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Title Page

Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH)

Riociguat in children with PAH

Bayer study drug	BAY 63-2521 / Riociguat		
Study purpose:	Safety		
Clinical study phase:	III	**Date:**	17 Feb 2020
Study No.:	BAY 63-2521 / 15681	**Version:**	4.0
Author:	PPD		

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-minutes-walking-distance
ACE	Angiotensin Converting Enzyme
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase (also known as SGPT)
AST	Aspartate Aminotransferase (also known as SGOT)
AT1	Angiotensin Type 1
BDG	Bayer Drug Groupings
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
DMC	Data Monitoring Committee
DMP	Data Management Plan
eCRF	electronic case report form
ECG	Electrocardiogram
EMA	European Medicines Agency
ERA	Endothelin Receptor Antagonists
FAS	Full Analysis Set
FC	Functional Class
GGT	Gamma-glutamyltransferase
IDT	Individual Titration Dose
LOS	Listing Only Set
LTE	Long-Term Extension
MedDRA	Medical Dictionary for Regulatory Activities
NC	North Carolina
NT-proBNP	N-Terminal pro–Brain Natriuretic Peptide
PAH	Pulmonary Arterial Hypertension
PASP	Pulmonary Arterial Systolic Pressure
PCA	Prostacyclin Analogue
PDE5	Phosphodiesterase 5
PedsQL	Pediatric Quality of Life Inventory
PH	Pulmonary Hypertension
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	Proton Pump Inhibitor
PT	Preferred Term
QoL	Quality of Life
SAE(s)	Serious Adverse Event(s)
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure

SC	Steering Committee
SD	Standard Deviation
SDG	Standardised Drug Grouping
SF-10	Health Survey for Children
SOC	System Organ Class
SOP	Standard Operating Procedures
TID	Three Times a Day
TAPSE	Tricuspid Annular Plane Systolic Excursion
TTCW	Time To Clinical Worsening
UK	United Kingdom
USA	United States of America
VRM	Validity Review Meeting
VRR	Validity Review Report
WHO	World Health Organization
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

This international, multicenter, single-arm, open-label study is designed to evaluate the safety, tolerability and pharmacokinetics of a body-weight adjusted riociguat regimen in children from ≥6 years to <18 years of age who have been diagnosed with idiopathic pulmonary arterial hypertension (IPAH), hereditable PAH, or PAH associated with connective tissue disease or congenital heart disease with shunt closure. The study consists of two periods: the *main study treatment period (24 weeks)* and an optional *Long-term extension (LTE) phase.*

Two analyses are planned for this study:

(1) at the end of the main study treatment period (24 weeks treatment) including the data from the main study treatment period, the safety follow-up as far as available, and the LTE phase for subjects who already entered the LTE phase.

(2) at the end of the LTE phase: including the data from both periods, i.e. the main study treatment period and the LTE phase.

This statistical analysis plan (SAP) describes the statistical methods and data presentations of analysis (1), i.e. main study treatment period.

The SAP is based on

- Statistical Analysis Plan version 3.0 , dated 24 AUG 2016
- Integrated clinical study protocol version 5.0 [1], including
    - Global Amendment 12, dated 23 AUG 2019
    - Local Amendment 11 (Romania), dated 05 APR 2019
    - Local Amendment 10 (Taiwan), dated 29 MAY 2018
    - Global Amendment 9, dated 13 MAR 2018
    - Local Amendment 8 (Germany), dated 03 NOV 2017
    - Local Amendment 7 (Japan), dated 07 MAR 2017
    - Global Amendment 6, dated 09 JAN 2017
    - Global Amendment 5, dated 31 MAY 2016
    - Local Amendment 4 (Japan), dated 16 MAR 2016
    - Global Amendment 3, dated 24 NOV 2015
    - Local Amendment 2 (Poland), dated 03 NOV 2015
    - Local Amendment 1 (UK), dated 25 AUG 2015
    - Clinical study protocol version 1.0, dated 13 MAR 2015

Planned LTE analysis and also a country-specific analysis for Japan will be covered by separate SAPs.

2. Study Objectives

A descriptive analysis of the safety and efficacy parameters will be performed.

The primary objectives: To evaluate safety, tolerability and pharmacokinetics of oral riociguat treatment.

Secondary objectives: Exploratory efficacy, i.e. to characterize the pharmacodynamic profile of riociguat comprising the following exploratory parameters:

- exercise capacity (6-minutes-walking-distance (6MWD) test),
- functional capacity (measured by WHO Functional class (FC)),
- laboratory biomarkers (N-terminal pro–brain natriuretic peptide (NT-proBNP), or brain natriuretic peptide (BNP)),
- Quality of life (QoL) measurements (Health Survey for Children (SF-10), child health questionnaire and Pediatric Quality of Life Inventory (PedsQL), Generic Core Scales self report),
- echocardiographic parameters,
- time to clinical worsening (TTCW).

Other objectives:

- to assess taste and texture of the pediatric formulation(s) by use of a questionnaire,
- to assess change in right heart catheterization (RHC) parameters (if available) obtained from RHC performed before study enrollment and during study conduct.

3. Study Design

3.1 Design overview

This is an international, multicenter, single-arm, open-label study to evaluate the safety, tolerability and pharmacokinetics of a body-weight adjusted riociguat regimen in subjects aged between ≥6 years old and <18 years old who have been diagnosed with IPAH, hereditable PAH, or PAH associated with connective tissue disease or congenital heart disease with shunt closure. These subjects must be on stable treatment with PAH medications (Endothelin Receptor Antagonists (ERA) and/or Prostacyclin Analogues (PCA)) prior to receiving the first dose of riociguat [2] [3].

