Actelion Pharmaceuticals Ltd*
(a Janssen Pharmaceutical Company of Johnson & Johnson)

Statistical Analysis Plan

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, group sequential, adaptive, Phase 3 study with open-label extension period to assess the efficacy and safety of selexipag as an add-on to standard of care therapy in subjects with inoperable or persistent/recurrent after surgical and/or interventional treatment Chronic Thromboembolic Pulmonary Hypertension

SELECT: SELExipag in inoperable or persistent/recurrent Chronic Thromboembolic pulmonary hypertension

Protocol AC-065B302; Phase 3

JNJ-67896049 (selexipag)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	27 September 2021	Not Applicable	Initial release
2	26 October 2021	1. Updates in Section 5.3: • 5.3.3.2.1: Main Imputation Approach "All observed PVR values will be used to derive the imputed values." updated to "Observed PVR values (excluding those PVR values beyond the analysis time window) will be used to derive the imputed values." • 5.3.3.3.1: Main Analysis Addition of "PVR values beyond the analysis time window will also be imputed using the rules defined in Section 5.3.3.2.1, for subjects who are alive and do not have a post baseline value." • 5.3.3.3.3: Supplementary Analysis 2 Updated from "A further analysis will be conducted using observed data only ie, with no imputation, on the HES, to assess the impact of delayed/missing RHC assessments (assumed to be mainly due to COVID-19) on the analysis of PVR at Week 20." to "A further analysis will be conducted using observed data only (including the delayed PVR values beyond the analysis time window) ie, with no imputation, on the HES, to assess the impact of delayed/missing RHC assessments (assumed to be mainly due to COVID-19) on the analysis of PVR at Week 20."	
		2. Update to footnote in Table 19.	Clarification on handling of specific subgroup analyses.
3	11 July 2022	Abbreviated CSR: reduction/change in scope.	Early termination of the study.

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analyses for the abbreviated clinical study report (CSR) of study AC-065B302. Plans for the analysis and reporting of the double-blind (DB) and open-label (OL) periods will be presented.

On 13 December 2021, the results of the planned interim analysis (IA) on the primary endpoint, pulmonary vascular resistance (PVR) versus placebo at Week 20, were presented to the Independent Data Monitoring Committee (IDMC) by the independent Statistical Support Group (SSG). This planned IA did not demonstrate efficacy on the primary endpoint; hence the IDMC recommended to stop the study for futility (see IDMC Charter Section 7 for details). Based upon the recommendation from the IDMC, the sponsor decided to discontinue the study on 14 December 2021; this was communicated to sites on 15 December 2021.

Following the decision to prematurely terminate the study it was decided that an abbreviated CSR would be produced to summarize key efficacy and safety data only. Such analyses are described in this SAP. The study team remains blinded to the results of the IA conducted by the SSG, until database lock occurs for the abbreviated CSR planned analyses. A separate SAP or SAP(s) (not described here) will be developed for all other analyses.

This SAP is referring to the documents listed in Table 2 and contains definitions of analysis sets, key derived variables, and statistical methods for the analysis of efficacy and safety for the AC-065B302 SELECT study.

Table 2: Study Documents

Document	Date, Version
Study Protocol Amendment 3 [EDMS-RIM-265242, 2.0]	29 September 2020, Final Version 4
IDMC Charter [EDMS-RIM-348405, 1.0]	23 February 2021, Final Version 4.0

The SAP for the SSG and open session of IDMC regular data review meetings is provided in a separate document. A further IDMC SAP for closed sessions is written and maintained by the SSG (see IDMC Charter Section 8 for details).

Titles, mock-ups, and programming instructions for all statistical output (tables, listings, and figures) are provided in a separate data presentation specifications (DPS 1) document.

Source data for the analyses are provided as Statistical Analysis Software (SAS®) data sets according to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM). All descriptive or formal statistical analyses will be performed using SAS® (Version 9.4), unless otherwise specified.

1.1. Objectives and Endpoints

Section 2 and Section 6 of the study protocol outline the objectives and endpoints of the study, respectively.

Changes to protocol planned analyses are described in see Section 6.2 Appendix 2.

1.2. Study Design

This is a prospective, multi-center, randomized, DB, placebo-controlled, add-on to standard of care, parallel-group, group sequential, adaptive Phase 3 study with an OL extension period (Figure 1).

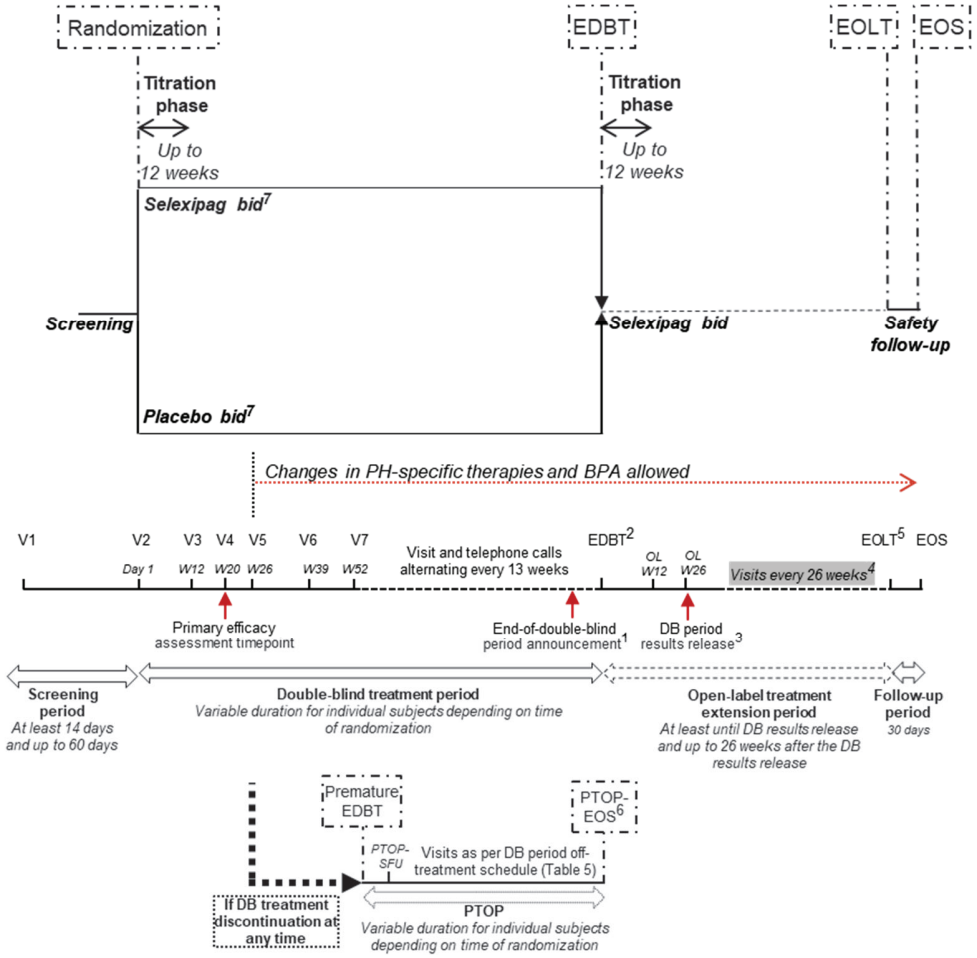
Up to 280 subjects will be randomized in a 1:1 ratio to receive either selexipag or placebo during the DB period. Subjects completing the DB period will enter the OL extension period and will receive selexipag (see protocol Section 5.1.3.2 for OL treatment initiation).

Subjects will be recruited in two sequential cohorts. Approximately the first 90 randomized subjects will constitute the hemodynamic cohort and, in addition to the overall study assessments, will undergo a right heart catheterization (RHC) (and left heart catheterization [LHC], if needed) at Week 20 (see protocol Section 7.2.3.1.2). The remaining subjects will constitute the non-hemodynamic cohort, who do not require a post-baseline hemodynamic assessment. Both cohorts are combined for the evaluation of secondary (and exploratory) efficacy endpoints, which do not require a post-baseline hemodynamic assessment.

Treatment allocation will be stratified by (see Section 1.2.5.1.2):

- Treatment with PH-specific therapies (ie, endothelin receptor antagonists [ERAs], and/or phosphodiesterase type 5 [PDE-5] inhibitors or soluble guanylate cyclase [sGC] stimulators [riociguat]: one versus two versus naive [naive capped at 40%]) and
- CTEPH population: inoperable (with or without BPA) versus persistent-recurrent after PEA (including PEA followed by BPA).

Figure 1: Study design



bid = twice daily; BPA = balloon pulmonary angioplasty; DB = double-blind, EDBT = End-of-Double-Blind-Treatment; EOLT = End-of-Open-Label-Treatment; EOS = End-of-Study; FU = follow-up, OL = open-label; PH = pulmonary hypertension; PTOP = post-treatment observation period, SFU = safety follow-up; V = visit; W = week.

(1) End-of-double-blind period announcement: when the overall target number of clinical worsening events has been reached, or earlier following recommendation of the IDMC or sponsor's decision.
(2) EDBT visit to occur within 4 weeks of End-of-double-blind period announcement [see (1)].
(3) DB period results to be released approx. 6 months after last EDBT/PTOP-EOS visit.
(4) *Variable duration of OL treatment extension period for individual subjects depending on time randomization, with visits every 26 weeks ONLY FOR SUBJECTS WHO WERE TRANSITIONED TO THE OL TREATMENT EXTENSION PERIOD BEFORE IMPLEMENTATION OF THE AC-065B302 PROTOCOL AMENDMENT 2.*
(5) EOLT visit to occur any time within 26 weeks of the DB period results release [see (3)].
(6) PTOP-EOS visit to occur within 4 weeks of End-of-double-blind period announcement [see (1)].
(7) For subjects with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking a moderate CYP2C8 inhibitor (eg, clopidogrel, deferasirox, teriflunomide), the dosing frequency of study treatment is once daily (qd), which must be taken in the morning [see protocol Section 5.1.9].

At the time of the decision to terminate the study, a total of 128 subjects had been randomized, of whom 91 subjects were randomized in the hemodynamic cohort.

1.2.1. Study Periods

In both hemodynamic and non-hemodynamic cohorts, the study comprises the following periods: screening period, treatment periods, follow-up period, and post-treatment observation period (see Figure 1).

Screening period: Lasts at least 14 days and up to 60 days; starts with the signature of the Informed Consent Form (ICF) and ends with the subject's randomization at Visit 2, Day 1.

The two treatment periods are:

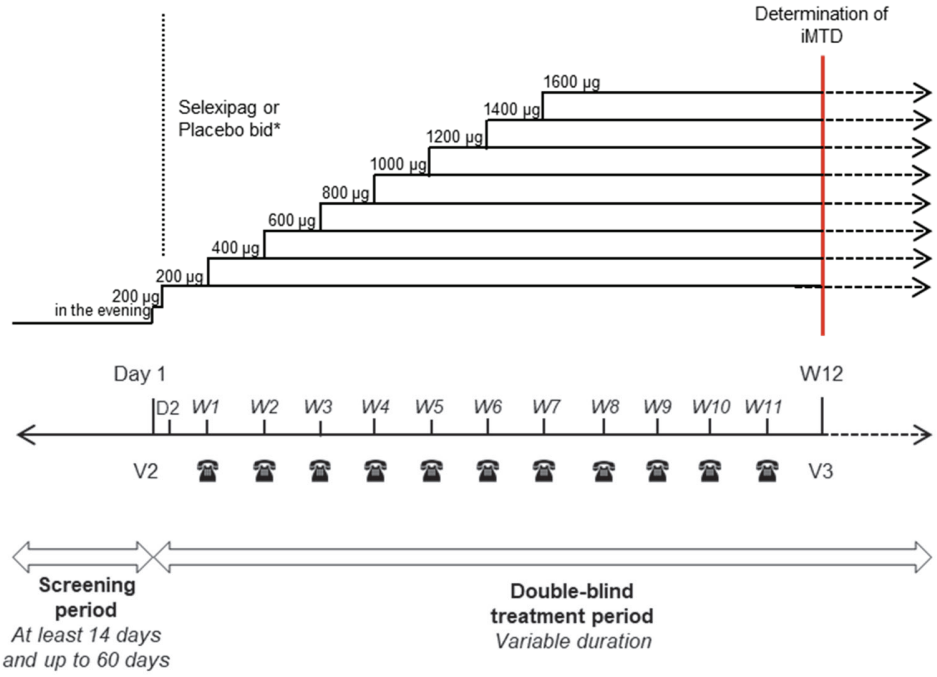
- **Double-blind treatment period**: Starts with the administration of the first dose of DB study treatment in the evening of the day of randomization (Visit 2) (except in case of once daily [qd] dosing, where the subjects must take the study treatment in the morning) and with a titration phase of up to 12 weeks (see Figure 2). It ends on the day of the last dose of DB study treatment with the EDBT visit. The EDBT visit will occur shortly (within 4 weeks) after the announcement of end-of-double-blind period, for all subjects who have not discontinued study treatment prematurely. The end-of-double-blind period will be announced by the sponsor when the overall target number of clinical worsening events has been reached, or earlier following the recommendation of the IDMC or sponsor's decision (see protocol Section 8.3).
- **Open-label treatment period**: For subjects who have completed the DB treatment period, the OL treatment extension period will last at least until the DB period results release and up to a maximum of 26 weeks after the DB period results release or upon sponsor's decision for early termination. It starts with the first dose of the OL study treatment in the evening of the day of the last dose of DB study treatment, ie, the EDBT visit (except in case of qd dosing, where the subjects must take the study treatment in the morning). All subjects will have a titration phase of up to 12 weeks. It ends with the End-of-Open-Label-Treatment (EOLT) visit that occurs any time within 26 weeks of the DB period results release or upon sponsor's decision for early termination.

Follow-up period: Starts on the day after the last dose of OL study treatment and ends 30−35 days thereafter with the safety follow-up (SFU) telephone call.

Post-treatment observation period (PTOP): Subjects who prematurely discontinue the DB treatment period will enter the PTOP and will continue to perform the visits and assessments as scheduled until the PTOP-EOS visit, provided the subject's consent for this limited participation in the study has not been withdrawn.

Up to the point of the decision to prematurely terminate the study, there were 15 subjects who had transitioned to the OL treatment period, under study protocol amendment 1, version 2. Subjects who were randomized from study protocol amendment 2, version 3 onwards or transitioned to protocol amendment 2, version 3, during DB treatment, remained in the DB treatment period or PTOP.

Figure 2: Titration phase



bid = twice daily; D = day; iMTD = individual maximum tolerated dose; V = visit; W = week. ☎ = weekly telephone calls.

* For subjects with moderate hepatic impairment (Child-Pugh B) or who are concomitantly taking a moderate CYP2C8 inhibitor (eg, clopidogrel, deferasirox, teriflunomide), the dosing frequency of the study treatment is once daily (qd), which must be taken in the morning [see protocol Section 5.1.9].

If the dose regimen is not well tolerated or symptoms cannot be fully managed with symptomatic treatment, the duration of the titration step can be prolonged to two weeks (see protocol Section 5.1.3).

1.2.2. Study Duration

The study starts with the first act of recruitment (ie, first ICF signed) and ends with the last telephone call or visit of the last subject.

The subjects will be treated in the DB treatment period for a variable duration depending on each subject's individual date of randomization. The actual duration depends on actual accrual rate and clinical worsening event rate (see protocol Section 10.6.3) as well as recommendations of the IDMC (see protocol Section 10.4) and sponsor's decision (see protocol Section 8.3). Following the decision to prematurely terminate the study, the actual duration is determined by the date that decision was communicated to sites, plus the time for each randomized subject's EDBT visit and subsequent SFU phone call.

Subjects who complete the DB treatment period will enter the OL treatment extension period, which lasts at least until the release of results from the DB treatment period and up to a maximum of 26 weeks after the DB period results release, or upon sponsor's decision for early termination.

Subjects who were transitioned to the OL treatment extension period before implementation of the AC-065B302 Protocol amendment 2: Those subjects transitioned to the OL treatment extension period after 52 weeks of DB treatment will be treated in the OL treatment period for a variable duration depending on each subject's individual date of randomization. They will remain in the

OL treatment extension period until EOLT occurring anytime within 26 weeks of the DB period results release (see Figure 1 and Table 4), or upon sponsor's decision for early termination.

Subjects who prematurely discontinue the DB study treatment will enter a PTOP and cannot enter the OL treatment extension period (see protocol Section 3.1.1.4).

For an individual subject, the EOS visit is defined as the last telephone call/visit performed in the study (see protocol Section 8.1).

1.2.3. Study Visits and Assessment Schedule

Visit and assessment schedules are presented in Table 3 for the DB treatment period, Table 4 for the OL treatment period, and Table 5 for the PTOP (protocol Tables 3, 4 and 5, respectively).

Table 3: Double-blind treatment period: visit and assessment schedule

PERIODS	Name	SCREENING	DOUBLE-BLIND TREATMENT										
	Duration	At least 14 days and up to 60 days											
VISITS	Number	1	2	Titration phase	3	4	5	6	7	TC every 26 weeks[10]	Visit every 26 weeks[10]	EDBT	U1, 2, 3, etc.
	Name	Screening/ Rescreening	Randomization		Week 12	Week 20	Week 26	Week 39	Week 52	Week 65, 91, 117, etc.	Week 78, 104, 130, etc	Announced[11] or for premature EDBT within 7 days after last DB dose	Unscheduled visit[1]
	Time	Day −60 to Day −14	Day 1	Weekly from Week 1 to Week 11 (± 3 days)	Day 85 (± 7 days)	Day 141 (± 7 days)	Day 183 (± 7 days)	Day 274 (± 7 days)	Day 365 (± 7 days)	Day 456, 638, 820 etc. (± 7 days)	Day 547, 729, 911, etc. (± 7 days)		Any time
Informed consent		X											
Eligibility		X	X										
Medical history/Demographics		X											
Previous/concomitant therapy		X	X	X	X	X	X	X	X	X	X	X	W
Physical examination*		X	X		X	X	X	X	X		X	X	W
Height		X											
Vital signs (BP, HR), Weight		X	X		X	X	X	X	X		X	X	W
Local 12-lead ECG		X							X			X	(X)
RHC (and LHC, if needed)		X[2]				X[3,4]							(X)
V/Q scan, PA, CTPA, MRA[5]		X											
Hematology and clinical chemistry**		X	X[6]		X	X	X	X	X		X	X	(X)
Serum pregnancy test**		X											(X)
Urine pregnancy test*			X	← monthly (±7 days) →									(X)
6MWT/BDI or Borg CR10®		X	X										
Post-dose 6MWT/BDI or Borg CR10®[3]					X	X	X	X	X		X	X	W
WHO FC		X	X		X	X	X	X	X		X	X	W
Actigraphy**		X	← Every day, 24 hours per day →										
PAH-SYMPACT®**,[7]		X	X		X	X	X	X					
EQ-5D-5L, WPAI©: GH**		X	X		X	X	X	X	X				
CGI-S			X		X	X	X	X	X		X	X	
CGI-C					X	X	X	X	X		X	X	
NT-proBNP**		X	X		X	X	X	X	X		X	X	(X)
Dose titration				☎[8]	iMTD								
DB Study treatment dispensing/return		–	X		X	X	X	X	X		X	X	
SAEs/AEs[9]		X	X	X	X	X	X	X	X	X	X	X	W

6MWT = 6-minute walk test; AE = adverse event; BDI = Borg dyspnea index; Borg CR10® = Borg category-ratio 10 Scale®; BP = blood pressure; BPA = balloon pulmonary angioplasty; CGI-C = Clinician Global Impression of Change; CGI-S = Clinician Global Impression of Severity; CT = computed tomography; CTPA = computed tomography pulmonary angiogram; DB = double-blind; ECG = electrocardiogram; eCRF = electronic Case Report Form; EDBT = End-of-Double-Blind-Treatment; EOS = end of study; EQ-5D-5L = Euro Quality of Life-5Dimension-5-Level; FC = functional class; HR = heart rate; IDMC = Independent data management committee; iMTD = individual maximum tolerated dose; LHC = left heart catheterization; MRA = magnetic resonance angiography; NT-proBNP = N-terminal pro b-type natriuretic peptide; PA = pulmonary angiography; PAH-SYMPACT® = Pulmonary arterial hypertension symptoms and impact questionnaire; PEA = pulmonary endarterectomy; RHC = right heart catheterization; SAE = serious adverse event; V/Q scan = ventilation/perfusion scan; WHO = World Health Organization; WPAI©: GH = Work Productivity and Activity Impairment Questionnaire: General Health. ☎ = telephone call.

1 Unscheduled visits may be performed at any time during the DB treatment period. Assessments (marked with an '(X)' or 'W') are performed at the discretion of the investigator.
If the unscheduled visit is performed due to increase from baseline in WHO FC, deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD, suspicion of clinical worsening (as defined in protocol Section 7.1.2), any change in dose, initiation of PH-specific therapies, or up-titration of DB study treatment beyond Week 12, the mandatory
assessments to be performed are marked with a 'W'. If an RHC (and LHC, if needed) is done at an unscheduled visit, this information must be collected in the eCRF.

2 RHC (and LHC, if needed) must have been performed at least 90 days after full anticoagulation and at least 90 days after last surgical (PEA) or interventional (BPA) treatment for subjects with persistent/recurrent CTEPH.
For the hemodynamic cohort, a historical RHC (and LHC, if needed) is allowed, provided it was performed within 30 days prior to Screening*, at least 90 days after last change in PH-specific therapies (ie, change in dose or initiation of new class of drugs) and as per guidance in protocol Appendix 1.
For the non-hemodynamic cohort, historical RHC (and LHC, if needed) is allowed, provided it was performed within 6 months prior to Screening*.
If no historical results are available, RHC (and LHC, if needed) must be performed during the Screening period (as per guidance in protocol Appendix 1 for the hemodynamic cohort).

* In case of rescreening in the hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used, provided there have been no changes in PH-specific therapy(ies) since the first Screening Visit. In case of rescreening in the non-hemodynamic cohort within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used.

3 Assessment to be performed within 2–5 hours post-dose.

4 Only for subjects in the hemodynamic cohort and must be done after the post-dose 6MWT.

5 Performed in the 14-month period prior to randomization and after last surgical (PEA) and/or interventional (BPA) treatment for subjects with persistent/recurrent CTEPH (protocol Section 7.2.2). If no historical results are available, the assessments must be performed during the Screening period.

6 If the results of the screening blood samples from the central laboratory are not available in time for randomization of the subject, an additional blood sample may be drawn to verify eligibility based on a local laboratory test.

7 PAH-SYMPACT® questionnaire to be completed for the seven consecutive days following the visit at site (ie, starting the day following the visit day) for the symptom part, and on the seventh day of the symptoms diary data collection period, together with the symptom part (ie, in the evening) for the impact part.

8 Scheduled telephone calls as per up-titration scheme (protocol Section 5.1.3.1).

9 All AEs and SAEs that occur after signing the Informed Consent Form and until the EOS, as defined in protocol Section 8.1, must be reported (see also protocol Section 9).

10 After Week 52, the phone and on-site visits will be alternating every 13 weeks (~3 months).

11. The EDBT visit occurs within 4 weeks after the end-of-double-blind period announcement, ie, within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor's decision.

* Assessment not collected in eCRF.

