Title page

Long-term extension, multi-center, multi-national study to evaluate the safety and tolerability of oral BAY 63-2521 (1 mg, 1.5 mg, 2 mg, or 2.5 mg TID) in patients with symptomatic Pulmonary Arterial Hypertension (PAH), PATENT-2 study

PATENT-2 study

Bayer study drug	BAY 63-2521/Riociguat/Adempas		
Study purpose:	Long-term extension		
Clinical study phase:	III	**Date:**	25 JUL 2019
Study No.:	12935	**Version:**	5.0
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This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

6MWD	6 minute walking distance
6MWT	6 minute walking test
AS	Atrial septostomy
ATC	Anatomical Therapeutic Chemical Classification System
BP	Blood pressure
CCB	Calcium channel blocker
ECG	Electrocardiogram
EQ-5D	EuroQol Questionnaire
ERA	Endothelin Receptor Antagonist
FC	Functional Class
HEOR	Health Economics and Outcomes Research
ICH	International Conference on Harmonisation
i.e.	id est (that is)
ITT	Intent to treat
LPFT	Last patient first treatment
LPH	Living with Pulmonary Hypertension Questionnaire
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NT pro-BNP	N-terminal pro-brain natriuretic peptide
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PDE5I	Phosphodiesterase type 5 inhibitors
PH	Pulmonary Hypertension
PPI	Proton pump inhibitor
PVR	Pulmonary vascular resistance
SAS	Statistical Analysis System
TID	ter in die (3 times a day)
WHO	World Health Organization
WHO-DD	World Health Organization – Drug Dictionary

1. Introduction

This SAP for the final analysis is based on the following study protocol versions:

- 12935 / version 2.0, 11 September 2008
- Amendment 1 (Japan) / Version 1.0 / 01 Oct 2008
- Amendment 2 (UK) / Version 1.0 / 08 Jan 2009
- Amendment 3 (NZ) / Version 1.0 / 18 Mar 2009
- Amendment 4 (Spain) / Version 1.0 / 09 Jun 2009
- Amendment 5/ Version 1.0 / 10 Jun 2009
- Amendment 6/ Version 1.0 / 22 Mar 2010
- Amendment 7 (Japan) / Version 1.0 / 23 Mar 2010
- Amendment 8 / Version 1.0 / 15 Feb 2011
- Amendment 9 (US, CAN) / Version 1.0 / 28 Feb 2011
- Amendment 10 / Version 1.0 / 30 Nov 2011

- Amendment 11/ Version 1.0/ 13 DEC 2012
- Amendment 12 (Korea)/ Version 1.0 / 03 APR 2013
- Amendment 13 (China)/Version 1.0/ 08 JUL 2014
- Amendment 14 (France)/ Version 1.0/ 28 OCT2015

There is a set of global and project standard tables. References are given in the TLF specifications document associated with this SAP.

2. Study Objectives

To assess the long-term safety and tolerability of riociguat in treatment naive patients and patients pretreated with an Endothelin Receptor Antagonist or a Prostacyclin Analogue with symptomatic Pulmonary Arterial Hypertension (PAH). The trial provides patients, who have completed 12 weeks of riocigua double blind treatment (PATENT-1, study 12934), the option of long-term treatment with riociguat.
For this study it is planned to enroll subjects in the following countries:
United States of America, Canada, Sweden, Denmark, Norway, China, Singapore, Taiwan, South Korea, Austria, Germany, Switzerland, Netherlands, Belgium, France, Italy, Spain, Ireland, South Africa, United Kingdom, Argentina, Brazil, Mexico, Australia, New Zealand, Japan, Czech Republic, Poland.
A list of countries that actually enrolled patients will be given.

3. Study Design

This is an open-label, multicenter, multinational, long-term extension (blinded with respect to dose up to Visit 5 [end of titration phase], in order to maintain the blinding of the PATENT-1 study).