At least 20 children on treatment with bosentan or other ERAs are planned to be enrolled in the study, making every effort to enroll equal number of subjects in each of the ≥12 to <18 year and the ≥6 to <12 year age cohort with a minimum of 5 subjects in each age cohort. In case of inadequate availability of subjects in the age group ≥6 to <12 years total enrolment is planned to be stopped only if at least 5 subjects of this younger age group have been enrolled. Enrollment starts with subjects from 12 to <18 years of age.

The main study comprises 3 periods: pre-treatment phase (Day -14 to Day -1), main study treatment period (24 weeks) and safety follow-up phase (60±8 days). The main study treatment period is divided into the individual titration phase (8 weeks) and maintenance phase (16 weeks). Subjects completing the optional LTE will also perform the safety follow-up visit after 60 ± 8 days after LTE.

After providing written informed consent and assent (if applicable), subjects undergo a screening evaluation to determine their eligibility. Eligible subjects – once on stable background treatment with ERA and/or PCA- start body-weight adjusted individual dose titration (IDT) regimen. After the individual titration phase of maximum of 8 weeks, subjects enter the 16-week maintenance phase. The last dose administered at Visit 4 (see Figure 3–1 below) is determinated as individual optimal dose and subject receives that treatment during the maintenance phase.

Subjects of the older age cohort (≥12 to <18 years) are treated first. After 5 subjects of this age cohort have reached their optimal dose and received this dose until assessment of their first control X-ray of left hand at week 24, an independent Data Monitoring Committee (DMC) provides recommendations to the Steering Committee (SC) whether to continue with enrolment in this age cohort and open enrolment in the subsequent lower age cohort (≥6 to <12 years). Only after obtaining positive safety and efficacy data in the first 5 patients, enrolment in the group from 6 to less than 12 years of age will be started.

Children who require treatment with riociguat for more than 24 weeks will be offered participation in an extension study and continuation until market approval of riociguat for the pediatric population unless local requirements prevent it, or until they are ≥18 years of age (whatever comes first). Subjects reaching adulthood can be transitioned to commercially-available Adempas.

3.2 Dosing overview

The individual optimal study dose will be defined during the titration phase of 8 weeks. The last dose administered during the titration phase will be administered during a 16-week maintenance phase. Subjects of the older age cohort (≥12 to <18 years) are treated first. After 5 subjects of this age cohort were treated for 24 weeks, an independent DMC will provide recommendations to the further conduct of the study.

Riociguat is administered to all subjects using an individual dose titration scheme according to a body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for PAH. The individual optimal (maintenance) dose is to be determined based on patient's monitoring of systolic blood pressure, well-being and clinical status. For children with <50 kg body weight at screening, a body weight adjusted dosing will be applied. Children with ≥50 kg body weight at screening will receive adult doses.

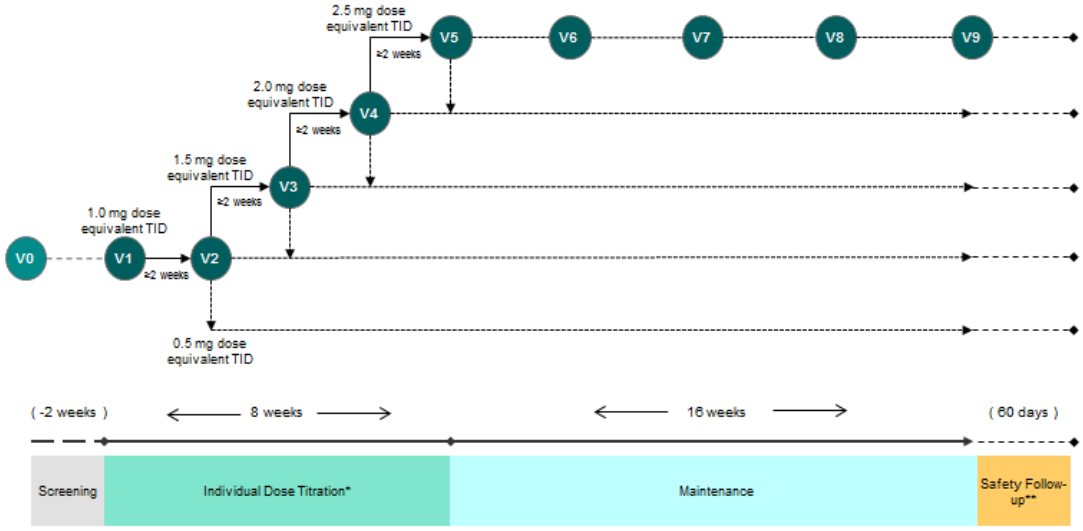
In subjects with a body-weight below 50 kg at screening, riociguat is administered as oral suspension TID with or without food. Subjects with a body-weight ≥50 kg at screening receive riociguat as tablet formulation.

The following tablet strengths are available: 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg. An oral suspension formulation of 0.15 mg/mL is also available.

Subjects with <50 kg body weight at screening start with body-weight adjusted riociguat dose equivalent to the exposure of 1.0 mg TID in adults. Subjects with ≥ 50 kg body weight at screening start with dose 1.0 mg TID. During the individual titration period, the dose is up-titrated every 2 weeks (±2 days) at the discretion of the investigator, based on subject's peripheral systolic blood pressure (SBP) and general tolerability measured at trough before intake of the next higher dose of riociguat. The maximum dose is the dose equivalent to the exposure of 2.5 mg in adults TID. Dose reductions for safety reasons are allowed at any time. The individual dose titration period does not exceed 8 weeks.

