Bayer

CLINICAL STUDY PROTOCOL

Title: Long-term extension, multi-centre, 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**

Test Drug: BAY 63-2521 (INN Riociguat)

Sponsor's Name and Address: Bayer HealthCare AG
D-51368 Leverkusen

Study Number/Version/Date: 12935 / Version 2.0/ 2008-Sep-11

The following Amendments have been incorporated into this Integrated Protocol.

AMENDMENT NUMBER	VERSION NUMBER	DATE
Amendment 5	1.0	10-June-2009
Amendment 6	1.0	22-March-2010
Amendment 8	1.0	15-Feb-2011
Amendment 11	1.0	13-Dec-2012

INTEGRATED PROTOCOL DATE 13 Dec 2012

STUDY 12935

AMENDMENT 5, 6, 8 and 11 INCORPORATED

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Glossary and Abbreviations

6MWD	6-minute walking distance
AE	adverse event or experience
ALT	alanine aminotransferase (also known as SGPT, *qv)*
ALP	alkaline phosphatase
AST	aspartate aminotransferase (also known as SGOT, *qv)*
CCW	concalc for Windows
cGMP	cyclic guanosine monophosphate
CHE	Cholinesterase
CK	creatine kinase
CRF	case report form
eCRF	electronic case report form
CT	computed tomography
CTEPH	chronic thromboembolic pulmonary hypertension
CYP3A4	cytochrome P450 isoenzyme 3A4 (etc)
d	Day
EC	ethical committee
ECG	Electrocardiogram
eg	*exempli gratia*, for example
EQ-5D	EuroQol questionnaire
g	standard acceleration due to gravity at the Earth's surface, by definition: $g = 9.80665\ m/sec^2$
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
GLDH	glutamate dehydrogenase
h	Hour
H	Height
HDPE	High Density Polyethylen
HEOR	Health Economics, Outcomes and Reimbursement
HPLC	high pressure liquid chromatography
ie	*id est,* that is
IR	immediate release
INR	international normalized ratio (prothrombin time expressed in relation to normal value)
IRB	Institutional Review Board
iv	Intravenous
IVR / IVRS	interactive voice response system
LPH	Living with Pulmonary Hypertension questionnaire
M-1	metabolite M-1
mg	Milligram
mmHg	millimeter of mercury
MRR	Medical Research Report
NO	Nitric oxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
O_2	Oxygen

$PaCO_2$	arterial partial pressure of carbon dioxide
PaO_2	arterial partial oxygen pressure
PEA	Pulmonary endarterectomy
PDE5	phosphodiesterase type-5
PH	pulmonary hypertension
PK	Pharmacokinetic
PTT	partial thromboplastin time
PvO_2	venous oxygen pressure
PVOD	Pulmonary-veno-occlusive disease
QC	quality control
SAE	serious adverse event
SaO_2	oxygen saturation
SAS	Statistical Analysis System
SBP	systolic blood pressure
tid	*ter in die* (3 times a day)
WHO	World Health Organization

1. INTRODUCTION

Please see INTRODUCTION of the BAY 12394 (PATENT-1) protocol.

In addition, the following aspects should be considered with respect to the long-term extension trial:

Based on the currently available scientific evidence, a large proportion of Pulmonary Artery Hypertension (PAH) patients cannot be cured. Therefore, it can be assumed that their disease will progress over the years, requiring a long-term medical treatment to maintain their quality of life and to increase their life expectancy.

Although the experiences with BAY 63-2521 with respect to the treatment of PAH are limited, in the light of the severity of the underlying disease it is justified to offer all patients who participated in the PATENT-1 trial a long-term treatment with BAY 63-2521 (until commercially available).

In this context, it should be highlighted that BAY 63-2521 revealed a positive benefit-risk ratio in the trials conducted in Pulmonary Hypertension (PH) patients to date (trials # 11874 and # 12166), allowing continuation of the development program. Moreover, in a first interim analysis of the extension phase of trial # 12166 (includes 21 patients with a BAY 63-2521 treatment up to one year) the improvements in walking distance observed within the first 12 weeks of treatment were sustained without any significant safety concerns.

For further information refer to the Investigator Brochure. The Investigator's Brochure will be updated at regular intervals during the conduct of the trial. New versions of the Investigator's Brochure will be made available to the investigators without delay

2. STUDY OBJECTIVES

To assess the long-term safety and tolerability of BAY 63-2521 in treatment naive patients and patients pretreated with an Endothelin Receptor Antagonist or a Prostacycline Analogue with symptomatic Pulmonary Arterial Hypertension (PAH).

The trial provides patients, who have completed 12 weeks of BAY 63-2521 double blind treatment (PATENT-1 trial, #12934), the option of long-term treatment with BAY 63-2521.

Efficacy assessments are included to provide an indication of maintenance of efficacy with long-term treatment.

3. INVESTIGATOR(S) AND OTHER STUDY PARTICIPANTS

Principal Investigator/Coordinating Investigator of the study

Name:	PPD
Address:	PPD
	PPD
	PPD
	PPD

The Study Manager and the Medical Expert will appoint the coordinating investigator responsible for signing the MRR.

Information regarding additional key personnel involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the sponsor and on site if requested.

4. INVESTIGATIONAL PLAN

4.1 Study Design and Plan

Multicentre, multinational, open label one arm study in patients with symptomatic PAH.

Study Phases:

- Treatment Phase:
  - Titration Phase: 8 weeks
  - Main-Study Phase: Duration until BAY 63-2521 receives official approval and will be commercially available
- Safety Follow Up Phase: 30 days

BAY 63-2521 will be administered orally as a tablet in doses of 0.5 mg, 1.0 mg, 1.5 mg, 2.0 mg, and 2.5 mg tid.

Titration Phase (8 weeks):

General aspects:

During the first eight weeks of the trial, patients from the Placebo Arm and from the BAY 63-2521 1.5 mg Dose Arm (applies only to patients who reached the 1.5 mg tid level) of PATENT-1 trial will be up-titrated, if tolerated, up to 2.5 mg BAY 63-2521 tid according to an individual dose titration scheme.

To maintain the blinding of PATENT-1, the PATENT-2 study medication (BAY 63-2521) is blinded with respect to the dose during the Titration Phase and investigators will not know at which dose level a certain patient enters the PATENT-2 trial.

Patients from the BAY 63-2521 Individual Dose Titration Arm and the BAY 63-2521 1.5 mg Dose Arm will enter the extension trial on the same dose level

which they have received on the last day of PATENT-1, while patients from the Placebo Arm will start at Visit 1 with a BAY 63-2521 dose of 1.0 mg tid.

To allow a blinded individual dose titration, the titration will be performed with the aid of an IVR-System. At each Titration Visit (with the exception of Visit 1) the investigator needs to decide, based on the patient's systolic blood pressure, if the study medication dose should be modified. The respective decision (increase, maintain or decrease dose) must be entered in the IVR-System that will automatically allocate the right dose in accordance with the respective titration scheme. Afterwards, the investigator will be informed by the system, which of the blinded medication bottles (blinded with respect to the dose) needs to be handed over for the next titration period (starts always with the morning dose).

Independently from the patient's allocation to a specific treatment arm in PATENT-1, the investigators will apply the following blood pressure based titration rules for their dose decision in PATENT-2:

The individual study medication dose of the next titration step will be determined every 2 weeks according to the peripheral SBP measured at trough before intake of the morning dose under consideration of the following algorithm (= individual dose titration scheme):

- If trough SBP ≥95 mmHg, increase dose (+0.5 mg tid).
- If trough SBP 90 - 94 mmHg, maintain dose.
- If trough SBP <90 mmHg without symptoms of hypotension, reduce dose (-0.5 mg tid).
- If any SBP <90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, stop study treatment; restart after 24 hours with reduced dose (-0.5 mg tid).

In general, if the investigator requests an increase or decrease of study medication dose via the IVR-System, the subsequent dose modification will not exceed plus/minus 0.5 mg study medication.

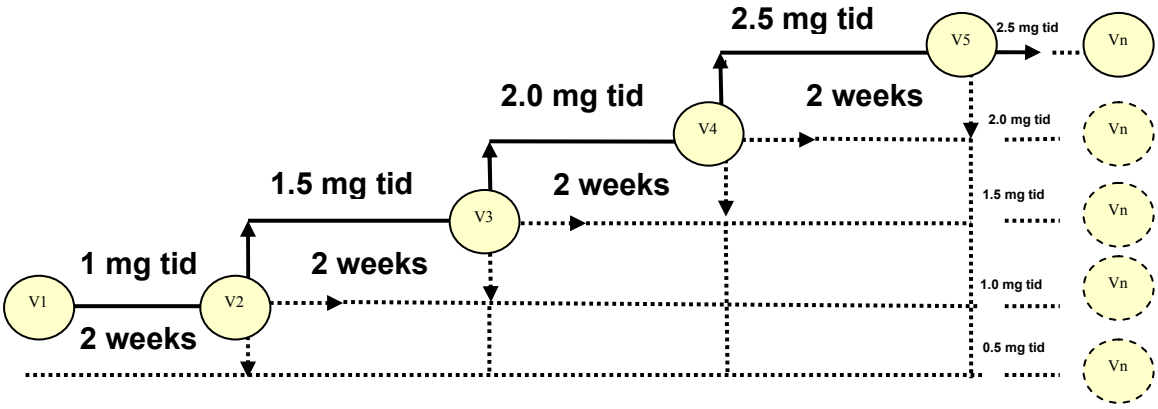
Although the individual dose titration scheme is solely based on the patient's systolic blood pressure, investigators are obliged to consider in addition the patient's well being. Therefore, it is allowed in case of study medication side effects, to suspend a foreseen up-titration step and to maintain the dose.

To request an increase of study medication dose is only possible at the planned study visits Visit 2, Visit 3 and Visit 4.

The Titration Phase ends at day 56 (Visit 5). At this visit the actual dose of the patients will be unblinded by the IVR-System.

Patients from the PATENT-1 Placebo Arm:

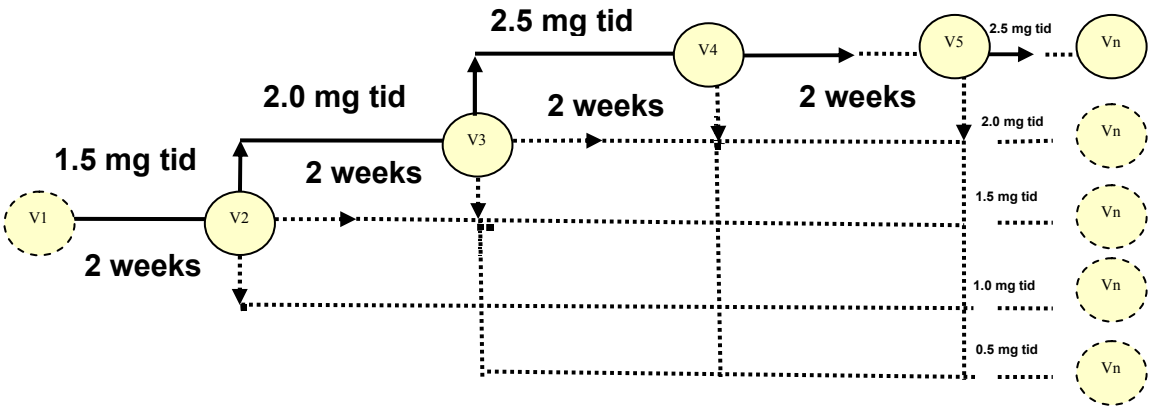
For patients from the PATENT-1 Placebo Arm the starting dose will be 1 mg BAY 63-2521 tid. The individual BAY 63-2521 dose will be titrated every 2 weeks according to the peripheral SBP measured at trough before intake of the next morning dose. At the end of the Titration Phase (Visit 5) patients will have reached BAY 63-2521 doses between 0.5 mg tid and 2.5 mg tid.



