Actelion Pharmaceuticals Ltd

Statistical Analysis Plan

A multicenter, randomized, double-blind, placebo-controlled study in participants with sarcoidosis-associated pulmonary hypertension (SAPH) to assess the efficacy and safety of oral selexipag.

Protocol AC-065D301; Phase 2

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
1.0	14 May 2019	Not Applicable	Initial release.
2.0	05 April 2022	Changes in primary/secondary/exploratory endpoints.	Update the full SAP according to major protocol amendments 2, 3 and 4 (full change in study objectives/strategy). See protocol version 2 (05 Dec 2019), version 3 (21 Sep 2020) and version 4 (25 Feb 2022) for all details.
3.0	01 December 2022	Update the SAP for a synoptic CSR	Update after announcement of study termination by the Sponsor (26 Sep 2022). Reporting simplified. All listings are kept, and all the analyses already planned and produced for DMC.

1. INTRODUCTION

This Statistical Analysis Plan (SAP) presents the planned analyses for the primary endpoint, pulmonary vascular resistance (PVR) up to Week 26, exploratory efficacy endpoints and safety endpoints. It also covers the needs for regular internal data monitoring committee (DMC) meetings. This current SAP presents a simplified version of the previous final SAP covering the analyses to be performed following the Sponsor decision to prematurely terminate the study due to slow enrollment (decision on 26 Sep 2022). Reporting is simplified: all listings and all the analyses already planned and produced for DMC are kept. For efficacy, all parameters will be listed only.

This SAP is referring to the documents listed in Table 2.

Table 2 Study Documents

Document	Date,	Version
Study Protocol	25 February 2022	Amendment 3 (Version 4)
Internal DMC Charter	28 January 2020	Version 1

1.1. Objectives and Endpoints (as per protocol)

Objectives	Endpoints
Primary	
• To assess the effect of selexipag versus placebo on pulmonary vascular resistance (PVR) in participants with sarcoidosis associated pulmonary hypertension (SAPH) up to Week 26.	• PVR on study intervention up to Week 26 expressed as percent of the baseline value.
Exploratory	
• To evaluate the effect of selexipag versus placebo on time to clinical worsening (TTCW).	• TTCW up to End-of-Main-Observation-period (EOMOP) defined as at least one of the following components: o All-cause death o Unplanned pulmonary hypertension (PH)-related hospitalization o Increase in WHO functional class (FC) o Lung transplantation o Atrial balloon septostomy o Initiation of parenteral or new class of PH-specific therapy for clinical worsening

Objectives	Endpoints
• To evaluate the effect of selexipag versus placebo on exercise capacity.	• Change from baseline in 6MWD, Borg CR Scale® (CR10), oxygen saturation, and WHO FC at Week 39 and over time. • Proportion of participants with oxygen desaturation post-6-minute walk test (6MWT) at Week 39 and over time (identified by decrease in oxygen saturation [SpO2] by at least 5% from pre-6MWT).
• To evaluate the effect of selexipag vs placebo on daily life physical activity (DLPA) and sleep parameters	• Change from baseline to Week 39 in actigraphy-assessed DLPA as measured by: o Total DLPA in counts per minute o Total volume of activity (above sedentary) o Daily time spent (minutes) in non-sedentary activity o Percentage of daily time spent in non-sedentary activity o Moderate to vigorous physical activity (MVPA) o Time spent in the different activity categories • Change from baseline to Week 39 in sleep parameters: o Total sleep time (TST; minutes) o Wake after sleep onset (WASO; minutes) o Number of awakenings o Sleep efficiency (percentage)
• To evaluate the effect of selexipag versus placebo on WHO FC.	• Proportion of participants with improvement, worsening and no change from baseline in WHO FC at Week 39 and over time.
• To evaluate the effect of selexipag versus placebo on death or PH-related hospitalizations	• Rate of all-cause death or unplanned PH-related hospitalization up to EOMOP. • Time to all-cause death up to EOMOP.

Objectives	Endpoints
• To evaluate the effect of selexipag versus placebo on patient-reported outcomes (PROs) assessed by the 12-Item Short Form Health Survey (SF-12), King's sarcoidosis questionnaire (KSQ), Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT), and Patient Global Assessment of Severity (PGA-S)	• Change from baseline up to Week 39 in SF-12 scores. • Change from baseline up to Week 39 in KSQ scores. • Change from baseline up to Week 39 in PAH-SYMPACT scores. • Change from baseline up to Week 39 in PGA-S scores.
• To evaluate the effect of selexipag versus placebo on clinician-reported outcomes (CROs) assessed by the Clinician Global Impression of Severity (CGI-S) and Clinician Global Impression of Change (CGI-C)	• Change from baseline up to Week 39 in CGI-S scores. • Change from baseline up to Week 39 as measured by CGI-C scores.
• To evaluate the effect of selexipag on the number of PH low-risk criteria	• Absolute and change from baseline in the number of low-risk criteria based on WHO FC, 6MWD, N-terminal pro b-type natriuretic peptide (NT-proBNP), and cardiac index (CIn) up to Week 26.
• To evaluate the effect of selexipag on NT-proBNP	• Change from baseline in NT-proBNP serum levels up to Week 39.
• To evaluate the effect of selexipag on disease and pathway-related serum biomarkers	• Change from baseline in serum biomarkers and associations between serum biomarker levels and clinical response and baseline characteristics up to Week 39.
• To evaluate the change in hemodynamic variables other than PVR	• Change from baseline in other hemodynamic variables (including cardiac output [CO], CIn, mean right atrial pressure [mRAP]) up to Week 26.
Safety	
• To assess the overall safety of selexipag	• Intervention-emergent AEs. • Intervention-emergent prostacyclin-associated AEs. • Serious adverse events (SAEs) up to End-of-Study (EOS). • AEs leading to premature discontinuation of study intervention. • Intervention-emergent AEs of special interest (eg, hypotension, anemia, hyperthyroidism). • Change in vital signs (systolic and diastolic arterial blood pressure and pulse rate) and body weight from baseline to all assessed timepoints during the study.