Dosing steps and dose equivalents in adults are shown in Figure 3–1 :

Figure 3–1: Dosing Schedule



TID = three times a day; V = Visit

At each titration visit, the individual dose is assigned based on the following algorithm where peripheral SBP will be measured (by oscillometry with the same calibrated oscillometry unit in each center) at trough before intake of the first dose of the day.

Dose titration algorithm

- If SBP is less than 5 mmHg lower than the age-, sex- and height-adapted level of the 50th SBP percentile [4], increase riociguat dose (+0.5 mg dose-equivalent TID)
- If SBP is ≥ 5 mmHg but less than 10 mmHg lower than the age-, sex- and height-adapted level of the 50th blood pressure (BP) percentile, maintain dose of riociguat.
- If SBP is ≥ 10 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, reduce riociguat dose (- 0.5 mg dose-equivalent TID).
- If any SBP is ≥ 5 mmHg lower than the age-, sex- and height-adapted level of the 50th BP percentile, with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with reduced dose (- 0.5 mg dose-equivalent TID).

Down-titration of riociguat is possible for safety reasons at any time point. If at any time, the subject has symptoms of hypotension, temporarily stop the medication and restart after 24 hours with a reduced dose (decrease dosage by 0.5 mg dose-equivalent TID).

At the end of the individual titration phase (Visit 4), the subjects should have reached their individually adjusted dose (maximum equivalent dose of 2.5 mg riociguat TID). The established individual equivalent dose is then taken as optimal dose to be administered during the 16-week maintenance phase. Dose reductions for safety reasons are allowed in the maintenance phase, but a subsequent re-increase is not possible. During the LTE phase the dose may be up-titrated at the investigator's discretion.

Subjects not tolerating the body-weight adjusted riociguat 0.5 mg TID are to withdraw from study.

During the LTE, subjects receiving stable equivalent dose of 1.0 mg, 1.5 mg, 2.0 mg, or 2.5 mg TID as oral suspension can switch to the tablet formulation at the discretion of the investigator.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package Statistical Analysis Software (SAS) release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). All variables will be analyzed by descriptive statistical methods.

1. The number of data available and missing data, mean, standard deviation (SD), minimum, 25% and 75% quartiles, median, and maximum will be calculated for metric data. Mean, median, quartiles and SD will be reported to one decimal place greater than the data were collected. Minimum and maximum values will be reported with the same precision as they were collected. The same metrics will be calculated for the change in parameters between Baseline and visits after Baseline.
2. Frequency tables will be generated for categorical data. These include the counts and percentages of each category including the category 'missing' as a separate category, if applicable. Percentages will be calculated using a denominator of all subjects in the specified population, and the percentage values will be reported to one decimal place. If an incidence is < 0.1 % but > 0 %, it will be displayed as "<0.1%".
3. If no data exists for a table, an empty table will be provided. The text in that table should read "No data matched the selected criteria".
4. For tables that fit horizontally on a single page, and that are more than one page in length, "Continued" will be added to the bottom of all but the last page. The word "Continued" must be added to the title for all pages after the first page and to the bottom of the page for all pages from the first to the second to last page.
5. For event-based tables the number of subjects should be displayed next to the treatment with the syntax "(N=x)". For tables where the N is the number of subjects and also used as the denominator "N=x (100%)" is to be used.
6. In frequency tables, if "n=0", then only "0" should be displayed; "(0.0%)" will not be displayed.
7. When numerator and denominator values are "0", do not use brackets. Use the following: "0/0", not "0/0 (%)".
8. All listings will be presented for subjects with their subject identifier, age at screening, sex and race.

The structure of analyses datasets and layout of analysis data displays will follow Bayer standards in the following order of priority: Riociguat Global Standards, Global Medical Standards, and Global Standards for Data Display. Study-specific specifications may be added if required and not covered by the Global Standards.

4.2 Handling of Dropouts

A subject who discontinues study participation prematurely for any reason, as specified in the protocol in section 8.9, is defined as a "dropout" if the subject has already started treatment. Dropouts will not be replaced.

In all subjects who prematurely discontinue study drug at any time after Visit 1 and before Visit 9 for reasons other than withdrawal of informed consent, an end-of-treatment visit has to be performed. The same procedures as at Visit 9 will be performed with the exception of the X-ray of left hand.

For all subjects stopping study medication either at the end of treatment or prematurely discontinuing the study at any time, a safety follow-up visit 60 days (±8 days) after last study medication intake should be performed.

If the subject or parent(s)/legal representative(s) withdraw(s) consent to treatment with study drug, the investigator asks to continue with study visits as planned, only with the aim to collect potential study outcomes and AEs. If the subject/parent(s)/legal representative(s) state to the investigator that they no longer authorize to continue to obtain outcome data, this is respected and documented in the source records, and no further study data are collected.

In all subjects who prematurely discontinue study drug for other reasons than withdrawal of informed consent, study visits takes place as planned to collect potential study outcomes and AEs. The analysis will be performed independently of the fact whether a patient had drug intake or not.

A subject who discontinues the study prior to the first intake of the study treatment is defined as 'screening failure'.

The number of screening failures and dropouts as well as the respective reasons will be summarized.

The frequency of enrolled subjects not completing screening, treatment phase, safety follow-up for those not entering the long-term extension and associated reasons will be summarized.

A Kaplan-Meier plot of the time from start of study treatment to end of study treatment will be provided. Subjects continuing study treatment in the LTE phase will be censored on his/her end of main phase.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the electronic case report form (eCRF). Missing data proportions will be reported.

