subgroup categories will refer to e.g. ‘concomitant ERA’, ‘concomitant PDE 5 inhibitors’, ‘concomitant prostacyclins’ and ‘concomitant oral anticoagulation’ see section 9.3.16 Details will be found in the SAP.

A comprehensive list of medically relevant subgroups will be added to the SAP.

Tables which show the incidence proportion of adverse events overall and by MedDRA preferred term within the primary SOC will also be presented. Incidences of adverse events and serious adverse events starting more than 2 days after end of treatment will be tabulated separately.

9.7.4 Analysis of secondary outcome(s)

The secondary safety outcomes will be analyzed similar to the primary outcomes. Subgroup analyses will be conducted for selected secondary endpoints (e.g. 6 Minutes Walking Test, NYHA/WHO FC, hospitalization).

Analyses of adverse events will be conducted for PH subgroups (inoperable vs. post- surgery CTEPH patients, monotherapy vs. combination therapy PAH patients) .

Adverse events of interest will be analysed in detail. Adverse events of interest are

- Symptomatic hypotension
- Hemoptysis/ pulmonary haemorrhage

Further analyses of information on adverse events of interest as given by the detailed questionnaire and the AE page will be evaluated.

Kaplan Meier plots will describe the time until the individual events of interests

For the effectiveness variables summary statistics and changes form baseline will be calculated for

- 6 Minutes Walking Test,
- Borg Dyspnoea Index
- EQ5D VAS
- Hemodynamic measurements
- Biomarkers

NYHA/WHO FC will be analyzed by frequency tables including changes from baseline.

The variables of hospitalization due to PH and drug utilization (reason and drug switch or interruption or discontinuation of Adempas®) will be analyzed by frequency tables and summary statistics.

9.7.5 Analysis of safety data

Other safety outcomes, e.g. laboratory values, cardiac rhythm, and lung function, will be analyzed by frequency tables or summary statistics and changes from baseline.

9.7.6 Bias, confounding and effect-modifying factors

Several sources for bias are identified, i.e. reporting, survivor, as well as selection biases. To decrease the reporting bias source data verification will be performed in at least 10% of the centers in countries

where legally permitted. For survivor bias see section 9.8. To reduce patient selection bias physicians must document consecutive patients who receive Adempas® and provide informed consent.

Baseline characteristics of the patients will be examined and described in detail.

9.7.7 Data quality

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

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

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

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request, the respective document, <6>, is listed in Annex 1.

National and international data protection laws as well as regulations on observational non-interventional studies will be followed. Electronic records used for capturing patient documentation (eCRF) will be validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) [25]. The documentation is available upon request. The respective document,< 3>, is listed in Annex 1.

9.7.8 Quality review

In a subset of patients (at least 10% of all sites/patients) source data verification will be conducted. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors will access medical records on site for data verification. Detailed measures for quality reviews will be described in the Quality Review Plan (QRP). The QRP is available upon request. The respective document, <8>, is listed in Annex 1.

9.7.9 Storage of records and archiving

The sponsor will make sure that all relevant documents of this PASS including CRFs and other patient records will be stored after end or discontinuation of the study at least for 15 years. Other instructions for storage of medical records will remain unaffected.

The investigators participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to also store documents for a retention period of at least 15 years.

9.7.10 Certification/qualification of external parties

NA

9.8 Limitations of the research methods

Typical limitations inherent to the study design of registries have recently been summarized in a state-of –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 large majority of patients to be included will be prevalent cases of PAH/CTEPH. 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 [27] .

With regard to safety results, such as frequency and kind of adverse reactions, it will be impossible to compare the results under Adempas® treatment with those on other therapies, as we have only comprehensive AE/SAE information available for Adempas® treated patients. Planned documentation of safety for Adempas® is 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.