** Transferred electronically by an external service provider.

Table 4: Open-label treatment period: visit and assessment schedule

PERIODS	Name	TRANSITION	OPEN-LABEL TREATMENT					SAFETY FOLLOW-UP
	Duration		At least until the DB period results release or up to a maximum of 26 weeks after the DB period results release					30 days
VISITS[1]	Number	EDBT	Titration phase	OL 1	OL 2	*Visits every 26 weeks*[7]	EOLT	Safety follow-up (Telephone call)
	Name			OL-Week 12	OL-Week 26	*OL-Week 52, 78, 104, etc*		
	Time	Announced[6]	Weekly from OL-Week 1 to OL-Week 11 (± 3 days)	Day 85 after EDBT (± 7 days)	Day 183 after EDBT (± 7 days)	*Day 365, 547, 729 after EDBT, etc (± 7 days)*	Any time within 26 weeks of the DB period results release or for premature EOLT within 7 days after last OL dose	30 (+ 5) days after last OL dose
Previous/concomitant therapy			X	X	X	*X*	X	X
Physical examination*				X	X	*X*	X	
Vital signs (BP, HR), Weight				X	X	*X*	X	
Hematology and clinical chemistry**				X	X	*X*	X	
Urine pregnancy test*			← monthly (±7 days) →					
Post-dose 6MWT/BDI or Borg CR10®[2]					X	*X*	X	
WHO FC					X	*X*	X	
Dose titration			☎[3]	iMTD				
OL Study treatment dispensing/return		X[4]		X	X	*X*	X	
SAEs/AEs[5]			X	X	X	*X*	X	X

6MWT = 6-minute walk test; AE = adverse event; BDI = Borg dyspnea index; Borg CR10® = Borg category-ratio 10 Scale®; BP = blood pressure; CGI-C = Clinician Global Impression of Change; CGI-S = Clinician Global Impression of Severity; DB = double blind; eCRF = electronic Case Report Form; EDBT = End-of-Double-Blind-Treatment; EOLT = End-of-Open-Label-Treatment; EOS = end of study; EQ-5D-5L = Euro Quality of life-5-Dimension-5-Level; FC = functional class; HR = heart rate; IDMC = Independent data management committee; iMTD = individual maximum tolerated dose; LHC = left heart catheterization; NT-pro BNP = N-terminal pro b-type natriuretic peptide; OL = open label; PAH-SYMPACT® = Pulmonary arterial hypertension symptoms and impact questionnaire; PTOP-SFU = Post-treatment observation period-Safety follow-up; RHC = right heart catheterization; SAE = serious adverse event; WHO = World Health Organization. ☎ = telephone call

1 Unscheduled visits may be performed at any time during the OL treatment period. Assessments are performed at the discretion of the investigator. If any RHC (and LHC, if needed) is done at an unscheduled visit, this must be collected in the eCRF.

2 Assessment to be performed within 2–5 hours post-dose.

3 Scheduled telephone calls as per up-titration scheme (see protocol Section 5.1.3.2).

4 First OL dose to be taken on the evening of the EDBT visit or in the morning of the day after EDBT visit in case of qd regimen. (see protocol Section 5.1.3.2).

5 All AEs and SAEs that occur after first dose of OL study treatment and up to 30 days after study treatment discontinuation must be reported (see also protocol Section 9).

[6] The EDBT visit occurs within 4 weeks after the end-of-double-blind period announcement ie within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor's decision.
[7] ONLY for subjects who were transitioned to the OL treatment extension period before implementation of the AC-065B302 protocol *AMENDMENT 2*.
* Assessment not collected in eCRF.
** Transferred electronically by an external service provider.

Table 5: PTOP: visit and assessment schedule

PERIODS	Name		DOUBLE-BLIND PERIOD - OFF-TREATMENT[1] (after premature discontinuation of double-blind study treatment)								SURVIVAL FOLLOW-UP
VISITS	Number							TC every 26 weeks[8]	Visit every 26 weeks[8]	PTOP-EOS	SFU 1, 2, 3, etc
	Name	PTOP-SFU[2] (telephone call)	PTOP-Week 12	PTOP-Week 20	PTOP-Week 26	PTOP-Week 39	PTOP-Week 52	PTOP-Week 65, 91, 117, etc	PTOP-Week 78, 104, 130, etc	Announced[5]	Survival Follow-up
	Time	30 (+5 days) after last DB dose	Day 85 (± 7 days)	Day 141 (± 7 days)	Day 183 (± 7 days)	Day 274 (± 7 days)	Day 365 (± 7 days)	Day 456, 638, 820 etc. (± 7 days)	Day 547, 729, 911, etc. (± 7 days)		Yearly after study discontinuation until death or announcement[6]
Previous/concomitant therapy		X	X	X	X	X	X	X	X	X	
Physical examination*			X	X	X	X	X		X	X	
Vital signs (BP, HR), Weight			X	X	X	X	X		X	X	
Local 12-lead ECG							X			X	
Hematology and clinical chemistry**			X	X	X	X	X		X	X	
6MWT/BDI or Borg CR10®			X	X	X	X	X		X	X	
WHO FC			X	X	X	X	X		X	X	
Actigraphy**			← Every day, 24 hours per day →								
PAH-SYMPACT®**, 3			X	X	X	X					
EQ-5D-5L, WPAI©: GH**			X	X	X	X	X				
CGI-S			X	X	X	X	X		X	X	
CGI-C			X	X	X	X	X		X	X	
NT-proBNP**			X	X	X	X	X		X	X	
SAEs/AEs[4]		X	X	X	X	X	X	X	X	X	
Survival											X[7]

6MWT = 6-minute walk test; AE = adverse event; BDI = Borg dyspnea index; Borg CR10® = Borg category-ratio 10 Scale®, PTOP = Post-Treatment Observation Period; FC = functional class; SAE = serious adverse event; SFU = safety follow-up; WHO = World Health Organization.

1 Depending on the time point of premature double-blind treatment discontinuation, the sequence and/or the applicability of visits may change. If one of the site visits falls within the time window of the premature EDBT visit [as defined in protocol Section 5.1.1.10], only the assessments of the premature EDBT are to be performed.

2 If the PTOP-SFU falls within the time window of any of the other PTOP visits, then the PTOP-SFU is combined with the corresponding PTOP site visit. In this case, the PTOP-SFU assessments are to be done in addition to the assessments of the respective visit.

3 PAH-SYMPACT® questionnaire to be completed for the seven consecutive days following the visit at site (ie, starting the day following the visit day) for the symptom part, and on the seventh day of the symptoms diary data collection period, together with the symptom part (ie, in the evening) for the impact part.

4 All AEs and SAEs that occur after signing the Informed Consent Form and until the EOS, as defined in protocol Section 8.1, must be reported (see also protocol Section 9).

[5] The PTOP-EOS visit occurs within 4 weeks after the end-of-double-blind period announcement, ie, within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor's decision.
[6] The end of the survival follow-up period for alive subjects will be announced and corresponds to the end-of-double-blind period announcement ie, within 4 weeks of reaching the overall target number of clinical worsening events, or earlier following recommendation of the IDMC, or sponsor's decision.
[7] Only for subjects who prematurely discontinue from DB study treatment and who disagree to continue to perform visits and assessments until the end of the PTOP, survival information will be collected yearly [see protocol Section 7.2.3.9].
[8] After Week 52, the phone and on-site visits will be alternating every 13 weeks (~3 months).
* Assessment not collected in electronic Case Report Form.
** Transferred electronically by an external service provider.

Following the decision to terminate the study, the sites were instructed to proceed as follows:

	Visits Required
Subjects in Screening	• Contact the subject and screen fail subject in IWRS
Subjects on DB Treatment	• Complete EDBT visit within 4 weeks (no later than 12-Jan-2022)* • 30-35 days after the EDBT, complete SFU (telephone call)
Subjects on OL Treatment	• Complete EOLT visit within 4 weeks (no later than 12-Jan-2022)* • 30-35 days after the EOLT, complete SFU (telephone call)
Subjects in PTOP	• Complete PTOP-EOS visit within 4 weeks (no later than 12-Jan-2022) • If the subject has not already completed the PTOP-SFU, this must be completed 30-35 days after last dose
Subjects currently in SFU	• Complete SFU visit (telephone call) as per protocol (30-35 days after last dose)
Subjects in survival follow-up	• Contact subject within 4 weeks (no later than 12-Jan-2022) and discontinue subject from the study**

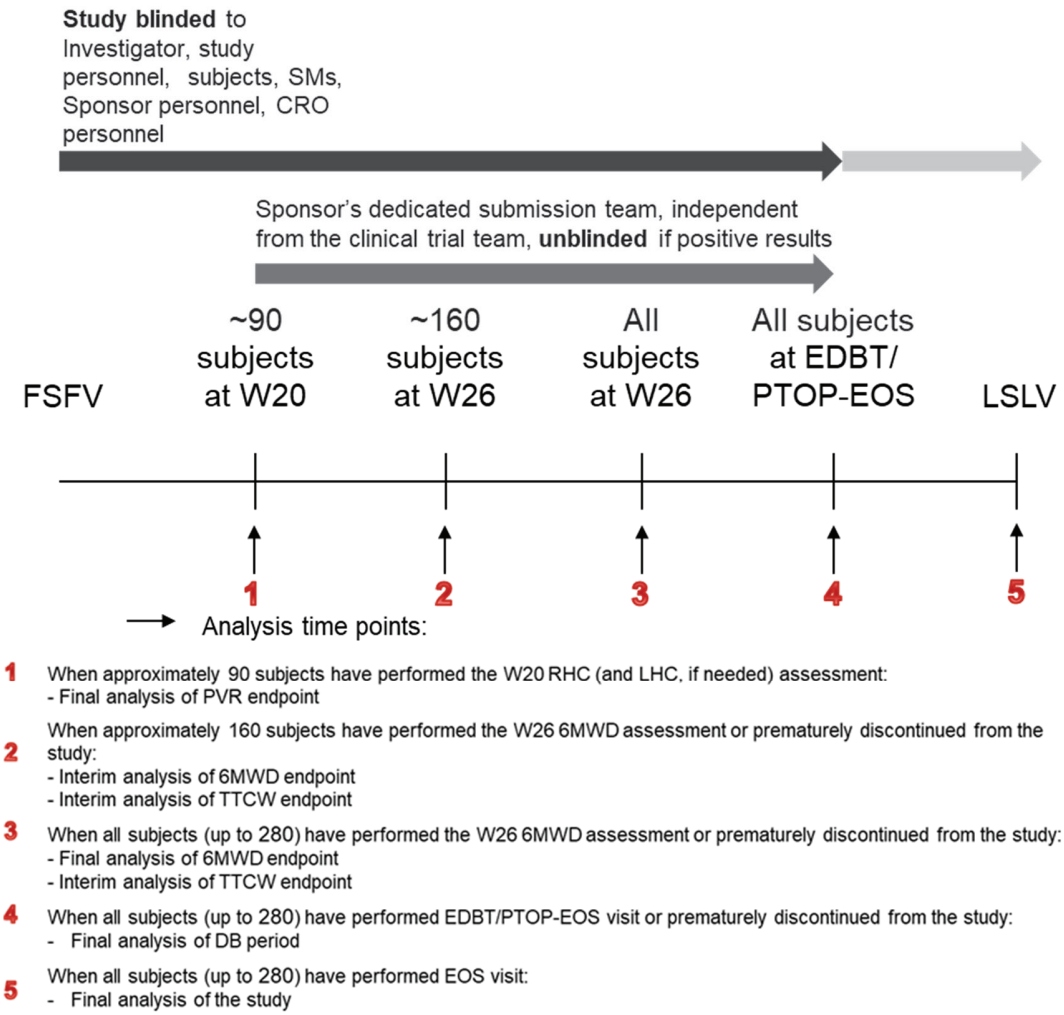
* Study treatment should be stopped at the EDBT/EOLT visit. If subject discontinued treatment prior to the EDBT/EOLT visit, subject should return for their EDBT/EOLT visit within 7 days of discontinuation of treatment.

** Delays in EOT visits due to: Holidays (Christmas and New Year) between announcement and requested EOT date; COVID-19 situation at sites where some site staff not returning until mid Jan2022; Post-Trial Access (PTA) requests for individual patients seeing clinical benefit of selexipag (PTA requests following premature termination due to futility were unexpected and had to be handled on a country-by-country basis).

1.2.4. Analysis Time Points

The database was to be locked, and the data extracted and analyzed at five planned analysis time points during the study (Figure 3):

Figure 3: Study Analyses



6MWD = 6-minute walk distance; CRO = Contract Research Organization; EDBT = End-of-Double-Blind-Treatment; FSFV = First subject first visit; LHC = Left heart catheterization; LSLV = Last subject last visit; PTOP-EOS = Post-treatment observation period end-of-study; PVR = pulmonary vascular resistance; RHC = Right heart catheterization; SM = Site manager; TTCW = Time to clinical worsening; W = week.
The diagram is not to scale.

The first analysis time point was when approximately 90 randomized subjects (= subjects who participated in the hemodynamic cohort) had completed the Week 20 RHC (and LHC, if needed) or prematurely discontinued from the study. The final analysis of the primary endpoint (PVR) was performed by the independent SSG for the IDMC. The details of decision rules and actions to be taken following this analysis are presented in the IDMC Charter Section 7.

Due to early termination of the study, analysis time points 2 and 3 are no longer applicable and analysis time points 4 and 5 are combined and constitute the final analysis reporting of the study, when all randomized subjects up to the point of early termination have performed their EOS visit, conducted by the sponsor, according to this abbreviated CSR SAP. The primary endpoint analyses, as conducted at analysis time point 1 by the SSG, will also be performed by the sponsor, as part of this SAP.

1.2.5. Randomization and Blinding

1.2.5.1. Method of Treatment Assignment and Randomization

1.2.5.1.1. Randomization

After the ICF has been signed, the investigator/delegate contacts the Interactive Response Technology (IRT) system at Visit 1 (Screening Visit) to obtain a subject number.

In case of rescreening, the subject number attributed at the time of first screening will be used for the rescreened subject.

At Visit 2 (Randomization Visit), after having verified that the subject meets all inclusion criteria (including confirmation of CTEPH and inoperability by the corresponding adjudication committee (AC) [country-specific adjudication committee (CSAC) or central adjudication committee (CAC)]) and none of the exclusion criteria, the investigator/delegate contacts the IRT system to randomize the subject. The IRT assigns a unique randomization number to the subject and assigns the treatment kit number, which matches the treatment arm assigned by the randomization list to the randomization number. The randomization list is generated by an independent Contract Research Organization (CRO), Almac Clinical Technologies, using SAS® version 9.4.

1.2.5.1.2. Stratification

Treatment allocation will be stratified by:

- Treatment with **PH-specific therapies** (ie, ERAs, PDE-5 inhibitors, sGC stimulators [riociguat]; **one** versus **two** versus **naïve** [naïve capped at 40%]), and
- **CTEPH population; inoperable [with or without BPA]** versus **persistent-recurrent** after PEA [including PEA followed by BPA])

PH-specific therapies currently considered are as follows:

Category	**Subcategory**	**Ingredient names**
Antihypertensives for pulmonary arterial hypertension	ERAs	ambrisentan, bosentan, sitaxentan, macitentan
	PDE-5 Inhibitors	avanafil, lodenafil, sildenafil, tadalafil, udenafil, vardenafil
	sGC stimulator	riociguat
Prostanoids*		epoprostenol, treprostinil, iloprost, beraprost
*Note as per protocol - Exclusion criteria 3: Treatment with prostacyclin (epoprostenol), prostacyclin analogs (ie, treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (ie, selexipag/Uptravi®) within 90 days prior to randomization (Visit 2), except those given at vasodilator testing during RHC. Categories are identified by searching the coded WHODRUG preferred terms for occurrence of any of the ingredient names. eg, 'sildenafil' and 'sildenafil citrate' will both be assigned to PDE-5 inhibitors. The searching methods will be adopted according to the dictionary format in the SDTM. Avanafil, lodenafil, udenafil and vardenafil are only approved for treatment of erectile dysfunction but are included if the investigator indicates “Underlying study disease (CTEPH)” on the eCRF. Source: https://www.whocc.no/atc_ddd_index/		

If applicable, the list of PH-specific therapies will be updated prior to each planned analysis in the respective SAP amendment.

1.2.5.2. Blinding and Unblinding

1.2.5.2.1. Blinding

The first treatment period of this study up to EDBT will be performed in a DB fashion. The investigator and study personnel, the subjects, the site managers (SM), sponsor personnel and CRO personnel involved in the conduct of the study will remain blinded to the study treatment until the fourth analysis time point, ie, until all randomized subjects have completed EDBT/PTOP-EOS Visit or prematurely discontinued from the study, and when the DB database is locked and the data extract is performed, or when the study is terminated prematurely.

Until the time of sponsor unblinding (see Section 1.2.5.2.2), the randomization list is kept strictly confidential and accessible only to authorized persons (ie, an independent SSG and Secure Data Office [SDO]), who are not involved in the conduct of the study.

The investigational treatment and its matching placebo are indistinguishable, and all treatment kits will be packaged in the same way.

1.2.5.2.2. Unblinding

1.2.5.2.2.1. Unblinding for IDMC meetings

An independent SSG not otherwise involved in the design, conduct and analysis of the study will have access to the randomization codes in order to prepare unblinded reports for review by the IDMC (see IDMC Charter). The randomization codes will be made available to the independent SSG in accordance with the sponsor's Quality System (QS) documents.

1.2.5.2.2.2. Unblinding for the first analysis time point (final analysis of PVR)

Full randomization information of all subjects randomized so far were made available to the independent SSG for the final analysis of PVR. In accordance with the IDMC Charter, the IDMC will review the unblinded results and provide a recommendation on continuation or premature study termination (see IDMC Charter Section 7).

Following the decision to prematurely terminate the study, the study team remains blinded to the results of the IA conducted by the SSG, until database lock occurs for the abbreviated CSR planned analyses, which combines analysis time points 4 and 5 as described above in Section 1.2.4.

1.2.5.2.2.3. Unblinding for the final analysis

Full randomization information will be made available to the sponsor clinical trial team (CTT) for data analysis only after all randomized subjects have completed the DB treatment period, or the PTOP or prematurely discontinued from the study, and when the DB part of the database is locked and the data extract is performed, in accordance with current standard operating procedures.

Following each subject's completion of the DB treatment period they will enter the OL extension period. In order to preserve the blind of each individual subject until the DB part of the database is locked, all subjects will be up-titrated with OL selexipag (see protocol Section 5.1.3.2).

1.2.5.2.2.4. Other unblindings

Sponsor personnel responsible for clinical study supply distribution will need to be unblinded at a supply level to ensure adequate supply of study treatment. These persons will be clearly identified with their unblinding documented in the Trial Master File (TMF).

For the other unblindings, ie, unblinding for suspected unexpected serious adverse reactions and emergency procedure for unblinding, please refer to protocol Section 5.1.6.5 and Section 5.1.6.6, respectively.

2. STATISTICAL HYPOTHESES

2.1. Hypotheses for the Primary Endpoint

The hypotheses for the primary endpoint PVR at Week 20 are formulated in terms of geometric mean of PVR pre-post (Baseline-Week 20) percent in subjects treated with selexipag ($GM_{selexipag}$) versus placebo ($GM_{placebo}$):

$$H_0: GM_{selexipag} = GM_{placebo}$$

$$H_A: GM_{selexipag} \neq GM_{placebo}$$

2.2. Hypotheses for Secondary Endpoints

Secondary Endpoints	Hypotheses
Change from baseline in 6MWD to Week 26 (key secondary endpoint).	The hypotheses are formulated in terms of mean 6MWD pre-post (Baseline-Week 26) change in subjects treated with selexipag ($\mu_{selexipag}$) versus placebo ($\mu_{placebo}$): $H_0: \mu_{selexipag} = \mu_{placebo}$ $H_A: \mu_{selexipag} \neq \mu_{placebo}$
TTCW (key secondary endpoint)	The null hypothesis is that there is no difference between selexipag ($S_{selexipag}(t)$) and placebo ($S_{placebo}(t)$) for the distribution of time to the first CHMP-defined clinical worsening event. The alternative hypothesis is that there is a difference: $H_0: S_{selexipag}(t) = S_{placebo}(t)$ $H_A: S_{selexipag}(t) \neq S_{placebo}(t)$
Change from baseline to Week 26 in BDI/Borg CR10®	The null hypothesis is that there is no difference between selexipag and placebo in the mean pre-post (Baseline-Week 26) change.

3. SAMPLE SIZE DETERMINATION

Full details regarding sample size determination for the study are provided in the protocol Section 10.6.

The study consists of two cohorts: approximately the first 90 subjects randomized will form the hemodynamic cohort, targeting the primary endpoint of PVR at Week 20. The remaining subjects will be randomized to enrich information on all secondary endpoints. If subject enrollment is not

terminated for futility or efficacy at analysis time point 1 or 2, the total sample size will be 280 subjects.

At the time of the decision to terminate the study, a total of 128 subjects had been randomized, of whom 91 subjects were randomized in the hemodynamic cohort.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

An overview of analysis sets is provided in Table 6.

Table 6: Overview of Analysis Sets

Analysis Sets	Description
Screened Analysis Set (SCR)	Includes all subjects who are screened and have a subject identification number. The screen failure subjects are those who are not randomized via the interactive voice recognition system, eg, not eligible or withdrawal of consent.
Full Analysis Set (FAS)	Includes all subjects assigned to a study treatment. In order to adhere to the intention-to-treat principle as much as possible: • Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received); and • All available data are included.
Hemodynamic Set (HES)	The HES is a subset of subjects in the FAS and comprises all randomized subjects in the hemodynamic cohort. In order to adhere to the intention-to-treat principle as much as possible: • Subjects are evaluated according to the study treatment they have been assigned to (which may be different from the study treatment they have received); and • All available data are included.
Efficacy Evaluable Set (EES) for Week 26 efficacy endpoints	The EES is a subset of subjects in the FAS and includes all subjects who have reached their Week 26 visit (according to the analysis time window for the specific Week 26 efficacy endpoint) or have discontinued earlier (for any reason except Sponsor decision = Study Termination). An EES is defined for: • 6MWD: From Day 2 to Day 273 (see Table 8) • Other efficacy endpoints: From Day 2 to Day 229 (see Table 8)
Per-protocol Analysis Set (PPS)	The PPS includes a subset of subjects in the FAS who were in compliance with the protocol. The PPS comprises all subjects who received study treatment and who complied with the protocol sufficiently to be likely to exhibit the treatment effects. Criteria for sufficient compliance include exposure to study treatment, availability of measurements and absence of major protocol deviations that have an impact on the treatment effect. A PPS is defined for: • PVR Per-protocol Analysis Set (PPS): Includes all subjects in the HES who do not have major protocol deviations that have an impact on treatment effect in PVR.

	The full list of criteria for sufficient compliance and the full list of protocol deviation codes for exclusion from the PPS are detailed in Section 6.4 Appendix 4.
Safety Analysis Set (SAF)	Includes all subjects who received at least one dose of study treatment. Subjects are evaluated according to the study treatment they have received (which may be different from the study treatment they have been randomized to): • If a subject has taken at least one dose of selexipag, she/he is assigned to the selexipag treatment group. • If a subject has taken only placebo, she/he is assigned to the placebo treatment group.

Table 7 defines all analysis sets and their specific usage at all analysis time points. For decision-making at analysis time point 1, PVR was evaluated on the HES. Week 26 efficacy endpoints will be evaluated on the EES. All other efficacy analyses will be evaluated on the FAS, unless otherwise specified. Safety endpoints will be evaluated on the SAF.

Table 7: Analyses sets and their usage at each analysis time-point

Analysis Time point	Analysis	Analysis Set				
		FAS	HES	PPS	EES**	SAF
1	Final PVR		X	X		
1	Exposure and safety					X
1	Others*	X	X			
EOS	Final 6MWD	X			X	
EOS	Final TTCW	X				
EOS	Final hemodynamic parameters other than PVR		X			
EOS	Final DB	X			X	X
EOS	Final OL	X				X

* Demographic and baseline characteristics, medial history, previous and concomitant medications, efficacy endpoints other than PVR, 6MWD and TTCW.
** For Week 26 efficacy endpoints.
The "X" indicates the analysis sets to be used for the main analyses for the respective endpoints and time points.
6MWD = 6-minute walk distance; DB = double-blind; EES = Efficacy Evaluable Set (EES) for Week 26 efficacy endpoints;
FAS = Full analysis set; HES = Hemodynamic set; OL = open-label; PPS = Per-protocol analysis set;
PPS = PVR Per-protocol analysis set; SAF = Safety analysis set; TTCW = Time to clinical worsening.