In general they will not be substituted or replaced, except for the parameters described below.

General rules

- **Efficacy variables**

  Last visit is defined as last observed value post-baseline (including unscheduled visits, but not including follow-up), if not specified otherwise.

  - 6 Minute Walking Distance

    If a subject dies before Week 24 or during follow-up after termination before Week 24, the worst value = 0 is used.

- WHO Functional Class

  If a subject dies before Week 24 or during follow-up after termination before Week 24, the worst value = IV (4) is used.

- **Safety variables**

  Last visit is defined as last observed value post-baseline (including unscheduled visits, but not including follow-up), if not specified otherwise.

  Treatment emergent events, phases, period and relative days will be derived according to standard guidelines.

  A complete date is not needed for the statistical tables, but an imputation on the phase of the study for adverse events and concomitant medications (pre, during or post) is required. The 'minimum' rule will be used for start dates which is first day of month or 1st of January. The 'maximum" rule will be used for end dates which is last day of month or 31st of December.

- **Child Health Questionnaire (SF-10)**

  Scores will be provided by QualityMetric Score was generated by QualityMetric.

- **Pediatric Quality of Life Inventory™ (PedsQL™)**

  In the case of missing single questionnaire items, the missing data rules in the scaling and scoring document will be followed. Specifically, if more than 50% of the items in the scale are missing, the Scale Scores should not be computed. If 50% or more items are completed: Impute the mean of the completed items in a scale.

4.4 Interim Analyses and Data Monitoring

No interim analyses are planned for this study.

An independent DMC is established for this study to provide the SC and the sponsor with recommendations related to the protection of the subjects safety, including stopping recruitment and study treatment. For that purpose, the DMC will regularly review all incidences of serious adverse events and adverse events of special interest. Organizational aspects, responsibilities, and processes are described in the DMC charter [5].

At least one DMC meeting per year will be held to review the subjects enrolled. In any case one DMC meeting will take place when the first 5 subjects of the age cohort (≥12 to <18 years) finish the main treatment phase and have reached their optimal dose and received this dose until assessment of their first control X-ray of left hand at week 24. After this DMC meeting, the DMC will give recommendations to the SC whether to continue with enrolment in this age cohort and open enrollment in the subsequent lower age cohort (≥6 to <12 years). Only after obtaining positive safety and efficacy data in the first 5 patients, enrolment in the group from 6 to less than 12 years of age will be started. The subsequent meetings are planned to occur when additional 5 patients, independently of age cohort, finish the main treatment period.

For all subjects reaching week 24 of the main study treatment period and all subjects continuing in the LTE, the left hand X-rays is evaluated by the DMC. The DMC is provided with all relevant documentation on an ongoing basis including all cases of clinical worsening (as defined in protocol section 6.3) that occur after intake of first dose of study medication, in the main study treatment period - including the 60 day safety follow-up period (only for those patients not entering the LTE).

The mock-ups for the DMC outputs are described within relevant sections of this SAP. A separate DMC SAP is not foreseen.

4.5 Data Rules

Unless otherwise specified, baseline is the last available non-missing value prior and up to the time of the first intake of study medication, i.e. first dose of riociguat. Change from baseline is calculated as the value at the post-baseline time point minus the baseline value, i.e. value at time point – value at baseline.

Post-treatment values will be considered treatment-emergent if they start within 2 calendar days after the last day of study drug administration, i.e. the treatment-emergent window will be 2 days.

All data from the electronic case report form (eCRF) will be organized and analyzed according to the scheduled visits. Any additional or unscheduled measurements will be included in the listings according to the date/time of assessment. In the case of multiple observations at a specific visit, the observation that is closest to the target visit will be used in the analyses. If observations have the same distance (before and after) to the target visit, the latest one will be used. If the repeated measurements are all taken on the same day, then the last measurement will be used.

Subgroup analyses will be performed by age cohort (≥6 to <12 years and ≥12 to <18 years) and by concomitant PAH medication (ERA only, ERA + PCA, PCA only) specified at Screening. The patients are assigned to the concomitant PAH medication groups specified before date of treatment according to Standardised Drug Grouping (SDG)/Bayer Drug Groupings (BDG), section 6.1.6. Patient´s assignment to PAH medication grouping is depicted in Table 4–1:

Table 4–1: Concomitant PAH medication grouping

Group	SDG (BDG)	
	Endothelin receptor antagonists	**Prostacyclins (including analogues and receptor agonists)**
ERA only	Yes	No
ERA + PCA	Yes	Yes
PCA only	No	Yes

Listings will be sorted by subject identifier, visit (if applicable), date and time.

Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings with dashes for the missing parts, e.g. like --MMMYYYY. Listing should only present the collected dates, not imputed dates.

Rounding for all variables will occur only as the last step, immediately prior to presentation in listings and tables. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending 5-9 up will be employed.

Every table, listing and figure will be produced with an electronic date stamp to document when it was produced.

4.6 Validity Review

Validity Review Meeting (VRM) will be performed according to applicable Syneos Health Standard Operating Procedures (SOP) and will be led by the Syneos Health Lead Data Manager. Details are available in the data management plan (DMP).

The results of the VRM will be documented in the Validity Review Report (VRR) and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meeting will be documented in an amendment and, if applicable, in a supplement to this SAP.

All protocol deviatons will be listed. All important deviations will be summarized by age cohort and concomitant PAH medication.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the VRM and documented in the VRR (see section 4.6).