9.9 Other aspects

NA

10 Protection of human subjects

10.1 Ethical conduct of the study

This study is a non-interventional study where Adempas® is prescribed in the customary manner in accordance with the terms of the marketing authorization. There is no assignment of a patient to a particular therapeutic strategy. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory authority approvals/authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, FDA and applicable local law(s) and regulation(s) (e.g. Regulation (EU) No 520/2012 [28]). Recommendations given by other organizations will be followed as well (e.g. EFPIA [29], ENCePP [30]). ICH-GCP guidelines will be followed whenever possible.

For PASS: In addition, the guidelines on good pharmacovigilance practices (GVP [31] [32]) will be followed; the relevant competent authorities of the EU member states will be notified Independent ethics committee (IEC) or institutional review board (IRB)

In all countries where reference to an IEC/IRB is required, documented approval from appropriate IECs/IRBs will be obtained for all participating centers prior to study start. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The IEC/IRB must supply to the sponsor, upon request, a list of the IEC/IRB members

involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to applicable laws and regulations.

10.3 Patient information and consent

Before documentation of any data, informed consent is obtained by the patient in writing. In countries where required by law or regulation, the investigator must have the IECs/IRB written approval/favorable opinion of the written informed consent form and any other written information to be provided to patients prior to the beginning of the observation.

10.4 Patient insurance

In this study, data on routine treatment of patients in daily practice are documented and analyzed with the help of epidemiological methods. Treatment including diagnosis and monitoring of therapy follows exclusively routine daily practice. Current medical daily practice is observed, and for the patient no risks beyond regular therapy exist – there is no additional hazard arising from study participation. As no study related risks exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the investigators and, respectively, the institutions involved provide sufficient protection for both patient and investigator.

No study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.5 Confidentiality

Bayer as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to the sponsor. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

11 Management and reporting of adverse events/adverse reactions

11.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE

can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.33 [33]

The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g. that require unscheduled diagnostic procedures or treatments or result in withdrawal from the study).

Symptomatic hypotension and hemoptysis have been defined as adverse events/SAE of special interest and additional documentation is required in the CRF

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator drug
- An effect related to off-label use or occupational exposure
- Medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- Drug exposure via mother/ father (exposure during conception, pregnancy, childbirth and breastfeeding)
- An effect related to lack of drug effect
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)

As mentioned above no causal relationship with a study medication is implied by the use of the term "adverse event".

Hospitalizations will not be regarded as adverse events, if they:

- were planned before inclusion in the study,
- are ambulant (shorter than 12 hours),
- are part of the normal treatment or monitoring of the studied disease, i.e. they were not due to a worsening of the disease.
- are required for carrying out a routine right heart catheterization (RHC) procedure for conducting diagnostic invasive hemodynamic measurements to evaluate a patient's underlying disease (without taking into account any clinical suspicion or finding with regard to the worsening of the underlying disease). In this context, a RHC is a procedure and not an adverse event.

An Adverse Reaction (AR) is defined as a response to a medicinal product which is noxious and unintended. An Adverse Reaction (AR) is any AE judged as having a reasonable suspected causal relationship to Adempas®

Causal relationship: The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of

the CRF. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are "yes" or "no".

An assessment of "no" would include:

- The existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site)
- Non-plausibility (e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration)

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment. Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics should be considered.

An AE is serious (SAE) if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important.

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is ‘sudden death’ where no cause has been established. In this instance, ‘sudden death’ should be regarded as the AE and ‘fatal’ as its reason for being ‘serious’.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be automatically considered as Serious, UNLESS at least one of the following exceptions is met:

Hospitalizations will not be regarded as adverse events, if they:

- were planned before inclusion in the study,
- are ambulant (shorter than 12 hours),
- are part of the normal treatment or monitoring of the studied disease, i.e. they were not due to a worsening of the disease.
- are required for carrying out a routine right heart catheterization (RHC) procedure for conducting diagnostic invasive hemodynamic measurements to evaluate a patient’s underlying disease (without taking into account any clinical suspicion or finding with regard to the worsening of the underlying disease). In this context, a RHC is a procedure and not an adverse event.