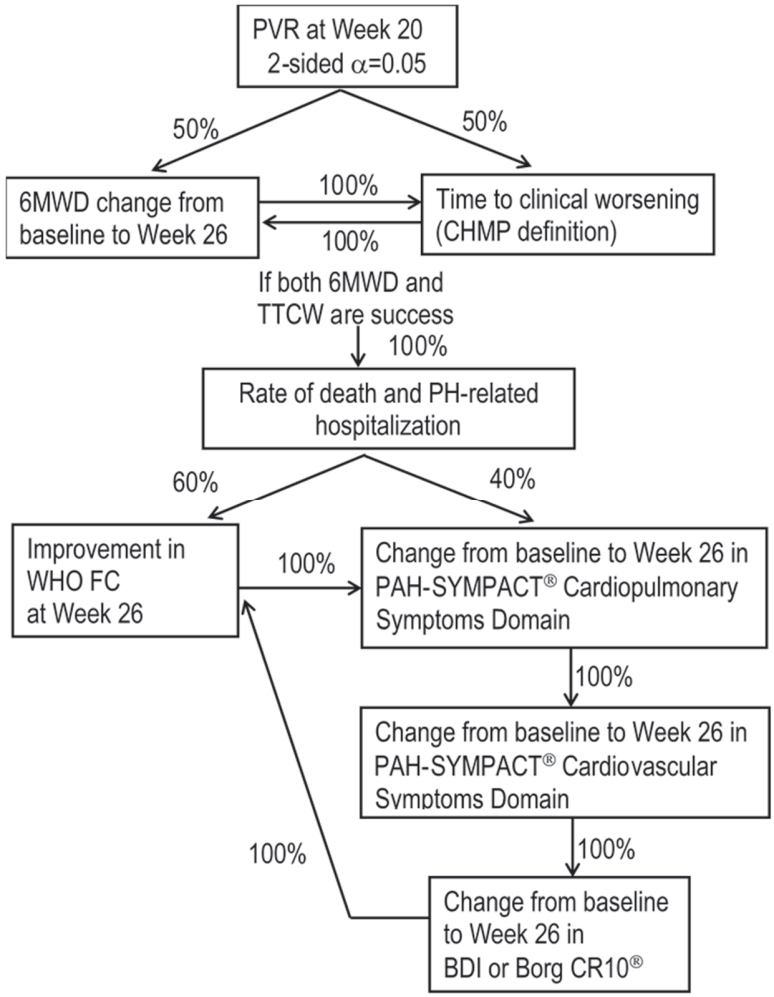
5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Overall Testing Strategy

The primary and secondary efficacy endpoints were to be tested in a specified hierarchy (Figure 4) and at multiple time points (see Section 1.2.4).

Figure 4: Testing strategy for primary and secondary endpoints (2-sided type I error rate, α = 5%)



6MWD = 6-minute walk distance; BDI = Borg dyspnea index; Borg CR10®= Borg category-ratio 10 Scale®; CHMP = Committee for Medicinal Products for Human Use; PAH-SYMPACT®= Pulmonary Arterial Hypertension Symptoms and Impact®; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; TTCW = Time to clinical worsening; WHO FC = World Health Organization functional class.

The primary endpoint analysis as described in Section 5.3, was performed at analysis time point 1, when approximately 90 randomized subjects (= subjects who participated in the hemodynamic cohort) had completed the Week 20 RHC (and LHC, if needed) or prematurely discontinued from the study. This analysis constitutes the first and final analysis of the PVR endpoint and was tested on the HES at 2-sided alpha of 5%. Failure to meet success on the primary endpoint led to termination of the study for futility, as no remaining alpha is available to formally test secondary endpoints.

Following the decision to prematurely terminate the study due to futility at analysis time point 1, the pre-planned testing hierarchy is no longer applicable, and all efficacy analyses other than PVR are exploratory. Further, early termination of the study has a significant impact on the amount of data available for the analysis of key secondary, supportive, and exploratory endpoints (eg, number of subjects reaching the Week 26 endpoint, low number of CW events), which may result in limited interpretation of some of the analyses.

Key and supportive secondary efficacy variables and their analyses are described in Section 5.4, as well as important exploratory efficacy variables as described in Section 5.5 and safety analyses as described in Section 5.6, using analysis sets as specified in Table 7.

5.1.2. Visit and Analysis Time Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits (including unscheduled visit results) to analysis visits. Listed below are the visit and analysis time windows and the target days for each visit. The reference day is Study Day 1 for the DB period or the first OL dose for the OL period. Each assessment will be assigned to one corresponding visit label and analysis time window. If a subject has two or more actual visits in a given visit window, the visit closest to the target day will be used as the analysis visit for that visit window. The other additional visit(s) will not be used in the table summaries or analyses unless otherwise specified (for example, they can be used for determination of clinically important endpoints). If two visit assessments are equidistant from the target day within a visit window, the later visit assessment is used. For endpoints evaluated at specific time points, assessments at different visits may be used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be eligible to be used for a later time point except for the endpoint. Table 8 presents scheduled visits with the corresponding visit labels, target study days and analysis time windows for efficacy and safety data parameters.

Table 8: Visit and Analysis Time Windows

Parameter	Analysis Period	Scheduled Visit Number	Time Interval (label on output)	Analysis Time Window[6] (Day)	Target Time Point (Day)[5]
Efficacy* RHC	Screening	1	Screening	< 1	-60 to -14
	DB	4[4] (DB-W20)	Endpoint at W20	2 to 189[1]	141
Efficacy* 6MWD	Screening	1	Screening	< 1	-60 to -14
	DB	2	Baseline	<=1	1
	DB	3	Week 12	2 to 113	85
	DB	4	Week 20	114 to 162	141
	DB	5	Week 26	163 to 229	183
	DB	6	Week 39	230 to 320	274
	DB	7	Week 52	321 to 456	365
	DB	8[7]	Week 78	457 to 638	547
	DB	9	Week 104	639 to 820	729
	DB	10	Week 130	821 to 1002	911
	DB	11	Week 156	1003 to 1184	1093
		etc	etc	etc	etc
	DB		Endpoint at W26	2 to 273[1]	183
	DB		DB-Endpoint	2 to end of DB	
Efficacy parameters*[2] (excl. RHC and 6MWD)	Screening	1	Screening	< 1	-60 to -14
	DB	2	Baseline	<=1	1
	DB	3	Week 12	2 to 113	85
	DB	4	Week 20	114 to 162	141

Table 8: Visit and Analysis Time Windows

Parameter	Analysis Period	Scheduled Visit Number	Time Interval (label on output)	Analysis Time Window[6] (Day)	Target Time Point (Day)[5]
	DB	5	Week 26	163 to 229	183
	DB	6	Week 39	230 to 320	274
	DB	7	Week 52	321 to 456	365
	DB	8[7]	Week 78	457 to 638	547
	DB	9	Week 104	639 to 820	729
	DB	10	Week 130	821 to 1002	911
	DB	11	Week 156	1003 to 1184	1093
		etc	etc	etc	etc
	DB		Endpoint at W26	2 to 229[1]	183
	DB		DB-Endpoint	2 to end of DB	
Safety parameters*[3]	Screening	1	Screening	< 1	-60 to -14
	DB	2	Baseline	<=1	1
	DB	3	Week 12	2 to 113	85
	DB	4	Week 20	114 to 162	141
	DB	5	Week 26	163 to 229	183
		6	Week 39	230 to 320	274
	DB	7	Week 52	321 to 456	365
	DB	8[7]	Week 78	457 to 638	547
	DB	9	Week 104	639 to 820	729
	DB	10	Week 130	821 to 1002	911
	DB	11	Week 156	1003 to 1184	1093
		etc	etc	etc	etc
Re-Baseline in OL**	OL	102[7]	OL-Baseline	<= [1]	[1]
	OL	103	OL-Week 12	[2] to [134]	[85]
	OL	105	OL-Week 26	[135] to [274]	[183]
	OL	107[8]	OL-Week 52	[275] to [456]	[365]
	OL	108	OL-Week 78	[457] to [638]	[547]
	OL	109	OL-Week 104	[639] to end of OL	[729]
		etc	etc	etc	etc
	OL		OL-Endpoint	[2] to end of OL	

6MWD = 6-minute walk distance; DB = Double blind; OL = Open label; RHC = Right heart catheterization

* Time Interval and Target Time Point are relative to Visit 2 (Study Day 1)

** Target Time Point and Analysis Time Window specified in [xx] are relative to the start date of OL; first OL dose to be taken on the evening of the EDBT visit or in the morning of the day after EDBT visit in case of qd regimen (see protocol Table 4).

1) Missing data will be imputed.

2) Efficacy parameters: TTCW, BDI/Borg CR10®.

3) Safety parameters: Vital Signs, Weight, laboratory tests.

4) Only for subjects in the hemodynamic cohort.

5) Target time point as defined in the protocol visit and assessment schedules.

6) Analysis time windows are wider than the assessment schedules specified in protocol. The analysis time windows will be applied to all collected data including scheduled, unscheduled and PTOP visits. PTOP flag will be included in the ADaM.

7) Scheduled Visit Number = After Week 52, phone and on-site visits will be alternating every 13 weeks (~3 months).

8) ONLY FOR SUBJECTS WHO WERE TRANSITIONED TO THE OL TREATMENT EXTENSION PERIOD BEFORE IMPLEMENTATION OF THE AC-065B302 PROTOCOL AMENDMENT 2.

Note: "Endpoint at Week XX" is the value used for the analysis endpoints, as applicable.

5.1.3. Study Day and Relative Day

Visit 2 is the date of randomization and usually also the date of the first study treatment administration. In general, in the DB period, for baseline characteristics, as well as efficacy endpoints the Study Day 1 or Day 1 refers to date of randomization; while for medical history, previous and concomitant medications exposure and safety endpoints the Study Day 1 or Day 1 refers to date of the first study treatment administration. If the date of randomization and the date of the first study treatment administration are different, the study day would not be the same for all endpoints.

For the OL period, Study Day 1 or Day 1 refers to date of the first study treatment administration in the OL treatment period.

All assessments at all visits will be assigned a study day relative to the respective Study Day 1.

Study day for an event/assessment on or after the respective Study Day 1 (≥ date of Study Day 1) is calculated as:

Event/assessment date - (date of Study Day 1) + 1.

Study day for an event/assessment prior to the respective Study Day 1 (< Study Day 1 date) is calculated as:

Event/assessment date - (date of Study Day 1).

There is no 'Day 0'.

5.1.4. Baseline and Endpoint

In the DB period, baseline is defined as the last observation prior to or at the randomization date for baseline characteristics, as well as for all efficacy endpoints; while for medical history, previous and concomitant medications, exposure, and safety endpoints baseline is defined as the last observation prior to the date of the first study treatment administration. OL-baseline is relative to the start date of the first study treatment administration in the OL treatment period.

Endpoint is defined as the available post-baseline result that is closest to the protocol defined target time point(s) within the respective analysis time-window(s) (see Section 5.1.2). Unscheduled visit results are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the post-baseline result that is closest to the protocol defined target time point(s) within the respective analysis time-window(s).

For the primary and key secondary endpoints, if there is no post-baseline result available within the respective analysis time-window, the imputation rules will be applied according to Section 5.3.3.2 and Sections 5.4.1.3.2 and 5.4.2.3.2, respectively.

5.1.5. Study Periods

An overview of the study periods is provided in Section 1.2.1 and Table 3, Table 4 and Table 5.

5.1.6. Study Completion

As per protocol Section 8.1, subjects who perform the EOS telephone call/visit are considered as study completers:

- For subjects who complete their study treatment up to the EOLT visit, the EOS visit corresponds to the safety telephone call which occurs 30–35 days after the last OL dose.
- For subjects who prematurely discontinue the DB study treatment, the EOS visit corresponds to the last visit in the PTOP period, ie, the PTOP-EOS visit. It occurs within 4 weeks after the end-of-double-blind period announcement, ie, within 4 weeks of reaching the overall target number of clinical worsening events (protocol Section 10.6.3), or earlier following recommendation of the IDMC (protocol Section 10.4) and sponsor's decision (protocol Section 8.3).
- For subjects who prematurely discontinue the OL study treatment, the EOS visit corresponds to the safety telephone call (ie, 30–35 days after last OL dose).

Subjects who prematurely withdraw from the study, per protocol Section 8.2, are not considered as study completers:

- For subjects who prematurely withdraw from the study, the EOS date is defined as the date of either death, last unsuccessful follow-up contact attempt, consent withdrawal, physician decision or sponsor decision, depending on the reason for study discontinuation.

5.1.7. Imputation Rules for Missing Adverse Event Date/Time of Onset

5.1.7.1. Treatment-emergent AEs

AEs with completely missing onset dates will be considered as treatment-emergent (avoiding under reporting of treatment-emergent AEs). AEs with partially missing onset dates will also be included as treatment-emergent when the month (if it exists) and the year occur on or later than the month and year of the initial study treatment date.

5.1.7.2. Imputation Rules

The date value is split into day, month, and year parts as outlined below:

	Day	Month	Year
Partial AE Start Date	Not used (missing and will be imputed)	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

Completely missing start dates will not be imputed. Partial AE start dates are imputed with reference to the treatment start date (TRTSDT) as outlined in the matrix of start year (YYYY) vs start month (MON) below.

The ***Italic bold*** font indicates the imputed values.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	Do not impute	Do not impute	Do not impute	Do not impute
YYYY < TRTY	(D) = ***31DEC***YYYY Before Treatment Start	(C) = ***01***MONYYYY Before Treatment Start	(C) = ***01***MONYYYY Before Treatment Start	(C) = ***01***MONYYYY Before Treatment Start
YYYY = TRTY	(B) = min(***TRTSDT, AE resolution)*** Uncertain	(C) = ***01***MONYYYY Before Treatment Start	(B) = min(***TRTSDT, AE resolution)*** Uncertain	(A) = ***01***MONYYYY After Treatment Start
YYYY > TRTY	(E) = ***01JAN***YYYY After Treatment Start	(A) = ***01***MONYYYY After Treatment Start	(A) = ***01***MONYYYY After Treatment Start	(A) = ***01***MONYYYY After Treatment Start

The following table is the legend to the matrix above.

Relationship	
Before Treatment Start	Partial date indicates AE start date prior to Treatment Start Date
After Treatment Start	Partial date indicates AE start date after Treatment Start Date
Uncertain	Partial date insufficient to determine the sequence of AE start date and Treatment Start Date
Imputation Calculation	
(A) After Treatment Start	**01**MONYYYY (The closest date to the treatment start date for imputation)
(B) Uncertain	min**(TRTSDT, AE resolution)** (AE happed just after the treatment start)
(C) Before Treatment Start	**01**MONYYYY (Start-month point will be used for imputation)
(D) Before Treatment Start	**31DEC**YYYY (End-year point will be used for imputation)
(E) After Treatment Start	**01JAN**YYYY (The closest date to the treatment start date for imputation)

Note: Imputation rules for concomitant medications follow the same approach as for AEs.

5.2. Subject Dispositions

The number of subjects screened and the number of screen failures, as well as the reason for screen failures will be summarized overall. If a subject is rescreened, they will be counted only once in the SCR. If a subject was rescreened and screen failed for a second time, they will be counted only once as a screen failure and only the later reason for screen failure will be considered. If a subject was rescreened and subsequently randomized, they will not be considered as a screen failure. The number of subjects rescreened, and the number of subjects rescreened and not randomized will be summarized in the screen failure disposition table.

The number and percentage of subjects in the following disposition categories will be summarized throughout the study by treatment group and overall:

- Subjects randomized
- Subjects receiving study treatment in DB period

- Subjects completed the EDBT
- Subjects who prematurely discontinued DB treatment
  - Reasons for discontinuation of DB study treatment
  - Subjects discontinued before Week 20
  - Subjects discontinued before Week 26
- Subjects who entered PTOP
- Subjects completed the PTOP
- Subjects who started selexipag treatment in the OL treatment period
- Subjects who completed the End-of-Open-Label-treatment (EOLT)
- Subjects who prematurely discontinued OL study treatment before EOLT
  - Reasons for discontinuation of OL study treatment
- Study completion
  - Study completers (as defined in Section 5.1.6 and protocol Section 8.1).
  - Reasons for premature withdrawal from study

Listings of subjects will be provided for the following categories:

- Subjects' randomization information
- Subjects who were mis-stratified (PH-specific therapies and CTEPH population) in the IRT system.
- Subjects who were randomized yet did not receive DB study treatment
- Subjects who started DB study treatment after but not on day of randomization
- Subjects who received wrong study treatment to their randomized assignment
- Subjects who prematurely discontinued (DB and OL) treatment, including flags for the following:
  - Subjects who prematurely discontinued DB treatment before Week 20
  - Subjects who prematurely discontinued DB treatment before Week 26
- Subjects who entered PTOP
- Subjects who were unblinded by investigator during the DB study period

5.3. Primary Endpoint Analysis

The primary endpoint, primary estimand and the primary analyses methods are described below in Sections 5.3.1, 5.3.2 and 5.3.3, respectively. Sections 5.3.3.3.2, 5.3.3.3.3 and 5.3.3.4 provide a summary of sensitivity, supplementary and subgroup analyses which are planned to support the primary efficacy endpoint.

5.3.1. Definition of Endpoint

The primary efficacy endpoint of this study is the PVR at Week 20, assessed at rest, within 2–5 hours post-dose, expressed as percent of baseline PVR.

The Week 20 value is the one identified for the Week 20 analysis time window (see Table 8).

At each assessment, PVR (dyn.sec/cm^5) is derived as follows:

$$PVR = 80 \times \frac{mPAP - PAWP}{CO},$$

where mPAP is mean pulmonary artery pressure measured in mmHg, PAWP is pulmonary artery wedge pressure measured in mmHg, and CO is cardiac output measured in L/min. Following the Actelion Heart Catheterization Guidance (see protocol Appendix 1), left ventricular end diastolic pressure (LVEDP) is to be recorded when PAWP is not available or not reliable. In this case, LVEDP will replace PAWP in the calculation of PVR. The results from the sponsor derived PVR (in dyn.sec/cm5) in the analysis dataset are used for analysis. Smaller PVR values indicate better condition.

The primary endpoint PVR at Week 20 is expressed as percent of the baseline value, ie:

$$PVR\ pre\text{-}post\ percent = \left(\frac{PVR\ at\ Week\ 20}{PVR\ at\ baseline}\right) \times 100\ (\%)$$

5.3.2. Estimand

Primary trial objective:

To evaluate the effect of selexipag versus placebo on PVR at Week 20 in subjects with inoperable CTEPH (ie, technically non operable) and persistent/recurrent CTEPH after surgical (pulmonary endarterectomy [PEA]) and/or interventional (balloon pulmonary angioplasty [BPA]) treatment.

Estimand scientific question of interest:

What is the effect on percent change from baseline to Week 20 in PVR, when subjects diagnosed with CTEPH, as defined by the study eligibility criteria, are assigned to selexipag versus placebo?

Estimand

A. Treatment:

- Experimental: Selexipag
- Control: Placebo

B. Population: Subjects with inoperable CTEPH or persistent/recurrent CTEPH after surgical (PEA) and/or interventional (BPA) treatment in the HES.

C. Variable: PVR at Week 20, expressed as percent of the baseline value, ie, the PVR pre-post percent defined above. For subjects who die without a Week-20 PVR assessment, the PVR pre-post percent will be imputed as defined in Section 5.3.3.2.1.

D. Summary measure (Population-level summary): difference in means of natural logarithm transformed PVR pre-post percent between selexipag and placebo, or equivalently ratio of geometric means of PVR pre-post percent between selexipag and placebo, ie,

$$\frac{Geometric\ mean(PVR\ pre\text{-}post\ percent\ in\ selexipag)}{Geometric\ mean(PVR\ pre\text{-}post\ percent\ in\ placebo)}$$

The main estimator of the treatment effect will be evaluated using an ANCOVA model for natural logarithm transformed PVR pre-post percent with treatment group, stratification factors and natural logarithm transformed baseline PVR value as covariates.

E. Intercurrent events (IE) and their corresponding strategies: IEs and their corresponding strategies are summarized in Table 9 below.

Table 9: Intercurrent Events and Corresponding Strategies for the Main Estimand of PVR

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Premature discontinuation of DB treatment for any reason	Treatment policy strategy: The occurrence of the IE is considered irrelevant in defining the treatment effect of interest ie, the value of the variable of interest is used regardless of whether or not the IE occurs (to reflect intention-to-treat (ITT) principle). Data for the variable of interest will still be collected after the IE (in PTOP).
Receiving additional therapy (see protocol Section 5.1.11.4 and 5.2.5)	
Death	Composite variable strategy: The IE is considered in itself to be informative about the subject's outcome and is therefore incorporated into the definition of the variable. Deaths occurring prior to the Week 20 assessment will be addressed by imputing the Week 20 PVR value, using the rules defined in Section 5.3.3.2.1.

5.3.3. Analysis Methods

5.3.3.1. Statistical Model

Hypotheses and statistical model:

The hypotheses for the primary endpoint PVR at Week 20 are described in Section 2.1.

An ANCOVA model will be applied on the $\log_e$-transformed PVR pre-post percent. Model covariates will include randomized treatment, stratification factors (PH-specific therapies and CTEPH population [see Section 1.2.5.1.2]) and the $\log_e$-transformed baseline PVR value. The residuals of the $\log_e$-transformed pre-post percent values are assumed to follow a normal distribution.

Improvement in PVR by selexipag over placebo is indicated by a small (< 1) ratio of the geometric mean ($GM_{selexipag}/GM_{placebo}$).

5.3.3.2. Handling of Missing Data

5.3.3.2.1. Main imputation approach

Imputation methods for PVR will be specific to the reason for missing data.

The baseline reference value for PVR is based on the last right heart catheterization (RHC) (and LHC, if needed) performed prior to randomization (see protocol Section 7.2.3.1.1).

If PVR cannot be calculated due to missing PAWP and LVEDP, the following conventions will be applied for the calculation at a visit at which both mPAP and CO are assessed:

1. If PAWP and LVEDP are missing both at baseline and post-baseline, the missing PAWP is imputed using the median of all values observed at the respective time point in all subjects from the same randomized treatment group.
2. If PAWP and LVEDP are missing either at baseline or at post-baseline, the available PAWP for the subject is used as a substitute for the missing PAWP.

In the case of a missing PVR value at Week 20, the last available post-baseline value obtained before the Week 20 analysis time window is carried forward. It is assumed that this will mainly occur in subjects who have an unscheduled RHC performed at the time of a PH-related disease progression prior to the Week 20 analysis time window. This imputation will be performed except in the following cases:

- If a subject dies without a Week 20 value, then the missing pre-post percent value is imputed with the largest pre-post percent value at Week 20 amongst all subjects in the same treatment group and analysis set (as in Zeng 2012 and Ghofrani 2017). The resulting imputed Week 20 PVR is the product of this imputed pre-post percent value and the respective baseline PVR value. Subjects who die before the Week 20 assessment are likely to have experienced considerable deterioration prior to death. This imputation approach assigns the worst observed value in the same treatment group to such subjects; hence presenting the potentially worst-case scenario.
- If the subject is alive and does not have a post-baseline value, then the missing pre-post percent value is imputed with the 50^{th} percentile of the pre-post percent values from all subjects in the same treatment group and analysis set (as in Ghofrani 2017). The resulting imputed Week 20 PVR is the product of this imputed pre-post percent value and the respective baseline PVR value. Subjects who are still alive at Week 20 are likely to be in relatively good condition. This imputation approach assigns the median value in the same treatment group to such subjects; hence presenting a neutral scenario.