Patients from the PATENT-1 1.5 mg Dose Arm:

Patients from the PATENT-1 1.5 mg Dose Arm will enter the extension trial on the same dose which they have received on the last day of PATENT-1 (Visit 6).

- In case that starting dose of PATENT-2 is 1.5 mg tid, the individual optimal BAY 63-2521 dose will be determined every 2 weeks according to the peripheral SBP measured at trough before intake of the next morning dose. At the end of the Titration Phase (Visit 5) respective patients will have reached BAY 63-2521 doses between 0.5 mg tid and 2.5 mg tid.



- In case that starting dose of PATENT-2 is 1.0 mg tid or 0.5 mg tid, the dose cannot be further increased until Visit 5. If the investigator requests a dose increase above that level via the IVR-System, the patient will undergo a sham titration. Nevertheless, in case that the investigator requests a dose decrease (eg for safety reason), dose modifications are possible (i.e. from 1.0 mg tid to 0.5 mg tid), but without a subsequent re-increase before Visit 5. Patients who do not tolerate the lowest BAY 63-2521 (0.5 mg tid) must be withdrawn from the trial (see section 4.3)

Patients from the PATENT-1 Individual Dose Titration Arm:

Patients from the BAY 63-2521 Individual Dose Titration Arm of the PATENT-1 study will enter the extension trial on the same dose which they have received on the last day of PATENT-1 (Visit 6). Although the investigator will apply during the

Titration phase the same titration rules as for the PATENT-1 placebo patients, the individual dose cannot be increased above the dose received at last day of PATENT-1. If the investigator requests a dose increase above that level via the IVR-System, the patient will undergo a sham titration. Nevertheless, in case that the investigator requests a dose decrease (eg for safety reason), dose modifications are possible, but without a subsequent re-increase before Visit 5.

Main-Study Phase (Duration until BAY 63-2521 receives official approval and will be commercially available):

From Visit 5 on (begin of the Main-Study Phase) investigators are allowed to modify the BAY 63-2521 dose in a dose range between 0.5 mg tid and 2.5 mg tid according to the patient's need. In contrast to the Titration Phase, patients may be up-titrated between regular scheduled visits. In this context, investigators have to consider the patient's blood pressure (refer to the individual dose titration scheme), potential BAY 63-2521 side effects and the progression of the underlying Pulmonary Hypertension.

Safety Follow Up Phase (30days)

For all patients stopping study treatment at any time a Safety Follow Up Visit 30 days after stop of study medication intake should be performed.

General Note: Stop of study medication and dose reductions for safety reasons (eg patient suffers from severe symptomatic hypotension) are allowed at <u>any</u> point in time during the Titration and the Main-Study Phase. In case of intended dose reductions the investigator will contact the IVR-System, which can be done independently from any planned study visit, and request a dose reduction (- 0.5 mg study medication).

4.2 Selection of Study Population

4.2.1 Inclusion Criteria

- Patients who have completed 12 weeks of treatment in the double blind trial PATENT-1.

- Patients must have given their written informed consent to participate in the study after having received adequate previous information and prior to any study-specific procedures.

4.2.2 Exclusion Criteria

- Patient's participating in another clinical trial

- Patients who have an ongoing serious adverse event from PATENT-1 that is assessed as related to BAY 63-2521 are not allowed to participate in the extension trial.

- Pregnant women (i.e. positive serum ß-human-chorionic-gonadotropin test or other signs of pregnancy) or breast feeding women, or women with childbearing potential not using a combination of safe contraception methods.

- Patients with a medical disorder, condition, or history of such that would impair the patient's ability to participate or complete this study in the opinion of the investigator or the sponsor.

- Pertinent non compliance with the conditions for the trial or instructions by the investigator during PATENT-1 participation.

- Patients with hypersensitivity to the investigational drug or inactive constituents.

4.3 Removal of Patients from Study

A patient who withdraws is one who discontinued in a clinical study for any reason. Patients may be withdrawn from the study for the following reasons:

- At their own request.
- At the specific request of the sponsor (eg detection of a new significant safety concern related to the study drug).
- Occurrence of adverse events or intercurrent diseases which the investigator judges unacceptable for continuation of participation in the study.
- Occurrence of adverse drug reactions, which have from the investigator's point of view, a negative impact on the patient's individual Risk-Benefit Ratio (Investigators are obliged to reassess the patient's individual Risk-Benefit Ratio on a continuous basis. Factors like anticipated treatment effect, progression of underlying disease, occurrence of side effects and alternative treatment options have to be considered).
- Pertinent non-compliance with the conditions for the trial or instructions by the investigator
- Although not intended, patients may interrupt their intake of study medication due to various reasons (eg hospitalization in a remote hospital without study medication access, safety reasons, side effects).

  - In case that an interruption took place during the Titration Phase and lasts longer than 3 days at a stretch (9 missing doses), it is not allowed to restart the study medication again (respective patients must be withdrawn from the trial). In case of shorter interruptions, it is at the discretion of the investigator if the study medication can be restarted.

  - In case that an interruption took place during the Main Study Phase and lasts longer than 14 days at a stretch, it is not allowed to restart the study

medication again (respective patients must be withdrawn from the trial). In case of shorter interruptions, it is at the discretion of the investigator if the study medication can be restarted.

- In case of pregnancy or breast feeding.
- Participation in another clinical trial
- In case that the patient fulfills one of the stopping criteria specified in Section 4.5.7"Prior and Concomitant Therapy".
- In case no further dose reduction is possible and patient does not tolerate the lowest possible BAY 63-2521 dose (0.5.mg tid).

Patients who withdraw should take part at the Termination Visit and the Safety Follow Up Visit (refer to Section 4.6.3). Moreover, it is the investigator's responsibility, in case of permanent discontinuation of the study medication, to decide together with the patient about the initiation of an alternative treatment.

4.4 Premature Termination of Study/Closure of Centre

The sponsor has the right to close this study, and the investigator/sponsor has the right to close a centre, at any time, although this should occur only after consultation between involved parties. The EC/IRB must be informed.

Reasons to close the study prematurely may be for example:

- If patients can be transferred to another clinical study or treatment program with BAY 63-2521 that ensures that patients who benefit can be treated with the compound until the drug receives official approval and will be commercially available.
- The occurrence of a new relevant safety related finding that has a negative impact on Risk-Benefit Ratio of the compound.

Should the study/centre be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

4.5 Treatments

4.5.1 Treatments to be administered

Test-Drug:	BAY 63-2521
Dosage:	1.0 - 2.5 mg (Individual Dose Titration) [a]
Route of administration:	oral
Time and frequency of administration:	tid[b]

[a]In case of side effects (eg symptomatic hypotension) doses of 0.5 mg tid are allowed

[b]The respective single daily doses should be taken 6-8 hours apart.

(For the individual dose titration refer to Section 4.1.)

4.5.2 Identity of Investigational Product(s)

Study medication will be labeled according to the requirements of local law and legislation. Label text will be approved according to agreed Bayer procedures, and a copy of the labels will be made available to the study site upon request.

BAY 63-2521 will be provided by BAYER Clinical Drug Supplies as tablets at a dose of 0.5mg, 1mg, 1.5 mg, 2mg and 2.5mg. The 5 tablets strengths are identical in appearance.

BAY 63-2521 tablets will be packed in HDPE bottles.

Storage requirements

All investigational drugs used during the trial will be stored at the investigational sites in a place inaccessible to unauthorized personnel, ie a locked cabinet.

4.5.3 Method of Assigning Patients to Treatment Groups

Not applicable

4.5.4 Selection of Doses in the Study

The dose selection for this study was based on the following rationale:

The dose range of 1.0 - 2.5 mg tid was tested in healthy volunteers in a multiple-dose study (# 11260). The highest dose of 2.5 mg tid showed a clear increase in adverse events and further escalation was stopped. A dose of 0.5 mg was identified in healthy volunteers (study 11258) as the no-effect dose while 1.0 mg already showed clinically relevant hemodynamic effects in some patients in the proof of concept study 11874. In the same study a strong lowering of systemic blood pressure was observed in one patient at the highest dose level (5 mg). Therefore 1.0 mg tid was selected as the minimal dose and 2.5 mg tid as the maximum dose for further studies in patients (for further details refer to the Investigator Brochure). In an ongoing Phase II trial (12166) in patients with PAH and CTEPH the respective dose range is tested in combination with an individual dose titration scheme. Based on interim analyses dose between 1.0 mg tid and 2.5 mg tid are effective and safe.

4.5.5 Selection and Timing of Dose for Each Patient

BAY 63-2521 will be administered tid as IR tablets with or without food.

During the eight weeks lasting Titration Phase, patients from the Placebo Arm and from the BAY 63-2521 1.5 mg Dose Arm (applies only to patients who reached the 1.5 mg tid level) of PATENT-1 trial will be up-titrated, if tolerated, up to 2.5 mg BAY 63-2521 tid according to the individual dose titration scheme. In contrast to that, patients from the PATENT-1 Individual Dose Titration Arm will remain on their “optimal dose” from PATENT-1 (for further details refer to Section 4.1).

After an individual BAY 63-2521 dose has been determined all patients will enter the Main-Study Phase (Visit 5). During the Main-Study Phase investigators are allowed to modify the BAY 63-2521 dose according to the patients need. In contrast to the Titration Phase, patients may be up-titrated between regular scheduled visits. The maximum allowed BAY 63-2521 dose is 2.5 mg tid, the minimum 0.5 mg tid (for further details refer to Section 4.1).

4.5.6 Blinding

Titration Phase:

To ensure the blinding of the treatment regimen of PATENT-1 study, the dosing of BAY 63-2521 will be kept blinded during the Titration Phase of PATENT-2.

Main Study Phase:

During the Main-Study Phase the blinding of dosing will be removed and patients will be treated with "open label" medication.

4.5.7 Concomitant Therapy

The intake of the following concomitant medications is not allowed during the Titration Phase and the Main-Study Phase of the trial:

- Specific (eg Sildenafil or Tadalafil) or unspecific Phosphodiesterase Inhibitors (eg Dipyridamole, Theophylline)
- NO donors (eg Nitrates)

Patients, who require respective medications, need to be withdrawn from the study (refer to Section 4.3"Removal of Patients from Study").

Treatment naive patients from PATENT-1

It is not allowed to start a concomitant Endothelin Receptor Antagonists- / Prostacycline Analogues therapy during the Titration Phase of the trial (after Visit 5

concomitant treatment is allowed). Patients, who require a concomitant Endothelin Receptor Antagonists- / Prostacycline Analogues therapy during the Titration Phase need be withdrawn from the study medication (refer to Section 4.3 "Removal of Patients from Study").