However it should be noted that other invasive procedure or treatment during any hospitalization may fulfill the criteria of ‘medically important’ and as such may be reportable as a SAE dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

11.2 Collection

Starting with the first application of Adempas® all non-serious adverse events (AE) must be documented on the AE Report Form or in the CRF / EDC system and forwarded to the sponsor within 7 calendar days of awareness. All serious AEs (SAE) must be documented and forwarded immediately (within 24 hours of awareness). For each AE, the investigator must assess and document the seriousness, duration, relationship to study drug, action taken and outcome of the event.

If a pregnancy occurs during the study, although it is not a serious adverse event, it should be reported within the same time limits as a serious adverse event. The outcome of a pregnancy should be followed up carefully and any abnormal result of the mother or baby should be reported.

The documentation of any AE/SAE ends with the completion of the observation period of the patient. However, any AE/SAE occurring up to 30 days after the last intake of Adempas® has to be documented, even if this period goes beyond the end of observation.

As long as the patient has not received any Adempas®, AEs /SAEs do not need to be documented as such in this non-interventional study. However, they are part of the patient's medical history.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

11.3 Management and reporting

Non-serious AEs

The outcome of all reported AEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the responsible study staff to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with Adempas® that qualify for expedited reporting will be submitted to the relevant authorities according to EU PV legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU, Module VI) and according to national regulations by the sponsor; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Bayer drugs the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Serious AEs

Any SAE or pregnancy entered into the CRF / EDC system will be forwarded immediately (within 24 hours of awareness) to the pharmacovigilance country person being responsible for SAE processing. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the pharmacovigilance country person in charge to provide further information.

Submission to the relevant authorities according to national regulations will be done by the sponsor for SAEs occurring under Adempas® treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting have to be followed.

For SAEs that occurred while administering non-Bayer drugs the investigator has to account for and comply with the reporting system of the product's Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

11.4 Evaluation

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case

reports, refer to section 11.2 and 11.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

12 Plans for disseminating and communicating study results

This study will be registered at “www.clinicaltrials.gov". Results will be disclosed in a publicly available database within the standard timelines.

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the sponsor. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines [34], STROBE [35]). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the sponsor.

13 List of References

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Annex 1. List of stand-alone documents

Table 3: List of stand-alone documents

Number	Document name	Date	Title
1	AD1301_SC members	1/28/2014	List of Steering committee members
2	AD1301_countries	Will be available at end of recruitment	List of all countries
3	AD1301_INV_CRF	Will be available at time of first country ready to enroll	CRF draft
4	AD1301_EDC_summary	Will be available at time of first country ready to enroll	EDC System description
5	AD1301_EDC_validation	Will be available at time of first country ready to enroll	EDC System Validation
6	AD1301_DAT_DMP	Will be available at time of first country ready to enroll	Data Management Plan
7	AD1301_DAT_SAP	Will be available before study database lock	Statistical Analysis Plan
8	AD1301_DAT_QRP	Will be available at time of first country ready to enroll	Quality Review Plan

Annex 2. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013; Doc.Ref. EMA/540136/2009

Study title: EXPERT, **EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	12
1.1.3 Study progress report(s)	☒	☐	☐	24
1.1.4 Interim progress report(s)	☒	☐	☐	24
1.1.5 Registration in the EU PAS register	☒	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	14
2.1.2 The objective(s) of the study?	☒	☐	☐	14

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	14
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	15
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	25

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	15
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	15
4.2.2 Age and sex?	☒	☐	☐	17
4.2.3 Country of origin?	☒	☐	☐	17
4.2.4 Disease/indication?	☒	☐	☐	17

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.5 Co-morbidity?	☒	☐	☐	20
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	16

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	23
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	15
6.2 Does the protocol discuss the validity of endpoint				

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	26
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	26

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	23
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	23 23
8.1.3 Covariates?	☒	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event,				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	24
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	24
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1Is sample size and/or statistical power calculated?	☒	☐	☐	23

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	24
10.3 Are descriptive analyses included?	☒	☐	☐	24
10.4 Are stratified analyses included?	☒	☐	☐	25
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	26
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	27
11.3 Are methods of quality assurance described?	☒	☐	☐	27
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☒	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	26
12.1.2 Information biases?	☒	☐	☐	26
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☒	☐	☐	28