Observed PVR values (excluding those PVR values beyond the analysis time window) will be used to derive the imputed values.

5.3.3.2.2. Alternative imputation approach

As an alternative approach for missing values, multiple imputation will be applied (Carpenter 2008, O'Kelly 2014), under the assumption of missing at random, with slight modification based on the reason for missingness.

The randomly imputed value for a missing $\log_e$-transformed PVR pre-post percent value (due to missing at baseline or at Week 20) will be generated from a normal distribution with a mean value that depends on the reason for missingness, and a variance estimated from the complete cases within the subject's treatment group and analysis set.

Reasons for missing information are derived from collected data in the electronic Case Report Form (eCRF) and are expected to be justified by a change in outcome (such as WHO FC, AE, etc.). For each missing pre-post percent value, the reason for missingness is categorized to worsening, no change or improvement. The criteria for the categorization and the corresponding means and standard deviations (SD) for the normal distributions to generate imputed values of $\log_e$-transformed PVR pre-post percent are summarized in Table 10 below.

Table 10: Categorization of missing data and the corresponding means and standard deviations for the normal distributions to generate imputed log_e-transformed pre-post percent values of PVR

Category	Criterion	Mean[a] for imputation	SD[a,b] for imputation
Worsening	If subject has: A worsening in WHO FC (increase from baseline) is reported at or before the time point of missing data, or Any treatment-emergent SAE occurrence, or Study treatment or study is prematurely discontinued with the main reason given as lack of efficacy, treatment failure, tolerability or efficacy related.	The upper quartile of the log_e-transformed pre-post percent values	One quarter of the difference between the maximum and the median of the observed log_e-transformed pre-post percent values
Improvement	If subject has: No above-mentioned SAEs or premature discontinuation, and An improvement in WHO FC (decrease from baseline) is reported at or before the time point of missing data.	The lower quartile of the log_e-transformed pre-post percent values	One quarter of the difference between the minimum and the median of the observed log_e-transformed pre-post percent values
No change	All other cases with missing data.	The median of the log_e-transformed pre-post percent values	The SD of observed log_e-transformed pre-post percent values per treatment group and analysis set

SD = standard deviation.

[a] Mean and standard deviation for a normal distribution, determined based on complete cases in the respective treatment group and analysis set.

[b] The standard deviation to be used to generate imputed pre-post percent values is designed to create an appropriate distribution of imputed values around the upper quartile, the median and the lower quartile for the worsening, no change and improvement categories, respectively.

With the respective means and SDs, missing log_e-transformed pre-post percent values will be imputed randomly from normal distributions to create a total of 100 analysis sets with complete data. ANCOVA models as described in Section 5.3.3.1 will be applied to each of these 100 analysis sets. Results will be aggregated following Rubin's rule, ie, the final estimate is the mean of per-imputation point estimates and the final variance is the sum of the average within-imputation variance and 1.01 times the between-imputation variance (Rubin 1987). On final point and variance estimates, 95% CL will be determined before back-transformation.

In summary, the randomly imputed value of $\log_e$-transformed pre-post percent for a subject will be generated from:

- normal distributions based on complete cases for each treatment arm
- Mean/SD adjusted for reasons for missingness

Step 1: Derive the quartiles, maximum and minimum within treatment group from the non-missing values of the $\log_e$-transformed PVR pre-post percent change from baseline to Week 20.

Step 2: Impute the missing data by drawing a value from a normal distribution with a Mean and SD depending on the subject categorization in Table 10.

Step 3: Repeat step 2, 100 times

Step 4: Estimate treatment difference using ANCOVA analysis with stratification factors (PH-specific therapies and CTEPH population) and the $\log_e$-transformed baseline PVR value as covariates and treatment as factor in the model for each of the imputed datasets generated in step 3.

Step 5: Use the SAS MIANALYZE procedure to estimate the combined treatment difference and standard error from the estimates obtained in step 4.

5.3.3.3. Main, Sensitivity and Supplementary Analyses

5.3.3.3.1. Main analysis

For the main estimand defined in Section 5.3.2, the main analysis refers to the final analysis of PVR at Week 20 with observed or imputed values (using the main imputation approach in Section 5.3.3.2.1), tested on the HES (pre-planned with approximately 90 subjects) at a full 2-sided significance level of 5% using the ANCOVA model (see Section 5.3.3.1). Missing PVR assessments at baseline or at Week 20 will be imputed specific to the reason for missing data and death occurring prior to the Week 20 visit will be addressed by imputing the Week 20 PVR value, using the rules defined in Section 5.3.3.2.1. PVR values beyond the analysis time window will also be imputed using the rules defined in Section 5.3.3.2.1, for subjects who are alive and do not have a post-baseline value.

From the ANCOVA model, PVR pre-post percent will be summarized by treatment group using covariate-adjusted geometric means and corresponding 2-sided 95% CL. The between-group ratio of geometric means with corresponding 2-sided 95% CL and p-value will be displayed as the placebo-corrected treatment effect.

For each treatment group, the arithmetic mean and 95% CL of the natural logarithm of the pre-post percent will be inversely transformed using the exponential function and multiplied by 100 to provide the geometric mean of the pre-post percent and the corresponding 95% CL, expressed as a percent.

Absolute values at baseline and at Week 20 as well as absolute pre-post changes from baseline to Week 20 in PVR will also be summarized using descriptive statistics.

A listing of observed and imputed values and changes from baseline to Week 20 for PVR will be provided for the HES by treatment group. Observed data after EDBT (PTOP) and imputed data will be flagged.

A listing of hemodynamic parameters (as per Table 16) will also be provided on the FAS (HES subjects will be flagged).

5.3.3.3.2. Sensitivity analyses

For the main estimand defined in Section 5.3.2, the following sensitivity analyses will be performed to assess the robustness of the main analysis results. All these analyses will be performed on the HES. Given the descriptive nature of these analyses, no adjustments for multiplicity testing will be considered

1. An analysis using the alternative imputation approach (Section 5.3.3.2.2) to assess the imputation assumptions of the main statistical analysis for PVR at Week 20.
2. An analysis of PVR at Week 20 using the main imputation approach for missing data (Section 5.3.3.2.1) but including all observed post-baseline PVR values ie, no imputation for values beyond the analysis time window, to assess the impact of delayed RHC assessments (assumed to be mainly due to COVID-19).
3. The median treatment effect using the Hodges-Lehmann estimate and the corresponding 95% asymptotic (Moses) CL will be derived and displayed, to assess relaxation of the assumption for the main ANCOVA model (Section 5.3.3.3.1).
4. An analysis following the main analysis approach in Section 5.3.3.3.1 but where the ANCOVA model covariates will include randomized treatment, stratification factors (PH-specific therapies and CTEPH population as per the eCRF (rather than the IRT stratification factors) and the $\log_e$-transformed baseline PVR value.

5.3.3.3.3. Supplementary analyses

In support of the main estimand, two supplementary estimands using subsets of the HES will be evaluated as described below. Given the descriptive nature of these analyses, no adjustments for multiplicity testing will be considered.

1. An analysis of PVR at Week 20 using the main imputation approach (Section 5.3.3.2.1) will be conducted in the subset of the HES meeting the PPS criteria to assess the robustness of the results of the main statistical analysis against protocol deviations leading to exclusion from the PPS.
2. A further analysis will be conducted using observed data only (including the delayed PVR values beyond the analysis time window) ie, with no imputation, on the HES, to assess the impact of delayed/missing RHC assessments (assumed to be mainly due to COVID-19) on the analysis of PVR at Week 20.

5.3.3.4. Subgroup Analyses

In order to assess the consistency of the treatment effect across different subject subgroups for the primary efficacy variable, subgroup analyses will be performed according to the demographic and baseline disease characteristics at randomization as defined in Table 14 on the HES. No multiplicity adjustment will be introduced; the subgroup analyses are descriptive in nature.

Subgroup analyses will be conducted according to the ANCOVA method for the main analysis as described in Section 5.3.3.3.1.

The treatment effect within subgroups will primarily be displayed with their corresponding 95% CLs and presented in a forest plot. The forest plot will also include as a reference the 'overall' treatment effect based on the main analysis (as described in Section 5.3.3.3.1).

Subjects with undetermined subgroup information due to missingness will not be included in the subgroup analyses.

5.4. Secondary Endpoint(s) Analysis

Following the decision to prematurely terminate the study due to futility at analysis time point 1, all efficacy analyses other than PVR are exploratory and therefore the presented p-values for each secondary endpoint will be for exploratory purposes only. For each secondary endpoint, a 2-sided 95% CL for treatment effect will also be presented.

Details of the key secondary efficacy endpoints of 6MWD at Week 26 and TTCW are provided in Section 5.4.1 and 5.4.2 and for the supportive secondary efficacy endpoint BDI/Borg CR10® in Section 5.4.3.

5.4.1. 6MWD at Week 26 (key secondary endpoint)

5.4.1.1. Definition of Endpoint

6MWD at Week 26 is defined as the change from baseline to Week 26 in 6MWD (in meters):

6MWD pre-post change (m) = 6MWD (m) at Week 26 − 6MWD (m) at baseline.

The baseline reference value (baseline) for the 6MWD is the distance obtained from the last 6-minute walk test (6MWT) performed prior to or at randomization. The Week 26 value is the one identified for the Week 26 analysis time window (see Table 8).

The longer 6MWD values indicate better condition.

5.4.1.2. Estimand

The main estimand defining the treatment effect for the 6MWD at Week 26 endpoint has the following attributes:

A. Treatment:

- Experimental: Selexipag

- Control: Placebo

B. Population: Subjects with inoperable CTEPH or persistent/recurrent CTEPH after surgical (PEA) and/or interventional (BPA) treatment in the Efficacy Evaluable Set (EES).

C. Variable: 6MWD at Week 26, expressed as change from baseline value. For subjects who die without a Week-26 6MWD assessment, the Week-26 6MWD will be imputed as defined in Section 5.4.1.3.2.1.

D. Summary measure (Population-level summary): The main estimator of the treatment effect will be evaluated using descriptive statistics.

E. Intercurrent events (IE) and their corresponding strategies: IEs and their corresponding strategies are summarized in Table 11 below.

Table 11: Intercurrent Events and Corresponding Strategies for the Main Estimand of 6MWD

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Premature discontinuation of DB treatment for any reason	Treatment policy strategy: The occurrence of the IE is considered irrelevant in defining the treatment effect of interest ie, the value of the variable of interest is used regardless of whether or not the IE occurs (to reflect intention-to-treat (ITT) principle). Data for the variable of interest will still be collected after the IE (in PTOP).
Receiving additional therapy	
Death	Composite variable strategy: The IE is considered in itself to be informative about the subject's outcome and is therefore incorporated into the definition of the variable. For subjects who died without any visit performed in the Week 26 analysis time window, 0m is imputed for the 6MWD at Week 26 assessment, as defined in Section 5.4.1.3.2.1.

5.4.1.3. Analysis Methods

5.4.1.3.1. Statistical model

Hypotheses and statistical model:

The hypotheses for the key secondary endpoint 6MWD at Week 26 are described in Section 2.2.

6MWD values at baseline and at Week 26 as well as pre-post changes from baseline to Week 26 will be summarized using descriptive statistics, on the EES.

5.4.1.3.2. Handling of missing data

5.4.1.3.2.1. Main imputation approach

Missing values of 6MWD at Week 26 will be imputed as follows:

- Rule 1: For subjects unable to walk at Week 26, a 0 is imputed for 6MWD at Week 26. This includes:
  - Subjects who died without any visit performed in the Week 26 analysis time window

  - Subjects for whom the Week 26 Visit corresponds to a scheduled (or unscheduled) visit and who were unable to walk due to clinical worsening (ie, the reason is entered in the eCRF as 'Clinical worsening (PH-related)')

- Rule 2 (if Rule 1 does not apply): The second-lowest observed 6MWD value at Week 26 in the same analysis set, according to treatment group, is imputed.

5.4.1.3.3. Main, sensitivity and supplementary analyses

5.4.1.3.3.1. Main analysis

For the main estimand defined in Section 5.4.1.2, the above-mentioned summary using descriptive statistics will be presented. Missing 6MWD assessments at Week 26 will be imputed using the rules defined in Section 5.4.1.3.2.1.

A listing of observed and imputed values and changes from baseline to Week 26 for 6MWD will also be provided by treatment group, on the EES. Observed data after EDBT (PTOP) and imputed data will be flagged.

Further descriptive analyses of 6MWD over time, on the FAS, are outlined in Section 5.5.2.

5.4.2. TTCW (key secondary endpoint)

5.4.2.1. Definition of Endpoint

The other key secondary efficacy endpoint is TTCW, where clinical worsening is defined (adapted from the CHMP definition [EMEA 2008]) as at least one of the following components, confirmed by the CEC:

- All-cause death
- Non-planned PH-related hospitalization
- PH-related deterioration identified by at least one of the following:
  - Increase from baseline in WHO FC*;
  - Deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD*;
  - New or worsening of signs or symptoms of right heart failure, defined as a reported AE with one of the following preferred terms: "CTEPH", "pulmonary hypertension", "right ventricular failure", "right ventricular dysfunction" and "acute right ventricular failure".

  *Confirmed by a second measurement performed on a different day within 14 days.

The CEC confirms which component corresponds to the onset of clinical worsening, selecting only one component from the highest level ie, All-cause death, Non-planned PH-related hospitalization, or PH-related deterioration. In the case of PH-related deterioration, multiple sub-components can be selected if they have the same onset date and should this be the case, then the conditions are ordered hierarchically as follows (decrease of severity from 1 to 3; where the most severe component will be taken as the onset of clinical worsening):

1. New or worsening of signs or symptoms of right heart failure
2. Increase from baseline in WHO FC
3. Deterioration from baseline by at least 15% in exercise capacity

The CEC adjudicate clinical worsening events from DB and PTOP periods only (as per CEC charter).

5.4.2.2. Estimand

The main estimand defining the treatment effect for the TTCW endpoint has the following attributes:

A. Treatment:

- Experimental: Selexipag
- Control: Placebo

B. Population: Subjects with inoperable CTEPH or persistent/recurrent CTEPH after surgical (PEA) and/or interventional (BPA) treatment in the FAS.

C. Variable: TTCW will be calculated from date of randomization to the date of onset of the first CEC confirmed (applicable for DB summaries only) component event (Section 5.4.2.1). For subjects who have not experienced an event by the respective cut-off date, their time will be right censored at the earliest date of the following: EDBT visit, the last PTOP visit or last contact. Longer times to clinical worsening indicate better condition.

D. Summary measure (Population-level summary): HR of selexipag versus placebo.

E. Intercurrent events (IE) and their corresponding strategies: IEs and their corresponding strategies are summarized in Table 12 below.

Table 12: Intercurrent Events and Corresponding Strategies for the Main Estimand of TTCW

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Premature discontinuation of DB treatment for any reason	Treatment policy strategy: The occurrence of the IE is considered irrelevant in defining the treatment effect of interest ie, the value of the variable of interest is used regardless of whether or not the IE occurs (to reflect intention-to-treat (ITT) principle). Data for the variable will still be collected after the IE (in PTOP).
Receiving additional therapy	
Hospitalization not related to PH	
• All-cause death • Non-planned PH-related hospitalization • PH-related deterioration (Section 5.4.2.1)	Composite variable strategy: An IE is considered in itself to be informative about the subject's outcome and is therefore incorporated into the definition of the variable. Value of the variable at the time of IE component: $\text{TTCW} = \begin{cases} \text{t(IE component), if IE component occurs} \\ \text{Censored, if IE component does not occur} \end{cases}$

5.4.2.3. Analysis Methods

5.4.2.3.1. Statistical model

Hypotheses and statistical model:

The hypotheses for the key secondary endpoint TTCW are described in Section 2.2.

Kaplan-Meier estimates for the survival functions will be provided. The HR will be estimated using a Cox model, including treatment group and all stratification factors as covariates.

Improvement by selexipag over placebo is indicated by a small (<1) HR, ie, (hazard with selexipag)/(hazard with placebo).

5.4.2.3.2. Handling of missing data

For subjects who have not experienced any event by the respective analysis cut-off date, their time will be right censored at the earliest date of the following: EDBT visit, the last PTOP visit or last contact.

5.4.2.3.3. Main, sensitivity and supplementary analyses

5.4.2.3.3.1. Main analysis

The frequency of each component event will be presented by treatment group and separately for the DB and OL treatment periods.

TTCW will be summarized for the DB and OL treatment periods, where Kaplan-Meier estimates for the survival functions will be provided together with 2-sided 95% CL. The HR and the corresponding 2-sided 95% CL in the DB treatment period will be estimated using a Cox model, including treatment group and all stratification factors as covariates. Kaplan-Meier plots will also be provided for the DB treatment period only.

Listings will be provided including a description of clinical worsening events with flags to indicate CEC confirmation status, occurrence of any events during the PTOP and censored times.

5.4.2.3.3.2. Sensitivity analyses

For the main estimand defined in Section 5.4.2.2, the following sensitivity analysis will be performed to assess the robustness of the main analysis results.

> An analysis following the main analysis approach in Section 5.4.2.3.3.1 but where the stratification factors (PH-specific therapies and CTEPH population) will be utilized as per the eCRF, rather than the IRT stratification factors.

5.4.3. Supportive Secondary Endpoint(s)

The hypothesis for the supportive secondary endpoint is described in Section 2.2.

5.4.3.1. Change from baseline to Week 26 in BDI/Borg CR10®

Dyspnea is assessed by two scales in this study: the BDI scale or the Borg CR10® scale (protocol Appendix 4 and Appendix 5, respectively], at time points indicated in the study visits and assessment schedules in Table 3, Table 4 and Table 5, immediately after stopping the 6MWT.

If a subject started the study using the BDI scale, then that scale will be used for the duration of their participation in the study. This also applies for the Borg CR10® scale.

The scales are used to rate the strength of the subject's perception on dyspnea and exertion. The numeric points on the scale are anchored by (categorical) verbal expressions. Responses can range from 0 to 10 for the BDI scale and from 0 to beyond a score of 10 for the Borg CR10® scale.

The lower BDI/Borg CR10® values indicate better condition.

5.4.3.1.1. Definition

Absolute pre-post change from baseline to Week 26 in BDI/Borg CR10® is defined as:

BDI/Borg CR10® pre-post change = BDI/Borg CR10® at Week 26 − BDI/Borg CR10® at baseline.

Improvement by selexipag over placebo is indicated by a negative (<0) difference in the mean pre-post change, ie, (mean pre-post change with selexipag) – (mean pre-post change with placebo).

5.4.3.1.2. Analysis Methods

The null hypothesis is that there is no difference between selexipag and placebo in the mean pre-post change.

The BDI/Borg CR10® pre-post changes will be analyzed by means of an ANCOVA model including treatment, baseline index value and stratification factors as covariates. Least squares estimates for each treatment group will be displayed with means and 95% CLs.

BDI/Borg CR10® values at baseline and at Week 26 as well as pre-post changes from baseline to Week 26 will also be summarized using descriptive statistics, on the EES.

A listing of observed values and changes from baseline to Week 26 for BDI/Borg CR10® will also be provided by treatment group, on the EES.

Further descriptive analyses of BDI/Borg CR10® over time, on the FAS, are outlined in Section 5.5.1.

Handling of missing data

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.5. Exploratory Endpoint(s) Analysis

Unless otherwise indicated, all exploratory efficacy analyses will be performed on the FAS. Given the exploratory nature of these analyses, no adjustment for multiplicity will be done.

5.5.1. Change from baseline up to EOS, by visit, in BDI/Borg CR10® collected immediately at the end of each individual 6MWT

Dyspnea is assessed by either the BDI scale or the Borg CR10® scale, as described in Section 5.4.3.1.

Analyses for change from baseline up to EOS (including OL), by visit, will be presented.

5.5.1.1. Definition

Absolute pre-post change from baseline to each post-baseline visit in BDI/Borg CR10® is defined as:

BDI/Borg CR10® pre-post change = BDI/Borg CR10® at a post-baseline visit − BDI/Borg CR10® at baseline.

5.5.1.2. Analysis Methods

Absolute values at baseline and at each visit, as well as absolute changes from baseline, by visit and separately for the DB and OL treatment periods, will be summarized by treatment group on the FAS using descriptive statistics.

Handling of missing data

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.5.2. Change from baseline up to EOS, by visit, in exercise capacity, as measured by the 6MWD

Analyses for change from baseline up to EOS (including OL), by visit, will be presented.

5.5.2.1. Definition

Similar to the key secondary endpoint analysis described in Section 5.4.1 except for the variable which uses data up to EOS:

Variable: 6MWD up to end of EOS, expressed as change from baseline value.

5.5.2.2. Analysis Methods

Absolute values at baseline and at each regular collection timepoint up to EOS, as well as absolute changes from baseline up to EOS, for each regular collection timepoint and separately for the DB and OL treatment periods, will be summarized by treatment group on the FAS using descriptive statistics.

A listing of observed values for 6MWD over time will be provided for the FAS. PTOP type data will be flagged.

Handling of missing data

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.5.3. Change from baseline to Week 20 in other hemodynamic parameters (cardiac output [CO], cardiac index [CI] and mean right atrial pressure [mRAP]) measured at rest

5.5.3.1. Definition

Hemodynamic parameters are collected in the study, based on RHC results and RHC methodology as described in Section 7.2.3.1 of the protocol and in the sponsor heart catheterization guidance in Appendix 1 of the protocol.

Table 13 provides a list of all hemodynamic parameters of interest, their source and derivation rules (if applicable). Whenever duplicate/triplicate measurements are collected, the relevant mean/most accurate assessment, as appropriate, should be used for the derivations described in Table 13.

Table 13: Overview of hemodynamic parameters

Hemodynamic Parameter	Source	Derivation
Pulmonary artery wedge pressure (PAWP)	eCRF	As collected
Left ventricular end diastolic pressure (LVEDP)	eCRF	As collected, if available
Systolic pulmonary artery pressure (sPAP)	eCRF	As collected (2 measurements and their average calculated by the eCRF)
Diastolic pulmonary artery pressure (dPAP)	eCRF	As collected (2 measurements and their average calculated by the eCRF)
Mean pulmonary artery pressure (mPAP)	eCRF	As collected (calculated by the eCRF)
Thermodilution Cardiac output (CO)	eCRF	As collected (3 measurements and their average calculated by the eCRF)
Fick Cardiac output (CO)	eCRF	As collected (3 measurements and their average calculated by the eCRF)
Heart Rate	eCRF	As collected
Mean right atrial pressure (mRAP)	eCRF	As collected
Mixed venous oxygen saturation (SvO2)	eCRF	As collected
Systolic Systemic Arterial Pressure (s-SAP)	eCRF	As collected
Diastolic Systemic Arterial Pressure (d-SAP)	eCRF	As collected
Pulmonary Vascular Resistance (PVR) Wood Units	eCRF	As collected (calculated by the eCRF)
Pulmonary Vascular Resistance (PVR) dyn.sec/cm5	eCRF	As collected (conversion by the eCRF)
Cardiac index (CI)	eCRF	As collected (calculated by the eCRF)
Total pulmonary resistance (TPR)	eCRF	As collected (calculated by the eCRF)

The variables which will be used for this exploratory analysis are change from baseline to Week 20 in the following hemodynamic parameters:

- CO
- CI
- mRAP

5.5.3.2. Analysis Methods

Absolute values at baseline and at Week 20 as well as absolute changes from baseline to Week 20 will be summarized by treatment on the HES using descriptive statistics.