Patients pre-treated with an Endothelin Receptor Antagonist or a Prostacycline Analogue from PATENT-1

It is not allowed to modify the concomitant Endothelin Receptor Antagonists- / Prostacycline Analogues therapy (eg dosage, type of medication) during the Titration Phase of the trial (After Visit 5 therapy modifications are allowed). Patients who require a modification of their Endothelin Receptor Antagonists- / Prostacycline Analogues therapy during the Titration Phase need to be withdrawn from the study medication (refer to Section 4.3"Removal of Patients from Study").

Other concomitant therapy

- Due to possible pharmacokinetic interactions between BAY 63-2521 and strong CYP3A4 inhibitors (eg Ketoconazol) concomitant treatment should be applied with caution (eg additional blood pressure monitoring). Such drugs may significantly increase BAY 63-2521 plasma concentrations. In this context, dose reduction of BAY 63-2521 should be considered (eg – 0.5 mg tid), in particular if the patient suffers a clinical relevant decrease in blood pressure (eg systolic blood pressure <90 mmHg with clinical symptoms). For further information refer to the Investigator Brochure.

- Antacids like aluminum hydroxide/magnesium hydroxide (eg Maaloxan ®) should not be taken simultaneously with BAY 63-2521, because a negative impact on the bioavailability of the study drug has been observed (please refer to the Investigator Brochure). To avoid such kind of interaction, antacids should be taken 1 hour after intake of BAY 63-2521 at the earliest.

- Pre- and co-treatment with Omeprazole led to a decrease in BAY 63-2521 bioavailability, indicating a lower bioavailability of BAY 63-2521 in neutral versus acidic milieu (for further information refer to the Investigator Brochure).

- Preliminary inspection of trough and peak plasma concentrations of BAY 63-2521 and BAY 60-4552 (Main BAY 63-2521 metabolite) in a cohort of patients treated with bosentan (n=6) compared to the patients not treated with bosentan (n=66) clearly indicate a decrease in BAY 63-2521/BAY 60-4552 plasma exposure, most probably due to the known CYP3A4 enzyme-inducing effects of concomitant bosentan. However, patients treated with bosentan profited in about the same magnitude in the 6 minute walk test as patients in the therapy naïve cohort did (for further information refer to the Investigator Brochure, trial 12166).

- Participation at a supportive physical training program, defined as a structured exercise and rehabilitation program supervised by a physician and/or a physiotherapist is not allowed during the Titration Phase of the study. However, later on during the Main Study Phase participation at respective training program is allowed, but need to be documented in the electronic CRF.

Concomitant treatment in case of clinical deterioration

In case of a clinically relevant deterioration of the patient's signs or symptoms of pulmonary hypertension the investigator may consider starting an alternative treatment with Endothelin Receptor Antagonists, and/or Prostacycline Analogues, and/or Phosphodiesterase Type-5 Inhibitors or to modify a preexisting Prostacycline Analogues treatment (ie increase of number of daily Iloprost inhalations from 6 to 9, or increase of Iloprost dosage from 2.5 to 5.0 microgram per inhalation, or start of an iv Prostacycline Analogue) at any point in time.

In case that the administration of the treatment is in conflict with the limitations mentioned above, the treatment with the study drug needs to be terminated (refer to Section 4.3"Removal of Patients from Study").

Due to possible synergistic effects on blood pressure Phosphodiesterase Type-5 Inhibitors should only be administered after an appropriate wash out time of 24 hours after last intake of BAY 63-2521.

4.5.8 Treatment Compliance

The packages of the investigational drug have to be brought back to the investigational site, and tablets will be counted for a compliance check. The respective compliance should be between 80% and 120% of calculated dose. Moreover, plasma concentrations will give additional information about patients' compliance.

4.6 Study Variables

The objective of the trial is to assess safety and tolerability of long-term treatment of BAY 63-2521 in patients with symptomatic PAH. In addition, efficacy assessments are included to provide an indication of maintenance of efficacy with long term treatment.

4.6.1 Safety Variables

- Treatment emergent adverse events
- Treatment emergent serious adverse events
- Laboratory parameters
- Blood pressure
- Heart rate
- ECG
- Blood gas parameter

4.6.2 Other Variables

- Change from baseline in 6 Minute Walking Distance
- Change from baseline in NT-pro BNP
- Change from baseline in WHO functional class
- Time To Clinical Worsening
- Change from baseline in Borg CR 10 Scale or Modified Borg Dyspnoea Scale (if patients were enrolled in trial 12934 before amendment 4 approval in their countries) (measured at the end of the 6MWD Test)
- Change from baseline in EQ-5D questionnaire
- Change from baseline in LPH questionnaire
- Change in use of healthcare resources

4.6.3 Assessment Periods

Visit 1 at Day 0

Patients who finalized at Visit 6 the PATENT-1 trial and underwent invasive hemodynamic measurements may remain in the clinic until the next day (optional hospital stay).

At the day after finalization of PATENT-1 trial (= Visit 1 of PATENT -2), patients who fulfill the in/exclusion criteria and signed the informed consent form will be included into PATENT -2.

Please Note: it is not permitted to include a patient into the extension study on the same day of V6 of PATENT -1 (applies even if Visit 6 investigations were performed at two consecutive days).

On Visit 1 prior to first administration of PATENT-2 study medication, blood pressure and heart rate will be measured.

Subsequently, the patients will be allocated via the IVR-System to their individual BAY 63-2521 starting dose. In this context, the IVR-System will consider the patient's treatment arm allocation from the PATENT-1 trial (for further details refer to Section 4.1).

Two to three hours after the first intake of study medication, blood pressure and heart rate measurement will be repeated (for further details about the order of the procedures and the temporal relationship refer to Section 10.1).

Between six to eight hours after first study medication intake, the patients should take the second dose of study medication (second measurement cycle). One to zero hours before intake of second dose of study medication, blood pressure and heart rate will be measured, pharmacokinetic blood samples will be collected and a 12-lead electrocardiogram will be recorded. 2-3 hours after intake of second dose of study medication the blood pressure and heart rate should be measured (for further details about the order of the procedures and the temporal relationship refer to Section 10.1).
In addition to the measurements related to the measurement cycles, Adverse Events will be questioned and documented. Adverse events that occur before intake of first dose of PATENT-2 medication will be allocated to PATENT-1.

The study medication should be taken six to eight hours apart. If during the profile visit the systolic blood pressure falls below 90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, the study medication should be reduced by 0.5 mg tid or if deemed necessary interrupted (see section 4.1).

If there are no medical objections, the patients will be discharged, after the second measurement cycle (blood pressure and heart rate are the main hemodynamic safety parameters that need to be considered). In this context, study medication for the next two weeks will be dispensed.

In case of medical objections (e.g. low blood pressure) patients should be hospitalized until a stable status is achieved (optional hospital stay).

During out-patient treatment until Visit 5, the patients will document the intake of the study medication on a patient diary which they will receive at Visit 1. The patients will return the patient diary to the investigator at each study visit until Visit 5. The exact time points of the last 3 preceding doses before the ambulatory visit will be documented in the CRF.

Note: All blood pressure, heart rate measurements and ECGs should be performed in supine position at rest (for more details refer to Section 4.6.4).

Visit 2 at Day 14 / Visit 3 at Day 28 / Visit 4 at Day 42[a]

[a]deviations from the scheduled visits of ±2 days are permissible

Patients will return to hospital for an ambulatory assessment every 2 weeks without taking their morning dose of study medication. Before the dose of the study medication will be adjusted according to the titration scheme (refer to Section 4.1), blood pressure and heart rate will be measured, blood samples for clinical chemistry, hematology, coagulation parameters, NT-pro BNP will be collected, and a 12-lead electrocardiogram will be recorded.

Subsequently, based on the patient's SBP at trough, an individual decision with respect to a dose modification will be made (for further details refer to Section 4.1). The respective decision will be entered into the IVR-System. Afterwards, under consideration of the IVR-System's reply, the study medication for the next 2 weeks will be dispensed to the patients.

Two to three hours after intake of the morning dose of study medication, blood pressure and heart rate measurement will be repeated (for further details about the order of the procedures and the temporal relationship refer to Section 10.1).

Four to five hours after the intake of the morning dose of study medication 6MWD Test and an evaluation of Borg CR 10 Scale or Modified Borg Dyspnoea Scale (if

applicable) will be performed (for further details about the order of the procedures and the temporal relationship refer to Section 10.1).

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In case that the SBP drops after intake of the morning dose below 90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, the study medication should be reduced by 0.5 mg tid or if deemed necessary interrupted for safety reasons (see section 4.1).

In addition to the measurements related to the cycle of measurements, the patient's concomitant medication will be updated, healthcare resource information will be collected, WHO functional class will be assessed, smoking status and Events of Special Interest as well as Adverse Events will be questioned and documented in the CRF.

The patients will be asked to return all unused study medication and the patient diary from the former visit for a compliance check.

Note: All blood pressure, heart rate measurements and ECGs should be performed in supine position at rest (for more details refer to Section 4.6.4).

Visit 5 at Day 56[a]

[a]deviations from the scheduled visit of ± 2 days are permissible

Patients will return to hospital for an ambulatory assessment without taking their morning dose of study medication. Before the dose of the study medication will be adjusted according to the titration scheme (refer to Section 4.1), blood pressure and heart rate will be measured, blood samples for clinical chemistry, hematology, coagulation parameters, NT-pro BNP, and pharmacokinetics will be collected, and a 12-lead electrocardiogram will be recorded. In addition, the patients will be asked to complete the EQ-5D and the LPH questionnaires.

Subsequently, based on the patient's SBP at trough, an individual decision with respect to dose modifications will be made (for further details refer to Section 4.1). The respective decision will be entered into the IVR-System. Afterwards, under consideration of the IVR-System's reply, the study medication for the next 4 weeks will be dispensed to the patients (Note: from that point in time on, the dose of the study medication will be unblinded).

Two to three hours after intake of the morning dose of study medication, blood pressure and heart rate measurement will be repeated (for further details about the order of the procedures and the temporal relationship refer to Section 10.1).

Four to five hours after the intake of the morning dose of study medication 6MWD Test and an evaluation of Borg CR 10 Scale or Modified Borg Dyspnoea Scale (if applicable) will be performed(for further details about the order of the procedures and the temporal relationship refer to Section 10.1).

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In case that the SBP drops after intake of the morning dose below 90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, the study medication should be reduced by 0.5 mg tid or if deemed necessary interrupted for safety reasons (see section 4.1).

In addition to the measurements related to the cycle of measurements, the patient's concomitant medication will be updated, healthcare resource information will be collected, WHO functional class will be assessed, smoking status and Events of Special Interest as well as Adverse Events will be questioned and documented in the CRF.

The patients will be asked to return all unused study medication and the patient diary from the former visit for a compliance check. The exact time points of the last 3 preceding doses before the ambulatory visit will be documented in the CRF.

Note: All blood pressure, heart rate measurements and ECGs should be performed in supine position at rest (for more details refer to Section 4.6.4).

Visit 6 [a] (changed with amendment 11)

[a] deviations from the scheduled visit of ± 2 days are permissible

Patients will return to hospital for an ambulatory assessment at Visit 6 without taking their morning dose of study medication.