All subjects entering the extension study first participated in a blinded 8-week titration phase. The dose of riociguat was increased, maintained, or decreased depending on whether peripheral systolic blood pressure (SBP) was ≥95 mmHg, 90 – 94 mmHg, or <90 mmHg, in accordance with the following rules:

- Subjects from the former placebo group of the PATENT-1 study started at Visit 1 with a riociguat dose of 1.0 mg tid. The individual riociguat dose was up-titrated in steps of 0.5 mg tid every 2 weeks up to a maximum of 2.5 mg tid.
- Subjects from the former riociguat 1.0–1.5 mg tid capped dose titration group of PATENT-1 entered the extension trial on the same dose level as they received on the last day of PATENT-1. Subjects whose last dose in PATENT-1 was 1.0–1.5 mg tid were up-titrated in steps of 0.5 mg tid every 2 weeks up to a maximum of 2.5 mg tid. Subjects whose last dose in PATENT-1 was 1.0 mg or 0.5 mg tid underwent sham titration, with no increase in dose of study drug before the end of the titration phase.
  (titration approach modified by protocol amendment 5)
- Subjects from the former riociguat 1.0-2.5 mg tid group of PATENT-1 entered the extension trial on the same dose level as they received on the last day of PATENT-1. Subjects underwent sham titration, with no increase in dose of study drug before the end of the titration phase.

During the main study phase, investigators (unblinded to dose) could modify the riociguat dose in a range between 0.5 mg tid and 2.5 mg tid according to the subject's need.

Dose reductions for safety reasons were allowed at any time.

For further details see integrated study protocol, amendment 11, version 1.0, Section 4.1.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

4.2 Handling of Dropouts

There is no definition of dropouts in the CSP.

4.3 Handling of Missing Data

Although efficacy variables will be summarized in a purely descriptive manner, imputation for missing values will still be made, for comparability of the results with study 12934, at week 12 and end of study. The imputation to the end of the study will only be done at the conclusion of the extension study.

For subjects completing the study as planned, the measurements taken at the end of study will be used. However, should a subject stop the study medication prematurely, the values recorded at the termination visit will be used.

Where a subject dies or withdraws due to clinical worsening with no subsequent visit, the following rules will be used: 6MWD worst possible value (0 m), Borg CR 10 Scale® worst possible value (10), EQ-5D and LPH worst possible score. Death or withdrawal due to clinical worsening are components of time to clinical worsening, so will be included as an event by definition. For WHO functional class, in the case of withdrawal due to clinical worsening with no termination visit, the worst possible score (IV) will be used, in the case of death the worst possible value plus one (V).

In the case of withdrawal for other reasons with no post-baseline measurements, the baseline will be taken. If the subject completes the study as planned, but there is no efficacy measurement at the end of the study, the last post-baseline value will be used.

PVR and NT pro-BNP are efficacy measures designed to show the direct effects of study treatment on biomarkers, and so it would not be appropriate to use an imputation rule in the case of death or missing post-baseline data. In the case of premature stop of study medication, measurements taken at the termination visit or last visit post-baseline will be used.

4.4 Interim Analyses and Data Monitoring

It is planned to produce two formal statistical summaries. The first will be when all patients enrolled in the long-term extension at LPFT of the PATENT-1 study have reached Visit 5 and the PATENT-1 study has been unblinded. The second will be at the conclusion of this extension study. Additional summaries will be performed, at least on a yearly basis, to monitor long-term safety.

4.5 Data Rules

Efficacy analysis datasets will be created that include key demographic data that will be used for the descriptive subgroup analyses. These datasets will also include results from the imputations of missing values in the period up to week 12 and end of study, such that the descriptive efficacy analyses can be performed without the need for major pre-processing within the statistical analysis programs.

4.6 Blind Review

All subjects receiving treatment in the long-term extension will be valid for the descriptive safety and efficacy analyses. Hence, there will be no formal validity assignment.

5. Analysis Sets

The safety and efficacy analyses will be performed in subjects entering and treated in the long-term extension. Formally, these can be considered the long-term safety population.

A subject is valid for the long-term safety and efficacy analysis, if at least one dose of study medication in the extension period was administered.

5.1 Assignment of analysis sets

A subject is valid for the long-term safety and efficacy analysis, if at least one dose of study medication in the extension period was administered.

6. Statistical Methodology

The statistical evaluation will be performed according to the company Global Standards for demography and safety analyses when these have been published (see section 1 for table templates), the statistical methods given in the protocol and, if applicable, any relevant protocol amendments.