Handling of missing data

In case of missing data, no imputation will be performed and only observed data will be summarized.

5.6. Safety Analyses

All safety analyses will be based on the SAF according to actual treatment received, unless otherwise specified.

Summaries will be performed separately for the DB and OL treatment periods, where applicable.

For all continuous safety variables, descriptive statistics by treatment group will include the N, mean, SD, median, and range [minimum, maximum]. Categorical variables will be summarized by treatment group using frequency counts and percentages.

5.6.1. Extent of Exposure

5.6.1.1. Exposure Duration

The number and percentage of subjects who receive study treatment will be summarized separately for the DB and OL treatment periods.

Study treatment duration in days is defined as (date of last dose of study treatment – date of first dose of study treatment) +1.

Descriptive statistics for study treatment duration will be presented. Subject-years of exposure is calculated as days of exposure/365.25. Subject-months of exposure is calculated as days of exposure/30.4.

Duration of exposure will be summarized with number and percentage in the following duration categories (where applicable): <1 month, 1 - <3 months, 3 - <6 months, 6 - <12 months, 12 - <24 months, 24 - <36 months, ≥36 months.

Cumulative exposure will be summarized with number and percentage in the following duration categories (where applicable): ≥1 month, ≥3 months, ≥6 months, ≥12 months, ≥24 months, ≥36 months.

5.6.1.2. iMTD

The individual maximum tolerated dose (iMTD) will be expressed for twice daily (bid) dosing frequency.

- If once daily (qd) dosing frequency is applied, it will be grouped together with the bid dose as the iMTD only when moderate CYP2C8 inhibitors are co-administered or for subjects with moderate hepatic impairment (Child-Pugh B): eg, 200 µg bid and 200 µg qd will be grouped together as an iMTD of 200 µg bid.
- For subjects with no co-administration of moderate CYP2C8 inhibitor or no moderate hepatic impairment (Child-Pugh B), dose X µg qd will be considered as equivalent to X/2 µg bid.

The iMTD of each treatment period (DB or OL) will be defined by the following rules as per the selexipag standard:

- Subjects who entered the study defined maintenance period (= who completed the study titration period):
  - The iMTD is defined as the last bid/qd dose at the end of titration period, ie, the dose administered on study day 85 after the first dose of treatment in the DB treatment period or on study day 85 after the first dose of treatment in the OL period.
- Subjects who did not enter the study defined maintenance period (= who discontinued the study treatment during the study titration period):
  - The iMTD is defined as the latest bid/qd dose that was not ended for the following reasons: "Dose reduced due to an AE", "Dose reduced not due to an AE", "Temporarily interrupted due to an AE", "Temporarily interrupted not due to an AE" or "Premature discontinuation".
  - If the latest bid/qd dose is 200 µg and was ended for "Dose reduced due to an AE", "Dose reduced not due to an AE", "Temporarily interrupted due to an AE", "Temporarily interrupted not due to an AE" or "Premature discontinuation", then the iMTD is defined as zero.

The bid/qd iMTD for each treatment period will be summarized with descriptive statistics, the number and percentage of subjects in each iMTD dose level and in each iMTD dose category: Low (200-400 µg bid), Medium (600, 800 and 1000 µg bid) and High (1200, 1400 and 1600 µg bid). For subjects who discontinued during the up-titration period, then iMTD = 0 since iMTD was not determined in those subjects, then their 0 dose will be included in the < 200 mcg bid category.

5.6.1.3. Others

For each study treatment period, the mode dose for a subject is defined as the dose that was administered for the longest duration, irrespective of interruptions, for that subject within the respective treatment period. In case of in a tie, the highest dose will be taken as the mode dose.

For each study treatment period, the weighted average dose for a subject is defined as the average of daily bid dose intensity for that subject within the respective treatment period. The exposure SDTM dataset will have records of all dose levels administered. If the end date of bid dose level

X and the start date of bid dose level Y are the same, it will be assumed that the subject took dose X in the morning and dose Y in the evening. In this case, the daily bid dose intensity on that day is calculated as (X + Y)/2. If a subject took qd dose level Z, the daily bid dose intensity will be calculated as Z/2.

The mode doses and the weighted average doses of all subjects will be summarized with descriptive statistics for the titration period in DB (up to and including study day 84), the maintenance period in DB (start on study day 85), the entire DB treatment period, the titration period in OL (up to and including study day 84 after treatment initiation in the OL period), the maintenance period in OL (start on study day 85 after treatment initiation in OL period), and the entire OL treatment period.

Study treatment administration will also be listed.

5.6.2. Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be summarized separately for the DB and OL treatment periods and defined as follows:

- DB: Any AE occurring at or after the initial administration of study treatment through the day of last dose in the double-blind treatment period plus 3 days (EDBT +3 days) and prior to start of OL study treatment (as subjects transition without interruption to the OL period) is considered to be treatment-emergent. For subjects who transition to the OL treatment period and have their first OL dose (evening dose) on the same day as their EDBT dose (morning dose), then their event(s) are assigned to the DB treatment period.
- OL: Any AE occurring after the initial administration of study treatment in the OL treatment period through the day of last dose in the OL treatment period plus 3 days is considered to be treatment-emergent. For subjects who transition to the OL treatment period, any AE from Day 2 of the OL treatment period is assigned to OL (regardless of the +3 days from EDBT).

If the event occurs on the day of the initial administration of study treatment, and either event time or time of administration (morning or evening) are missing, then the event will be assumed to be treatment-emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment-emergent unless it is known to be prior to the first administration of study treatment based on partial onset date or resolution date.

For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group, by system organ class (SOC) and preferred term (PT) in descending order of frequency in the selexipag treatment group.

Summary tables will be provided, for DB and OL treatment periods, for:

- overall summary tables of treatment-emergent AEs
- treatment-emergent AEs
- treatment-emergent serious AEs (SAEs)

- treatment-emergent AEs leading to permanent discontinuation of study treatment
- treatment-emergent AEs by severity
- treatment-emergent AEs related to study treatment
- treatment-emergent SAEs related to study treatment
- treatment-emergent AEs leading to hospitalization
- treatment-emergent AEs leading to dose interruption/dose modification of study treatment.
- treatment-emergent AEs with fatal outcome
- all SAEs up to 30 days after study treatment discontinuation
- all SAEs up to EOS (defined as in protocol Section 8.1)

In addition to the summary tables, listings will be provided, for DB and OL treatment periods, for subjects who had:

- treatment-emergent AEs
- treatment-emergent SAEs
- treatment-emergent AEs leading to permanent discontinuation of study treatment
- treatment-emergent AEs with fatal outcome

5.6.2.1. Adverse Events of Special Interest (AESI)

Incidence of treatment-emergent AESI, for DB and OL treatment periods, will also be summarized by treatment group, by AESI category and PT (in descending order of frequency in AESI category, in the selexipag treatment group). See Section 6.8 Appendix 8 for the list of categories of AESI.

In addition, each treatment-emergent AESI category will be summarized by preferred terms (PTs) and treatment group and will include:

- Number and % of subjects with at least one AESI
  - Relative risk with 95% CI for selexipag vs. placebo
- Number and % of subjects with at least one AESI leading to permanent discontinuation of study treatment
- Number and % of subjects with at least one serious AESI
- Number and % of subjects with at least one related AESI
- Number and % of subjects with at least one fatal AESI
- Number and % of subjects with at least one event within the worst severity category where the following hierarchical order is considered to determine worst severity: Severe, Moderate, Mild, Missing
- For recurrent events:

- Cumulative number of recurrent AESIs (note: this includes the total number of events as subjects may have multiple PTs under an AESI category, and multiple events in a given PT)
- Average annualized event rate (AER)

  where AER (per 100-SY) $= \left(\frac{Cumulative\ number\ of\ recurrent\ events}{SY\ treatment\ exposure} \times 100\right)$
- Subject Years (SY) of treatment exposure (calculated as indicated in Section 5.6.1.1) and is further based on first dose of study treatment up to EDBT +3days / EOLT +3days, as applicable
- Outcome for cumulative number of recurrent AESIs
  - Number and % of fatal events
  - Number and % of not recovered/not resolved events
  - Number and % of events that recovered/resolved with sequelae
  - Number and % of recovered/resolved events
  - Number and % of events with unknown outcome

In addition to the AESI summary tables, listings by treatment group and AESI category will also be provided for DB and OL treatment periods. Further listings for other AESI categories, for the DB and OL treatment periods, will also be provided.

5.6.2.2. Deaths

Deaths will be summarized by treatment group and separately for the DB and for the overall study period.

Summary tables will be provided for:

- all deaths in the DB period up to EDBT + 30 days (up to start of the OL period)
- all deaths up to EOS (defined as in protocol Section 8.1)

Frequencies for the following parameters will be included in the summary tables:

- Number of subjects who died
- Cause of death
- Relationship to study treatment (yes/no)

The summary will be based on the Death Information eCRF page, and relationship to the study treatment will be mapped through the corresponding AE, if available.

A listing of subjects who died will be provided including the study day of death in relation to Study Day 1 and days off treatment.

5.6.2.3. Subgroup Analyses

The following treatment-emergent AEs in the DB treatment period will also be summarized for specific subgroups as defined below:

- treatment-emergent AEs
- treatment-emergent SAEs

by

- Gender (Male vs. Female)
- Age (18-64 years vs. 65-74 years vs. ≥75 years)

Subgroup analyses will not be conducted for the OL treatment period (only 15 subjects entered the OL treatment period).

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

All laboratory data will be reported in International System (SI) units [except for eGFR, where the conventional unit will be used, as per Section 6.10 Appendix 10 (mL/min/1.73m^2)]. All laboratory data provided by central laboratory will be considered regardless of whether they correspond to scheduled (per protocol) or unscheduled visits. Local laboratory data (scheduled or unscheduled) will be included in listings and used only to find marked abnormalities. If a value below limit of quantification (LOQ) is recorded, the LOQ value itself will be used in the summaries instead. It will be clearly noted in the listings if a value is below LOQ.

List of parameters:

Clinical Chemistry	**Hematology**
Alanine aminotransferase (ALT)	Basophils
Alkaline phosphatase	Basophils/Leukocytes (fraction of 1)
Aspartate aminotransferase (AST)	Eosinophils
Bilirubin	Eosinophils/Leukocytes (fraction of 1)
Creatinine	Erythrocytes Mean Corpuscular Volume
Direct Bilirubin	Erythrocytes
Glomerular Filtration rate Adj for BSA	Hematocrit
Potassium	Hemoglobin
Sodium	Leukocytes
Thyrotropin [Thyroid Stimulating Hormone (TSH)]	Lymphocytes
Thyroxine (T4)	Lymphocytes/Leukocytes (fraction of 1)
Thyroxine, Free (FT4)	Monocytes
Triiodothyronine (T3)	Monocytes/Leukocytes (fraction of 1)
Triiodothyronine, Free (FT3)	Neutrophils, Segmented
	Neutrophils, Segmented/Leukocytes (fraction of 1)
	Platelets

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled time points by treatment group, and separately for the DB and OL treatment periods. Change from baseline to each scheduled post-baseline visit will also be summarized.

Marked abnormalities in laboratory data are defined in Section 6.10 Appendix 10 (notable values/changes from baseline for thyroid parameters of interest are provided below).

Marked abnormalities will be summarized by treatment group, separately for chemistry and hematology laboratory parameters and separately for the DB and OL treatment periods, defined as follows:

- DB: Any abnormality occurring at or after the initial administration of study treatment through the day of last dose in the double-blind treatment period plus 3 days (EDBT +3 days) and prior to the start of OL study treatment (as subjects transition without interruption to the OL period) is considered to be treatment-emergent.
- OL: Any abnormality occurring after the initial administration of study treatment in the OL treatment period through the day of last dose in the OL treatment period plus 3 days is considered to be treatment-emergent.

If the abnormality occurs on the day of the initial administration of study treatment, and either the laboratory collection time or time of study treatment administration are missing, then the abnormality will be assumed to be treatment-emergent. If the date of the abnormality is recorded as partial or completely missing, then the abnormality will be considered to be treatment-emergent unless it is known to be prior to the first administration of study treatment based on partial onset date or resolution date. If the abnormality was present at baseline, then any post-baseline abnormality will be considered to be treatment-emergent only if the post-baseline abnormality is in a category worse than at baseline.

In case the abnormality is defined based on the lower or upper limit of the normal reference range (eg, Alanine aminotransferase) and the corresponding lower or upper limit is not available, the abnormality will not be derived.

In case the marked abnormality is defined as an increase from the baseline (eg, Hemoglobin), comparison of the central laboratory baseline value with the local laboratory post-baseline value to assess the marked abnormality is allowed.

The number and percentage of subjects with treatment-emergent marked abnormal values will be presented for each chemistry and hematology laboratory parameter for which marked abnormalities are defined, by treatment group, and separately for the DB and OL treatment periods.

In addition to the summary tables, chemistry and hematology laboratory data will be listed, together with a derived marked abnormality flag. Separate listings of marked abnormality chemistry and hematology laboratory values will also be provided.

The following summaries will also be provided for thyroid parameters of interest:

The number and percentage of subjects with clinically notable TSH change from baseline (as defined below) by treatment group, and separately for the DB and OL treatment periods.

- TSH ≤0.1 mIU/L
- TSH >0.1 mIU/L and <0.45 mIU/L
- TSH ≥5.33 mIU/L and < 10 mIU/L
- TSH ≥10 mIU/L

5.6.3.2. Vital Signs and Physical Examination Findings

Vital signs will be summarized at scheduled time points, by treatment group and separately for the DB and OL treatment periods.

Continuous vital sign parameters including weight, pulse, blood pressure (systolic and diastolic) and body mass index (BMI) at each assessment time point as well as the change from baseline to each post-baseline assessment visit will be summarized with descriptive statistics. BMI will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation.

Notable vital signs will be summarized by treatment group and separately for the DB and OL treatment periods, defined as follows:

- DB: Any abnormality occurring at or after the initial administration of study treatment through the day of last dose in the double-blind treatment period plus 3 days (EDBT +3 days) and prior to the start of OL study treatment (as subjects transition without interruption to the OL period) is considered to be treatment-emergent.
- OL: Any abnormality occurring after the initial administration of study treatment in the OL treatment period through the day of last dose in the OL treatment period plus 3 days is considered to be treatment-emergent.

Incidence of treatment-emergent notable vital signs, as defined below will be summarized for subjects who had at least 1 post-baseline assessment for that vital sign.

- Systolic blood pressure (SBP) <90 mmHg (baseline status is not considered)
- Decrease of >40 mmHg in SBP from baseline
- Diastolic blood pressure (DBP) <50 mmHg (baseline status is not considered)
- Decrease of >20 mmHg in DBP from baseline
- All above four notable criteria fulfilled: SBP <90 mmHg and with >40 mmHg decrease from baseline and DBP <50 mmHg and with >20 mmHg decrease from baseline
- Pulse <50 bpm or Pulse >120 bpm (baseline status is not considered)
- Weight >15% decrease or increase from baseline

In addition, the following table summary will be provided, separately for the DB and OL treatment periods, at each visit for:

- Weight: the incidence of increases/decreases from baseline >15% will be summarized by a frequency distribution.
- BMI: categorized as Underweight: BMI < 18.5 kg/m^2, Normal: 18.5 kg/m^2 ≤ BMI < 25 kg/m^2, Overweight: 25 kg/m^2 ≤ BMI < 30 kg/m^2, Obese: BMI ≥ 30 kg/m^2. The frequency and percentage of subjects in each category will be presented.

A listing of subjects with treatment-emergent clinically notable vital signs will be presented, separately for the DB and OL treatment periods. A listing of all vital sign measurements will also be provided, with clinically notable vital signs flagged.

Physical examination assessments are not collected in the eCRF. The date of the physical examination is collected in the eCRF and clinically relevant findings (other than those related to CTEPH) that are present prior to signing of informed consent should be recorded on the Medical History eCRF page. Physical examination findings made after signing of informed consent, which meet the definition of an AE (see protocol Section 9.1.1), should be recorded on the AE page of the eCRF.

5.6.3.3. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) is performed at timepoints indicated in the schedule of assessment as shown in Table 3 during the DB treatment period and Table 5 during the PTOP, with an overall interpretation of "Normal", "Abnormal" or "Not evaluable" being captured on the ECG Test Results eCRF.

The ECG is interpreted locally and stored at the site.

Clinically relevant ECG findings that are present prior to the initiation of study treatment should be documented in the Medical History section of the eCRF. Clinically relevant ECG findings found after the study treatment initiation that were not present at Screening or that worsened during the study should be reported as an AE (see protocol Section 9.1.1) as appropriate.

Descriptive statistics (n, %) will be presented at scheduled time points, by treatment group.

Shift from baseline to each scheduled post-baseline visit will be summarized with the number and percentage of subjects in the combination of baseline vs. post-baseline categories, by treatment group.

A listing of abnormal ECG results will also be provided, including unscheduled visit data.

5.6.3.4. Other Safety Parameters

5.6.3.4.1. Procedures

Therapeutic or diagnostic procedures are collected on the imaging and the heart catheterization eCRFs and the procedure eCRF. BPA and PEA are procedures of specific interest as reported on

the medical history eCRF and are identified by preferred terms that code to BPA (eg, "angioplasty" and "arterial angioplasty") and PEA (eg, "endarterectomy" and "pulmonary endarterectomy").

The number and percentage of subjects who underwent any therapeutic or diagnostic procedure, and for which indication (per protocol, medical history, trial indication (CTEPH), prophylaxis, other, AE), as well as procedures of interest (related to BPA and PEA), will be presented separately for DB and OL treatment periods, including baseline and post-baseline summaries (as applicable).

A listing of all procedures will also be provided, including if the procedure was elective (yes/no).

5.7. Other Analyses

5.7.1. Definition of Subgroups

Table 14 summarizes the subgroups which will be used in this study.

Table 14: Definition of Subgroups

Subgroup	Category
Stratification factor 1: PH-specific therapies (as per IRT) [$]	• One • Two • Naïve
Stratification factor 2: CTEPH population (as per IRT) [$]	• Inoperable (with or without BPA) • Persistent-recurrent after PEA (including PEA followed by BPA)
CTEPH sub-population [*]	• Inclusion criteria 3a: Inoperable CTEPH • Inclusion criteria 3b: CTEPH after BPA • Inclusion criteria 3c: CTEPH after PEA or PEA followed by BPA ▪ CTEPH after PEA ▪ CTEPH after PEA followed by BPA
Gender	• Male • Female
Age Group	• 18-64 years • 65-74 years • ≥75 years
Race	• Black or African American • American Indian or Alaska Native • Native Hawaiian or Other Pacific Islander • Asian • White • Other • Not reported
Geographic region 1	• North America • Western Europe/Australia • Eastern Europe • Asia • Latin America
Geographic region 2	• US • Non-US
WHO FC at baseline	• I • II • III • IV

Table 14: Definition of Subgroups

Subgroup	Category
Dose group (iMTD)	• Low (200–400 µg bid) • Medium (600, 800 and 1000 µg bid) • High (1200, 1400 and 1600 µg bid)
NT-proBNP 1 **	• Low (<300 ng/L) • Medium (300 to 1400 ng/L) • High (>1400 ng/L)
NT-proBNP 2 ***	• Low • Medium • High

* As captured on the CTEPH sub-population eCRF.
** Based on 2015 European Society of Cardiology/European Respiratory Society guidelines cutoffs.
*** Based on NT-proBNP baseline tertiles.
$ Analysis model will not include the subgrouping variable as a covariate.

5.8. Interim Analyses

The database was to be locked, and the data extracted and analyzed at five time points during the study (see details in Section 1.2.4, Figure 3 and IDMC Charter).

Due to early termination of the study due to futility at analysis time point 1, analysis time points 2 and 3 are no longer applicable and analysis time points 4 and 5 are combined and constitute the final analysis reporting of the study, when all randomized subjects up to the point of early termination have performed their EOS visit, conducted by the sponsor, according to this SAP.

5.8.1. Independent Data Monitoring Committee (IDMC) or Other Review Board

5.8.1.1. Independent Data Monitoring Committee

An IDMC has overall responsibility for safeguarding the interests of subjects by monitoring unblinded safety and efficacy data obtained during the study and for reviewing the results of the interim analyses, thereby ensuring that the study is conducted in accordance with the highest scientific and ethical standards.

The IDMC is tasked to organize and conduct the interim analyses with the assistance of the independent SSG. The IDMC will make appropriate recommendations based on statistical analyses summaries provided by the SSG team, based on the IDMC SAP for closed session, prepared in accordance with the IDMC Charter.

All communication between the IDMC and the sponsor will be directed through a Sponsor Committee, as defined in the IDMC Charter, which includes senior medical and statistical members. The Sponsor Committee will make decisions based on the recommendations from the IDMC.

5.8.1.1.1. Outputs for IDMC meetings

For periodic data reviews and the pre-planned IAs at analysis time points 1, 2 and 3, summary tables will be created by the independent SSG, according to the IDMC SAP for closed session,

prepared by the SSG, using SAS® (SAS Institute Inc.) and R (R Core Team (2012) and based on the blinded SDTM and Analysis Data Models (ADaMs) provided by the sponsor. Summaries will be created for the data available at the time of the IDMC data cut-off. The summary tables in the IDMC data package will be displayed by treatment arm with masked treatment code label. The assignment of codes to the study treatment will not be provided in the report but will be provided separately and will be consistent throughout the study.

A separate data package will be created by the sponsor, for the open session, only presenting data for the overall pooled subject population (not by treatment group). The details of analyses and list of outputs and mock layouts are described in an IDMC specific SAP for SSG and Open Session of IDMC.

5.8.1.2. Other Review Boards

5.8.1.2.1. Steering committee

A Steering Committee (SC) has been appointed by the sponsor to contribute to the design of the protocol, oversee the conduct of the study, evaluate the results and support publications. The committee is governed by a dedicated SC Charter.

5.8.1.2.2. Adjudication committees

The study population includes subjects with CTEPH who are diagnosed as inoperable (ie, technically non-operable) or with persistent/recurrent CTEPH after surgical (PEA) and/or interventional (BPA) treatment. In accordance with the European Society of Cardiology and the European Respiratory Society Guidelines for the diagnosis and treatment of PH (Galiè 2016), an operability assessment for CTEPH subjects should be performed by a multidisciplinary CTEPH team. Therefore, in addition to the CTEPH diagnosis, the inoperability, and the persistence/recurrence of PH of CTEPH subjects considered eligible for study inclusion by the investigational sites will be confirmed by a multidisciplinary CTEPH team. For this purpose, two sets of independent adjudication committees (ACs) are established:

- Country-specific Adjudication Committees (CSACs) and
- Central Adjudication Committee (CAC) for countries without a CSAC.

The composition and operation of these committees is described in the ACs' Charter.