Before the patients take the morning dose of the study medication, a physical examination will be done and the patient's weight recorded, blood pressure and heart rate will be measured, blood samples for clinical chemistry, hematology, coagulation parameters, blood gas analysis, NT-pro BNP will be collected, and a 12-lead electrocardiogram will be recorded. In addition, the patients will be asked to complete the EQ-5D questionnaire.

Subsequently, the investigator will make a decision (needs to be entered into the IVR-System) with respect to the patient's BAY 63-2521 dose for the next treatment period. In this context, the investigator will consider the patient's blood pressure (refer to the individual dose titration scheme Section 4.1), potential BAY 63-2521 side effects and the progression of the underlying Pulmonary Hypertension.

Two to three hours after intake of the morning dose of study medication, blood pressure and heart rate measurement will be repeated (for further details about the order of the procedures and the temporal relationship refer to Section 10.1).

Four to five hours after the intake of the morning dose of study medication 6MWD Test and an evaluation of Borg CR 10 Scale or Modified Borg Dyspnoea Scale (if applicable) will be performed (for further details about the order of the procedures and the temporal relationship refer to Section 10.1).

In case that the SBP drops after intake of the morning dose below 90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, the study

medication should be reduced by 0.5 mg tid or if deemed necessary interrupted for safety reasons (see section 4.1).

In addition to the measurements related to the cycle of measurements, the patient's concomitant medication will be updated, healthcare resource information will be collected, WHO functional class will be assessed, smoking status and Events of Special Interest as well as Adverse Events will be questioned and documented in the CRF.

The patients will be asked to return all unused study medication.

For female patients with child bearing potential a pregnancy test will be performed.

Unblinded study medication will be dispensed for the next 90 days.

Note: All blood pressure, heart rate measurements and ECGs should be performed in supine position at rest (for more details refer to Section 4.6.4).

Visit 7 – Vn (every 90 days)[a*] (added with amendment 11)

[a] deviations from the scheduled visit of ± 14 days are permissible

Patients will return to hospital for an ambulatory assessment without taking their morning dose of study medication.

Before the patients take the morning dose of the study medication, a physical examination will be done and the patient's weight recorded, blood pressure and heart rate will be measured.

Subsequently, the investigator will make a decision (needs to be entered into the IVR-System) with respect to the patient's BAY 63-2521 dose for the next treatment period. In this context, the investigator will consider the patient's blood pressure (refer to the individual dose titration scheme Section 4.1), potential BAY 63-2521 side effects and the progression of the underlying Pulmonary Hypertension.

One hour after the intake of the morning dose of study medication 6MWD Test will be performed.

In case that the SBP drops below 90 mmHg with clinical symptoms of hypotension such as dizziness or presyncope, the study medication should be reduced by 0.5 mg tid or if deemed necessary interrupted for safety reasons (see section 4.1).

In addition to the measurements related to the cycle of measurements, the patient's concomitant medication will be updated, WHO functional class will be assessed and Events of Special Interest as well as Adverse Events will be questioned and documented in the CRF.

The patients will be asked to return all unused study medication.

For female patients with child bearing potential a pregnancy test must be performed locally.

Unblinded study medication will be dispensed for the next 90 days.

Note: All blood pressure, heart rate measurements should be performed in supine position at rest (for more details refer to Section 4.6.4).

Termination Visit

In case the decision has been made to stop the study medication prematurely or if the sponsor announces the official end of the study, a Termination Visit should be performed at the respective point in time or as soon as possible after stop of medication. In general, at the Termination Visit the same efficacy and safety relevant measurements should be performed as at Visit n (Exception: no pregnancy test needs to be performed). In particular, every effort should be made to perform the 6MWD Test. Deviations need to be documented in the electronic CRF.

Safety Follow Up Visit 30 days after stop of study medication [a]

[a] deviations from the scheduled visit of +5 days are permissible

For all patients who stopped the study medication either at the official end of the trial or prematurely, a Safety Follow-Up Visit 30 days after last study medication intake has to be performed.

At the Safety Follow Up Visit the following assessments should be performed: physical examination including determination of patient's weight, blood pressure and heart rate measurement (changed with amendment 11).

For female patients with child bearing potential a pregnancy test must be performed locally. Moreover, adverse events will be questioned and the concomitant medication pages in the electronic CRF will be updated.

Note: All blood pressure and heart rate measurements should be performed in supine position at rest (for more details refer to Section 4.6.4).

4.6.4 Observations and Measurements

(Visits and numbering updated with amendment 11)

Laboratory Parameters

All blood samples will be analyzed in a central laboratory until V6.

Laboratory procedures will be described in a separate laboratory manual.

At the latest at the end of the study when all planned analyses are completed, all blood samples will be destroyed.

- ***Hematology, clinical chemistry, coagulation test***

Hematology (white blood cell differential count, erythrocytes, hemoglobin, hematocrit, platelets)

Coagulation tests (PTT, INR)

Clinical chemistry (AST, ALT, ALP, GGT, GLDH, CK, lipase, CHE, creatinine, urea, uric acid, total bilirubin, total protein, serum albumin, sodium, potassium, calcium, phosphate)

Note: Calcium and phosphate will only be analyzed for patients who were included under amendment 8 of study 12934.

Frequency: At every visit until V6 (except Visit 1)

- ***NT-proBNP***

Frequency: At every visit until V6 with the exception of Visit 1 and Safety Follow Up Visit

Changes from baseline NT-proBNP will be considered as a secondary efficacy endpoint in PATENT-1. To ensure the blinding of the treatment regime of PATENT-1, the results of the NT-pro BNP determinations at PATENT -2 Visits 2-5 will not be forwarded to the investigators before lock of the PATENT-1 database. In contrast to that the results of the NT-pro BNP determination at PATENT-2, Visit 6 will be forwarded to the investigators.

- ***Pregnancy testing***

Methodology: Determination of ß- human chorionic gonadotropin in blood serum or urine

Frequency: Will be performed centrally at Visit 6 and locally at least at every Main-Study Phase Visit (V7-Vn) and at Safety Follow Up Visit. Based on country specific regulations further measurements might be performed.

In addition to the above mentioned serum ß- human chorionic gonadotropin tests, a urine test will be performed at Visit 6 of PATENT-1 study if the patient will

participate in the extension study. Female patients with childbearing potential can be enrolled into the extension study based on the result of this test.

Blood gas analysis

SaO_2(%)

PaO_2(mmHg

$PaCO_2$(mmHg)

Supplemental oxygen "yes" or "no" (If the patient receives supplemental oxygen the amount will be recorded in the electronic CRF in liter per minute)

Methodology: Capillary or arterial blood gas analysis

Frequency: At V6

Blood pressure and heart rate measurement

Blood pressure and heart rate will be measured after the patient has been at rest for 10 minutes in a supine position. The same arm is always used for these measurements.

Methodology: Non invasive measurement preferably with a mercury sphygmomanometer or a validated electronic device in accordance with published guidelines (eg American Heart Association. Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. Hypertension 2005;45;142-161)

Frequency: At every visit

Point in time: For details refer to appendix 10.1

Electrocardiography

For deriving the ECGs the patient should always be in supine position. The ECGs should be derived after a resting period of 15 min. The ECGs for the study will be

transferred electronically and assessed centrally. In addition, the investigator will print-out the ECGs locally and review the ECGs for potential AEs.

ECG procedures will be described in a separate manual.

Methodology: 12 lead ECG

Frequency: Every visit until V6

Point in time: For details refer to appendix 10.1

Exercise Testing / 6 Min Walking Distance (6MWD) Test

The 6 Min Walking Distance Test will be performed in accordance with the American Thoracic Society Guideline.

Methodology: During the Titration Phase the test has to be performed by a second person who is not involved in the process of study drug titration and is unaware of the immediate reaction of the patient's blood pressure and heart rate after dosing. This person will enter the test results on a separate work sheet and a different person (could be the same person as involved in titration) will enter them into the electronic CRF.

Frequency: At every visit with the exception of Visit 1 and Safety Follow-Up Visit

Point in time: For details refer to section 4.6.3and appendix 10.1For further details refer to Section 10.4.

Borg CR 10 Scale® or Modified Borg Dyspnoea Scale

The Borg CR 10 Scale or Modified Borg Dyspnoea Scale (if patient was enrolled before 12934 Amendment 4 approval in their country) will be measured together with 6MWD Test.

Methodology: The test will be explained to the patients before starting the 6MWD test. The patients will be asked to rank their exertion at the end of the 6MWD test. During the Titration Phase the test has to be performed by a person who is not involved in the process of study drug titration and is unaware of the immediate reaction of the patient's blood pressure and heart rate after dosing. This person will

enter the test results on a separate work sheet and a different person(could be the same person as involved in titration) will enter them into the electronic CRF.

In context with 12934 protocol amendment 4 the "Modified Borg Dyspnoea Scale" was replaced by the Borg CR 10 Scale®. For consistency reason, patients who were enrolled before approval of 12934 protocol amendment 4 in their country must use the "Modified Borg Dyspnoea Scale" throughout the main and the extension study.

Frequency: At every visit until V6 with the exception of Visit 1 and Safety Follow Up Visit

Point in time: Immediately after the 6MWD Test

For further details refer to section 4.6.3and Section 10.5.

Determination of WHO Functional Class

The patient's functional class will be determined according to the WHO classification.

Methodology: During the Titration Phase the evaluation has to be performed by a second physician who is not involved in the process of study drug titration and is unaware of the immediate reaction of the patient's blood pressure and heart rate after dosing. This physician will enter the test results on a separate work sheet and a different person(could be the same person as involved in titration) will enter them into the electronic CRF.

Frequency: At every visit with the exception of Visit 1 and Safety Follow-Up Visit

For further details refer to Section 10.6.

Events of Special Interest

Time To Clinical Worsening

The first occurrence of the following events of special interest need to be documented in the electronic CRF and will be considered for the calculation of the combined endpoint "Time To Clinical Worsening":

- Death (all-cause mortality)
- Heart/lung transplantation
- Atrial septostomy (AS)
- Hospitalization due to persistent worsening of Pulmonary Hypertension[a,b]
- Start of new PH specific treatment (Endothelin Receptor Antagonists, Prostacycline Analogues, Phosphodiesterase Type-5 Inhibitors) or modification of a preexisting Prostacycline Analogues treatment (ie increase of number of daily Iloprost inhalations from 6 to 9, or increase of Iloprost dosage from 2.5 to 5.0 microgram per inhalation, or start of an iv Prostacycline Analogue) due to worsening Pulmonary Hypertension.
- Persistent decrease of more than 15 % from baseline or more than 30% compared to the last study related measurement in 6MWD due to worsening pulmonary hypertension[b].

  The persistence of the decrease has to be confirmed by a second measurement performed after 14 days. In case that the period between first occurrence of the event and the Termination Visit is less than 14 days, the decrease needs to be confirmed at the Termination Visit.
- Persistent worsening of functional class due to deterioration of Pulmonary Hypertension[b]:

Patients who deteriorate from class II or III to class IV: The persistence of worsening has to be confirmed by a second measurement performed after 14 days. In case that the period between first occurrence of the event and the Termination Visit is less than 14 days, the decrease needs to be confirmed at the Termination Visit.