For all descriptive analyses, unless otherwise specified, it is planned to summarize the group of subjects as a whole (“all subjects”) and by the following groups:

- Patients randomized to riociguat individual titration in the main phase who stayed on riociguat in the LTE phase, referred to as "riociguat individual titration"
- Patients randomized to placebo in the main phase who switched to riociguat in the LTE phase, referred to as "placebo-riociguat"

By week 8 of the extension, all subjects should be receiving riociguat at the optimized dose, but prior to this there may be some differences between the treatment groups as those subjects in the placebo group will be receiving active medication for the first time, or those in the 1.5 mg group will be up-titrated above 1.5 mg for the first time.

6.1 Population characteristics

Demographic variables and baseline characteristics will be summarized by former treatment group for the long-term safety population.

New ("treatment-emergent") and current concomitant medication received during the long-term extension will be summarized, coded by ATC codes (WHO-DD).

Specific concomitant medications will also be summarized by class and corrected generic name:

1. PH specific medication (note, for the PAH indication PDE5Is are excluded entirely until after stop of riociguat):
- ERAs (bosentan, ambrisentan, sitaxsentan)
- Prostacycline (iloprost, epoprostenol, treprostinil)
- PDE5I (sildenafil, vardenafil, tadalafil)

2. Background therapy
- CCB
- diuretics
- digoxin
- oral anticoagulation
- oxygen

3. Safety relevant medication
- PPI (omeprazol, pantoprazol, rabeprazol, esomeprazol, etc)
- antacids (e.g. aluminum hydroxide, magnesium hydroxide)
- strong CYP3A4 inhibitors
- CYP3A4 inductors
- vasodilative drugs (e.g. antihypertensive medication)

Duration of study medication (in days), in total and by dose, will be summarized descriptively and by three-monthly intervals using frequency counts. Compliance (taken as a percentage of planned), over the first 12 weeks of the study and for the first four weeks after the titration,

will be summarized descriptively and in 10% intervals. Dose titration by visit, dose titration sequence and reasons for up- and down-titration by visit and dose (after titration) will also be summarized using frequency counts. Formally, the dose titration information should just be needed for the former riociguat 1.5 mg and placebo groups, but as the investigators and subjects remain fully blinded during the 8 week (sham) titration phase, in theory those subjects randomized to the riociguat Individual Dose Titration group, despite actually being on a stable dose of study medication, could also have a sham dose adjustment.

6.2 Efficacy

Efficacy variables are:

- 6 minute walking distance from the 6MWT
- PVR (no RHC required at any time during study, PVR only measured if RHC performed as part of regular diagnostic work up)
- NT pro-BNP
- WHO functional class
- Time to clinical worsening
- Borg CR 10 Scale®
- EQ-5D questionnaire
- LPH questionnaire

In the efficacy analyses, countries and centres will be clustered by geographic region, consistent with the pooling in study 12934.

All analyses will be descriptive. For non-categorical data, absolute values and changes from baseline will be summarized. Baseline will be week 0 of study 12934.
It is envisaged that WHO functional class will either remain the same, improve by one or two categories, or deteriorate by one category in most cases. A change score (end of study minus baseline) will be calculated, which could go from -3 (class IV at baseline and class I at end of study) to +4 (class I at baseline, death at end of study), but in practice for those patients still alive at the end of the study it will most likely range from -2 to +1

Time to clinical worsening is made up of several components:
1) all-cause mortality
2) heart/lung transplantation
3) Atrial septostomy (AS)
4) hospitalization due to persistent worsening of pulmonary hypertension
5) start of new PH-specific treatment
6) persistent decrease in 6MWD
7) persistent worsening of functional class
as defined in the protocol section 4.6.4.

The occurrence of the event of clinical worsening during the long-term extension will be summarized using categorical methods, but as an additional summary, the time to event will also be described. In determining whether an event is considered to be an event of clinical worsening the same rules as in study 12934 will be applied.

Change in the Borg CR 10 Scale® will be summarized using frequency counts.

The exploratory efficacy variables described in the Supplementary SAP of study 12934 will be summarized descriptively. This includes the subscales of the EQ5D and LPH and the additional haemodynamic variables. Also the sensitivity analysis of clinical worsening and the categorical analyses described in the Supplementary SAP of study 12934 will be performed.