5.8.1.2.3. Clinical Event Committee

A Clinical Event Committee (CEC) has been appointed by the sponsor to adjudicate, in a blinded fashion, components of the clinical worsening events. Full details for this procedure, as well as the composition and operation of the CEC, are described in the CEC Charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
AC	Adjudication Committee
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
ATC	anatomic and therapeutic class
bid	twice daily
BDI	Borg dyspnea index
BMI	body mass index
Borg CR10®	Borg category-ratio 10 Scale®
BPA	balloon pulmonary angioplasty
bpm	beats per minute
BSA	body surface area
CAC	Central Adjudication Committee
CEC	Clinical Events Committee
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression of Severity
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	cardiac index
CL	confidence limit(s)
CMH	Cochran-Mantel-Haenszel
CO	cardiac output
CRO	Contract Research Organization
CSAC	Country-specific Adjudication Committee
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTEPH	chronic thromboembolic pulmonary hypertension
CTT	Clinical Trial Team
CV	coefficient of variation
CW	clinical worsening
DB	double-blind
DBP	diastolic blood pressure
DLPA	daily life physical activity
dPAP	Diastolic pulmonary arterial pressure
d-SAP	Diastolic systemic arterial pressure
DPS	data presentation specifications
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDBT	End-of-Double-Blind-Treatment
EES	Efficacy Evaluable Set
EOLT	End-of-Open-Label-Treatment
EOS	End-of-Study
EOT	End-of-Treatment
ERA	endothelin receptor antagonist
EQ-5D-5L©	Euro Quality of life-5-Dimension-5-Level
FAS	Full Analysis Set
FC	Functional Class
FDA	Food and Drug Administration
FSFV	First subject first visit
FT3	Triiodothyronine, Free
FT4	Thyroxine, Free
FU	follow-up
HES	Hemodynamic Set

HR	hazard ratio
IA	interim analysis
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IE	inter-current event
IF	information fraction
iMTD	individual maximum tolerated dose
IQ	Interquartile
IRT	Interactive Response Technology
LHC	left heart catheterization
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LSLV	Last subject last visit
LVEDP	left ventricular end diastolic pressure
LWYY	Lin-Wei-Yang-Ying
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	mean pulmonary arterial pressure
mRAP	mean right atrial pressure
MVPA	moderate to vigorous physical activity
NT-proBNP	N-terminal pro b-type natriuretic peptide
OL	open-label
PAH	pulmonary arterial hypertension
PAH-SYMPACT®	PAH Symptoms and Impact® questionnaire
PAWP	pulmonary artery wedge pressure
PDE-5	phosphodiesterase type 5
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
PPS	PVR Per-Protocol Analysis Set
PRO	patient-reported outcome(s)
PT	preferred term
PTA	Post-Trial Access
PTOP	post-treatment observation period
PTOP EOS	post-treatment observation period end-of-study
PVR	pulmonary vascular resistance
qd	once daily
RHC	right heart catheterization
RR	rate ratio
SAE	serious adverse event
SAP	statistical analysis plan
SAF	Safety Analysis Set
SAS®	Statistical Analysis Software
SBP	systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SIS	Selexipag-Initiated Set
SFU	safety follow-up
sGC	soluble guanylate cyclase
SL	significance level
SM	Site manager
SMQs	Standardized MedDRA Query
SOC	system organ class
sPAP	Systolic pulmonary artery pressure
s-SAP	Systolic systemic arterial pressure
SSG	Statistical Support Group
SvO_2	Mixed venous oxygen saturation
T3	Triiodothyronine
T4	Thyroxine

TEAE	treatment-emergent adverse event
TPR	total pulmonary resistance
TSH	Thyroid Stimulating Hormone (Thyrotropin)
TTCW	time to clinical worsening
ULN	upper limit of normal
WASO	wake after sleep onset
WCC	WorldCare Clinical
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WPAI©: GH	Work Productivity and Activity Impairment: General Health

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Following the decision to prematurely terminate the study due to futility at analysis time point 1, it was decided that an abbreviated CSR would be produced to summarize key efficacy and safety data only. Such analyses are described in this SAP. The study team will remain blinded to the results of the IA conducted by the SSG, until database lock occurs for the abbreviated CSR planned analyses.

For the abbreviated CSR, some endpoints (and analyses) have been removed or adapted compared to the protocol planned analyses, to better evaluate the data that is available for them at the time of early termination of the study. Endpoints to be considered for the abbreviated CSR are primary and key secondary endpoints (and associated supportive and exploratory endpoints) and a full complement of safety.

All efficacy analyses other than PVR are exploratory. A summary is provided below:

- Primary Endpoint
  - PVR
    - No change in protocol specified analysis approach. Sensitivity and supplementary analyses will also be conducted, as per Section 5.3.
- Key Secondary Endpoints
  - Change from baseline in 6MWD to Week 26
    - ANCOVA analysis approach will not be conducted. Descriptive analyses will be performed (as per Section 5.4.1).
  - TTCW
    - Low number of events at the time of early termination: log rank test will not be performed; descriptive analyses only (as per Section 5.4.2).
- Supportive Secondary Endpoints
  - Change from baseline to Week 26 in BDI/Borg CR10®
    - No change in protocol specified analysis approach (as per Section 5.4.3).
- Exploratory Endpoints
  - Change from baseline up to EOS, by visit, in BDI/Borg CR10® collected immediately at the end of each individual 6MWT
    - Descriptive analysis will be performed (as per Section 5.5.1).
  - Change from baseline up to EOS, by visit, in exercise capacity, as measured by the 6MWD
    - Descriptive analysis will be performed (as per Section 5.5.2).
  - Change from baseline to Week 20 in other hemodynamic parameters (cardiac output [CO], cardiac index [CI] and mean right atrial pressure [mRAP]) measured at rest
    - Descriptive analysis will be performed (as per Section 5.5.3).

Secondary endpoints which will no longer be included in the abbreviated CSR:

- Improvement in WHO FC at Week 26
- Change from baseline to Week 26 in PAH-SYMPACT® cardiopulmonary symptoms domain and cardiovascular symptoms domain
- Change from baseline to Week 26 in NT-proBNP
- All-cause death or hospitalizations related to PH worsening (confirmed by the CEC)

Exploratory endpoints which will no longer be included in the abbreviated CSR:

- Changes in 6MWD, WHO FC and NT-proBNP from baseline to all regular collection timepoints up to the EDBT period.
  - Note: 6MWD is already included, by definition, in the above exploratory endpoint "Change from baseline up to EOS, by visit, in exercise capacity, as measured by the 6MWD."
- Rate of hospitalizations up to end of double-blind period
- Mean number of hospital days for all-cause hospitalization
- Mean number of hospital days related to PH worsening
- Improvement in WHO FC from baseline up to EOS, by visit
- Change from baseline to Week 26 in actigraphy-assessed daily life physical activity (DLPA)
- Change from baseline up to Week 39, by visit, in PAH-SYMPACT® scores (including cardiopulmonary symptoms domain, cardiovascular symptoms domain, physical impacts domain, and cognitive/emotional impacts domain)
- Change from baseline up to Week 52, by visit, in EQ-5D-5L
- Change from baseline up to Week 52, by visit, in WPAI©: GH scores
- Change from baseline to all regular collection timepoints up to end of double-blind period in the CGI-S scores and in the CGI-C scores
- Change from baseline to Week 20 in the number of low-risk criteria, defined as WHO FC I or II, 6MWD ≥440 m, NT-proBNP <300 ng/L and CI ≥2.5 L/min/m2 (Galiè 2016)

Updates and clarifications have also been included as follows:

- The primary efficacy endpoint and key secondary efficacy endpoints have been described in terms of estimands.
- Analysis Sets:
  - Efficacy Evaluable Set(s) have been defined for the Week 26 efficacy endpoints
    - The EES is a subset of subjects in the FAS and includes all subjects who have reached their Week 26 visit (according to the analysis time window for the specific Week 26 efficacy endpoint) or have discontinued earlier (for any reason except Sponsor decision = Study Termination). An EES is defined for:

  - ♦ 6MWD: From Day 2 to Day 273 (see Table 8)
  - ♦ Other efficacy endpoints: From Day 2 to Day 229 (see Table 8)
- PVR Per-protocol Analysis Set (PPS1) renamed to PPS since only one per-protocol analysis set now required. 6MWD Per-protocol Analysis Set (PPS2) and TTCW Per-protocol Analysis Set (PPS3) have been removed since per-protocol analyses are no longer applicable for those key secondary endpoints (descriptive analyses only).
- The Selexipag Initiated Set (SIS) has been removed since there is no need for this specific analysis set. Safety summaries are based on the SAF. As per protocol, all subjects in the OL treatment period received selexipag.

- Table 7: Analyses sets and their usage at each analysis time-point
  - Updated in line with corresponding updates in analysis sets and early termination of the study.
- Details regarding interim analysis and DB and OL analyses (Section 10.4 and 10.5 of the protocol) have been updated in line with early termination of the study
  - Due to early termination of the study for futility at analysis time point 1, analysis time points 2 and 3 are no longer applicable and analysis time points 4 and 5 are combined and constitute the final analysis reporting of the study, conducted by the sponsor, according to this SAP.
  - Efficacy and safety summaries will be presented at each analysis time point and performed separately for the DB and OL treatment periods, as applicable.
- Additional subgroups of interest (compared to those listed in protocol Section 10.3.5)
  - CTEPH sub-population (now collected directly on eCRF).
  - Age Group
  - WHO FC at baseline
  - NT-proBNP

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of subjects in each analysis set will be summarized by treatment group and overall. A by subject listing of subjects included in each analysis set will also be provided. In addition, the distribution of subjects by region, country/territory, and site ID will be presented.

Table 15 presents a list of the demographic variables that will be summarized by treatment group and overall, for the FAS (and HES at analysis time point 1; as described in Table 7). Demographics will also be summarized by region using the FAS.

By-subject listings of demographic data will also be provided based on the FAS (HES subjects will be flagged).

Separate summaries will be produced for the DB and OL treatment periods, where the OL summary will include summaries of those variables that are collected again after baseline or those that will be derived e.g., Age at start of OL, BMI at start of OL. At entry of OL, the only new information collected is weight (BMI can be derived), age will be derived from the age collected at screening to the start of OL; the rest are unchanged and correspond to the DB output.

Table 15: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables:	
Age (18-64 years, 65-74 years, ≥75 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not applicable, Multiple)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)	
Region (North America, Western Europe/Australia, Eastern Europe, Asia, Latin America)	
BMI (underweight: <18.5 kg/m^2, normal: 18.5 to <25 kg/m^2, overweight: 25 kg/m^2 to <30 kg/m^2, obese: ≥30 kg/m^2)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'.

Table 16 presents a list of the baseline PH characteristics variables that will be summarized by treatment group and overall, for the FAS (and HES at analysis time point 1; as described in Table 7). By subject listings of baseline data will also be provided based on the FAS (HES subjects will be flagged).

Separate summaries will be produced for the DB and OL treatment periods, where the OL summary will include summaries of those variables that are collected again after baseline or those that will be re-calculated e.g., Time from CTEPH diagnosis; the rest are unchanged and correspond to the DB output.

Table 16: Baseline pulmonary hypertension characteristics variables

Continuous Variables:	**Summary Type**
Time since initial CTEPH diagnosis (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Hemodynamic parameters • Heart rate (bpm) • PVR (Wood units, calculated eCRF) • PVR (dyn.sec/cm5, conversion eCRF) • PVR (dyn.sec/cm^5, derived) • mRAP (mmHg) • PAWP (mmHg)* • LVEDP (mmHg)* • sPAP (mmHg) • dPAP (mmHg) • mPAP (mmHg) • Cardiac Output (L/min) • Mixed Venous Oxygen Saturation (%) • s-SAP (mmHg) • d-SAP (mmHg) • Cardiac Index (L/min/m^2) • Total Pulmonary Resistance (dyn.sec/cm^5)	
6MWD (meters)	
NT-pro BNP (ng/L)	
Number of BPA performed	
Categorical Variables:	
CTEPH population (Inoperable, Persistent-Recurrent) (collected in IRT)	Frequency distribution with the number and percentage of subjects in each category.

CTEPH sub-population (collected in eCRF):
• Inclusion criterion 3a: inoperable CTEPH
• Inclusion criterion 3b: CTEPH after BPA
• Inclusion criterion 3c: CTEPH after PEA or PEA followed by BPA
  • CTEPH after PEA
  • CTEPH after PEA followed by BPA	

PH-specific therapy at baseline • One, two or naive (collected in IRT) • "ERAs Only", "PDE-5i Only", "sGC Only", "ERAs + PDE-5i", "ERAs + sGC", naïve (none of them) (collected in eCRF)	
WHO FC (I, II, III, IV)	
Borg Dyspnea Index (BDI) Borg CR10 Score	

6MWD = 6-minute walk distance; bpm = beats per minute; CTEPH = Chronic thromboembolic pulmonary hypertension; dPAP = Diastolic pulmonary arterial pressure; d-SAP = Diastolic systemic arterial pressure; ERA = Endothelin receptor antagonist; FC = Functional class; IRT = Interactive response technology; LVEDP = Left ventricular end diastolic pressure; mPAP = Mean pulmonary arterial pressure; mRAP = Mean right atrial pressure; NT-proBNP = N-terminal pro b-type natriuretic peptide; PAWP = Pulmonary artery wedge pressure; PDE-5 = Phosphodiesterase type-5; PH = Pulmonary hypertension; PVR = Pulmonary vascular resistance; sGC = Soluble guanylate cyclase; sPAP = Systolic pulmonary arterial pressure; s-SAP = Systolic systemic arterial pressure; WHO = World Health Organization.
*Following the Actelion Heart Catheterization Guidance (see protocol Appendix 1), LVEDP is to be recorded when PAWP is not available or not reliable.

6.4. Appendix 4 Protocol Deviations

In general, major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study.

Subjects with major protocol deviations will be identified during the conduct of the study in an ongoing manner using a comprehensive list of criteria (documented on the Major Protocol Deviation Criteria Form) as indicated in the Cross-Pharma TV-SOP-04282: Identification and Management of Clinical Trial Issues and Protocol Deviations for the definition of major protocol deviations.

Prior to each analysis time point all deviations will be closed, final and locked in the clinical trial management system and subjects with major protocol deviations will be summarized by the following categories/codes (DVDECOD).

- Entered but did not satisfy criteria (subject randomized but did not satisfy the inclusion/exclusion selection criteria)
- Received a disallowed concomitant treatment (subject took a forbidden concomitant medication)
- Received wrong treatment or incorrect dose (subject received wrong study treatment or incorrect dose)
- Developed withdrawal criteria but not withdrawn (subject developed withdrawal criteria during the study but was not withdrawn)
- Other (as per the full list on the study specific Major Protocol Deviation Criteria Form):

The specific major protocol deviations that will lead to exclusion from PPS are summarized in Table 17.

The number and percentage of subjects with major protocol deviations will be summarized using the FAS (and HES at analysis time point 1) and the impact on the primary endpoint will be assessed based on PPS. Subjects in PPS will be analyzed according to the assigned study treatment. Listings will also be provided for subjects with major protocol deviations in the FAS and subjects with major protocol deviations leading to exclusion from PPS in the HES.

Protocol Deviations resulting from COVID-19 impact are described in Section 6.11, Appendix 11.

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
INCLUSION CRITERIA					
1	Subject must have signed and dated the ICF.	Inclusion criterion 1 not met: Subject didn't *<specify: sign and/or date>* the ICF..	Inclusion Criterion 1 not met	Entered but did not satisfy criteria	Yes
2	Subjects must be ≥18 (or the legal age of consent in the jurisdiction in which the study is taking place) and ≤ 85 years old at Screening (Visit 1).	Inclusion criterion 2 not met: Subject was *<specify age>* years old.	Inclusion Criterion 2 not met	Entered but did not satisfy criteria	Yes
3	Subject must have eligibility confirmed by the AC (CSAC or CAC) prior to randomization.	Inclusion criterion 3 not met: Eligibility was not confirmed by the AC (CSAC or CAC) prior to randomization.	Inclusion Criterion 3 related to AC not met	Entered but did not satisfy criteria	Yes
4	Baseline RHC (and LHC, if needed) criteria: – performed at least 90 days after start of full anticoagulation – performed at least 90 days after last surgery/treatment (for subject with persistent/recurrent CTEPH after BPA or PEA [including PEA followed by BPA]) – CO measured with a minimum of 3 consecutive measurements that should not differ by > 10% when the thermodilution method is used and with 1 measurement when the Fick method is used.	Inclusion criterion 3 related to baseline RHC/LHC conditions not met: *<specify which criteria not met from the description list>*	Inclusion Criterion 3 related to baseline RHC/LHC conditions not met - Protocol Version 1 and 2	Entered but did not satisfy criteria	Yes
5	Historical RHC (and LHC, if needed) criteria for the hemodynamic cohort: – performed within 30 days prior to (re)screening – performed at least 90 days after last change in PH-specific therapies (i.e., change in dose or initiation of new class of drugs)	Inclusion criterion 3 related to historical baseline RHC/LHC conditions not met for the hemodynamic cohort: *<specify which criteria not met from the description list>*	Inclusion Criterion 3 related to baseline RHC/LHC conditions not met – hemodynamic cohort - Protocol Version 1 and 2	Entered but did not satisfy criteria	Yes
6	Historical RHC (and LHC, if needed) criteria for the hemodynamic cohort: – performed within 30 days prior to screening* – performed at least 90 days after last change in PH-specific therapies (i.e., change in dose or initiation of new class of drugs) *in case of rescreening within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used, provided there have been no changes in PH-specific therapy(ies) since the first Screening Visit.	Inclusion criterion 3 related to historical baseline RHC/LHC conditions not met for the hemodynamic cohort: *<specify which criteria not met from the description list>*	Inclusion Criterion 3 related to baseline RHC/LHC conditions not met – hemodynamic cohort - From Protocol Version 3 onwards	Entered but did not satisfy criteria	Yes
7	Historical RHC (and LHC, if needed) criteria for the non-hemodynamic cohort:	Inclusion criterion 3 related to historical baseline RHC/LHC conditions not met	Inclusion Criterion 3 related to baseline RHC/LHC	Entered but did not satisfy criteria	N/A

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
	– performed within 6 months prior to (re)screening.	for the non-hemodynamic cohort: historical RHC not performed within 6 months prior to (re)screening	conditions not met – non-hemodynamic cohort - Protocol Version 1 and 2		
8	Historical RHC criteria for the non-hemodynamic cohort: performed within 6 months prior to screening*. * In case of rescreening within 6 months of the first Screening Visit, the first screening RHC (and LHC if needed) can be used.	Inclusion criterion 3 related to historical baseline RHC conditions not met for the non-hemodynamic cohort: historical RHC not performed within 6 months prior to (re)screening	Inclusion Criterion 3 related to baseline RHC/LHC conditions not met – non-hemodynamic cohort - From Protocol Version 3 onwards	Entered but did not satisfy criteria	N/A
9	For the hemodynamic cohort, historical HC for eligibility: The HC guidance requirements for zeroing and heart catheterization measurement must have been followed and documented in the source notes if a historical HC is used. Otherwise, a new HC assessment will have to be performed for baseline measurements.	Subject was randomized based on a historic HC which was not conducted as per HC guidelines and no new HC was performed during screening: <specify>	Historic HC not performed as per HC guidelines and no new HC performed during screening.	Entered but did not satisfy criteria	Yes
10	Baseline RHC (and LHC, if needed) criteria: – PVR at rest ≥ 300 dyn.sec/cm5 or ≥ 3.75 WU – mPAP ≥ 25 mmHg, – Pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg or, if not available or unreliable, a left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg.	Inclusion criterion 3 related to baseline RHC/LHC data not met: *<specify which criteria not met from the description list>*	Inclusion Criterion 3 related to baseline RHC/LHC data not met - Protocol Version 1 and non-hemodynamic Version 3 onwards	Entered but did not satisfy criteria	Yes
11	Baseline RHC (and LHC, if needed) criteria: – PVR at rest ≥ 400 dyn.sec/cm5 or ≥ 5 WU – mPAP ≥ 25 mmHg, – Pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg or, if not available or unreliable, a left ventricular end diastolic pressure (LVEDP) ≤ 15 mmHg.	Inclusion criterion 3 related to baseline RHC/LHC data not met: *<specify which criteria not met from the description list>*	Inclusion Criterion 3 related to baseline RHC/LHC data not met – from Protocol Version 2 and hemodynamic Version 3 onwards	Entered but did not satisfy criteria	Yes
12	For the hemodynamic cohort, zeroing as per HC guideline must be done prior to the HC measurement.	Zeroing was not done according to the HC guidelines at screening: <specify>	Zeroing was not done before HC measurements at screening.	Entered but did not satisfy criteria	Yes
13	For the hemodynamic cohort, for sPAP and dPAP the 2 most representative and reliable measurements must be documented in the source notes.	sPAP and/or dPAP not documented with 2 representative and reliable measurements at screening: <specify which parameter was not measured and documented as per guidance sPAP and/or dPAP>	sPAP and/or dPAP not measured or documented as per HC guidance at screening.	Entered but did not satisfy criteria	Yes
14	For the hemodynamic cohort, for the HC, if thermodilution method is used to measure CO, the CO must be measured with at least 3	Thermodilution CO at screening not measured at least 3 times: <specify deviation>	Thermodilution CO at screening not measured at least 3 times.	Entered but did not satisfy criteria	Yes

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
	measurements documented in the heart catherization worksheet.				
15	For the hemodynamic cohort, for the HC, if thermodilution method is used to measure CO, 3 measurements must be within 10% of each other, i.e., the lowest of the 3 CO values must not be lower than 10% of the middle value AND the highest value must not be higher than 10% of the middle value.	Thermodilution CO values at screening: the upper and/or lower values are more than 10% +/- of the middle value: <specify and list the CO values>	Thermodilution CO the upper and/or lower values are more than 10% +/- of the middle value at screening.	Entered but did not satisfy criteria	Yes
16	HC is to be performed at screening.	HC is missing at screening: <specify>	HC missing at screening.	Entered but did not satisfy criteria	Yes
17	For the hemodynamic cohort CO must be measured at screening.	Missing CO at screening <specify>	Missing CO at screening.	Entered but did not satisfy criteria	Yes
18	For the hemodynamic cohort, sPAP must be measured at screening.	Missing sPAP at screening: <specify>	Missing sPAP at screening.	Entered but did not satisfy criteria	Yes
19	For the hemodynamic cohort, dPAP must be measured at screening.	Missing dPAP at screening. <specify>	Missing dPAP at screening.	Entered but did not satisfy criteria	Yes
20	For the hemodynamic cohort, PAWP or LVEDP, if PAWP is missing or not reliable must be available at screening.	Missing or not reliable PAWP and missing LVEDP at screening: <specify>	Missing or not reliable PAWP and LVEDP not available at screening.	Entered but did not satisfy criteria	Yes
21	Subjects must have available imaging assessments performed in the 14-month period prior to randomization (Visit 2) or during screening as follows: – Subject with Inoperable CTEPH must have at least two imaging assessments – Subject with Persistent/Recurrent CTEPH after BPA must have at least one imaging assessment	Inclusion criterion 3 related to baseline imaging not met: *<specify which criteria not met from the description list>*	Inclusion Criterion 3 related to baseline imaging not met – Protocol Version 1	Entered but did not satisfy criteria	N/A
22	Subjects must have available imaging assessments performed in the 14-month period prior to randomization (Visit 2) or during screening as follows: – Subject with Inoperable CTEPH must have at least two imaging assessments – Subject with Persistent/Recurrent CTEPH after BPA must have at least one imaging assessment performed after last interventional (BPA) treatment – Subject with Persistent/Recurrent CTEPH after PEA (including PEA followed by BPA)	Inclusion criterion 3 related to baseline imaging not met: *<specify which criteria not met from the description list>*	Inclusion Criterion 3 related to baseline imaging not met – from Protocol Version 2 onwards	Entered but did not satisfy criteria	N/A