Other Events of Special Interest

The first occurrence of the following event of special interest needs to be documented in the electronic CRF, but will not be considered for the calculation of the combined end point "Time To Clinical Worsening":

- Initiation of a supplemental long-term oxygen therapy (= oxygen application for more than 30 days at a stretch) or persistent modification of a pre-existing supplemental long term oxygen therapy (ie need for a persistent increase of the amount of delivered oxygen for more than 30 days) due to worsening pulmonary hypertension.[b]

[a]Transient deteriorations of clinical status requiring hospitalization, treatable by eg short time application of iv diuretics, positive inotropic agents or non-invasive ventilation and allowing patients discharge within 48 hours are not considered as persistent with respect to the event of special interest definition.

[b]In case of clinical deterioration the investigator has to assess carefully if the deterioration of the patient's condition (eg worsening functional class) is related to the underlying pulmonary hypertension or can be explained by an alternative cause (eg transient infection, musculoskeletal disease, surgical or medical intervention other than PH related, exacerbation of a concomitant lung disease, lacking compliance of medication intake). Only persistent clinical deteriorations caused by the underlying pulmonary hypertension will be considered as events of special interest.

Frequency: At every visit with the exception of Visit 1 and Safety Follow-Up Visit the investigator must check if an event of special interest has occurred in the period between start and termination of the study drug treatment. With respect to each subcategory (eg "hospitalization due to persistent worsening of pulmonary

hypertension") it is only necessary to document the first occurrence of such an event in the electronic CRF.

HEOR measurements

EQ-5D, LPH

EQ-5D and LPH are health questionnaires that evaluate the patient's health status and quality of life.

Methodology: Questionnaires need to be self-completed by the patients

EQ-5D Frequency: V5 and V6 only

LPH Frequency: Visit 5 only.

For further details refer to Section 10.7and Section 10.8.

Use of healthcare resources

For health economic calculations (see section 4.6.2) investigators need to collect information about the use of healthcare resources. This includes information about:

- Visits at healthcare professionals (eg type of healthcare professional visited)
- Hospitalizations and rehabilitation procedures (eg start and stop date of hospitalization)
- Diagnostic and therapeutic procedures (eg type of diagnostic procedure)

Frequency: From Visit 2 until Visit 6 investigators need to collect on an ongoing basis information about health care resources that the patient uses since intake of the first dose of PATENT-2 study medication. The respective information will be recorded in the electronic CRF.

4.6.5 Drug Concentration Measurements

For investigation of drug exposure and potential relationships to drug effects, plasma concentrations of BAY 63-2521 (and its main metabolite BAY 60-4552)

will be determined at the times given in the Trial Flow Chart (see Section 10.1) and in the Appendix 10.2using a sparse sampling approach in all participating patients.

Frequency: Visit 1 and Visit 5

BAY 63-2521 and metabolite M-1 (BAY 60-4552) concentrations in plasma will be measured by a validated HPLC-MS/MS method. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of QC samples will be reported together with concentrations in unknown samples in the MRR of this study. Drug concentrations are calculated from the chromatographic raw data in accordance with current Bayer guidelines (see Section 9). The data are evaluated using CCW software in its most recently released version.

4.7 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with GCP guidelines. Each centre will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the case report forms (CRF) for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

4.8 Documentation

An electronic data capture system will be used in this study (e-CRF). All entries made in the e-CRF must be verifiable against source documents. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained until notification given by the sponsor for destruction.

5. ETHICAL AND LEGAL ASPECTS

5.1 Ethics Committee (EC) or Institutional Review Board (IRB)

Documented approval from appropriate Ethics Committee(s)/IRBs will be obtained for all participating centers/countries prior to study start, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the Ethics Committee approval must be obtained and also forwarded to the sponsor. The Ethics Committees must supply to the sponsor, upon request, a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations.

5.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation form, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior EC/IRB/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the EC/IRB/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

5.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/ notifications, where required, must be in place and fully documented prior to study start.

5.4 Patient Information and Consent

A core Information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the ECs/IRB written approval/favorable opinion of the written Informed Consent Form and any other written information to be provided to patients. The written approval of the EC/IRB together with the approved Patient Information/Informed Consent Forms must be filed in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the patient should be documented appropriately in the patient's files.

5.5 Insurance

All patients participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

5.6 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the case report form, and if the patient name appears on any other document (eg, pathologist report), 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 patients will be informed in writing that representatives of the sponsor, EC/IRB, or Regulatory Authorities

may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients' records to be identified.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical and Analytical Plans

The aim of this long-term extension study is primarily the assessment of safety and tolerability, so no single primary variable has been identified. Patient numbers will be determined by those completing the PATENT-1 study and willing to enter the PATENT-2 study. As the extension is of an open label design with no comparator group, all statistical analyses will be descriptive. The summary tables will be presented for the overall group of patients, and also split by previous treatment groups in PATENT-1. Baseline will be week 0 in PATENT-1 (changed with amendment 11).

Statistical analysis of safety variables

For the analysis of safety, all patients entering PATENT-2 and receiving BAY 63-2521 will be included. For treatment-emergent adverse events, ECG and laboratory test abnormalities, frequency counts of incidence rates during the extension period (changed with amendment 11) and incidence per 100 patient years at risk will be presented. For ECG and laboratory test measurements, vital signs, changes from baseline will also be summarized using descriptive methods (mean, standard deviation, median, minimum, maximum).

Statistical analyses of other variables

Patients will be included in these analyses if they are included in the safety analysis and have both baseline and post-baseline data available for the variable being analyzed. For Time To Clinical Worsening, incidence tables of the overall rate and the particular event leading to clinical worsening will be presented, together with the Kaplan-Meier survival curve. Change in Borg CR 10 Scale or Modified Borg Dyspnoea Scale and functional class at each visit will be summarized by frequency counts. Patients with data on the Borg CR10 Scale and patients with data on the Modified Borg Dyspnoea Scale will be combined in the statistical analysis. Change in 6MWD, NT pro-BNP, EQ-5D and LPH at each visit will be summarized using descriptive methods.

The study endpoints related to health care resource utilization will be summarized using appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics. It is envisaged that all endpoints will be measured either on a semi-continuous scale or have ordered categories, and so exploratory statistical tests will be ANCOVA or the stratified Wilcoxon test, depending on the distribution.

Statistical summaries (changed with amendment 11)

It is planned to produce two formal statistical summaries. The first will be when all patients enrolled in the long-term extension at Last Patient First Treatment 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.

6.2 Determination of Sample Size

Not applicable

7. ADVERSE EVENTS

7.1 Contraindications/Warnings/Precautions/Interactions/Undesirable Effects

The potential for drug-drug pharmacodynamic interactions, leading to an exaggerated vasodilatation and excess blood pressure drop should always be considered if patients are treated concomitantly with other drugs with vasoactive properties.

Concomitant treatment with specific or unspecific Phosphodiesterase Inhibitors leading to higher production and decreased degradation of cGMP is not allowed during the trial (refer to Section 4.5.7"concomitant therapy").

Due to possible pharmacodynamic interactions, BAY 63-2521 must not be administered together with NO donors/nitrates (refer to Section 4.5.7 "concomitant therapy").

Due to possible pharmacokinetic interactions between BAY 63-2521 and strong CYP3A4 inhibitors (eg Ketoconazol) concomitant treatment should be applied with caution (eg additional blood pressure monitoring). Such drugs may significantly increase BAY 63-2521 plasma concentrations. In this context, dose reduction of BAY 63-2521 should be considered (eg – 0.5 mg tid), in particular if the patient suffers a clinical relevant decrease in blood pressure (eg systolic blood pressure <90 mmHg with clinical symptoms). For further information refer to the Investigator Brochure.

Antacids like aluminum hydroxide/magnesium hydroxide (eg Maaloxan ®) should not be taken simultaneously with BAY 63-2521, because a negative impact on the bioavailability of the study drug has been observed (please refer to the Investigator Brochure). To avoid such kind of interaction, antacids should be taken 1 hour after intake of BAY 63-2521 at the earliest.

Pre- and co-treatment with Omeprazole led to a decrease in BAY 63-2521 bioavailability, indicating a lower bioavailability of BAY 63-2521 in neutral versus acidic milieu (for further information refer to the Investigator Brochure).

Preliminary inspection of trough and peak plasma concentrations of BAY 63-2521 and BAY 60-4552 (Main BAY 63-2521 metabolite) in a cohort of patients treated with bosentan (n=6) compared to the patients not treated with bosentan (n=66) clearly indicate a decrease in BAY 63-2521/BAY 60-4552 plasma exposure, most probably due to the known CYP3A4 enzyme-inducing effects of concomitant bosentan. However, patients treated with bosentan profited in about the same magnitude in the 6 minute walk test as patients in the therapy naïve cohort did (for further information refer to the Investigator Brochure, trial 12166).

The BAY 63-2521 clearance was increased in smokers compared to non-smokers in a previous trial in patients with pulmonary hypertension (IMP 12166; see IB for more information). Therefore, patients should report their smoking status to the investigator.

Due to the pharmacological mode of action of a guanylate cyclase stimulator, treatment with BAY 63-2521 may unmask existing Pulmonary Veno-Occlusive disease (PVOD), leading to pulmonary congestion and subsequent pulmonary edema. Given the severity of the underlying disease this effect may be life-threatening. Clinical symptoms of uncovering of a PVOD may occur weeks to months after start of treatment with BAY 63-2521. Should signs of pulmonary edema occur when BAY 63-2521 is administered, the possibility of associated PVOD should be considered and BAY 63-2521 should be discontinued immediately.

The following undesirable effects of the compound have been observed in clinical trials: decrease in blood pressure (in healthy volunteers mainly diastolic blood pressure), postural hypotension, dizziness, syncope, increase in heart rate, nasal congestion, feeling hot, headache, dyspepsia, nausea, vomiting, gastritis, flushing, and hyperhidrosis (refer to the Investigator Brochure). Most of the undesirable

effects are caused by the vasodilators mode of action of the drug. The effects of the compound on smooth muscles may lead to gastrointestinal symptoms (eg dilation of the esophageal sphincter with heartburn, esophagitis and dysphagia; diarrhea; constipation).

In addition, the possibility of hitherto unforeseen side effects and allergic reactions to drugs, which can result in severe damage and even death, must always be considered.

Any new, relevant information about adverse drug reactions of BAY 63-2521 will be given to the patients (verbally and in writing).

Inadvertent overdosing with total daily BAY 63-2521 doses of 9 mg (13 and 32 days), 22.5 mg (14 and 15 days), and 25 mg (2 days) was reported for 5 subjects, which was tolerated without any adverse events (for further information refer to the Investigator Brochure).

Overdosage following administration of BAY 63-2521 should be treated as clinically indicated. There is no known antidote to BAY 63-2521.

Due to the pharmacological profile of BAY 63-2521, cardiovascular effects as described in the Investigator Brochure (Section 5.3.3.3) may be expected in case of overdose.

If symptoms develop after the investigational drug has been administered, any therapy that becomes necessary has to be guided by the predominant symptoms. Patients have to remain under medical supervision until all relevant adverse effects have subsided. If adverse events occur, the investigator has to decide whether or not to remove the patient from the trial (refer to Section 4.3). Emergency drugs and equipment has to be available to provide any treatment, which may become necessary.