Safety analysis set (SAF)

A subject will be included in the SAF (equivalent to full analysis set, FAS) if he/she is assigned to receive study medication and has received at least one dose of the study medication.

Listing only set (LOS)

All subjects who signed informed consent for treatment eligibility at screening but could not be assigned to safety analysis set defined above. Their data will be presented in individual subject data listings in CSR section 16.2.1 and will not be included in any statistical analyses.

6. Statistical Methodology

The analysis will include data from screening to week 24. Information collected at safety follow-up visit, for subjects not continuing in the LTE phase, will be included in tables, if applicable. LTE phase data collected until the cut-off date from subjects already in the LTE phase will be listed only.

The cut-off date will be defined after all treated subjects completed the 24 week treatment period assessments or safety follow-up visit is completed for all subjects who are not continuing in the LTE phase, except those who are lost to follow-up. The cut-off date will be defined by the sponsor, allowing time for data cleaning.

6.1 Population characteristics

Demographic and baseline characteristics of subjects will be summarized using descriptive statistics.

The variables to profile the study population include demographic data, medical history, concomitant PAH specific medication. If not stated otherwise, population characteristics will be tabulated overall. The actual body-weight adjusted dosing information will be included in the listings as applicable (e.g. where the collected data could be assigned to the treatment dose).

6.1.1 Inclusion-/Exclusion criteria

Data from the assessment of inclusion and exclusion criteria will be presented in listings for all subjects who signed informed consent/assent and failed the inclusion/exclusion criteria.

6.1.2 Disposition

Disposition will be described for the following study phase:

- Screening,
- Treatment,
- Safety follow-up (for those subjects who do not enter LTE)

and include numbers of subjects completing each study phase and reasons for non-completion.

The following will also be summarized:

- Subject validity and validity exclusion reasons,
- the number of subjects enrolled, assigned to study treatment, completing the main study, completing the safety follow-up and entering the LTE.

Summaries will be presented overall (all ages), by age group and by concomitant PAH medications.

Subject will be defined as main study completer, if he/she has completed the week 24 treatment period.

6.1.3 Demography

Demographic data includes age at screening (years), sex, race and smoking among others. This data will be listed and summarized in tables. Summaries will be presented overall (all ages), by age group and concomitant PAH medications for SAF set and will be repeated for subjects who discontinued treatment.

The above presentation will be part of the DMC package.

6.1.4 Baseline characteristics

The following baseline characteristics are observed at baseline. In case of repeated measures the last available value before the first application of the study drug will be used for summary tables.

Primary diagnosis of Pulmonary Hypertension (PH)-IIP, 6MWD, WHO functional class, BNP/NT-proBNP, SF10, PedsQL, bone age and morphology and tanner scale.

Primary diagnosis of Pulmonary Hypertension (PH)-IIP information presented in the corresponding listing will be part of the DMC package.

6.1.5 Medical history

Medical history will be evaluated by a frequency table, showing number of subjects with medical history findings coded according to the Medical Dictionary for Regulatory Activities (MedDRA), last available version at the time of database lock, and analyzed by system organ class (SOC) and preferred term (PT).

6.1.6 Prior and concomitant medication

Prior and concomitant medication will be listed and summarized in frequency tables. Medications will be coded according to the World Health Organization Drug Dictionary Enhanced (WHO-DDE), last available version at the time of database lock. For this study, separate outputs will be generated for previous and concomitant PAH specific medication and other (non PAH specific) medication.

Missing or incomplete start and stop dates of medication will be imputed as described in section 4.3 about Missing Data.

The medications will be classified as follows:

- Medications that began before the start of study drug (regardless of when they ended) are defined as ‘medication before start of study drug‘.
- Medications that started and stopped before the start of study drug are defined as ‘medication that started and ended before administration of study drug‘.
- Medications that are ongoing at, began after the start of study drug, or medications that were started after end of study drug are defined as ‘concomitant medication‘.
- Medications that began after the start of study drug, and those that were started after end of study drug are defined as ‘new concomitant medication’.

Medications will be tabulated overall (all ages), by age group and concomitant PAH medications for SAF.

SDG/BDG will be used to select concomitant medications of special interest: PAH specific medication, Background therapy/supportive PH therapy and Safety relevant medication. The selected concomitant medications will be summarized by parent SDG/BDG, SDG/BDG and substance name. The information will be provided separately and will be part of the analysis datasets specifications. Summaries will be done for all selected concomitant medications, new selected concomitant medications, and selected medications taken before start of study drug.

6.1.7 Study medication duration and exposure

Study medication can be administered as tables or as oral suspension formulation of 0.15 mg/mL. For the analysis the equivalent dose (mg) will be used. The derivation rule is:

- For tablets: No conversion needed. The dose (mg) is identical to the equivalent dose (mg).
- For oral suspension: The volume of suspension (ml) will be converted into equivalent dose (mg) as described in the protocol Table 5–2: Body weight-adjusted riociguat dosing schedule, considering the weight at that timepoint.

Treatment duration and exposure will be analyzed for the SAF set and presented overall (all ages), by age group and concomitant PAH medications. The cumulative treatment exposure will be analyzed for the SAF set and presented overall (all ages), by age group and concomitant PAH medications by suitable treatment exposure intervals.

Duration of treatment is defined as the number of weeks from start of treatment until the last day th e study drug administration in respective phase devided by 7 (i.e. [end date – start date + 1] / 7). Duration of treatment will be summarized by study phase descriptively and by suitable time intervals using frequency counts. Dose titration by visit, dose titration sequence

and reasons for up- and down-titration by visit and dose will also be summarized using frequency counts.