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
	must have at least one imaging assessment performed after last surgical (PEA) or interventional (BPA) treatment.				
23	Subject must have PH in WHO FC I-IV	Inclusion criterion 4 not met: WHO FC not assessed at (re)screening	Inclusion Criterion 4 not met	Entered but did not satisfy criteria	N/A
24	Subject must be able to perform the 6MWT with a minimum distance of 100 m and a maximum distance of 450 m at (re)screening visit (Visit 1).	Inclusion criterion 5 not met: 6MWD at (re)screening was *<specify 6MWD at (re)screening> or <not available>.*	Inclusion Criterion 5 not met	Entered but did not satisfy criteria	N/A
25	6MWT is to be performed at screening	6MWT not done at screening: <specify>	6MWT not done at screening.	Entered but did not satisfy criteria	N/A
26	For the 6MWT all the following requirements related to the subject must be followed: - wear comfortable clothing - wear appropriate shoes - must not have exercised vigorously within 2 hours before the 6MWT	The 6MWT requirements related to the subject at screening were not followed: <specify deviation>	The 6MWT guidance related to the subject were not followed at screening.	Entered but did not satisfy criteria	N/A
27	If the subject is used to take bronchodilators, he/she must take them at least 10 to 30 minutes before the 6MWT.	Bronchodilators were not taken 10 to 30 minutes before the 6MWT at screening: <specify>	Bronchodilators not taken as per 6MWT guidance at screening.	Entered but did not satisfy criteria	N/A
28	Walking aids (e.g., cane) and walkers are not allowed.	Forbidden walking aid was used during the 6MWT at screening: <specify>	Used forbidden walking aid during the 6MWT at screening.	Entered but did not satisfy criteria	N/A
29	The interval between two 6MWTs on the same day must be at least 2 hours.	There was less than 2 hours between 2 6MWTs performed at **randomization**: <specify>	Less than 2 hours between two 6MWTs at randomization.	Entered but did not satisfy criteria	N/A
30	Only two 6MWTs can be performed on the same day.	More than two 6MWT were performed at screening: <add description of the actual deviation>	More than 2 tests done screening.	Entered but did not satisfy criteria	N/A
31	The 6MWT must be performed indoors, along a long, flat, straight, enclosed corridor (or similar location) with a hard surface that can be blocked for traffic during the conduct of the test. The track must be marked at regular intervals. The turnaround points must be marked with a cone. A starting line, which marks the beginning and end of each lap needs to be marked on the floor. The use of treadmill and a continuous course, e.g., a circuit, is not allowed.	Corridor not compliant with 6MWT guidance requirements at screening: <add description of actual deviation>	Corridor does not meet 6MWT guidance requirements at screening.	Entered but did not satisfy criteria	N/A

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
32	The corridor must not be shorter than 20 m in length.	6MWT at screening was done in a corridor with track length shorter than 20 m: <add description of actual deviation>	Corridor length not as per 6MWT guidance at screening.	Entered but did not satisfy criteria	N/A
33	If a subject is oxygen dependent, the use of a portable device is allowed. The oxygen flow rate must remain constant from 30 minutes prior to each 6MWT, until the completion of all protocol-mandated assessments after the 6MWT. The way oxygen is delivered (delivery device, application route, way of carrying the delivery device) must be the same for all 6MWTs, unless a change is required for documented medical reasons.	Requirements for oxygen supplementation not followed at screening: <add description of actual deviation>	Requirements for oxygen supplementation not followed at screening.	Entered but did not satisfy criteria	N/A
34	A woman of childbearing potential must: Have a negative serum pregnancy test at (re)screening and a negative urine pregnancy test at randomization.	Inclusion criterion 6a not met: subject had *<a positive serum pregnancy test at (re)screening>* and/or *<a positive urine pregnancy test at randomization>*.	Inclusion Criterion 6a not met	Entered but did not satisfy criteria	N/A
35	A woman of childbearing potential must: – Agree to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation.	Inclusion criterion 6b not met: subject doesn't agree to undertake monthly urine pregnancy tests during the study and up to at least 30 days after study treatment discontinuation.	Inclusion Criterion 6b not met	Entered but did not satisfy criteria	N/A
36	A woman of childbearing potential must: – Agree to use one of the methods of birth control described in protocol Section 4.5.2 from (re)screening up to at least 30 days after study treatment discontinuation.	Inclusion criterion 6c not met: the subject doesn't agree to use one of the methods of birth control described in protocol Section 4.5.2 from (re)screening up to at least 30 days after study treatment discontinuation.	Inclusion Criterion 6c not met	Entered but did not satisfy criteria	N/A
37	At re-screening, 6MWT, physical examination, vital signs, local 12-lead ECG and central laboratory assessments must be repeated.	At re-screening, the following assessments were not repeated: *<specify assessment>*.	Assessments not repeated at re-screening.	Entered but did not satisfy criteria	N/A
EXCLUSION CRITERIA RELATED TO THE DISEASE					
38	Planned BPA within 26 weeks after randomization is forbidden.	Exclusion criterion 1 met: BPA is planned for the subject within the first 26 weeks after randomization.	Exclusion criterion 1 met	Entered but did not satisfy criteria	Yes
39	Change in dose or initiation of new PH-specific therapy within 90 days prior to the baseline RHC (and LHC, if needed) qualifying for enrollment for the hemodynamic cohort and within 90 days prior	Exclusion criterion 2 met: subject had a change in dose or initiation of new PH-specific therapy	Exclusion criterion 2 met	Entered but did not satisfy criteria	Yes

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
	to randomization (Visit 2) for the non-hemodynamic cohort is forbidden.				
40	Treatment with prostacyclin (epoprostenol), prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (i.e., selexipag/Uptravi®) within 90 days prior to randomization (Visit 2) is forbidden, except those given at vasodilator testing during RHC.	Exclusion criterion 3 met: subject was treated with prostacyclin (epoprostenol), prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (i.e. selexipag/Uptravi®) within 90 days prior to randomization (Visit 2).	Exclusion criterion 3 met	Entered but did not satisfy criteria	Yes
41	Change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to baseline RHC (and LHC, if needed) is forbidden.	Exclusion criterion 4 met: subject had a change in dose or initiation of new diuretics and/or calcium channel blockers within 1 week prior to baseline RHC/LHC.	Exclusion criterion 4 met	Entered but did not satisfy criteria	Yes
EXCLUSION CRITERIA RELATED TO COMORBIDITIES					
42	Severe coronary heart disease or unstable angina as assessed by the investigator is forbidden.	Exclusion criterion 5 met: subject has severe coronary heart disease or unstable angina.	Exclusion criterion 5 met	Entered but did not satisfy criteria	N/A
43	Myocardial infarction within the last 6 months prior to (re)screening is forbidden.	Exclusion criterion 6 met: subject had myocardial infarction within the last 6 months prior to (re)screening.	Exclusion criterion 6 met - Protocol Version 1 and 2	Entered but did not satisfy criteria	N/A
44	Myocardial infarction within the last 6 months prior to or during (re)screening is forbidden.	Exclusion criterion 6 met: subject had myocardial infarction within the last 6 months prior to or during (re)screening.	Exclusion criterion 6 met - From protocol Version 3 onwards	Entered but did not satisfy criteria	N/A
45	Decompensated cardiac failure if not under close supervision is forbidden.	Exclusion criterion 7 met: subject has decompensated cardiac failure without close supervision.	Exclusion criterion 7 met	Entered but did not satisfy criteria	N/A
46	Severe arrhythmias as assessed by the investigator is forbidden.	Exclusion criterion 8 met: subject has severe arrhythmias as assessed by the investigator.	Exclusion criterion 8 met	Entered but did not satisfy criteria	N/A
47	Cerebrovascular events (e.g., transient ischemic attack, stroke) within the last 3 months prior to (re)screening is forbidden.	Exclusion criterion 9 met: subject had cerebrovascular events (e.g., transient ischemic attack, stroke) within the last 3 months prior to (re)screening.	Exclusion criterion 9 met - Protocol Version 1 and 2	Entered but did not satisfy criteria	N/A
48	Cerebrovascular events (e.g., transient ischemic attack, stroke) within the last 3 months prior to or during (re)screening is forbidden.	Exclusion criterion 9 met: subject had cerebrovascular events (e.g., transient ischemic attack, stroke) within the last 3 months prior to or during (re)screening.	Exclusion criterion 9 met - From protocol Version 3 onwards	Entered but did not satisfy criteria	N/A

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
49	Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH is forbidden.	Exclusion criterion 10 met: subject has congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to PH	Exclusion criterion 10 met	Entered but did not satisfy criteria	Yes
50	Known or suspicion of pulmonary veno-occlusive disease (PVOD) is forbidden.	Exclusion criterion 11 met: subjects has known or suspected PVOD.	Exclusion criterion 11 met	Entered but did not satisfy criteria	Yes
EXCLUSION CRITERIA RELATED TO SELEXIPAG USE					
51	Known and documented severe hepatic impairment is forbidden.	Exclusion criterion 12 met: subject has known and documented severe hepatic impairment.	Exclusion criterion 12 met	Entered but did not satisfy criteria	Yes
52	Severe renal failure (estimated glomerular filtration rate < 30 mL/min/1.73 m2 or serum creatinine > 2.5 mg/dL or 221 µmol/L) at (re)screening is forbidden.	Exclusion criterion 13 met: subject has severe renal failure (estimated glomerular filtration rate < 30 mL/min/1.73 m2 or serum creatinine > 2.5 mg/dL or 221 µmol/L) at (re)screening.	Exclusion criterion 13 met	Entered but did not satisfy criteria	N/A
53	Known or suspected uncontrolled thyroid disease as per investigator judgment is forbidden	Exclusion criterion 14 met: subject has known or suspected uncontrolled thyroid disease as per investigator judgment.	Exclusion criterion 14 met	Entered but did not satisfy criteria	N/A
54	Being pregnant, planning to become pregnant or lactating is forbidden.	Exclusion criterion 15 met: subject is pregnant, planning to be become pregnant or lactating.	Exclusion criterion 15 met	Entered but did not satisfy criteria	N/A
55	Treatment with strong and moderate inhibitors of cytochrome P-450 2C8 (CYP2C8; e.g., gemfibrozil, clopidogrel, deferasirox, teriflunomide) within 14 days prior to randomization is forbidden.	Exclusion criterion 16 met: subject was treated with strong and moderate inhibitors of cytochrome P-450 2C8 (CYP2C8; e.g., gemfibrozil, clopidogrel, deferasirox, teriflunomide) within 14 days prior to randomization.	Exclusion criterion 16 met – Protocol Version 1	Entered but did not satisfy criteria	Yes
56	Treatment with strong inhibitors of cytochrome P-450 2C8 (CYP2C8; e.g., gemfibrozil) within 14 days prior to randomization is forbidden.	Exclusion criterion 16 met: subject was treated with strong inhibitors of cytochrome P-450 2C8 (CYP2C8; e.g., gemfibrozil) within 14 days prior to randomization.	Exclusion criterion 16 met – Protocol Version 2	Entered but did not satisfy criteria	Yes
57	Treatment with strong inhibitors of cytochrome P-450 2C8 (CYP2C8; e.g., gemfibrozil) or moderate inducers of CYP2C8 (e.g., rifampicin) within 14 days prior to randomization is forbidden.	Exclusion criterion 16 met: subject was treated with strong inhibitors of cytochrome P-450 2C8 (CYP2C8; e.g., gemfibrozil) or moderate inducers of CYP2C8 (e.g., rifampicin) within 14 days prior to randomization.	Exclusion criterion 16 met – from Protocol Version 3 onwards	Entered but did not satisfy criteria	Yes

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
58	SBP < 90 mmHg at (re)screening (Visit 1) or at randomization (Visit 2) is forbidden.	Exclusion criterion 17 met: subject had SBP < 90 mmHg at (re)screening (Visit 1) or at randomization (Visit 2).	Exclusion criterion 17 met	Entered but did not satisfy criteria	N/A
59	Known hypersensitivity to selexipag or drugs of the same class, or any of their excipients is forbidden.	Exclusion criterion 18 met: subjects has known hypersensitivity to selexipag or drugs of the same class, or any of their excipients.	Exclusion criterion 18 met	Entered but did not satisfy criteria	Yes
GENERAL EXCLUSION CRITERIA					
60	Planned or current treatment with another investigational treatment up to 3 months prior to randomization is forbidden.	Exclusion criterion 19 met: subjects has planned or current treatment with another investigational treatment up to 3 months prior to randomization.	Exclusion criterion 19 met	Entered but did not satisfy criteria	Yes
61	Any co-morbid condition that may influence the ability to perform a reliable and reproducible 6MWT, including use of walking aids (cane, walker, etc.) is forbidden.	Exclusion criterion 20 met: subject has any co-morbid condition that may influence the ability to perform a reliable and reproducible 6MWT, including use of walking aids (cane, walker, etc.).	Exclusion criterion 20 met	Entered but did not satisfy criteria	N/A
62	Any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of the results, such as drug or alcohol dependence or psychiatric disease is forbidden.	Exclusion criterion 21 met: subject has any known factor or disease that might interfere with treatment compliance, study conduct, or interpretation of the results, such as drug or alcohol dependence or psychiatric disease.	Exclusion criterion 21 met: known interfering factor or disease	Entered but did not satisfy criteria	N/A
63	Known concomitant life-threatening disease with a life expectancy < 12 months is forbidden.	Exclusion criterion 22 met: subject has a known concomitant life-threatening disease with a life expectancy < 12 months.	Exclusion criterion 22 met: known life-threatening disease	Entered but did not satisfy criteria	N/A
CONCOMITANT MEDICATION					
64	Change in dose or initiation of new PH-specific therapies (i.e., ERA, PDE-5 inhibitor, sGC stimulator) is forbidden from randomization and up to Week 26 (Visit 5).	Change in PH-specific therapies: <specify treatment>.	Change in PH-specific therapies	Received a disallowed concomitant treatment	Yes
65	Treatment with prostacyclin (epoprostenol), prostacyclin analogs (i.e., treprostinil, iloprost, beraprost) or prostacyclin receptor agonists (i.e., selexipag/Uptravi) is forbidden from randomization (Visit 2) and up to study treatment discontinuation.	Received prostanoids: <specify treatment>.	Received prostanoids	Received a disallowed concomitant treatment	Yes

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
66	Treatment with strong CYP2C8 (e.g., gemfibrozil) is forbidden from randomization and up to 30 days after study treatment discontinuation.	Received strong and/or moderate inhibitors of CYP2C8: <specify treatment>.	Received strong and/or moderate inhibitors of CYP2C8 – from Protocol Version 2 onwards	Received a disallowed concomitant treatment	Yes
DOSAGE & ADMINISTRATION					
67	Wrong medication kit received/dispensed in the double-blind study treatment period. NOTE: This PD leads to exclusion only if, after unblinding, the received/dispensed bottle did not contain the planned/randomized study treatment. If PD date is available (either date of first intake from an incorrect bottle or if this date is not available, use the date when the wrong bottle was dispensed), only exclude if occurred prior to the corresponding efficacy assessment date.	Received wrong medication kit during the double-blind study treatment period *<enter number>.*	Received wrong medication kit during the double-blind study treatment period.	Received wrong treatment or incorrect dose	Yes (see note)
68	The double-blind study treatment dose reached at Week 12 (Visit 3) must be kept stable at least until Week 26 (Visit 5) but can be adjusted for safety and tolerability reasons.	Double-blind study treatment not stable from Week 12 until Week 26 and was changed for reason other than subject's safety and tolerability.	Double-blind study treatment not stable from Week 12 until Week 26 except for safety and tolerability reasons.	Received wrong treatment or incorrect dose	Yes
69	Overall compliance is expected to be between 80% and 120%. NOTE: During double-blind treatment only.	Overall study drug compliance below 80% or above120%: <specify actual deviation>	Overall study compliance outside expected range.	Received wrong treatment or incorrect dose	Yes (see note)
70	Study treatment was not administered as per protocol (e.g., starting dose, dosing frequency adjustment due to moderate hepatic impairment or concomitant treatment with moderate CYP2C8 inhibitors, titration scheme, reinitiating after temporarily interruption and overdose defined as any single dose greater than 1600 µg or a total daily dose greater than 3200 µg. For subjects with moderate hepatic impairment or who are concomitantly taking moderate (a) CYP2C8 inhibitor(s) the dosing frequency is once daily, and an overdose is defined by the intake of a dose greater than 1600 µg or a total daily dose greater than 1600 µg.)	Study treatment was not administered as per protocol: <specify actual deviation>	Study treatment was not administered as per protocol.	Received wrong treatment or incorrect dose	Yes

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
WITHDRAWAL CRITERIA					
71	Study treatment must be discontinued if study treatment interruptions exceed 14 consecutive days.	Study treatment was not discontinued following a study treatment interruption for more than 14 days: <specify actual deviation>	Study treatment not discontinued despite interruption of more than 14 days.	Developed withdrawal criteria but not withdrawn	Yes
72	Study treatment must be permanently discontinued if a subject develops severe hepatic impairment.	Study treatment was not prematurely discontinued in subject with severe hepatic impairment. <specify actual deviation>	Study treatment not discontinued in subject with severe hepatic impairment.	Developed withdrawal criteria but not withdrawn	Yes
73	Study treatment must be discontinued if pulmonary veno-occlusive disease (PVOD) is confirmed.	Study treatment was not prematurely discontinued in subject with confirmed PVOD. <specify actual deviation>	Study treatment not discontinued in subject with confirmed PVOD.	Developed withdrawal criteria but not withdrawn	Yes
74	Study treatment must be permanently discontinued if strong inhibitors of CYP2C8 (e.g., gemfibrozil) treatments are started during the treatment period.	Study treatment was not prematurely discontinued in subject receiving concomitant strong inhibitors of CYP2C8: *<specify treatment>*.	Study treatment not withdrawn in subject who received strong inhibitors of CYP2C8.	Developed withdrawal criteria but not withdrawn	Yes
75	Study treatment must be permanently discontinued if any investigational treatments are started during the treatment period.	Study treatment was not prematurely discontinued in subject receiving an investigational treatment *<specify treatment>*.	Study treatment not withdrawn in subject who received an investigational treatment.	Developed withdrawal criteria but not withdrawn	Yes
76	Study treatment must be discontinued if a subject becomes pregnant.	Subject became pregnant and study treatment was not discontinued. <specify actual deviation>	Study treatment not discontinued in subject who became pregnant.	Developed withdrawal criteria but not withdrawn	N/A
77	Study treatment must be discontinued if the subject (or the participants legally acceptable representative) does not agree to continue with administration of study treatment.	Study treatment was continued despite the participants (or the participants legally acceptable representative) request to prematurely discontinue study treatment <specify actual deviation>	Study treatment not discontinued despite request to prematurely discontinue study treatment.	Developed withdrawal criteria but not withdrawn	N/A
78	Study treatment must be discontinued if the investigator considers that for safety or tolerability reasons (e.g., AE), it is in the best interests of the subject to discontinue study treatment.	Study treatment was not prematurely discontinued although the investigator considered this to be in the best interest of the participant: <specify actual deviation>	Study treatment not discontinued due to safety or tolerability concerns.	Developed withdrawal criteria but not withdrawn	N/A
79	A subject will be withdrawn from the study due to Sponsor's decision for any reason, including, but not limited to premature termination or suspension of the study	Sponsor decision to withdraw subject or terminate the study but subject was not withdrawn from study treatment within the time indicated by the sponsor: <specify>.	Study treatment not discontinued due to Sponsor decision.	Developed withdrawal criteria but not withdrawn	N/A
OTHER – STUDY PROCEDURES					

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
80	Study treatment must be approved for use before administration	Participant received study treatment which was not approved for use: <specify>	Administration of study treatment which was not approved for use	Other	Yes
81	Under normal circumstances, the investigator and study personnel, the subjects, sponsor personnel directly involved in the conduct of the trial, and CRO personnel involved in the conduct of the study will remain blinded to the study treatment until the fourth analysis time point (see protocol Section 5.1.6).	Non-justified unblinding of treatment group: <specify actual deviation and reason for unblinding>.	Non-justified unblinding.	Other	Yes
82	Informed consent process not followed (e.g., study-related activity performed prior to signing initial ICF(s); new study-related activity performed before the subject was re-consented, subject not re-consented)	Informed consent process not followed: <specify actual deviation>	Informed consent process not followed.	Other	N/A
83	The Visit 4/Week 20 must be performed on Day 141 ± 7 days (i.e., days 134-148) after randomization.	The Visit 4/Week 20 was performed outside the allowed time window.	Visit 4/Week 20 outside time window.	Other	Yes (only if beyond the analysis time window ie, beyond Week 27/Day 189)
84	The Visit 4/Week 20 must be performed.	The Visit 4/Week 20 was not performed.	Visit 4/Week 20 not performed.	Other	Yes
85	The Visit 5/Week 26 must be performed on Day 183 ± 7 days (i.e., days 176-190) after randomization.	The Visit 5/Week 26 was performed outside the allowed time window.	Visit 5/Week 26 outside time window.	Other	N/A
86	The Visit 5/Week 26 must be performed.	The Visit 5/Week 26 was not performed.	Visit 5/Week 26 not performed.	Other	N/A
87	For the hemodynamic cohort, at the Week 20 the CO must be measured with a minimum of 3 consecutive measurements that should not differ by > 10% when the thermodilution method is used and with 1 measurement when the Fick method is used. The mean value will be recorded in the electronic Case Report Form (eCRF).	At the Week 20 RHC CO was not measured as per Actelion RHC/LHC guidelines.	Week 20 CO not as per study guidelines.	Other	Yes
88	For the hemodynamic cohort, zeroing as per HC guideline must be done prior to the HC measurement.	Zeroing was not done according to the HC guidelines at Visit 4/Week 20: <specify>	Zeroing was not done before HC measurements at Visit 4/Week 20.	Other	Yes
89	For the hemodynamic cohort, for sPAP and dPAP the 2 most representative and reliable	sPAP and/or dPAP not documented with 2 representative and reliable	sPAP and/or dPAP not measured or documented as	Other	Yes

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
	measurements must be documented in the source notes.	measurements at Visit 4/Week 20: <specify which parameter was not measured and documented as per guidance sPAP and/or dPAP>	per HC guidance at Visit 4/Week 20.		
90	For the hemodynamic cohort, the same method for CO measurement must be used for both the baseline and any post-baseline HC.	Postbaseline CO at Visit 4/Week 20 was not measured with the same method as at baseline: <specify>.	Postbaseline CO method at Visit 4/Week 20 is not the same as for baseline CO measurement.	Other	Yes
91	For the hemodynamic cohort, for the HC, if thermodilution method is used to measure CO, the CO must be measured with at least 3 measurements documented in the heart catherization worksheet.	Thermodilution CO at Visit 4/Week 20 not measured at least 3 times: <specify deviation>	Thermodilution CO at Visit 4/Week 20 not measured at least 3 times.	Other	Yes
92	For the hemodynamic cohort, for the HC, if thermodilution method is used to measure CO, 3 measurements must be within 10% of each other, i.e. the lowest of the 3 CO values must not be lower than 10% of the middle value AND the highest value must not be higher than 10% of the middle value.	Thermodilution CO values at Visit 4/Week 20: the upper and/or lower values are more than 10% +/- of the middle value: <specify and list the CO values>	Thermodilution CO the upper and/or lower values are more than 10% +/- of the middle value at Visit 4/Week 20.	Other	Yes
93	For the hemodynamic cohort, HC is to be performed at Visit 4/Week 20.	HC is missing at Visit 4/Week 20: <specify>	HC not done at Visit 4/Week 20.	Other	Yes
94	For the hemodynamic cohort, HC is to be performed at Visit 4/Week 20; Day 141 ± 7 days (i.e., days 134-148) after randomization.	Visit 4 /Week 20 HC was performed outside the allowed time window	Visit 4/Week 20 HC outside time window.	Other	Yes (only if beyond the analysis time window ie, beyond Week 27/Day 189)
95	For the hemodynamic cohort, CO must be measured at Visit 4/Week 20.	Missing CO at Visit 4/Week 20: <specify>	Missing CO at Visit 4/Week 20.	Other	Yes
96	For the hemodynamic cohort, sPAP must be measured at Visit 4/Week 20.	Missing sPAP at Visit 4/Week 20: <specify>	Missing sPAP at Visit 4/Week 20.	Other	Yes
97	For the hemodynamic cohort, dPAP must be measured at Visit 4/Week 20.	Missing dPAP at Visit 4/Week 20: <specify>	Missing dPAP at Visit 4/Week 20.	Other	Yes
98	For the hemodynamic cohort, PAWP or LVEDP, if PAWP is missing or not reliable must be available Visit 4/Week 20.	Missing or not reliable PAWP and missing LVEDP at Visit 4/Week 20: <specify>	Missing or not reliable PAWP and LVEDP not available at Visit 4/Week 20.	Other	Yes
99	For the hemodynamic cohort, the Week 20 RHC (and LHC, if needed) must be performed within 2 to 5 hours post dose.	The Week 20 RHC/LHC was performed outside the 2 to 5 hours post dose window.	Week 20 RHC/LHC outside 2 to 5 hours post dose window.	Other	Yes

