Title Page

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CTEPH/PAH - OS

Trade Name: Adempas

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Study Completion Date:	29 JUN 2018

Performing Laboratory:
NA

Post Authorization Safety Study (PASS) Report Addendum – Study Information

Acronym/Title	**EXPERT, EXPosurE Registry RiociguaT in patients with pulmonary hypertension**
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Report version and date	**Addendum Version 1.0, 16 March 2020**
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**
Author	PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
Marketing authorization holder contact person	PPD

Confidentiality statement:

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1. Rationale

This addendum to the Clinical Study Report (CSR) of EXPERT provides a brief explanation of data and quality management in this non-interventional study based on an existing academic registry (COMPERA). It also provides results from post-hoc re-evaluations on data quality, particularly from the pharmacovigilance perspective, as an evaluation of long-term safety was the primary purpose of the study.

EXPERT was a non-imposed post-approval safety study (EU-RMP PASS, category 3) that was conducted on the technical and data platform of the academic COMPERA registry (Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; Clintrials.gov identifier: NCT01347216). Data were captured using the core Case Report Form (CRF) of COMPERA with study specific additions for EXPERT. The data cleaning followed the established processes in COMPERA, in which by default, laboratory values and hemodynamic parameters captured within the COMPERA-eCRF were not systematically cleaned and reviewed in detail for quality and plausibility, unless they were reported as (S)AEs. Additional data cleaning was conducted for the primary endpoints of the EXPERT study: (1) incidence of adverse events/serious adverse events and (2) incidence of all-cause mortality (reference to DMP and/or report).

2. Explanation on data and quality management

The data management procedures were re-evaluated post-hoc. In summary, data management activities have been planned and executed appropriately for the purpose of this PASS (see Data Management Plan and Data Management Report for reference).

In the laboratory and hemodynamic parameters the median of the values is displayed as a robust center estimate, which is only minimally affected by outliers, but it is acknowledged that in some cases the minimum and maximum values are implausible or sometimes impossible. Some of the entered values imply errors in the selected unit. The data cleaning strategy of these parameters was to inform the site personnel about values outside of a plausibility range, but to allow such entered values to be kept, if required.

No additional cleaning measures were taken on the laboratory parameters, because they were not part of the study objectives in focus for this study and were only included as supplementary information in the appendices of the CSR, but not in the main body of the CSR.

Considering the nature of the non-interventional study setting, the use of an existing academic database and the purpose of the study, it is deemed acceptable that some parameters not cleaned in detail would still include a small proportion of implausible values in the tables and listings (all tables provided for transparency). Data pertinent to the study endpoints (i.e. AEs/SAEs) were checked and cleaned in detail as needed.

During the study, quality review activities were conducted with the aim to evaluate the quality of the collected data at participating sites. Due to the primary objective of the study, it was checked whether safety reporting was conducted properly. Quality review was done in two waves.

- During the first wave, at the early study phase, structured interviews were conducted at 20 sites. This was done in order to ensure the training status especially on safety reporting topics at the participating sites

- During the second wave on-site data reviews were performed at 34 sites.

Six unreported SAE's were found and reported to the Sponsor. No other major issues were found.

3. Medical review, and post-hoc data quality check

Detailed medical reviews were performed at 6-monthly intervals by an interdisciplinary team. The team reviewed the data considered to be most relevant for the study purpose in detail, such as patient disposition, PAH/PH etiology, physical capacity, and treatment status. The main focus was adverse events (AEs) / SAEs as primary study endpoints and potential safety concerns to be included in the EU-RMP. AEs/SAEs/AE of special interest (AESIs) were reviewed in terms of type (SOC and preferred term), drug relationship, and outcome.

Single case reviews were performed in patients with certain characteristics, e.g. patients with atrial fibrillation/flutter; pregnancies; smokers; patients with low systolic blood pressure (< 95 mmHg) at baseline; patients with low creatinine clearance (< 30 mL/min) as selected by the investigators; patients with information from the hemoptysis questionnaire.

Listings were generated and reviewed, among others, on: non-serious adverse event terms matching an entry in the EudraVigilance Important Medical Event list; medication error (including patients with Adempas < 3 mg/d or > 7.5 mg/d); patients with concomitant use of Adempas and PDE-5 inhibitors; patient switching from PDE-5 inhibitors to Adempas; patients with a reported death; patients with off-label use (Dana Point groups 2, 3 and 5), patients with Interstitial lung disease; Haemoptysis (serious) / Pulmonary haemorrhage; Hypotension, Hypotension, Syncope; Haemorrhages; AEs in patients with creatinine clearance < 30 ml/min at baseline (as selected by the investigator). If, based on the respective medical review round, information was missing, specific queries were sent to the sites in regular intervals.

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) were to be reported as AEs and the sites were trained on respective rules for safety reporting.

Individual SAEs were reviewed and followed-up as appropriate, in accordance with the sponsor's standard operating procedures.

An additional post-hoc quality check was performed assessing all patients with documented hospitalization for causes "other than PH/PAH" to see if corresponding SAEs had been reported. A clear instruction had been linked with this eCRF-field to report as (S)AE if applicable.

Relative to the overall study population, the number of hospitalizations not reported as a corresponding SAE was considered to be low (27 patients with potential SAEs, in which 35 additional SAEs were considered; in 15 of these patients a potential SAE was considered for the first time; no safety signal identified). It was concluded from the increase in the overall number of SAEs, patients with SAEs, or the type of individual events, that these factors did not significantly change the study results or safety conclusions in the CSR. The reasons for hospitalization from this data check have been added as SAEs to the company safety database, whilst the study database was not re-opened (See Appendix 1).

4. Summary

In a post-hoc re-evaluation, the MAH checked and assessed the validity of the study data.

Due to the overall set-up and data cleaning procedures of the already existing academic COMPERA registry, by default, laboratory values and hemodynamic parameters captured within the COMPERA-eCRF were not systematically cleaned and reviewed in detail for quality and plausibility, unless they were reported as (S)AEs. Additional measures were taken with auto queries, and in the coding process, SAE reconciliation, medical and quality review to achieve a higher quality of the data. The MAH is of the opinion that these measures were appropriately planned and conducted for the purpose and nature of this non-interventional study.

An additional post-hoc quality check assessed the extent of hospitalizations not reported as potentially corresponding SAEs in the database, and revealed a low additional number of potentially unreported events, which were not considered to meaningfully change the study result or safety conclusion provided in the CSR.

Overall, the extent of implausible values was low and it is not considered to affect the quality of safety analysis, the primary endpoint of the study, mainly based on (S)AE data. Supportive descriptive analyses of laboratory and hemodynamic parameters are minimally affected by the small amount of implausible or missing values.

Based on the post-hoc re-evaluation of the data related to safety in particular, it can be stated that the implausible and missing data do not impact the overall conclusion concerning long-term safety of PAH/CTEPH patients treated with Adempas.

5. List of Appendices

Appendix 1*:CIOMS listings from Argus (ARGUS: GPV-2019-06-riociguat-cluster “Cases identified during an additional quality check on 06 Nov 2019”)

Signatures

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Product reference	**BAY 63-2521**
Procedure number	**NA**
Study Initiator and Funder	**Bayer AG**
Author	PPD

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

Date, Signature: 17.3.2020 , PPD