Extent of exposure will be summarized descriptively and by suitable dosing intervals using frequency counts.

Cumulative treatment duration will be summarized by total person years, excluding subjects with missing duration, and uses 365.25 days per year in the calculation. Cumulative treatment duration will include individual titration phase and maintenance phase.

Extend of exposure in mg will be calculated as follow:

- Tablets: sum of all doses [mg] within a time interval
- Oral suspension: sum of all drug amount [ml] within a time interval multiplied with 0.15 mg/mL. The dose will be in mg.

The overall extent of exposure is the sum of all extend of exposures of a patient.

6.2 Efficacy

6.2.1 Primary efficacy

Please refer to section 6.3.

6.2.2 Secondary efficacy

Efficacy is evaluated in exploratory manner based on SAF and assessed as change from baseline to end of treatment (week 24). All data except PedsQL data are part of the DMC package.

It includes following endpoints:

- **6-Minute Walking Distance (6MWD)**

6MWD will be analyzed descriptively by summary tables. Time points of efficacy assessments are at baseline and week 24.

- **WHO functional class**

WHO functional class will be analyzed descriptively using frequency tables. Time points of efficacy assessments are at baseline and week 24.

- **Laboratory biomarker (NT-proBNP or BNP)**

NT-proBNP or BNP will be analyzed descriptively by summary tables. Time points of efficacy assessments are at baseline and week 24.

- **Child Health-related Questionnaire (SF-10)**

SF-10 scores (Physical Summary Score, and Psychosocial Summary Score) will be analyzed descriptively by summary tables. Time points of efficacy assessments are at screening and week 24.

- **Generic Core Scales self-report (PedsQL)**

Summary scores of all three types of questionnaires (Young Child Report (age: 5-7), Child Report (age: 8-12), Teen Report (age: 13-18)) will be analyzed overall (all age groups together) and by age cohort (≥6 to <12 years and ≥12 to <18 years) by summary tables. Time points of efficacy assessments are at screening and week 24.

Following Summary Scores will be analyzed:

- Physical Functioning Dimension
- Emotional Functioning Dimension
- Social Functioning Dimension
- School Functioning Dimension
- Physical Health Summary Score (equal to Physical Functioning Dimension)
- Psychosocial Health Summary Score
- Total Score

- **Echocardiography**

There are following echocardiography parameters assessed:

Table 6–1: Echocardiography parameters

General description (in clinical study protocol)	Parameters in data
Pulmonary arterial systolic pressure (PASP)	Pulmonary artery systolic pressure
Tricuspid annular plane systolic excursion (TAPSE)	Tricuspid annular plane systol. Excursion
Pericardial effusion	Finding for pericardial effusion
	Pericardial effusion
Left ventricular eccentricity index	Left ventricular eccentricity index
Right atrial pressure	Estimate of mean right atrial pressure
Right ventricular pressure by tricuspide regurgitant jet velocity	Tricuspid regurgitation peak velocity
Acceleration time of pulmonary flow	Pulmonary artery acceleration time
Right heart dimensions (i.e. Right atrial and Right ventricular)	Right atrial diastolic area index
	Right atrial systolic area index
	Right atrial diastolic area
	Right atrial systolic area
	Right ventricular diastolic area
	Right ventricular systolic area
	Right ventricular diastolic area index
	Right ventricular systolic area index
	Right ventr. fractional area change
Cardiac output	Right Ventricular Cardiac Output
	Right Ventricular Cardiac Index

Assessments by Central Reader will be listed and analyzed descriptively by sample summary statistics. Time points of assessments are at baseline and week 24. Investigator´s assessments (Echocardiography Local) will be listed only.

Supplementary parameters (Diameter, vena cava inferior, baseline; Minimum inferior vena cava diameter; Left Ventricle-Short axis perpendicular; Left Ventricle-Short axis parallel; Pressure gradient of tricuspid valve; Respiratory collapsibility, v. cava inf.; right ventricular outflow tract – velocity time intergral; Right ventricular stroke volume; Heart Rate; Right

Ventricular Outflow Tract Area; Right Ventricular Outflow Tract Diameter) used to derive echocardiography parameters (Table 6–1) will be listed only.

- **Time to clinical worsening (TTCW):**

Time to clinical worsening is defined by the first of any of the following events:

- Hospitalization for right heart failure
  (Preferred term (PT) as described in Table 6–2 *AND* requires or prolongs hospitalization = 'Y')
- Death (all cause mortality)
  (all deaths during both treatment and follow-up period)
- Lung transplantation
  (PT = ‚Lung transplant')
- Pott's anastomosis and/or atrioseptostomy
  (Subject has either PT = 'Systemic-pulmonary artery shunt' *OR* PT = 'Balloon atrial septostomy' or both. The first event occured will be considered.)
- Increase in WHO FC from baseline
- Appearance/worsening symptoms of right heart failure and need for additional PAH therapy (PT as described in Table 6–2 *AND* therapy as described in Table 6–3 at same day or up to 6 days before or after.)

Table 6–2: Right heart failure

Preferred Term (at least one must apply)
Acute right ventricular failure
Chronic right ventricular failure
Right ventricular failure
Pulmonary arterial hypertension

Table 6–3: Need for additional PAH therapy

Drug class	Compound (at least one must apply)
Endothelin receptor antagonist	Ambrisentan
	Bosentan
	Macitentan
Phosphodiesterase-5 inhibitor	Sildenafil
	Tadalafil
	Udenafil
Prostacyclin analogue	Beraprost
	Epoprostenol
	Iloprost
	Treprostinil
Prostacyclin agonist	Selexipag

TTCW will be analyzed descriptively by sample summary statistics.