Objectives	Endpoints
	• Intervention-emergent marked laboratory abnormalities. • Change from baseline in supplemental oxygen rate. • Change from baseline in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (D_{LCO}). • Change from baseline in arterial blood gas parameters.

1.2. Study Design

This is a prospective, randomized, double-blind (DB), placebo-controlled, multicenter, interventional study in men and women ≥18 and ≤75 years of age with SAPH. Study intervention will be up-titrated to allow each participant to reach their individual maximum tolerated dose (iMTD), in the range of 200 µg to 1,600 µg twice daily. For participants with moderate hepatic impairment (Child-Pugh Class B) or who are concomitantly taking a moderate cytochrome P450 (CYP)2C8 inhibitor(s) the dosing frequency is once daily.

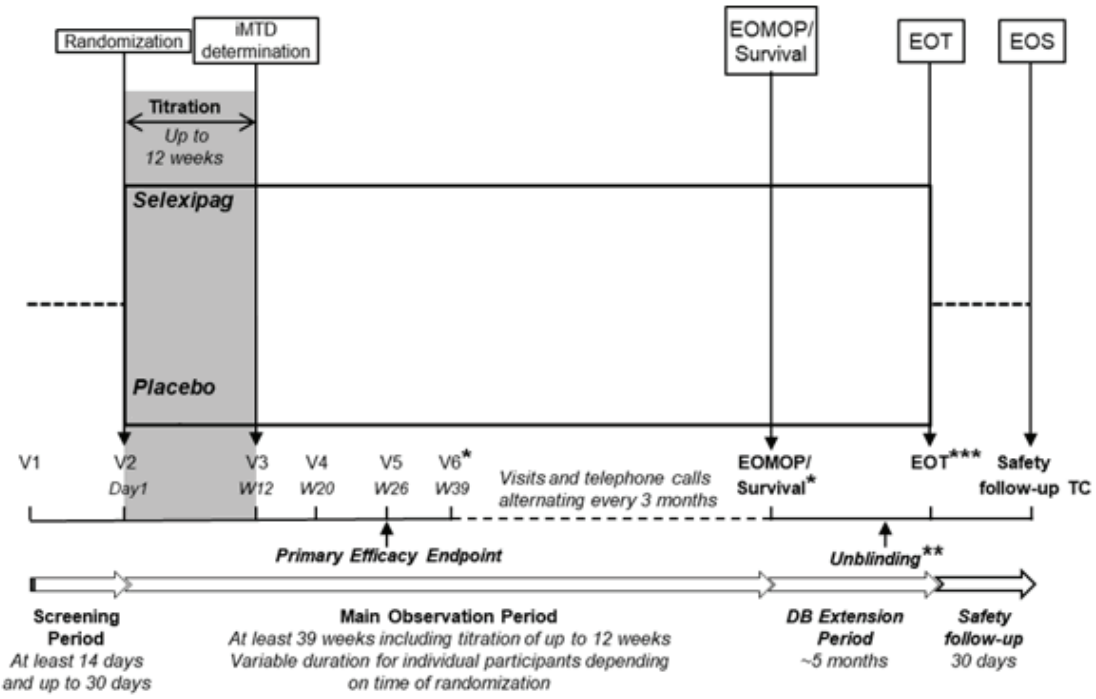
The study starts with the first Informed Consent Form (ICF) signed by the first participant and ends with the last safety follow-up telephone call (TC) or visit of the last participant. The study comprises the following periods:

- A screening period of up to 30 days: starts with the signature of the ICF and ends with the participant's randomization at Visit 2, Day 1. The screening period should last at least 14 days to allow collection of baseline data for daily life physical activity (DLPA), sleep parameters, and Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT™).
- Intervention and observation periods:
  - A main observation period (MOP) that starts with the participants' randomization at Visit 2, Day 1 and with a titration phase of up to 12 weeks. Participants receive double-blind study intervention (selexipag or placebo) during this period. It ends on the day of the EOMOP visit. The EOMOP visit is the data cut-off for the primary efficacy and safety analyses. The EOMOP visit for all participants is planned at 39 Weeks ±1 month after randomization of the last participant. The duration of the MOP will be different for each individual participant and will depend on the time of each participant's individual date of randomization.
    - Participants who prematurely discontinue study intervention before the EOMOP visit will continue to perform visits and assessments as scheduled until the EOMOP visit.
    - For participants who prematurely discontinue study intervention before the EOMOP visit and who disagree to perform visits and assessments as scheduled until the EOMOP visit, long-term follow-up information regarding their survival status will be collected yearly until death or the time of EOMOP.