The primary and secondary efficacy variables, except PVR, will be summarized descriptively for the following subgroups:

- therapy-naïve
- pre-treated
- pre-treated with Endothelin Receptor Antagonist
- pre-treated with Prostacyclin Analogue
- region
- idiopathic/familial PAH
- connective tissue disease
- associated (other forms) PAH
- WHO FC I/II at baseline
- WHO FC III/IV at baseline
- therapy-naïve and WHO FC I/II at baseline
- therapy-naïve and WHO FC III/IV at baseline
- pre-treated and WHO FC I/II at baseline
- pre-treated and WHO FC III/IV at baseline
- < 320m 6MWD at baseline
- ≥ 320m 6MWD at baseline
- < 380m 6MWD at baseline
- ≥ 380m 6MWD at baseline
- males
- females
- age < 65 years

- age ≥ 65 years
- race.

6.3 Pharmacokinetics/pharmacodynamics

BAY 63-2521 and BAY 60-4552 trough concentrations will be summarized per visit, separated according to actual dose. The analyses will be focused on descriptive statistics. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms), and CV, minimum, median, maximum value and the number of measurements. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the limit of quantification (LOQ). For the calculation of the mean value a data point below LOQ will be substituted by one half of the limit. In tables showing mean values, this means will be marked. Tables will be split by scheduled/ unscheduled visits.

Boxplots of plasma concentrations of BAY 63-2521 and BAY 60-4552 at each visit will be given for scheduled extension visits and the last visit of the main study 12934. Separate plots will be given for each of the former treatment groups ("Riociguat Individual Dose Titration", "Riociguat 1.5 mg Dose", "Placebo"). The plots will be restricted to patients that, while receiving riociguat, have been uptitrated at all planned times and have not been down-titrated until visit 5 of the extension study.

6.4 Safety

Safety variables are:
- Adverse events
- Mortality
- Laboratory parameters
- Vital signs
- ECG parameters
- Blood gas analysis

Baseline for continuous safety variables will be week 0 of study 12934.

The incidence of treatment-emergent adverse events during the extension will be tabulated by treatment group. Adverse events are considered to be treatment-emergent if they have started or worsened after first application of study medication up to 2 days after end of treatment with study medication. Further tables will be produced for serious and/or drug-related treatment-emergent adverse events. The incidence of adverse events during follow-up (that is, adverse events occurring more than 2 days after end of treatment with study medication) will be

tabulated separately. The incidence of adverse events that started in the main study 12934 and continue into study 12935 will also be tabulated separately.

In addition, given the varying length of time subjects are in the long-term study, the incidence of treatment-emergent adverse events will also be give per 100 subject years.

Mortality will be summarized descriptively. Any deaths in the study period will be listed, with day of death relative to start and stop of study drug and cause of death.

The safety evaluation of laboratory data will include

- listings of laboratory data out of normal range
- incidence rates of treatment-emergent laboratory values outside of normal range by treatment group
- incidence rates of pre-specified laboratory data abnormalities by treatment group
- descriptive analysis of continuous laboratory parameters, and their changes from baseline by visit and treatment group

The specific laboratory data abnormalities are consistent with those requested by the Data Monitoring Committee or as part of the company medical safety review, and include hepatic transaminases, bilirubin and creatinine (and calculated eGFR).
With global amendment 11, a laboratory value testing was completely removed from the study protocol.

Vital signs (systolic BP, diastolic BP, heart rate and weight) and blood gas analysis will be summarised by visit and treatment group for the population of subjects valid for safety.

For ECGs, the status pre-treatment and post treatment-initiation will be tabulated. The incidence rates of treatment-emergent ECG abnormalities will be tabulated by treatment group. A descriptive analysis of continuous ECG parameters and their changes from baseline by visit and treatment group will also be presented.

7. Document history and changes in the planned statistical analysis

SAP version 2.0 dated 30 Sep 2009

SAP version 3.0 dated 15 Mar 2012

SAP version 4.0 dated 29 May 2012

SAP version 5.0 dated 25 Jul 2019, Update to new template

8. References

Not applicable.