All Kaplan-Meier estimates will be summarized.

In addition, Kaplan-Meier plots will be generated for the TTCW. Subjects without signs of worsening at the time of the main study or LTE phase analysis will be right censored at the date of end of main phase or the date of subject's study termination, whatever occurs first.

For subjects with event: Time to clinical worsening (weeks) = integer[(date of first event – treatment start date + 1) / 7].

For subjects without event: Time to worsening (weeks) = integer[(date study termination/ end of main phase – treatment start date +1) /7]. Date of study termination is defined as date of last visit. Date end of main phase is defined as date of the last visit of the main phase (Visit 9 for subjects continuing in LTE phase or safety follow-up visit for subjects not continuing in LTE phase).

TTCW will be part of the DMC package.

6.2.3 Other efficacy

Taste and texture of the pediatric formulation(s)

Taste and texture is assessed by use of a questionnaire at the beginning (Day 0) and at the end of the main study (week 24 or end of treatment visit). The assessment is completed only for subjects who received study medication via oral suspension. It will be analyzed descriptively using frequency tables.

Right heart catheterization (RHC)

RHC may be conducted on medical reasons during the study. It will be analyzed descriptively by sample using summary statistics and tabulated with change in RHC parameters (if available) obtained from RHC performed before study enrollment and during study conduct.

6.3 Pharmacokinetics/pharmacodynamics

BAY 63-2521 and M1 (BAY 60-4552) peak and trough concentrations will be summarized per visit, separated according to actual dose for peak concentrations and according to previous dose for trough concentrations.

The analyses will be focused on descriptive statistics for patients with a valid PK value, and the frequency of patients with invalid or missing PK value by time point will be shown. 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.

Pharmacokinetic data from this study will be reported under a separate cover.

PK concentrations of the study drug and its metabolites will be listed and tabulated.

For pharmacodynamics see section 6.2.2.

6.4 Safety

The primary objective of this study is to evaluate safety and tolerability of riociguat in children with PAH. Primary endpoint of the study is: Change from baseline to end of treatment (week 24) of safety and tolerability.

Beside the number of subjects who discontinued prematurely, safety and tolerability will be assessed by incidence of adverse events and serious adverse events, recording of ECGs, vital signs, body weight, left hand X-ray and laboratory panel.

Safety data will be presented in data listings, and summarized in tables for subjects in the SAF.

AEs will be coded according to the MedDRA, last available version, and analyzed by SOC and PT.

6.4.1 Adverse event

Adverse events are considered to be treatment-emergent adverse events (TEAE) if they have started or worsened after first application of study drug up to 2 days after end of treatment with study drug.

The safety evaluation of AE data will include:

- Overall summary of AEs
- Overall summary of TEAEs
- TEAEs and by SOC and PT (overall, serious, study drug related, study drug related serious, of special interest, not related to study drug, TEAEs resulting in discontinuation of study drug, study drug related resulting in discontinuation)
- TEAEs by SOC and PT and by maximum intensity
  (overall, serious, study drug related, study drug related serious, TEAEs of special interest, TEAEs resulting in discontinuation of study drug)
- TEAEs by SOC and PT and by worst outcome
  (overall, serious, study drug related, study drug related serious, TEAEs of special interest, TEAEs resulting in discontinuation of study drug)
- Common (≥ 5%) TEAEs by PT, common (≥ 5%) serious TEAEs by PT, common (≥ 5%) study drug related TEAEs by PT
- Listings of serious TEAEs, serious TEAEs with outcome of death, serious TEAEs leading to discontinuation of study drug, TEAEs of special interest, TEAEs of special interest leading to discontinuation of study drug, TEAEs leading to discontinuation of study drug and deaths.

Adverse events of special interest are: Hemoptysis, Hypotension and Skeletal related events.

For each SOC and PT, summaries will be made with respect to the proportion of subjects having at least one occurrence of that event in dosing group (0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, 2.5 mg TID) and overall during the study.

All adverse event tables will be presented overall (all ages). In addition, presentation will be done by age group and concomitant PAH medications for overall summary tables and Common (≥ 5%) TEAEs by PT, common (≥ 5%) serious TEAEs by PT, common (≥ 5%) study drug related TEAEs by PT tables.

Non-TEAEs will be listed only.

Following outputs are part of the DMC package:

- Overall summary of TEAEs
- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- Study drug-related TEAEs by SOC and PT
- Serious study drug-related TEAEs by SOC and PT
- TEAEs of special safety interest by SOC and PT
- Listings of deaths
- Listings of all AEs with information of serious adverse events (SAEs), AEs leading to discontinuation of study drug and AEs of special interest.

In addition all adverse events terms and investigator terms are tabulated.

6.4.2 Laboratory data

Following laboratory parameters are collected: complete blood count (CBC) of hematology parameters and general chemistry parameters Creatinine, SGOT/AST, SGPT/ALT, blood urea nitrogen (BUN), gamma-glutamyltransferase (GGT), uric acid, total bilirubin, albumin, sodium, potassium, calcium, phosphate and glomerular filtration rate (calculated based on Schwartz formula for non Japan population and Japan-specific formula for Japan population). All data will be evaluated via local laboratory. Descriptive analysis of laboratory parameters (AST, ALT, BUN, creatinine, GGT, uric acid, total bilirubin, albumin, sodium, potassium, calcium, phosphate, CBC and Glomerular filtration rate) and their corresponding changes from baseline will be presented. Values that are outside the labor specific reference ranges will be considered as laboratory abnormality.