- A DB extension period extending intervention for participants who do not prematurely discontinue study intervention before EOMOP: The period starts in the evening of the day of the EOMOP visit and ends with the end-of-treatment (EOT) visit. This period will last approximately 5 months. All participants entering the DB extension period will continue taking blinded study intervention (selexipag or placebo) during this period. Study intervention allocation will be unblinded approximately 1 month before the expected EOT visit.
- A safety follow-up period starting on the day after the last dose of study intervention and ending with the safety follow-up call at the End-of-Study (EOS) visit. For an individual participant, EOS visit is defined as follows:
  - For participants who complete the treatment, EOS visit is defined as the safety follow-up visit (TC) 30 (+5) days after last dose of study intervention.
  - For participants who prematurely discontinue study intervention for any reason before EOMOP visit (except for withdrawal from the study) but complete the main observation period, EOS visit corresponds to the last visit, which is either the EOMOP visit or the safety follow-up TC, whichever occurs last.
  - For participants who prematurely discontinue study intervention for any reason before the EOMOP visit and who decline to continue with visits and assessments up to the EOMOP visit, but agree to the collection of long-term survival information, the EOS visit corresponds to the last visit or TC before study discontinuation.
  - For participants who prematurely discontinue study intervention between the EOMOP and EOT visits for any reason (except for withdrawal from the study), the EOS visit corresponds to the safety follow-up TC.
  - For participants who complete the treatment and who are entering a continued access program (ie, other open-label extension study or post-trial access), the EOS visit is defined as the EOT visit and enrollment in the continued access program must occur on the day of the last visit in the SPHINX study.

Following the study premature termination by the sponsor, the EOMOP will refer to a premature EOMOP.

See figure below for the study design schematic overview.



EOMOP = end-of-main-observation-period; EOS = end-of-study; EOT = end-of-treatment; iMTD = individual maximum tolerated dose; TC = telephone call, V = visit; W = week.

*The EOMOP visit has to be performed within ±1 month of planned Visit 6/ Week 39 of the last participant and it will be announced approximately 9 months in advance. For the last participant, the EOMOP visit will be the Visit 6/Week 39. For all other participants, if the EOMOP visit falls within the visit window of any other scheduled visit, these visits can be combined, and assessments will not be repeated. Survival information will be collected for participants who discontinued from study intervention and visits and assessments.
**Intervention group allocation will be provided to study sites approximately 1 month prior to EOT.
***Study intervention will be provided until the EOT visit, which is planned approximately 5 months after the last EOMOP visit. In case of premature discontinuation of study intervention, the premature EOT visit should be performed within 7 days after last study intervention dose and participants should continue to perform visits and assessments up to the EOMOP visit.

A sponsor Data Monitoring Committee (DMC), Clinical Event Committee (CEC), and Steering Committee (SC) will be established.

The sponsor DMC (internal) has overall responsibility for safeguarding the interests of participants and will review safety data throughout the study. The sponsor DMC will provide recommendations to the study team.

The CEC will be a sub-committee of the SC that will review and adjudicate the following cases: hospitalization, WHO FC increase, and initiation of PH-specific therapy (not to be performed because of study premature termination). An SC is involved in the study design and will provide guidance on the study conduct and study publications.

The End-of-Study (EOS) at study level is considered as the last visit or safety follow-up TC, whichever occurs last, for the last participant in the study.

1.2.1. Analysis Timepoints

Following the study premature termination by the sponsor, the final analysis will be performed at the final database lock only, when all participants have completed the safety follow-up phone call or discontinued prematurely.

1.2.2. DMC and Steering Committee

A sponsor Data Monitoring Committee (DMC) and a Steering Committee will be established.

The sponsor DMC (internal) has the overall responsibility for safeguarding the interests of participants and will review on regular basis the results of safety analyses performed by an unblinded statistical support group (SSG) independent from the study team. The DMC will provide recommendations to the study team. The committee is governed by a dedicated DMC charter.

A Steering Committee is involved in the study design and will provide guidance on the study conduct and study publications. The committee is governed by a dedicated Steering Committee charter.

1.2.3. Randomization and blinding

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study under the supervision of the sponsor. The randomization will be stratified by PH-specific therapy at baseline (yes vs no). The Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

The study period up to EOMOP will be performed in a DB fashion. Unblinding will occur after all patients completed EOMOP.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Under normal circumstances, the investigator and study personnel, the participants, sponsor personnel, and CRO personnel involved in the conduct of the study will remain blinded to the study treatment until EOMOP analysis timepoint, or until the study is stopped prematurely. In order to preserve the blind of each individual participant until EOMOP analysis timepoint, randomization codes and, if required, the translation of randomization codes into treatment and

control groups will be disclosed to those authorized and only for those participants included in the analyses for the DMC. An internal SSG will conduct the analyses and present unblinded results to the DMC (see specific DMC charter).

The investigator may in an emergency determine the identity of the treatment by contacting the IWRS. While the responsibility to break the treatment code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the Investigator Site file and in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a participant in the study, unblinded SUSAR information will be provided to DMC and respective health authorities and Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) only. SUSARs will be reported to investigators in a blinded fashion. The treatment assignment will not be communicated to site personnel or to sponsor study team.

