Science For A Better Life

Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Title	**EXPERT**, **EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension
Report version and date	Version 1.0, 22 MAY 2019
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 cyclasestimulators), 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 reallife 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 P
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%) 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 2.4) 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 15 to 93 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 (SD 131) 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%). The SOC most frequently affected were Respiratory, thoracic and mediastinal disorders (24.6%), followed by Infections and Infestations (23.5%), Gastrointestinal Disorders (19.0%), Nervous

	System Disorders (17.4%). The most frequently named PT were peripheral edema (7.4%), dizziness (8.6%), anemia (3.1%), pneumonia (5.5%), syncope (4.1%), and hypotension (4.4%). With respect to adverse events of special interest, any treatmentemergent 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%). 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. 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 0.5 (SD 2.7) additional outpatient visits at the PH center were reported, 0.3 (SD 3.1) days per week in home care, 1.1 (SD 7.4) days at a pulmonary rehabilitation facility/hospital, and 1.1 (10.7) hospitalisations.
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.
Marketing Authorisation Holder(s)	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.