In case of overdose, general measures to prevent absorption (eg, gastric lavage, activated charcoal) should to be taken.

Note: To keep the investigators up-to-date regarding any kind of safety relevant information the Development Core Safety Information (DCSI), which is an appendix of the Investigators' brochure, will be updated at regular intervals during the conduct of the trial. New versions of the investigator's brochure will be made available to the investigators without delay.

7.2 Adverse Event Monitoring

Patients must be carefully monitored for adverse events. Adverse events should be assessed in terms of their seriousness, severity, and relationship to the study drug.

7.3 Adverse Event Definitions

7.3.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered with a pharmaceutical product. The adverse event does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An adverse event occurring in the course of the use of a drug product in professional practice.
- An adverse event occurring from an overdose whether accidental or intentional.
- An adverse event occurring from drug abuse.
- An adverse event occurring from drug withdrawal.

- An adverse events where there is a reasonable possibility that the event occurred purely as a result of the patients participation in the study (eg adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during Wash-Out Phase) must also be reported as an adverse event even if it is not related to the investigational product.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an adverse event if it is already reflected as a data point captured in the **electronic** CRF (adapted with amendment 11). If, however, the event fulfills any of the criteria for a "serious" adverse event, it must be recorded and reported as such.

7.3.2 Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

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

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

- The admission results in a hospital stay of less than 12 hours.

OR

- The admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study).

OR

- The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Any hospitalization 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) will not be considered as a serious adverse event. In this context, a RHC procedure is considered as a procedure and not as an adverse event (changed with amendment 11).

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

Important medical event: Any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "WHO Adverse Reaction Terminology – Critical Terms List. These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

7.3.3 Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator Brochure (refer to Section 8.1. "Development Core Safety Information" of the Investigator Brochure). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. For example, an event more specific or more severe than described in the Investigator Brochure would be considered "unexpected". Specific examples would be; (a) acute renal failure as a labeled adverse event with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

7.3.4 Relationship of Adverse Event to Investigational Product

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of 'No' would include:

1. The existence of a clear alternative explanation eg, mechanical bleeding at surgical site.

OR

2. Non-Plausibility eg, the patient 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 adverse event is associated with the use of the investigational drug.

Factors to be considered in assessing the relationship of the adverse event to study drug 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 discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Patient's response after drug discontinuation (de-challenge) or patients response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment: The other drugs the patient is taking or the treatment the patient 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 test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual patient's pharmacodynamics should be considered.

7.3.5 Severity of the Adverse Event

The following classification should be used:

The severity of adverse events should be graded as follows:

Mild – usually transient in nature and generally not interfering with normal activities.
Moderate – sufficiently discomforting to interfere with normal activities
Severe – prevents normal activities.

7.3.6 Adverse Event Documentation

All adverse events occurring in the period between the patient has signed the informed consent and until 30 days after definite stop of study medication must be fully recorded in the patient's case record form. However, in case that more than 30 days after stop of study medication an adverse event occurred that has been considered as related by the investigator, this needs to be documented too.

Documentation must be supported by an entry in the patient's file. A laboratory test abnormality considered clinically relevant, eg, causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

7.4 Reporting of Serious Adverse Events/Pregnancy

Serious adverse events (SAEs), including laboratory test abnormalities fulfilling the definition of serious, that occurred in the period between the patient signed the informed consent and until 30 days after definite stop of study medication must immediately (within 24 hours of the investigator's awareness) be reported to the person detailed in the study file. A serious adverse event form must also be completed within 24 hours of the investigator's awareness and forwarded to the designated person as detailed in the study file. For reporting of serious adverse events an electronic adverse event as provided in the electronic CRF shall be used. If the electronic CRFis not available due to technical problems (eg information cannot be entered into the electronic CRF) serious adverse events need to be reported within 24 hours of the investigator's awareness by using print out forms (e.g. via fax). Each serious adverse event must be followed up until resolution or stabilization by submission of updated reports to the designated person.

If Global Pharmacovigilance requests supportive documents in context with a serious adverse event report (eg autopsy report, hospital report) these documents shall be forwarded to the person detailed in the study file (eg via fax).

The same rules apply to serious adverse events that occurred more than 30 days after definite stop of study medication, if the investigator considers them as related to the study medication.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to Bayer within the same timelines as a serious adverse event on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

7.5 Reporting of Safety Related Events of Special Interest

For this trial the following safety related event of special interest has been defined:

- Syncope

Any syncope has to be reported as "important medical event" (see section 7.3.2) and therefore as Serious Adverse Event (SAE) to the sponsor within 24 hours of becoming aware of the event.

8. USE OF DATA AND PUBLICATION

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, whilst free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the

results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

9. REFERENCES

Investigator Brochure: BAY 63-2521

American College of Chest Physicians. Diagnosis and Management of Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Chest 2004; 126; 7-10s

American Heart Association. Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. Hypertension 2005;45;142-161

American Thoracic Society. ATS Statement: Guidelines for Six-Minute Walk Test. American Journal of Respiratory and Critical Care Medicine 2002; Vol 166. pp 111-117

10.APPENDICES

10.1 Study Flow Chart

Tabular Schedule of Study Procedures										
Study Phase	PATENT-1	PATENT-2								
		Treatment Phase (Duration until BAY 63-2521 receives official approval and will be commercially available)							Safety- Follow-Up Phase (30 days + 5)	
		Titration Phase (8 weeks)					Main-Study Phase			
Blinding of study medication	Blinded treatment	Blinded with respect to the BAY 63-2521 dose					Unblinded			
Visit	V 6 of PATENT-1	V 1 [g]	V 2	V 3	V 4	V 5	V6	V7- V n (every 90 days)	Termination Visitc	Safety-Follow Up-Visit
Day	- 1	0	14±2	28±2	42±2	56±2	84±2	174±14 Vn+14	-	30 + 5
Week	-	0	2	4	6	8	12	24- n	-	-
In-patient hospitalization - optional	X[a]	X[b]	-	-	-	-		-	-	-
Informed consent	X									
Patient's Weight	X						X	X	X	X
Concomitant Medication	X		X	X	X	X	X	X	X	X
Collection of smoking status[h]	X		X	X	X	X	X			
Physical examination	X						X	X	X	X
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X	X

Tabular Schedule of Study Procedures

Study Phase	PATENT-1	PATENT-2								
		Treatment Phase (Duration until BAY 63-2521 receives official approval and will be commercially available)							Safety- Follow-Up Phase (30 days + 5)	
		Titration Phase (8 weeks)					Main-Study Phase			
Blinding of study medication	Blinded treatment	Blinded with respect to the BAY 63-2521 dose					Unblinded			
Visit	V 6 of PATENT-1	V 1 [g]	V 2	V 3	V 4	V 5	V6	V7- V n (every 90 days)	Termination Visitc	Safety-Follow Up-Visit
Day	- 1	0	14±2	28±2	42±2	56±2	84±2	174±14 Vn+14	-	30 + 5
Week	-	0	2	4	6	8	12	24- n	-	-
Blood gas analysis	X						X			
WHO functional class[d]	X		X	X	X	X	X	X	X	
6 MWD Test[d]	X		X	X	X	X	X	X	X	
Borg CR 10 Scale[d] or Modified Borg Scale[f]	X		X	X	X	X	X			
EQ-5D Questionnaire	X					X	X			
LPH Questionnaire	X					X				
Use of healthcare resources	X		X	X	X	X	X			
Standard lab. blood sampling	X		X	X	X	X	X			

Tabular Schedule of Study Procedures

Study Phase	PATENT-1	PATENT-2								
		Treatment Phase (Duration until BAY 63-2521 receives official approval and will be commercially available)							Safety- Follow-Up Phase (30 days + 5)	
		Titration Phase (8 weeks)					Main-Study Phase			
Blinding of study medication	Blinded treatment	Blinded with respect to the BAY 63-2521 dose					Unblinded			
Visit	V 6 of PATENT-1	V 1 [g]	V 2	V 3	V 4	V 5	V6	V7- V n (every 90 days)	Termination Visitc	Safety-Follow Up-Visit
Day	- 1	0	14±2	28±2	42±2	56±2	84±2	174±14 Vn+14	-	30 + 5
Week	-	0	2	4	6	8	12	24- n	-	-
NT-pro BNP	X		X	X	X	X	X			
PK blood sampling	X	X				X				
12-lead electrocardiogram	X	X	X	X	X	X	X			
Pregnancy test (if applicable)	X[e]						X	X[i]		X[i]
Dispense study medication		X	X	X	X	X	X	X		
Drug accountability	X		X	X	X	X	X	X	X	
Collection of patient Diary			X	X	X	X				
Event of special interest evaluation	X		X	X	X	X	X	X	X	X
Adverse event reporting	X[f]	X[f]	X	X	X	X	X	X	X	X

Flowchart updated (last with amendment 11)
Indexes:

[a]According to hospital routine, patients may be hospitalized for one day after the performance of invasive hemodynamic measurements.

[b]Patients will be discharged if there is no medical objection. Blood pressure monitoring and heart rate are the main hemodynamic safety parameters that need to be considered.

[c]A Termination Visit will only be performed in case of premature stop of study medication or if the sponsor announces the official end of the study. In such case, generally the same measurements and procedures should be performed as at Main-Study Visits (V7 – Vn). In particular, every effort should be made to perform the 6MWD Test. Deviations, particularly from the scheduled points in time need to be documented in the electronic CRF.

[d]During the Titration Phase these test have to be performed by a second person (for WHO functional class assessment a second physician) who is not involved in the process of study drug titration and is unaware of the immediate reaction of the patient's blood pressure and heart rate after dosing. This person will record the test results on a separate work sheet and a different person (could be the same person as involved in titration) will enter them into the electronic CRF
For consistency reason, patients who were enrolled in trial 12934 before approval of protocol amendment 4 in their country must use the "Modified Borg Dyspnoea Scale" throughout the main and the extension study (for further details see section 4.6.4).

[e]At Visit 6 of PATENT-1 a urine (if the patient will participate in the extension study) and a serum pregnancy test should be performed. Female patients with childbearing potential can be enrolled into the extension study based on the results of the urine test

[f]Adverse events that occur before intake of first dose of PATENT-2 medication will be allocated to PATENT-1.

[g]It is not permitted to include a patient into the extension study on the same day of V6 of PATENT-1 study (applies even if Visit 6 investigations were performed at two consecutive days).

[h]Patients will be asked if their smoking habits has changed since the previous visit and the results will be recorded in the electronic CRF

[i] Test to be done locally

Visit Details

Day			**Day 0**					
Visit 1			**First cycle of measurements** [c] **First study medication dose intake**			**Second cycle of measurements** [c] **Second study medication dose intake**		
Order of procedures	Starting point of procedures	Time interval (h)	00 ≥-01 <00	00 **00**[c]	00 ≥02 <03	00 ≥-01 <00	00 **00**[c]	00 ≥02 <03
↓	Blood pressure, heart rate[b]		X			X		
	12-lead ECG[a,b]					X		
	Pharmacokinetic blood sample[b]					X		
	Administration of BAY 63-2521[b]			**X**			**X**	
	Blood pressure, heart rate[b]				X			X
	Discharge from ward							X

[a]Single ECG

[b]The point in time when the respective procedures are performed will be documented in the case report form.