Participants who have had their treatment assignment unblinded may stay on study treatment after unblinding provided the following conditions are met: emergency unblinding for accidental or intentional overdose or medication error.

2. STATISTICAL HYPOTHESES

The primary objective is: " To assess the effect of selexipag versus placebo on pulmonary vascular resistance (PVR) in participants with sarcoidosis associated pulmonary hypertension (SAPH) up to Week 26."

As the study is prematurely terminated, no formal hypothesis will be tested, and all efficacy parameters will be listed only.

3. SAMPLE SIZE DETERMINATION

In a clinical study with bosentan in participants with SAPH (BOSAPAH-1), the observed GM ratio for *PVR post to pre percent* (defined in Section 5.3.1) was around 0.7 in 35 participants with SAPH at Week 16 (bosentan vs placebo). It was also 0.7 in the NS-304/-02 study in 35 participants with PAH at Week 17 (selexipag vs placebo, with CV of *PVR post to pre percent* 0.28 vs 0.08). In the CTEPH studies MERIT-1 (80 participants) and BENEFIT (157 participants) the observed CVs of *PVR post to pre percent* approached 0.4. The blinded interim estimate in 79 participants of the TRITON study gives a CV of 0.5.

Sample size is calculated based on the statistical requirements to detect a clinically relevant difference between the selexipag and placebo groups using a 1:1 randomization ratio, a two-sided Type I error of 5% and a Type II error of 10% (90% power).

The following assumptions were made:

- A ratio of the GM of Week 26 (or premature EOT) to Baseline PVR values equal to 0.70 ie, a 30% relative decrease (improvement) in GM as compared to placebo;
- A coefficient of variation of the ratio of 0.50;
- Normal distribution for the $\log_e$-transformed ratio of Week 26 (or premature EOT) to baseline PVR values.

Based on the above assumptions, 74 participants are required to establish the superiority of selexipag vs placebo with 90% power to correctly reject a false null hypothesis in favor of the alternative hypothesis.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis sets are detailed in the Table 3 below:

Table 3 Overview of the Different Populations for Analyses

Population	Description
Screened Analysis Set (SCR)	All participants who were screened and received a participant identification number.
Randomized Set (RS)	All participants assigned to a study intervention.
Safety Analysis Set (SAS)	All participants who received at least one dose of study intervention. Participants will be analyzed according to the intervention they actually received.

All baseline characteristics and safety analyses will be performed on the SAS. Efficacy will be listed only using the RS.

5. STATISTICAL ANALYSES

5.1. General Considerations

Following the sponsor decision to prematurely terminate the study due to slow enrollment (decision on 26 Sep 2022), the reporting is simplified: all listings and all the analyses already planned and produced for the sponsor DMC are kept for the final CSR. For efficacy, all parameters will be listed only.

Statistical analysis will be done by the sponsor or delegated to a Contract Research Organization under the responsibility of the sponsor. Unblinded analyses for the sponsor DMC will be performed by an SSG independent from the study team to protect from unblinding.

5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The period starts with the administration of the first dose of DB study treatment. The reference day is Study Day 1, which is the day of randomization. If a participant has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses,

but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 4) are the visit windows and the target days for each visit defined in the protocol.

Table 4 Visit Windows for double-blind treatment period

Parameter	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
All parameters§	1	Screening	< 1	[-30 to -1]
	2	Baseline	<=1	1
RHC (including PVR) / DLco / Spirometry / Arterial blood gas	5	Week 26	2 to 280	183
All Other parameters	3	Week 12	2 to 112	85
	4	Week 20	113 to 161	141
	5	Week 26	162 to 228	183
	6	Week 39	229 to 364	274
	7	Week 65	365 to 546	456
	8	Week 91	547 to 728	638
	9	Week 117	729 to 910	820
	10	Week 143	911 to 1092	1002

§ RHC is collected only during the screening period, not at baseline. *Relative to Study Day 1; DL_{CO} = diffusing capacity for carbon monoxide; RHC = right heart catheterization.

It is likely that only few participants (or none) will have an assessment after visit 10 and therefore those data will not be used in summary statistics and will be listed only.

5.1.2. Study Day and Relative Day

Study Day 1 or Day 1 refers to the day of randomization. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'

5.1.3. Baseline

Baseline is defined as the last observation on or before the day of first dose of study treatment.

5.1.4. Imputation Rules for Missing Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first dose of study treatment.
  - The day of first dose of study treatment, if the month/year of the onset of AE is the same as month/year of the first dose of study treatment and month/year of the AE resolution date is different
  - The day of first dose of study treatment or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose of study treatment date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the first dose of study treatment
  - Month and day of the first dose of study treatment, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the first dose of study treatment,
  - The AE resolution date.
- Completely missing onset dates will not be imputed, but the event will be assumed to be treatment emergent unless otherwise indicated.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

Concomitant therapy start dates will be imputed as follows:

- If the start date is missing day only, it will be set to first day of the month.
- If the start date has the year, but is missing the month, it will be set to January 1.
- If the start date is completely missing, it will not be imputed

Concomitant therapy end dates will be imputed as follows:

- If the end date is missing day only, it will be set to last day of the month.
- If the year is supplied, but is missing the month, it will be set to December 31, or the date of death if this is earlier.
- If the end date is completely missing, it will not be imputed

For missing or partial assessment dates:

- For scheduled visits, the date will be set to the date closest to the scheduled date, within the range allowed by the partial dates. (For screening assessments, use day -8 as the scheduled date.)
- For unscheduled visits with partial dates:
  - if the day of first dose of study treatment is within the period, it will be set to the day after first dose;
  - otherwise, if the day of first dose of study treatment is within the period, it will be set to the day of first dose;
  - otherwise, if only the day is missing, it will be set to first of the month.

otherwise, if the year is supplied, but is missing the month, it will be set to January1.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention
- Participants who completed the study
- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention
- Participants who terminated study prematurely
- Reasons for termination of study

A listing of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention.