Comments:

Survivor bias described on page 28

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	28
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	28
13.3 Have data protection requirements been described?	☒	☐	☐	29

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	33
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	33

Comments:

Name of the main author of the protocol: Christian Meier

Date: 28/Jan/2014

Signature: _____

Annex 3. Signature pages

Signature Page - Qualified Person responsible for Pharmacovigilance (QPPV)

Title	**EXPERT**, **EXP**osur**E** Registry **R**iociguaT in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not registered
Active substance (medicinal product)	Riociguat
Marketing authorization holder(s)	Bayer Pharma AG
Function	Qualified person responsible for pharmacovigilance (QPPV)
Name	Michael Kayser
Title	European Qualified Person for Pharmacovigilance
Address	Bayer Pharma AG, Aprather Weg 18a, 42096 Wuppertal, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 30-Jan-2014, Michael Kayser

Signature Page - Study Medical Expert

Title	**EXPERT**, **EXP**osur**E** Registry **R**iociguaT in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not registered
Active substance (medicinal product)	Riociguat
Marketing authorization holder(s)	Bayer Pharma AG
Function	Study medical expert
Name	Christian Meier
Title	Global Medical Affairs Physician General Medicine PH
Address	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 29.01.14, _____

Signature Page - Study Conduct Responsible

Title	**EXPERT**, **EXP**osur**E** Registry **R**iociguaT in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not registered
Active substance (medicinal product)	Riociguat
Marketing authorization holder(s)	Bayer Pharma AG
Function	Study conduct responsible
Name	Monika Brunn
Title	Global Project Manager NIS
Address	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 30.1.2014 Monika Brunn

Signature Page - Study Statistician

Title	**EXPERT**, **EXP**osur**E** Registry **R**iociguaT in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not registered
Active substance (medicinal product)	Riociguat
Marketing authorization holder(s)	Bayer Pharma AG
Function	Study statistician
Name	Annette Böckenhoff
Title	Global Integrated Analysis Statistician
Address	Bayer Pharma AG, Elberfeld 0470, 42117 Wuppertal, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 30.01.2014, A. Böckenhoff

Signature Page - Study Data Manager

Title	**EXPERT**, **EXP**osur**E** Registry **R**iociguaT in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not registered
Active substance (medicinal product)	Riociguat
Marketing authorization holder(s)	Bayer Pharma AG
Function	Study data manager
Name	Anja Laske
Title	Global Data Manager Non-Interventional Studies
Address	Bayer Vital GmbH, 51366 Leverkusen, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 29.01.14, Anja Laske

Signature Page - Study Epidemiologist

Title	**EXPERT**, **EXP**osur**E** Registry **R**iociguaT in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not registered
Active substance (medicinal product)	Riociguat
Marketing authorization holder(s)	Bayer Pharma AG
Function	Study epidemiologist
Name	Alexander Michel
Title	Director, Global Epidemiology
Address	Bayer Pharma AG, 13342 Berlin, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 30.1.14, On behalf of A. Michel

M. Soriano Gabarró

Signature Page - Study Health Economics and Outcomes Research (HEOR) Responsible

Title	**EXPERT**, **EXP**osur**E** Registry **R**iociguaT in patients with pulmonary hypertension
Protocol version identifier	Version 1
Date of last version of protocol	28th Jan 2014
IMPACT study number	16657
Study type	☐ non-PASS ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	Study not registered
Active substance (medicinal product)	Riociguat
Marketing authorization holder(s)	Bayer Pharma AG
Function	Study health economics and outcomes research (HEOR) responsible
Name	Margarita de la Orden Abad
Title	Head GHEOR Cardio-Pulmonary
Address	Bayer Pharma AG, Muellerstrasse 178, 13352 Berlin, Germany

The undersigned confirms that s/he agrees to conduct the study under the conditions described in this protocol.

Date, Signature: 30 Jan 14.