[c]The respective single daily doses of study medication should be taken 6-8 hours apart.

Ambulatory Visits **Visit 2 – Visit 5**			**Cycle of measurements**			
Order of procedures	Starting point of procedures	Time interval (h)	00 ≥-01 <00	00 **00**	00 ≥02 <03	00 ≥04 <05
↓	Blood pressure, heart rate[c]		X			
	12-lead ECG[a,c]		X			
	Pharmacokinetic blood sample[c, d]		X			
	Administration of BAY 63-2521[c]			**X**		
	Blood pressure, heart rate[c]				X	
	6 MWD test[b,c]					X
	Borg CR 10 Scale(or Modified Borg Dyspnoea Scale)[b,c]					X

[a]Single ECG

[b]During the Titration Phase these test have to be performed by a second person who is not involved in the process of study drug titration and is unaware of the immediate reaction of the patient's blood pressure and heart rate after dosing. This person will record the test results on a separate work sheet and a different person (could be the same person as involved in titration) will enter them into the electronic CRF.

[c]The point in time when the respective procedures are performed will be documented in the case report form.

[d]Pharmacokinetic blood sample will only be collected at Visit 5

Ambulatory visits V6			**Cycle of measurements**			
Order of procedures	Starting point of procedures	Time interval (h)	00 ≥-01 <00	00 00	00 ≥02 <03	00 ≥04 <05
↓	Blood pressure, heart rate [b]		X			
	12-lead ECG [a, b]		X			
	Administration of BAY 63-2521 [b]			X		
	Blood pressure, heart rate [b]				X	
	6 MWD test [b]					X
	Borg CR 10 Scale (or Modified Borg Dyspnoea Scale) [b]					X

[a] Single ECG (updated with amendment 11)

[b] The point in time when the respective procedures are performed will be documented in the case report form.

Ambulatory visits V7 – Vn, Termination Visit			**Cycle of measurements**		
Order of procedures	Starting point of procedures	Time interval (h)	00 ≥-01 <00	00 **00**	00 ≥00 <01
↓	Blood pressure, heart rate[a]		X		
	Administration of BAY 63-2521[a]			**X**	
	6 MWD test[a]				X

[a] The point in time when the respective procedures are performed will be documented in the case report form (updated with amendment 11).

10.2 Pharmacokinetic Sampling

The number of samples taken for the assessment of pharmacokinetics has been optimized to take the minimum amount of blood.

PK samples will be analyzed under the responsibility of the Institute of Clinical Pharmacology, BAYER AG, Wuppertal, Germany.

Visit 1

Point in time**:** -01-00 hours before administration of the second dose of BAY 63-2521 (Day 1)

V 5

At this study visit the patients should present themselves to the hospital without taking the morning dose of BAY 63-2521. During the visit the pharmacokinetic sample should always be taken at trough before administration of the morning dose of study medication.

Point in time: -01-00 hours before administration of BAY 63-2521 morning dose

Sample collection, processing and storage

The blood samples will be collected in specific tubes which will be provided by the central laboratory. Further details on collection, labeling, storage and shipping of samples are provided in a separate laboratory manual.

At the latest at the end of the study when all planned analyses are completed, all PK samples will be destroyed.

10.3 Blood Gas Analysis

Blood gases are to be obtained from the arterial blood or from arterialized capillary blood. All samples should be obtained with the patient resting in a sitting or supine position for at least 10 min. If

possible no supplementary oxygen should be given during the resting period and while blood samples are drawn. If the patient requires oxygen, care should be taken that all samples are drawn with the same flow of oxygen throughout the study whenever possible. Printouts from the analyzer have to be stored in the patient file and the measured values have to be transferred into the electronic CRF.

Blood gas measurement
Actual time
Date
SaO_2 (%)
PaO_2 (mmHg)
$PaCO_2$ (mmHg)
Supplemental oxygen “Yes” or “No”
If “Yes”,amount of supplemental O_2 (l/min)

10.4 6 Min Walking Distance (6MWD) Test

The 6MWD Test must be performed in accordance with the American Thoracic Society Guideline (American Thoracic Society. ATS Statement: Guidelines for Six-Minute Walk Test. American Journal of Respiratory and Critical Care Medicine 2002; Vol 166. pp 111-117)

According to the guideline, the 6MWD Test should be carried out indoors, along a long, flat, straight, enclosed corridor with hard surface that is seldom traveled. The walking course should be preferably 30 m in length but not less than 25 meters (longer walking courses should be shortened to 30 m). The length of the corridor and turnaround points should be marked.

Patients will be instructed to walk alone, not run, from one end to the other end of the walking course, at their own pace, while attempting to cover as much ground as possible in 6 min.

During the walk, patients are allowed to stop, lean against the wall and rest, but should resume walking as soon as they feel able to do so.

A “warm-up” period before the test should not be performed. The patients should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.

Investigators should not walk with the patients. Moreover, only standardized phrases for encouragement must be used during the test. To allow reproducibility, standardized phrases should be used every minute according to the following pattern:

- After the first minute, tell the patient the following (in even tones): “You are doing well. You have 5 minutes to go.”
- When the timer shows 4 minutes remaining, tell the patient the following: “Keep up the good work. You have 4 minutes to go.”
- When the timer shows 3 minutes remaining, tell the patient the following: “You are doing well. You are halfway done.”
- When the timer shows 2 minutes remaining, tell the patient the following: “Keep up the good work. You have only 2 minutes left.”
- When the timer shows only 1 minute remaining, tell the patient: “You are doing well. You have only 1 minute to go.”

To reduce the variability of the 6MWD Tests, it is of utmost importance that the eligibility-test, the baseline-test and all following tests are performed under the same conditions (truncated with amendment 11):

- Patients, who used walking aids already at the eligibility-test and the baseline-test (eg cane, walker), need to use the same walking aids at every subsequent 6MWD Test.

For quality reasons, the inhalation of supplemental oxygen and the use of walking aids during the 6MWD Tests must be documented in the CRF.

In case that a patient has never performed a 6MWD Test, a familiarization test should be performed during the Pre-Treatment Phase. To avoid any interactions, it is not permitted to perform the familiarization test on the same day as the eligibility 6MWD Test.

10.5 Borg CR 10 Scale® or Modified Borg Dyspnoea Scale

In context with 12934 protocol amendment 4 the "Modified Borg Dyspnoea Scale" was replaced by the Borg CR 10 Scale®. For consistency reason, patients who were enrolled before approval of 12934 protocol amendment 4 in their country must use the "Modified Borg Dyspnoea Scale" throughout the main and the extension study.

The Borg CR 10 Scale or the Modified Borg Dyspnoea Scale will always be measured in conjunction with the 6MWD Test.

The Borg CR 10 Scale or the Modified Borg Dyspnoea Scale will be explained to the patients before starting the 6MWD Test (questionnaires and instructions will be provided in local language). Patients will be asked to rank their exertion at the end of the 6MWD Test. If a patient has problems to understand the principles of rating, an attempt should be made to explain the principles in a neutral and unpersuasive manner.

The test result will be entered on same work sheet as the 6MWD Test result Later on the results will be transferred into the electronic CRF.

10.5.1 Borg CR 10 scale and test instructions

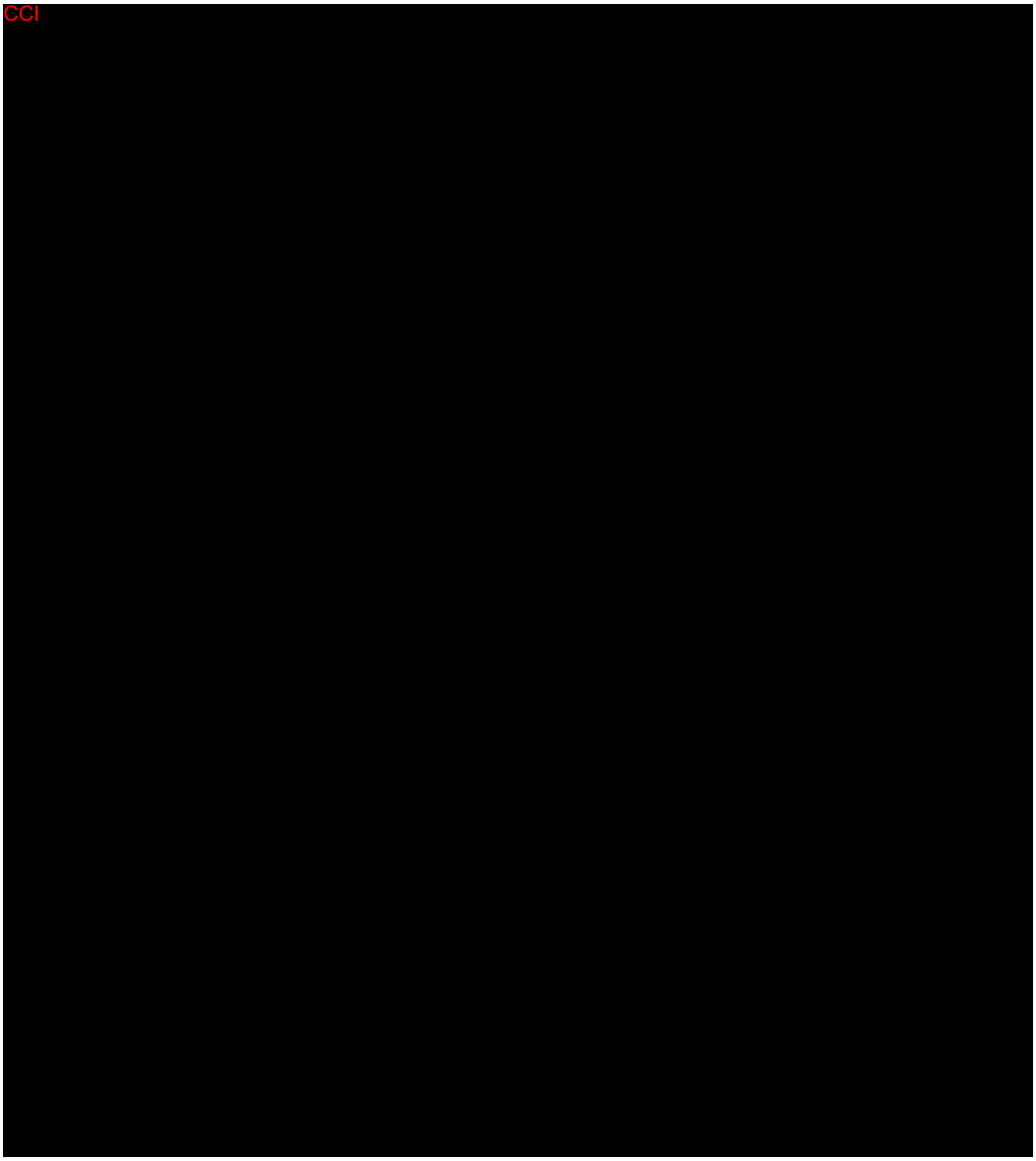
CCI

[redacted]

CCI

[redacted]

CCI

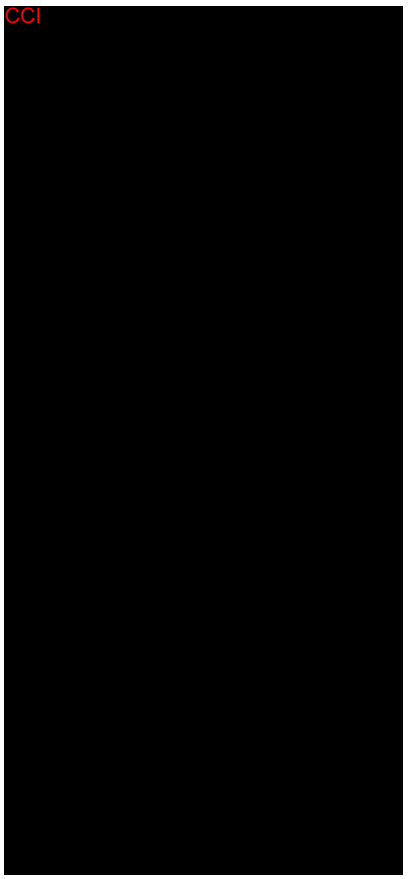


CCI

10.5.2 Modified Borg Dyspnoea Scale

CCI

CCI



CCI [redacted]

10.6 WHO functional class

The patient's functional class will be determined by using the WHO classification (Class I- IV / refer to American College of Chest Physicians. Diagnosis and Management of Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Chest 2004; 126; 7-10s):

I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near syncope.