5.3. Primary Endpoint(s) Analysis

PVR data will be listed only.

5.3.1. Definition of Endpoint(s)

The primary endpoint is the ratio of the PVR value post-treatment initiation up to Week 26 (post) vs the PVR value pre-treatment initiation at baseline (pre), expressed as a percentage, ie:

$$PVR\ post\ to\ pre\ percent = \left(\frac{PVR\ up\ to\ Week\ 26}{PVR\ at\ baseline}\right) \times 100\ (\%)$$

The baseline reference value for PVR is based on the last RHC performed prior to study intervention initiation.

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

$$PVR = 80 \times (mPAP - PAWP) / CO$$

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. If PAWP is missing, then the LVEDP will be used.

Handling of missing data

No imputation will be performed for missing PVR.

5.3.2. Analysis Methods

PVR data will be listed only using the Randomized Set (RS).

5.4. Secondary Endpoint(s) Analysis

Not applicable. For efficacy, the study has only primary and exploratory endpoints.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

All exploratory endpoints will be listed only using the Randomized Set (RS).

5.5.1. Time To Clinical Worsening (TTCW)

No event adjudication will be performed by the Clinical Event Committee (CEC). Therefore, no data will be reported for this endpoint.

5.5.2. 6-Minute Walk Distance (6MWD) and Borg CR Scale® (CR10)

6MWD and Borg Scale will be listed only using the Randomized Set (RS).

5.5.3. Proportion of participants with oxygen desaturation post 6MWT up to Week 39

Oxygen desaturation will be listed only using the Randomized Set (RS).

5.5.4. Proportion of participants with improvement/no change/worsening versus baseline in WHO FC up to Week 39

WHO FC will be listed only using the Randomized Set (RS).

5.5.5. Daily life physical activity (DLPA) and sleep parameters up to Week 39

Actigraph data as per source transfer as documented in the data transfer agreement (instead of derived data) may be reported in listings (on the Randomized Set (RS) as we may not have sufficient data for derivation.

If derived, the following variables will be computed and listed over time on the Randomized Set (RS):

- Total DLPA in counts per minute
- Total volume of activity (above sedentary)
- Daily time spent (minutes) in non-sedentary activity
- Percentage of daily time spent in non-sedentary activity
- Moderate to vigorous physical activity (MVPA)
- Time spent in the different activity categories

All actigraphy endpoints will be aggregated into 14-day windows for analysis. Baseline will be the average of the last 14 days prior to first dose of study drug (Day −1 to Day −14); post baseline assessments will be aggregated in 14-day intervals as shown in Table 5.

Likewise, the last 14 days prior to the last dose of study treatment will be used for determination of the EOT value. All patients will have an EOT value, unless patient withdrew within a week of treatment start or no actigraphy data available after the study day 7 (See section "Handling of missing data").

If enough valid data have been collected in a time window at an analysis visit (see Section Handling of missing data"), the average of the values assessed within the time window will be used as analysis value. Actigraphy data collected prior to Day −14 or after EOT will be listed only.

Table 5 Actigraphy assessment time windows

Analysis Visit	Start Day	End Day
Baseline	−14	−1
Week 3	8	21
Week 5	22	35
Week 7	36	49
Week 9	50	63
Week 11	64	77
Week 13	78	91
Week 15	92	105
Week 17	106	119
Week 19	120	133
Week 21	134	147
Week 23	148	161
Week 25	162	175
Week 27	176	189
Week 29	190	203
Week 31	204	217
Week 33	218	231
Week 35	232	245
Week 37	246	259
Week 39	260	273
EOT[1]	Last study treatment − 14 days*	Last study treatment − 1 day*

[1] EOT value will be computed out of the last two weeks prior to last study treatment, regardless if the last study treatment date was before, at, or after Day 273.
* EOT will have a valid value. If EOT value based on the period (EOT-14, EOT-1) is missing (not valid), the EOT period will be rolled back by one day, i.e., (EOT-15, EOT -2), (EOT-16, EOT-3), and so on until a non-missing (valid) value is available. The period can be rolled back until (1, 14).
EOT = End-of-Treatment.

Handling of missing data

Actigraphy variables will be considered valid (non-missing) for a specific time window if the data are available for at least 7 complete days (consecutive or not) within that time window of assessment.

For DLPA actigraphy endpoints, a complete day is defined as a record of at least 7 awake hours of data. If less than 7 complete days are available, the value of the time window will be set to missing.