Data will be summarized by visit using frequency tables for values within/outside reference ranges. Laboratory data outside the standard reference ranges and clinically relevant abnormal laboratory values will be flagged in listings.

Laboratory data will be presented overall (all ages).

Additionally a table of Treatment emergent specific laboratory abnormalities will be produced including SGOT/AST > 3*ULN, SGPT/ALT > 3*ULN, Bilirubin > 2*ULN, Glomerular filtration rate <30 mL/min/1.73m^2.

Laboratory data are part of the DMC package.

6.4.3 Pregnancy test

Results of the pregnancy tests (urine or serum) will be listed only.

6.4.4 Vital Signs

Vital signs (diastolic and systolic blood pressure, respiratory rate and heart rate) and their corresponding changes from baseline will be summarized by visit. In addition, at Day 0, pre-dose, 2 and 4 hours assessment will be evaluated. Body surface area measured at Screening will be listed only. The analysis of height, weight and BMI will be described in section 6.4.7.

Vital signs data will be presented overall (all ages) and by age group.

In addition a frequency table of systolic blood pressure for each visit compared to the age, sex, height - adapted SBP median by age group and concomitant PAH medications will be presented. The adapted SBP median is based on the age at visit and actual height at the respective visit, derived from Table 4-1 and Table 4-2 in the study protocol. For Japanese and Taiwanese the 5th and 95th height percentile are not defined and therefore 3rd and 97th height percentile will be used instead, respectively.

Vital signs data are part of the DMC package.

6.4.5 Electrocardiogram (ECG)

ECG will be will be summarized by visit. In addition, at Day 0, pre-dose, 2 and 4 hours assessment will be evaluated. Investigator assessment and other parameters, including changes from baseline, will be tabulated.

Data will be presented overall (all ages), by age group and concomitant PAH medications. Refer to table shells for more information about the subgroup presentation.

ECG outputs are part of the DMC package.

6.4.6 Left hand X-ray

Bone age and bone morphology will be evaluated centrally by external X-ray specialist based on left hand X-ray at Day 0, week 24 and every 12 months during the LTE until growth velocity is plateauing and growth plates are closed. Data will be summarized by visit and will be presented overall (all ages).

Left hand X-ray outputs are part of the DMC package.

6.4.7 Physical examination and growth chart

Subject's overall development is assessed by physical examination, growth chart (height and weight) evaluation and pubertal development using Tanner scale, see protocol section 18.3, and at the discretion of the investigator in case of clinical suspicion for bone and/or growth anomalies. Pubertal assessment using Tanner scale will be performed every 12 months. Abnormal physical examination findings are recorded as medical history, if they started before providing written informed consent/assent. If the abnormal finding started or deteriorated after providing written informed consent/assent, it is documented as adverse event.

Height, weight, BMI will be summarized by visit and will be presented overall (all ages), excluding subjects with down-syndrome. BMI will be presented for non-Asian, i.e. excluding Japanese and Taiwanese, population only.

In addition a frequeny table of growth parameter percentiles by visit and by age group and concomitant PAH medications will be presented for height, weight and BMI. Subjects with down-syndrome will be excluded. The percentiles are based on CDC growth standards [6] and growth chart for Japan for Japanese and Taiwanese subjects provided by sponsor [7].

For the calculation of percentiles, age in months at each visit will be calculated. Due to the fact, that only year of birth is collected the calculation of age in months will be:

(year of visit – year of birth)*12

Pubertal assessment using Tanner scale will be summarized as shift table for change from baseline by visit.

Growth parameters by visit and Tanner scale listing are part of the DMC review.

7. Document history and changes in the planned statistical analysis

- SAP final version 1.0, dated 12 OCT 2015
- SAP final version 2.0, dated 15 JAN 2016. SAP was updated to reflect protocol changes and is based on protocol version 2, Amendment 3, from 24 NOV 2015.
- SAP final version 3.0, dated 24 AUG 2016. SAP was updated to reflect protocol changes and is based on protocol version 3, Global Amendment 5, from 31 MAY 2016 and stand-alone Amendment 4, from 08 MAR 2016. Further updates were done to reflect the changes of the DMC Charter and is based on the DMC Charter version 3.0, from 01 JUN 2016.
- SAP final version 4.0, dated 17 JAN 2020. SAP was updated to reflect protocol changes and is based on protocol version 5.0, Global Amendment 9, from 13 MAR 2018, version 4.0, Global Amendment 6, from 09 JAN 2017 and stand-alone Amendments 7 from 07 MAR 2017 and 8 from 03 NOV 2017 and describes analysis of the main study treatment period. Further updates were done to specify PAH medications, BDGs, echocardiography parameters, pharmacokinetics/pharmacodynamics and definition of time to worsening.

8. References

1. Clinical Study Protocol No. BAY 63-2521 / 15681 (Bayer AG). Open-label, individual dose titration study to evaluate safety, tolerability and pharmacokinetics of riociguat in children from 6 to less than 18 years of age with pulmonary arterial hypertension (PAH). Version 5.0, Global Amendment 9, 13 MAR 2018.
2. EMA 2009. Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension.. In: USE, C. F. M. P. F. H. (ed.) EMEA/CHMP/EWP/356954/2008.
3. EMA 2012a. Paediatric addendum clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. In: USE, C. F. M. P. F. H. (ed.) EMA/CHMP/213972/2010.
4. NHBPEP 2004. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics, 114, 555-76.
5. PATENT- Child DMC Charter v 5.0, dated 22 AUG 2019
6. http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm
7. http://jspe.umin.jp/medical/files/fuhyo2.pdf