II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.

III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.

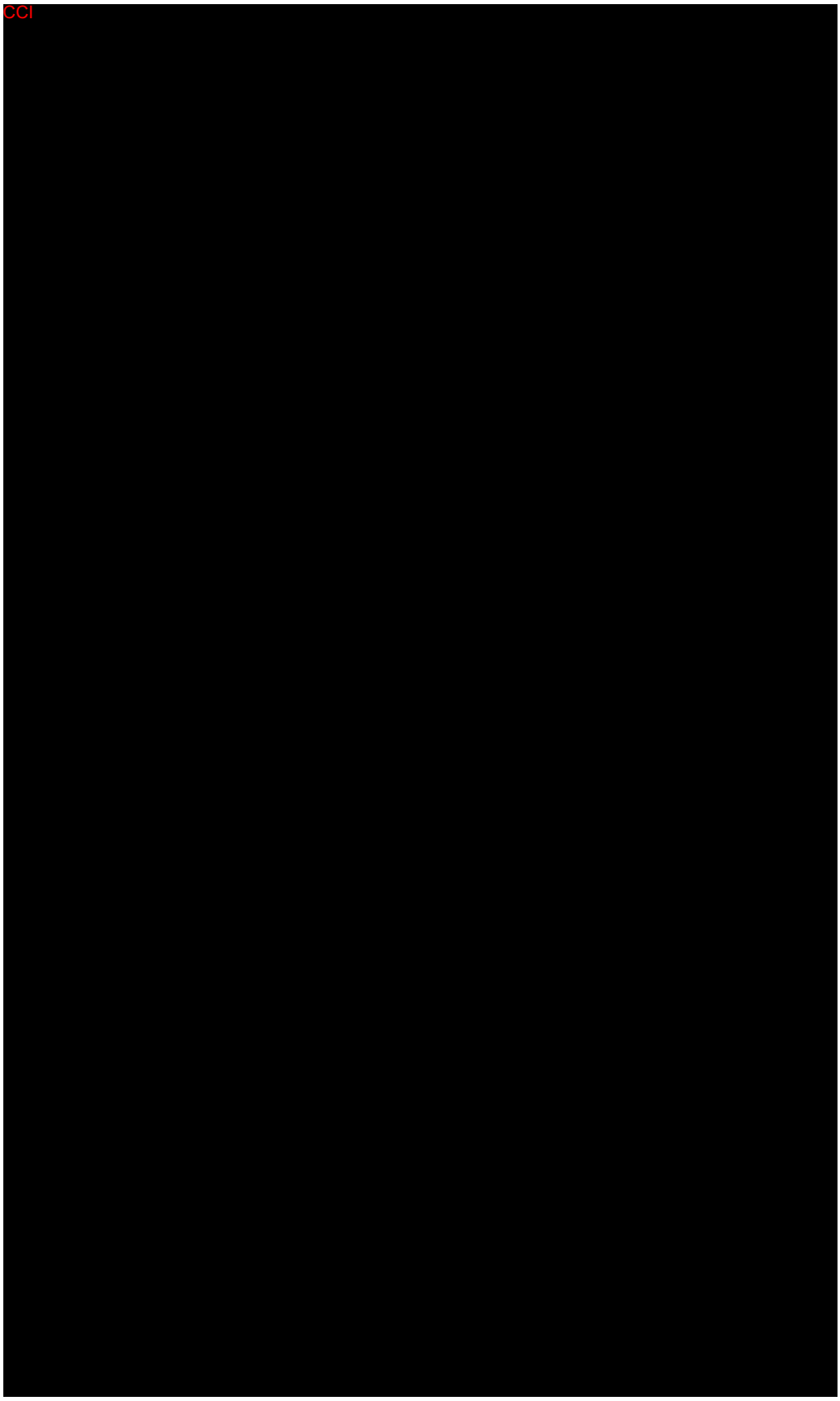
IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

10.7 EQ-5D

CCI [redacted] The EQ-5D is a self-report questionnaire and needs to

be completed by the patient (questionnaires will be provided in local language). However, if the patient has problems completing the questionnaire, an attempt should be made to explain the questions in a neutral and unpersuasive manner.

After the patient has filled in the questionnaire, the questionnaire is transferred to the study personnel, who will enter the content into the electronic CRF.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[redacted]

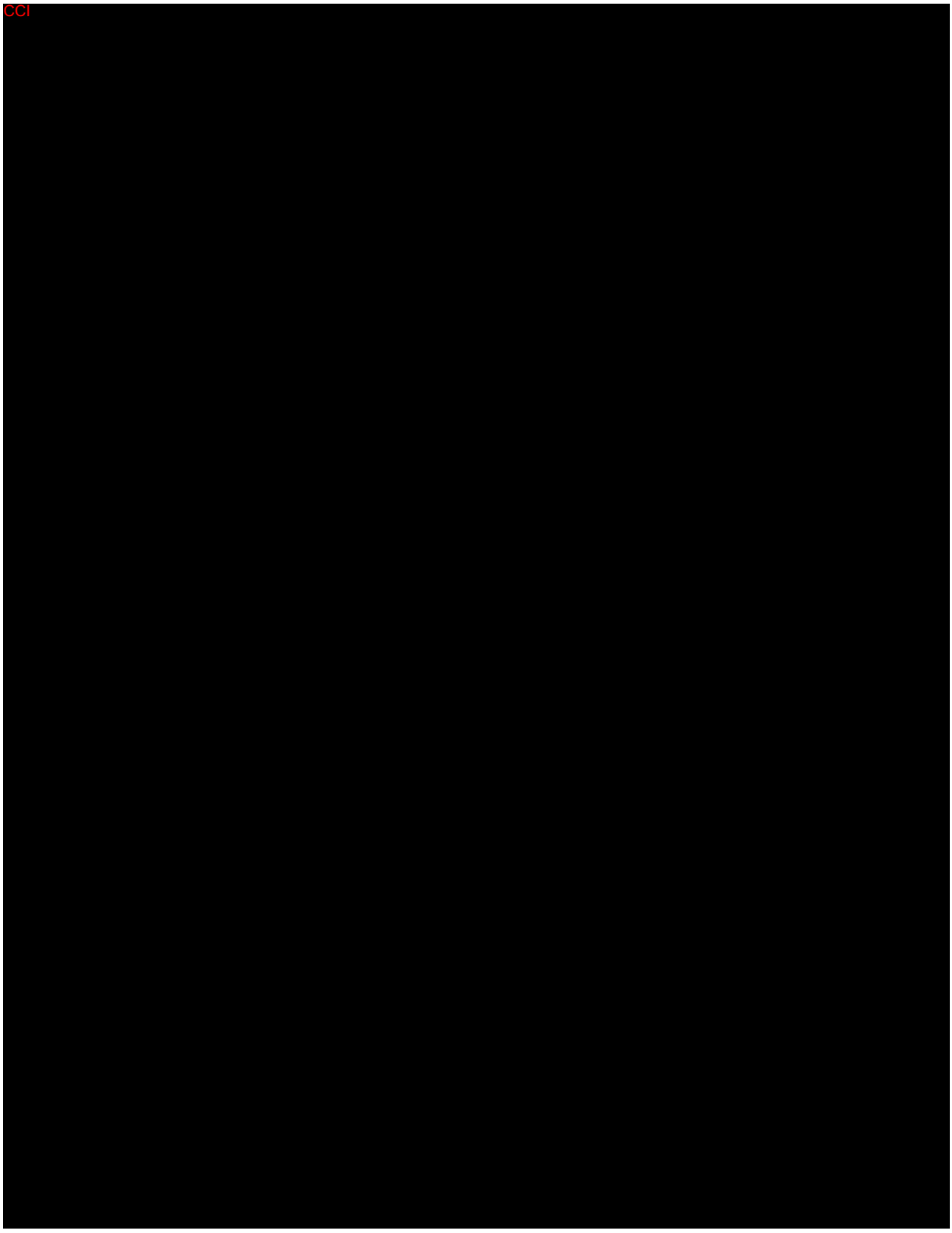
10.8 Living with Pulmonary Hypertension questionnaire (LPH)

CCI [redacted]

The LPH is a self-report questionnaire and needs to be completed by the patient (questionnaires will be provided in local language). However, if the patient has problems completing the questionnaire, an attempt should be made to explain the questions in a neutral and unpersuasive manner.

After the patient has filled in the questionnaire, the questionnaire is transferred to the study personnel, who will enter the content into the electronic CRF.

CCI [redacted]


CCI

10.9 Role of the Steering Committee (SC)

The Steering Committee has the overall scientific responsibility of the study. It will guide the trial in all aspects of safety and efficacy and has to assure that all relevant information coming from the sponsor (e.g. from the Global Pharmacovigilance department), from other study committees (e.g. from the Data Monitoring Committee) and from the investigators will thoroughly be reviewed and all relevant decisions with regard to the conduct will be taken in due time. In particular the Steering committee has the following responsibilities:

- Primary responsibility for designing the study
- Primary responsibility for the content of protocol amendments
- To ensure a scientifically sound and safe conduct of the study
- To decide on Data Monitoring Committee recommendations together with the sponsor
- Primary responsibility for the final study report

10.10 Role of the Data Monitoring Committee (DMC)

It is the main responsibility of the Data Monitoring Committee (DMC) to protect the safety of the patients participating in the BAY 63-2521 phase III program. In this context, the DMC will regularly review accumulating study data with the responsibility to provide an independent recommendation on the advisability of continuing the study as planned.

The DMC will conduct its reviews based on unblinded data summaries. During the course of the trial the DMC and the SC should closely interact and alert each other in order to assess all safety relevant information. The DMC should also closely interact with the sponsor´s Global Pharmacovigilance department.

In case of unacceptable safety profile, the DMC can recommend to stop the trial. However, the final decision will be made by the SC together with the sponsor.

DMC will stop when all patients are on open label dose of Riociguat (changed with amendment 11).

For further details refer to the DMC Charter.