In case of premature discontinuation of study drug, the average of the last non-missing 14-day window prior to the last dose of study treatment will always be used as an EOT value. If the EOT value corresponding to the period (EOT-14, EOT-1) is missing (not valid), the EOT period will be rolled back by one day, i.e., (EOT-15, EOT-2), (EOT-16, EOT-3), until a non-missing (valid) value is available. This corresponds to a last observation carried forward (LOCF) up to Week 39/EOT approach. If no post-baseline actigraphy data have been collected for at least 7 days over a 14-day time window, no EOT value will be computed, and the post-baseline value will be set as missing.

5.5.6. Time to all-cause death up to EOMOP

Deaths will be listed only using the Randomized Set (RS).

5.5.7. Rate of all-cause death or unplanned PH-related hospitalizations up to EOMOP

Unplanned PH-related hospitalizations will be listed only using the Randomized Set (RS).

5.5.8. Change from baseline up to Week 39 in SF-12 scores

SF-12 individual questions responses will be listed only using the Randomized Set (RS). If available for analysis, the physical and mental component summary scores will be reported according to the instrument's instruction (and applying the OPTUM process).

5.5.9. Change from baseline up to Week 39 in the KSQ scores

KSQ individual questions responses will be listed only using the Randomized Set (RS).

5.5.10. Change from baseline up to Week 39 in the PAH-SYMPACT scores

PAH-SYMPACT individual questions responses will be listed only using the Randomized Set (RS).

5.5.11. Change from baseline up to Week 39 in the PGA-S scores

PGA-S individual questions responses will be listed only using the Randomized Set (RS).

5.5.12. Change from baseline up to Week 39 in the CGI-S scores

CGI-S individual questions responses will be listed only using the Randomized Set (RS).

5.5.13. Change from baseline up to Week 39 in the CGI-C scores

CGI-C individual questions responses will be listed only using the Randomized Set (RS).

5.5.14. Change from baseline up to Week 39 in NT-proBNP serum levels

NT-proBNP values will be listed only using the Randomized Set (RS).

5.5.15. Change from baseline up to Week 39 in other hemodynamic variables (including cardiac output [CO], CIn, mean right atrial pressure [mRAP])

Other hemodynamic variables (including cardiac output [CO], CIn, mean right atrial pressure [mRAP]) will be listed only using the Randomized Set (RS).

5.5.16. Change from baseline up to Week 39 in the number of low-risk criteria

This endpoint is derived based on other endpoints and will not be computed for this study, due to the very limited number of study participants.

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual intervention received, unless otherwise specified. Analyses will be conducted for the entire study period only.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

Exposure will be summarized for the entire study period, by treatment group and overall using the SAS.

The number and percentage of participants who receive study intervention will be summarized. The number and percentage of participants at each dose level will also be summarized by visit.

Descriptive statistics for duration of study intervention (N, mean, SD, median, and range (minimum, maximum)) will be summarized. Participant-[years] of intervention are calculated as [days of intervention/365.25]. Participant-[years] will be presented by intervention group.

Cumulative exposure will be summarized using week categories.

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

Total dose days of intervention is defined as the total number of days that study intervention was administered to the participant (excluding days off study intervention).

The number (%) of participants with a dose adjustment/dose not administered will be summarized by intervention group. Reasons for dose adjustments/doses not administered will also be summarized.

Descriptive statistics will be presented for the following parameters: Maximum Study Treatment Total Daily Dose and Weighted-Average Study Treatment Total Daily Dose (separately for titration and maintenance periods); Individual Total Daily Maintenance Dose of Study Treatment; Maximum Tolerated Total Daily Dose of Study.

The mean daily dose of study treatment is calculated as (sum of total daily dose)/study treatment duration.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 3 days is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration 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 intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries will be displayed by treatment (selexipag or placebo) and will include all events up to 3 days after the last dose of study drug or EOS, whichever occurs first.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study intervention
- AEs by severity
- AEs by relationship to study intervention
- All SAEs up to 30 days after the last study treatment

In addition to the summary tables, listings will be provided for participants who:

- Had AEs
- Had SAEs
- Had AEs leading to discontinuation of study intervention
- Had AEs of COVID-19
- AEs of special interest (Appendix 8)

Deaths will be displayed by actual intervention received. Frequencies for the following parameters will be included in the summary table:

- Number of participants who died
- Cause of death
- Relationship to study intervention (yes/no)

A listing of participants who died will be provided.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set and will be presented by study treatment for the entire study period. Local laboratory data will be included in listings and used only to find marked abnormalities.

The laboratory tests are summarized in table below:

Laboratory Assessments	**Variables**
Hematology	Hemoglobin Hematocrit Erythrocyte count Platelet count Leukocyte count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Total and direct bilirubin Creatinine Sodium, potassium Serum albumin Glomerular filtration rate, using the Modification of Diet in Renal Disease formula Thyroid hormones: Free and total triiodothyronine (T3) Free and total thyroxine (T4) Thyroid stimulating hormone (TSH)
Other Tests	A serum pregnancy test for women of childbearing potential will be performed at Screening. Urine pregnancy tests will be performed at randomization and monthly thereafter. Urine pregnancy tests are either performed on-site during a scheduled visit or at home with the pregnancy test validated kit provided by the site. The results of the urine pregnancy tests will not be collected in the eCRF. Results of pregnancy tests will be documented in the participant's records (pregnancy test card). The date of the urine pregnancy test reported on the pregnancy card will be collected in the eCRF. Additional serum or urine pregnancy tests may be performed, if pregnancy is suspected during the study, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. NT-proBNP will be analyzed as part of the efficacy assessments.