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
100	For the hemodynamic cohort, the Week 20 RHC (and LHC, if needed) must be performed after the post-dose 6MWT	The Week 20 RHC/LHC was performed before the post-dose 6MWT	Week 20 RHC/LHC performed before post-dose 6MWT.	Other	N/A
101	6MWT is to be performed at randomization	6MWT not done at randomization: <specify>	6MWT not done at randomization.	Other	N/A
102	6MWT is to be performed at Visit5/Week 26.	6MWT not done at Visit 5/Week 26: <specify>	6MWT not done at Visit5/Week 26.	Other	N/A
103	At Week 26, the 6MWT must be performed within 2 to 5 hours post dose.	At Week 26 the 6MWT was performed outside the post dose time window of 2 to 5 hours post dose.	Week 26 6MWT outside time window.	Other	N/A
104	6MWT is to be performed at PTOP-Week 26 visit.	6MWT not done at PTOP-Week 26 visit: <specify>	6MWT not done at PTOP-Week 26 visit.	Other	N/A
105	For the 6MWT all the following requirements related to the subject must be followed: - wear comfortable clothing - wear appropriate shoes - must not have exercised vigorously within 2 hours before the 6MWT	The 6MWT requirements related to the subject at randomization were not followed: <specify deviation>	The 6MWT guidance related to the subject were not followed at randomization.	Other	N/A
106	For the 6MWT all the following requirements related to the subject must be followed: - wear comfortable clothing - wear appropriate shoes - must not have exercised vigorously within 2 hours before the 6MWT	The 6MWT requirements related to the subject at Visit 5/Week 26 were not followed: <specify deviation>	The 6MWT guidance related to the subject were not followed at Visit 5/Week 26.	Other	N/A
107	For the 6MWT all the following requirements related to the subject must be followed: - wear comfortable clothing - wear appropriate shoes - must not have exercised vigorously within 2 hours before the 6MWT	The 6MWT requirements related to the subject at PTOP-Week 26 visit were not followed: <specify deviation>	The 6MWT guidance related to the subject were not followed at PTOP-Week 26 visit.	Other	N/A
108	If the subject is used to take bronchodilators, he/she must take them at least 10 to 30 minutes before the 6MWT.	Bronchodilators were not taken 10 to 30 minutes before the 6MWT at randomization: <specify>	Bronchodilators not taken as per 6MWT guidance at randomization.	Other	N/A
109	If the subject is used to take bronchodilators, he/she must take them at least 10 to 30 minutes before the 6MWT.	Bronchodilators were not taken 10 to 30 minutes before the 6MWT at Visit 5/Week 26: <specify>	Bronchodilators not taken as per 6MWT guidance at Visit 5/Week 26.	Other	N/A

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
110	If the subject is used to take bronchodilators, he/she must take them at least 10 to 30 minutes before the 6MWT.	Bronchodilators were not taken 10 to 30 minutes before the 6MWT at PTOP-Week 26 visit: <specify>	Bronchodilators not taken as per 6MWT guidance at PTOP-Week 26 visit.	Other	N/A
111	Walking aids (e.g., cane) and walkers are not allowed.	Forbidden walking aid was used during the 6MWT at randomization: <specify>	Used forbidden walking aid during the 6MWT at randomization.	Other	N/A
112	Walking aids (e.g., cane) and walkers are not allowed.	Forbidden walking aid was used during the 6MWT at Visit 5/Week 26: <specify>	Used forbidden walking aid during the 6MWT at Visit 5/Week 26.	Other	N/A
113	Walking aids (e.g., cane) and walkers are not allowed.	Forbidden walking aid was used during the 6MWT at PTOP-Week 26 visit: <specify>	Used forbidden walking aid during the 6MWT at PTOP-Week 26 visit.	Other	N/A
114	The interval between two 6MWTs on the same day must be at least 2 hours.	There was less than 2 hours between 2 6MWTs performed at randomization: <specify>	Less than 2 hours between two 6MWTs at randomization.	Other	N/A
115	The interval between two 6MWTs on the same day must be at least 2 hours.	There was less than 2 hours between 2 6MWTs performed at Visit 5/Week 26: <specify>	Less than 2 hours between two 6MWTs at Visit 5/Week 26.	Other	N/A
116	The interval between two 6MWTs on the same day must be at least 2 hours.	There was less than 2 hours between 2 6MWTs performed at PTOP-Week 26 visit: <specify>	Less than 2 hours between two 6MWTs at PTOP-Week 26 visit.	Other	N/A
117	Only two 6MWTs can be performed on the same day.	More than two 6MWT were performed at randomization: <add description of the actual deviation>	More than 2 tests done randomization.	Other	N/A
118	Only two 6MWTs can be performed on the same day.	More than two 6MWT were performed at Visit 5/Week 26: <add description of the actual deviation>	More than 2 tests done Visit 5/Week 26.	Other	N/A
119	Only two 6MWTs can be performed on the same day.	More than two 6MWT were performed at PTOP-Week 26 visit: <add description of the actual deviation>	More than 2 tests done PTOP-Week 26 visit.	Other	N/A
120	The 6MWT must be performed indoors, along a long, flat, straight, enclosed corridor (or similar location) with a hard surface that can be blocked for traffic during the conduct of the test. The track must be marked at regular intervals. The turnaround points must be marked with a cone. A starting line, which marks the beginning and end of each lap needs to be marked on the floor. The use of treadmill and a continuous course, e.g., a circuit, is not allowed.	Corridor not compliant with 6MWT guidance requirements at randomization: <add description of actual deviation>	Corridor does not meet 6MWT guidance requirements at randomization.	Other	N/A

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
121	The 6MWT must be performed indoors, along a long, flat, straight, enclosed corridor (or similar location) with a hard surface that can be blocked for traffic during the conduct of the test. The track must be marked at regular intervals. The turnaround points must be marked with a cone. A starting line, which marks the beginning and end of each lap needs to be marked on the floor. The use of treadmill and a continuous course, e.g., a circuit, is not allowed.	Corridor not compliant with 6MWT guidance requirements at Visit 5/Week 26: <add description of actual deviation>	Corridor does not meet 6MWT guidance requirements at Visit 5/Week 26.	Other	N/A
122	The 6MWT must be performed indoors, along a long, flat, straight, enclosed corridor (or similar location) with a hard surface that can be blocked for traffic during the conduct of the test. The track must be marked at regular intervals. The turnaround points must be marked with a cone. A starting line, which marks the beginning and end of each lap needs to be marked on the floor. The use of treadmill and a continuous course, e.g., a circuit, is not allowed.	Corridor not compliant with 6MWT guidance requirements at PTOP-Week 26 visit: <add description of actual deviation>	Corridor does not meet 6MWT guidance requirements at PTOP-Week 26 visit.	Other	N/A
123	The corridor must not be shorter than 20 m in length.	6MWT at randomization was done in a corridor with track length shorter than 20 m: <add description of actual deviation>	Corridor length not as per 6MWT guidance at randomization.	Other	N/A
124	The corridor must not be shorter than 20 m in length.	6MWT at Visit 5/Week 26 was done in a corridor with track length shorter than 20 m: <add description of actual deviation>	Corridor length not as per 6MWT guidance at Visit 5/Week 26.	Other	N/A
125	The corridor must not be shorter than 20 m in length.	6MWT at PTOP-Week 26 visit was done in a corridor with track length shorter than 20 m: <add description of actual deviation>	Corridor length not as per 6MWT guidance at PTOP-Week 26 visit.	Other	N/A
126	For participants who have not previously performed a 6MWT, a training 6MWT must be performed before the first protocol-mandated 6MWT is performed.	Missing training 6MWT before the first protocol mandated 6MWT: <add description of actual deviation>	Missing training 6MWT before first protocol-mandated 6MWT.	Other	N/A
127	If a subject is oxygen dependent, the use of a portable device is allowed. The oxygen flow rate must remain constant from 30 minutes prior to each 6MWT, until the completion of all protocol-mandated assessments after the 6MWT. The way	Requirements for oxygen supplementation not followed at randomization: <add description of actual deviation>	Requirements for oxygen supplementation not followed at randomization.	Other	N/A

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
	oxygen is delivered (delivery device, application route, way of carrying the delivery device) must be the same for all 6MWTs, unless a change is required for documented medical reasons.				
128	If a subject is oxygen dependent, the use of a portable device is allowed. The oxygen flow rate must remain constant from 30 minutes prior to each 6MWT, until the completion of all protocol-mandated assessments after the 6MWT. The way oxygen is delivered (delivery device, application route, way of carrying the delivery device) must be the same for all 6MWTs, unless a change is required for documented medical reasons.	Requirements for oxygen supplementation not followed at Visit 5/Week 26: <add description of actual deviation>	Requirements for oxygen supplementation not followed at Visit 5/Week 26.	Other	N/A
129	If a subject is oxygen dependent, the use of a portable device is allowed. The oxygen flow rate must remain constant from 30 minutes prior to each 6MWT, until the completion of all protocol-mandated assessments after the 6MWT. The way oxygen is delivered (delivery device, application route, way of carrying the delivery device) must be the same for all 6MWTs, unless a change is required for documented medical reasons.	Requirements for oxygen supplementation not followed at PTOP-Week 26 visit: <add description of actual deviation>	Requirements for oxygen supplementation not followed at PTOP-Week 26 visit.	Other	N/A
130	A woman of childbearing potential must practice an acceptable method of contraception while receiving study treatment and until 30 days after last dose of study treatment - see section 4.5.2 of the protocol.	Woman of childbearing potential not using an acceptable method of contraception: <specify actual deviation>.	Subject non-compliant with contraception method use	Other	N/A
131	For female of childbearing potential, after randomization, urine pregnancy tests will be performed monthly (±7 days) until 30 days after study treatment discontinuation.	Pregnancy test missed <specify month>.	Subject non-compliant with pregnancy test.	Other	N/A
132	A SAEs or pregnancy is to be reported within the 24 hours' time frame of the investigator's knowledge of the event.	An SAE or pregnancy not reported or not reported in time: <specify>	SAE/pregnancy not reported or not reported in time.	Other	N/A
133	The Safety follow-up phone call must be performed 30-35 days after the last DB study treatment dose in case of premature discontinuation of DB study treatment.	The SFU call was *<not performed 30-35 days after the last DB study treatment dose>* or *<was not performed>*.	PTOP1 Safety follow-up telephone call not performed as per protocol.	Other	N/A

Table 17: Major Protocol Deviations Leading to Exclusion from PPS

Sequence No.	Description	Protocol Deviation Description (DVTERM)	PD Criterion	Protocol Deviation Coded Term (DVDECOD)	Exclude from PPS
134	Safety follow-up phone call must be performed 30-35 days after the last OL study treatment dose.	Safety follow-up phone call was *<not performed 30-35 days after the last OL study treatment dose>* or *<was not performed>*.	Visit 13 safety follow-up telephone call not performed as per protocol.	Other	N/A
135	PH-specific therapies stratification reported in IRT is different from the actual stratification reported in eCRF	Incorrect stratification based on PH-specific therapies	Incorrect stratification based on PH-specific therapies	Other	Yes
136	CTEPH population stratification reported in IRT is different from the actual stratification reported in eCRF	Incorrect stratification based on CTEPH population	Incorrect stratification based on CTEPH population	Other	Yes
137	An unscheduled visit must be performed within 14 days of the following occurring at an on-site visit: o Increase from baseline in WHO FC.	Unscheduled on-site visit not performed following increase from baseline in WHO FC	Unscheduled on-site visit not performed following increase from baseline in WHO FC	Other	N/A
138	An unscheduled visit must be performed within 14 days of the following occurring at an on-site visit: o Increase from baseline in WHO FC.	Unscheduled on-site visit performed outside the 14 days' time window following increase from baseline in WHO FC	Unscheduled on-site visit performed outside the 14 days' time window following increase from baseline in WHO FC	Other	N/A
139	An unscheduled visit must be performed within 14 days of the following occurring at an on-site visit: o Deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD.	Unscheduled on-site visit not performed following deterioration from baseline in 6MWD	Unscheduled on-site visit not performed following deterioration from baseline in 6MWD	Other	N/A
140	An unscheduled visit must be performed within 14 days of the following occurring at an on-site visit: o Deterioration from baseline by at least 15% in exercise capacity, as measured by the 6MWD.	Unscheduled on-site visit performed outside the 14 days' time window following deterioration from baseline in 6MWD	Unscheduled on-site visit performed outside the 14 days' time window following deterioration from baseline in 6MWD	Other	N/A

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

Prior medications are defined as any therapy used and discontinued before the day of first dose (partial or complete) of study treatment.

Concomitant medications are defined as any therapy used on or after the same day as the first dose of study treatment, including those that started before and continue on after the first dose of study treatment.

- Concomitant medications at baseline are defined as any therapy used on the first dose of study treatment, including those that started before and continue on after the first dose of study treatment.
- Concomitant medications initiated during the study treatment period are defined as any therapy used on or after the first dose of study treatment.

Summaries of prior and concomitant medications will be presented by Anatomical Therapeutic Chemical (ATC) term and treatment group.

The number and proportion of subjects who receive each prior/concomitant medication will be summarized as well as the number and proportion of subjects who receive at least 1 prior/concomitant medication by treatment group and overall, for the FAS (and HES at analysis time point 1; as described in Table 7). In addition, concomitant medications of special interest will be presented; these include PH-specific therapies, anticoagulants/antithrombotics and oxygen therapy (see Section 6.9 Appendix 9 for a list of medications in each category).

The following summary tables will be provided:

- Prior medications
- Concomitant medications at baseline
- Concomitant medications initiated during the DB treatment period (any therapy initiated on or after the first dose of study treatment in the DB treatment period).
- Concomitant medications of special interest at baseline (special interest therapies used on the day of the first dose of study treatment, including those that started before and continue on after the first dose of study treatment)
  - Concomitant PH-specific therapy at baseline, by medication subcategory and medication name
  - Concomitant anticoagulants/anti-thrombotics at baseline, by medication subcategory and medication name
  - Long term concomitant oxygen therapies present at baseline.
- Concomitant medications initiated during the OL treatment period (any therapy initiated on or after the first dose of study treatment in the OL treatment period)

Prior and concomitant medications will also be listed based on the FAS (HES subjects will be flagged).

6.6. Appendix 6 Medical History

All relevant medical history/current medical conditions based on the investigator's judgment (eg, chronic and ongoing acute conditions, serious past conditions) present before and/or at the time of signing informed consent are collected on the Medical History eCRF page.

The verbatim terms used in the eCRF reported by investigators to identify medical history events will be coded using the MedDRA.

The number and percentage of subjects in each category will be summarized by treatment group and overall, for the FAS (and HES at analysis time point 1; as described in Table 7), by system organ class (SOC) and preferred term (PT), in descending order of frequency in the SOC and PT in the selexipag treatment group.

By subject listings of medical history data will also be provided based on the FAS (HES subjects will be flagged).

6.7. Appendix 7 Intervention Compliance

Study treatment compliance is based on study treatment accountability collected on the Study Drug Dispensing & Accountability eCRF page and the Study Drug Compliance eCRF page:

- Study drug compliance for the whole treatment period is calculated from the first dose of study treatment to EDBT (overall treatment compliance).

where,

- Compliance during the DB treatment period (irrespective of any temporary study treatment dose adjustments and/or interruptions) is calculated as follows:

$$Compliance\ (\%) = \frac{(number\ of\ tablets\ dispensed\ at\ all\ visits - number\ of\ tablets\ returned\ at\ all\ visits)}{total\ expected\ number\ of\ tablets\ \ taken\ during\ the\ DB\ treatment\ period} x100$$

where,

for bid dosing frequency:

$$Expected\ number\ of\ tablets\ taken\ during\ the\ DB\ treatment\ period = [DB\ treatment\ end\ date\ (EDBT) -\ DB\ treatment\ start\ date\ (Day\ 1) + 1]x2$$

for qd dosing frequency:

$$Expected\ number\ of\ tablets\ taken\ during\ the\ DB\ treatment\ period = [DB\ treatment\ end\ date\ (EDBT) -\ DB\ treatment\ start\ date\ (Day\ 1) + 1]$$

Compliance will be summarized descriptively (N, mean, SD, median, and range [minimum, maximum]) by study treatment group for the FAS and actual treatment group for the SAF, respectively, over the DB treatment period.

The number and percentage of subjects who have at least 80% compliance through the DB treatment period in the FAS and SAF will also be summarized by treatment group.

Similar and separate summaries will be provided for the OL treatment period.

By subject listing of compliance data will also be provided on the SAF.

6.8. Appendix 8 Adverse Events of Special Interest

The following categories of AESI have been considered as either potential/identified important risks in selexipag RMP or represent otherwise an event of interest for this study. These have been reported in selexipag studies, based on the Standardized MedDRA Query (SMQs)/PTs in the current MedDRA version.

Any modifications of terms (according to the MedDRA SMQs/PTs) may occur based on later dictionary updates and/or external guidance and the latest definitions will be used at the time of analyses.

Details will be provided in an AESI definition file (doc_aesi) that is saved at the selexipag compound level and version controlled in the Entimo Integrated Clinical Environment (or equivalent system).

- Anaemia
- Bleeding events
- Gastrointestinal disturbances denoting intestinal intussusception (manifested as ileus or obstruction)
- Hyperthyroidism
- Hypotension
- Light-dependent non-melanoma skin malignancies
- Major adverse cardiovascular events (MACE)
- Medication errors
- Ophthalmological effects associated to retinal vascular system
- Pulmonary venoocclusive disease associated with pulmonary oedema
- Renal function impairment / acute renal failure
- Other topics:
  - Pregnancy
  - Prostacyclin associated reactions
  - COVID-19 infection

6.9. Appendix 9 Medications of Special Interest

Concomitant medications of special interest for PH-specific therapies (as per Section 1.2.5.1.2), and oxygen therapy, are tracked in an excel spreadsheet "med_of_interest.xls", which is located in the AC-065B302 SELECT programming study area for each reporting effort. Reviews and updates to this spreadsheet will be performed if there are additional terms included in the data for these specific concomitant medications of special interest at the time of each reporting event and/or if there is a change/update to the WHO-DD at the time of each reporting event.

A separate spreadsheet (sdg_b3c3_september1_2021_126_antithrombotic_drugs.xslx), which is provided by the coding specialist based on the current coding version, tracks the anticoagulant/anti-thrombotic medications of special interest.

6.10. Appendix 10 Marked Abnormal Laboratory Values

The following protocol defined marked laboratory abnormalities will be used.

Hematology (SI units)

Laboratory test name (CDISC Synonym[s])	LL	LLL	HH	HHH
Hemoglobin	< 100 g/L	< 80 g/L	> 20 g/L above baseline	> 40 g/L above baseline
Hematocrit; Erythrocyte Volume fraction (EVF); Packed Cell Volume (PCV) *(male)*	< 0.32 L/L	< 0.20 L/L	> 0.60 L/L	> 0.65 L/L
Hematocrit; Erythrocyte Volume fraction; Packed Cell Volume *(female)*	< 0.28 L/L	< 0.20 L/L	> 0.55 L/L	> 0.65 L/L
Platelets *(assuming no platelet cluster)*	< 75×10^9/L	< 50×10^9/L	> 600×10^9/L	> 999×10^9/L
Leukocytes; White Blood Cells	< 3.0×10^9/L	< 2.0×10^9/L	> 20.0×10^9/L	> 100.0×10^9/L
Neutrophils (Abs)	< 1.5×10^9/L	< 1.0×10^9/L	NA	NA
Eosinophils (Abs)	NA	NA	> 5.0×10^9/L	NA
Lymphocytes (Abs)	< 0.8×10^9/L	< 0.5×10^9/L	> 4.0×10^9/L	> 20×10^9/L

CDISC=Clinical Data Interchange Standards Consortium; NA = not applicable; ULN = upper limit of normal.
Greyed fields represent alert criteria for expedited notification to respective investigational site.

Blood chemistry (SI units)

Laboratory test name (CDISC Synonym[s])	LL	LLL	HH	HHH
Alanine Aminotransferase	NA	NA	> 3 × ULN	> 5 × ULN*
Aspartate Aminotransferase	NA	NA	> 3 × ULN	> 5 × ULN*
Alkaline Phosphatase	NA	NA	> 2.5 × ULN	> 5 × ULN
Bilirubin; Total Bilirubin	NA	NA	> 2 × ULN	> 5 × ULN
Creatinine	NA	NA	> 1.5× ULN	> 3 × ULN
Sodium	NA	< 130 mmol/L	> 150 mmol/L	> 155 mmol/L
Potassium	< 3.2 mmol/L	< 3.0 mmol/L	> 5.5 mmol/L	> 6.0 mmol/L
Glomerular Filtration Rate	< 60 ml/min/ 1.73 m2	< 30 ml/min/ 1.73 m2	NA	NA

* Additional thresholds are to be reported, namely > 8 × ULN.
CDISC=Clinical Data Interchange Standards Consortium; NA = not applicable; ULN = upper limit of normal.
Greyed fields represent alert criteria for expedited notification to respective investigational site.

6.11. Appendix 11: COVID-19

A COVID-19 Appendix is available for the AC-065B302 SELECT study, issued as a separate document to the protocol. This COVID-19 Appendix provides guidance on the conduct of the study during the COVID-19 pandemic; including guidance on what should be done in the event that subjects cannot attend scheduled visits due to the COVID-19 pandemic (with a focus on trying to collect mandated assessments as per protocol, as far as remains possible).

Statistical considerations to evaluate the impact of COVID-19 pandemic:

- Perform sensitivity/descriptive analyses to assess the impact of COVID-19:
  - As described in Section 5.3.3.3.2 and 5.3.3.3.3 for the primary endpoint.
  - As described below for other assessments.

Subject Disposition and Study Completion/Withdrawal:

The following summaries will be added to the disposition reporting described in Section 5.2, for those subjects who prematurely discontinued DB treatment or prematurely discontinued OL study treatment or prematurely discontinued the study due to:

- Adverse event - COVID-19 related
- Death - COVID-19 related
- Other – COVID-19 related

Prior and Concomitant Therapies:

Subjects who received one or more concomitant medications for COVID-19 infection will be summarized.

A listing of concomitant medications for COVID-19 infection will also be provided.

Protocol Deviations:

In terms of handling safety and efficacy data, COVID-19 related protocol deviations are captured on the eCRF and their impact on study safety and efficacy outcomes will be evaluated.

The number and percentage of subjects with major protocol deviations related to COVID-19 will be provided, added to the major protocol deviation summary table described in Section 6.4 Appendix 4.

Separate listings of subjects with major (and minor) protocol deviations related to COVID-19 will also be provided.

Adverse Events and Deaths:

The following will be added to the overall AE table summaries described in Section 5.6.2:

- COVID-19 associated AEs
- COVID-19 associated SAEs
- COVID-19 associated non-serious AEs

where, COVID-19 associated AEs are based on events that code to a COVID-19 MedDRA term.

The following listings will also be provided:

- Listing of subjects with treatment-emergent COVID-19 associated AEs during the DB treatment period.
- Listing of subjects with treatment-emergent COVID-19 associated AEs during the OL treatment period.
- Listing of subjects who died due to COVID-19 infection.

7. REFERENCES

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