Descriptive statistics (including change from baseline) will be presented for all chemistry and hematology laboratory tests at scheduled time points by treatment group.

An abnormality (abnormality based on criteria defined in tables in Appendix 10) will be attributed to the baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- Treatment emergent (TE) will be concluded if the postbaseline value is worse than the baseline value.
- If the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low), then the postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Treatment-emergent marked laboratory abnormalities will be summarized for each laboratory variable for which marked abnormalities are defined providing their incidence and frequency.

In addition, the proportion of participants with the following treatment-emergent liver abnormalities will be summarized:

- ALT ≥3× upper limit of normal (ULN), ALT ≥5×ULN, ALT ≥8×ULN
- AST ≥3×ULN, AST ≥5×ULN, AST ≥8×ULN
- ALT or AST ≥3×ULN, ALT or AST ≥5×ULN, ALT or AST ≥8×ULN
- ALT or AST ≥3×ULN and concomitant (collected on the same day) bilirubin ≥2×ULN and both (ALT or AST and bilirubin) increased compared to baseline
- ALT or AST ≥3×ULN and bilirubin ≥2×ULN at any time and both (ALT or AST and bilirubin) increased compared to baseline

All laboratory data will be listed together with derived marked abnormality flag. A separate listing of marked abnormality laboratory values will be provided.

5.6.3.2. Vital Signs and Physical Examination Findings

Vital signs will be displayed for the participants included in the safety analysis set and will be presented by study treatment for the entire study period.

Continuous vital sign parameters including weight, pulse, blood pressure (systolic and diastolic), and Body Mass Index (BMI) will be summarized at each assessment time point. Body Mass Index will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at [screening/the nearest visit] will be used in the calculation. Change from baseline will be summarized. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Abnormality criteria (based on criteria defined below in Table 6) will be applied to baseline and postbaseline values. For baseline values, increase or decrease criteria are not applied.

Postbaseline values will be considered treatment-emergent if they meet both value and change criteria in the Table 6 below. If the baseline value is missing, a postbaseline abnormality will always be considered as treatment-emergent.

Incidence of treatment-emergent clinically important vital signs during intervention, as defined in Table 6, will be summarized for participants who had a baseline assessment and at least 1

postbaseline assessment for that vital sign. A listing of participants with treatment-emergent clinically important vital signs will be presented, along with a listing of all vital sign measurements.

Table 6 Clinically Important Vital Signs

Vital Sign	Criteria
Pulse	>120 bpm and with >30 bpm increase from baseline
	<50 bpm and with >20 bpm decrease from baseline
Systolic blood pressure	>180 mm Hg and with >40 mm Hg increase from baseline
	<90 mm Hg and with >30 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >30 mm Hg increase from baseline
	<50 mm Hg and with >20 mm Hg decrease from baseline

5.6.3.3. Electrocardiogram

Listings will be produced for all ECG data including unscheduled visit data on the SAS. A listing of clinically relevant ECG abnormalities will also be provided.

5.6.3.4. Other Safety Parameters

Descriptive statistics of values and changes from baseline in supplemental oxygen rate, DLCO, FVC and arterial blood gas will be summarized over time on the SAS by treatment group for the entire study period.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Not applicable.

5.7.2. Immunogenicity

Not applicable.

5.7.3. Pharmacodynamics

Not applicable.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

5.7.5. Biomarkers

Biomarker analysis is optional for each participant. A biomarker-specific ICF should be signed prior to collection of any samples for biomarker analysis.

Biomarker samples will be used to generate plasma and serum marker data for computational analyses. These analyses are considered exploratory and the results will be reported separately from the CSR.

Available biomarkers data at time of final database lock will be listed only.

5.7.6. Health Economics

Not applicable.

5.7.7. Other Variables and/or Parameters

Not applicable.

5.7.8. Definition of Subgroups

No subgroup analysis will be performed.

5.8. Interim Analyses

Not applicable.

5.8.1. Data Monitoring Committee (DMC) or Other Review Board

There is no formal efficacy interim analysis for this study. The sponsor DMC (internal DMC) has overall responsibility for safeguarding the interests of participants and will review on regular basis the results of analyses performed by an unblinded internal statistical support group (SSG) independent from the study team. The DMC will provide recommendations to the study team. Outputs needed for DMC meetings will be flagged in list of outputs in this SAP (DPS part 1) and will focus only on baseline characteristics, protocol deviations, concomitant medications and all safety data (adverse events and laboratory data).

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
BSA	body surface area
CI	confidence interval
CL	total systemic clearance
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End of treatment
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IQ	interquartile
IVRS	interactive voice response system
IWRS	interactive web response system
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

This current SAP presents a simplified version of the previous final SAP covering the analyses to be performed following the Sponsor decision to prematurely terminate the study due to slow enrollment (decision on 26 Sep 2022). Reporting is simplified: all listings and all the analyses already planned and produced for DMC are kept. For efficacy, all parameters will be listed only.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group, and overall.

Table 7 and Table 8 present a list of the demographic variables and baseline disease characteristics that will be summarized by intervention group and overall for the SAS.

Table 7 Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m2)	
Categorical Variables	
Age ([18-25 years, 26-50 years, 51-64 years, and >=65 years])	Frequency distribution with the number and percentage of participants 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, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Region (US, Latin America, Europe)	

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

Table 8 Baseline disease characteristics

Continuous Variables:	**Summary Type**
Time from SAPH diagnosis (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
6MWD (m)	
NT-proBNP (ng/L)	
Calculated PVR (dyn.sec/cm5)	
Cardiac Outputs (L/min), mPAP (mmHg), mRAP (mmHg), PAWP (mmHg), LVEDP (mmHg), sPAP (mmHg), dPAP (mmHg), Mixed venous oxygen saturation (%),Cardiac Index (L/min/m2), sSAP (mmHg), dSAP (mmHg)	
Total pulmonary resistance	
Categorical Variables	
PH therapies (ERA, PD5-inhibitors, Riociguat)	Frequency distribution with the number and percentage of participants in each category.
WHO FC (I, II, III, IV)	

For each participant time since SAPH diagnosis (months) will be derived as:

- (Date of randomization – date of diagnosis + 1) / 12

Demographics and baseline characteristics will also be listed on the SAS.

All available hemodynamic parameters should be included, as available in the clinical database.

6.4. Appendix 4 Protocol Deviations

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

Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be displayed by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

See TV-FRM-04718 "Major Protocol Deviation Criteria" for detailed definitions of major protocol deviations.

A separate listing for all protocol deviations related to COVID-19 will be also produced.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the last available version of World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention (including those ongoing at first dose). Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

All prior and concomitant medications will be listed for the SAS.

6.6. Appendix 6 Medical History

All Medical history will be listed for the SAS.

6.7. Appendix 7 Intervention Compliance

Study intervention compliance will be summarized descriptively for the SAS.

The number and percentage of participants who have at least 80% study intervention compliance through the EOMOP period will be summarized by treatment group.

Study intervention compliance will be calculated as follows:

Compliance = [(number of tablets dispensed − number of tablets returned) / total number of tablets that should have been taken during the period] × 100.

Compliance will be also listed.

6.8. Appendix 8 Adverse Events of Special Interest

The following adverse events of special interest will be used for selexipag. These are based on the important identified and potential risks in the latest Risk Management Plan and on-going discussion with Pharmacovigilance Risk Assessment Committee.

AE Special Interest Category
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
Pregnancy
Pulmonary venoocclusive disease associated with pulmonary oedema
Renal function impairment / acute renal failure
Prostacyclin associated reactions*

*Prostacyclin associated reactions will be summarized separate from other AESIs

A specific file containing all preferred terms for each category as per last coding version will be maintained.

6.9. Appendix 9 Medications of Special Interest

Concomitant and prior medications of special interest are defined as follows:

Concomitant/Prior Medication Special Interest Category	**Standard ATC Name**	**Note**
PAH-specific medications	Sildenafil	Medications with ATC name containing any of the listed standard ATC names are considered as PAH-specific medications.
PAH-specific medications	Tadalafil	
PAH-specific medications	Vardenafil	
PAH-specific medications	Iloprost	
PAH-specific medications	Epoprostenol	
PAH-specific medications	Beraprost	
PAH-specific medications	Treprostinil	
PAH-specific medications	Selexipag	
PAH-specific medications	Riociguat	
PAH-specific medications	Macitentan	
PAH-specific medications	Bosentan	
PAH-specific medications	Ambrisentan	

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on tables below.

Blood chemistry marked abnormalities (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

CDISC = Clinical Data Interchange Standards Consortium; NA = not applicable; ULN = upper limit of normal.

Blood chemistry marked abnormalities (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; EVF; PCV (male)	< 0.32 L/L	< 0.20 L/L	> 0.60 L/L	> 0.65 L/L
Hematocrit; EVF; PCV (female)	< 0.28 L/L	< 0.20 L/L	> 0.55 L/L	> 0.65 L/L
Platelets (assuming no platelet cluster)	$< 75 \times 10^9$/L	$< 50 \times 10^9$/L	$> 600 \times 10^9$/L	$> 999 \times 10^9$/L
Leukocytes; white blood cells	$< 3.0 \times 10^9$/L	$< 2.0 \times 10^9$/L	$> 20.0 \times 10^9$/L	$> 100.0 \times 10^9$/L
Neutrophils (Abs)	$< 1.5 \times 10^9$/L	$< 1.0 \times 10^9$/L	NA	NA
Eosinophils (Abs)	NA	NA	$> 5.0 \times 10^9$/L	NA
Lymphocytes (Abs)	$< 0.8 \times 10^9$/L	$< 0.5 \times 10^9$/L	$> 4.0 \times 10^9$/L	$> 20 \times 10^9$/L

CDISC = Clinical Data Interchange Standards Consortium; EVF = erythrocyte volume fraction; NA = not applicable; PCV = packed cell volume.

7. REFERENCES

Frye BC, R. I. (2020). Safety and efficacy of abatacept in patients with treatment-resistant SARCoidosis (ABASARC) - protocol for a multi-center, single-arm phase IIa trial. *Contemp Clin Trials Commun.*, 19:100575.