Statistical Analysis Plan

LASARE: A Phase I Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of 4P004 Versus Placebo Injected in the Target Knee Joint of Patients with Grade 2 to 4 Osteoarthritis on the Kellgren and Lawrence Severity Index.

Protocol Number:	4MB-LAS-P
Test Drug:	Liraglutide
Sponsor:	4Moving Biotech
Date:	2023-11-27
Version:	1.0

Names and Addresses

The signatories agree to comply in all respects with this statistical analysis plan.

	Name / Address
SPONSOR **Sponsor's legal representatives**	[redacted]
CLINICAL CRO **CRO's legal representatives**	[redacted]
CDISC Packages and Statistical Analysis **CRO's legal representatives**	[redacted]

Approvals

Sponsor's Representative:	
Company:	
Signature:	
	.....
Date:	_ _ / _ _ _ / _ _ _ _
Artialis' representative:	
Signature:	
	.....
Date:	_ _ / _ _ _ / _ _ _ _
Statistician:	
Company:	
Signature:	
	.....
Date:	_ _ / _ _ _ / _ _ _ _

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1 Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
CrCl	Creatinine clearance
Cmax	Maximum concentration
CRF	Case report form
CSR	Clinical study report
DLT	Dose Limiting toxicity
DSMB	Data and safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European medical agency
EoS	End of Study
FU	Follow up
GLP-1(R)	Glucagon-like peptide 1 (receptor)
ICF	Informed consent form
ICH	International council for harmonisation
IA	Intra-articular
IMP	Investigational medicinal product
KL	Kellgren and Lawrence classification
MedDRA	Medical dictionary for regulatory activities
MTD	Maximum tolerated dose
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OARSI	Osteoarthritis research society international
PCSA	Potentially clinically significant abnormality
PK	Pharmacokinetic(s)
PT	Preferred term
PTE	Pre-treatment event
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
T1/2	Elimination half-life
TEAE	Treatment-emergent adverse event
TK	Target Knee
Tmax	Time to maximum concentration
ULN	Upper limit of normal

2 Introduction

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for clinical research study LASARE "A Phase I Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of 4P004 Versus Placebo Injected in the Target Knee Joint of Patients with Grade 2 to 4 Osteoarthritis on the Kellgren and Lawrence Severity Index".

This study is being completed to characterize the safety and the tolerability of single IA administration of 4P004 at escalating doses [redacted]) in participants with knee OA and to determine the maximum tolerated dose (MTD) defined by occurrence of Dose Limiting Toxicities (DLTs).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the EMA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

The following documents were reviewed in preparation of this SAP:
- Clinical Trial Protocol (4MB-LAS-P Version 3.0 July 2023)
- AdClin SOP "Clinical Data Analysis"
- ICH Guidance Topic E9 "Statistical Principles for Clinical Trials" [https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf]

3 Purpose

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for the Clinical Trial Protocol 4MB-LAS-P, version 3.0 (17-07-2023), of the clinical research study LASARE "A Phase I Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of 4P004 Versus Placebo Injected in the Target Knee Joint of Patients with Grade 2 to 4 Osteoarthritis on the Kellgren and Lawrence Severity Index". The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts.

Of note, since the study is primarily designed for safety and tolerability, complementary analyses may be performed to support the clinical development program. Any analysis performed but not identified in this SAP will be clearly identified in the respective CSR.

4 Study Objectives

The primary objectives are

- To characterize safety and tolerability of single IA administration of 4P004 at escalating doses [redacted] in participants with knee OA grade 2 to 4 osteoarthritis (OA) on the Kellgren and Lawrence severity index (KL 2-4).
- To determine the maximum tolerated dose (MTD) defined by occurrence of Dose Limiting Toxicities (DLTs) in participants with knee OA KL 2-4.

The secondary objective is

- To characterize the plasma pharmacokinetics (PK) of liraglutide when administered as single IA doses at escalating dose levels in participants with knee OA KL 2-4.

The exploratory objective is

- To collect biological fluids (blood, urine)

5 Study Design

5.1 Overall Study Design and Plan

Phase I study for IA injection, double-blind, placebo-controlled, randomized, multicenter, single ascending dose is designed to assess the safety, tolerability and pharmacokinetic of 4P004 in participants with target knee OA KL 2-4.

Participants were enrolled in 4 cohorts; in each cohort participants receive either 4P004 or placebo (6:2).

For the highest dose cohort, a sentinel dosing was planned and implemented.

Recruitment of participants

Participants are recruited via investigators' patient registry or via advertising.

- *A Screening visit* at D-7 (D-14 to D-4) is performed at study site and if the participant still agrees to participate in the study after the investigator has answered all his/her questions, the participant will sign the informed consent form. This visit should take place 4 to 14 days before the randomization day. During this visit, the eligibility of the participant will be evaluated.
- *The Randomization visit* (Day 1 to Day 2) is performed at study site and the participant is randomized in the study after review of inclusion & exclusion criteria. The participant will be hospitalized for 24 hours. *The IMP IA injection will be performed* by the investigator after a venous infusion line has been set up. Participant will be monitored during the 24-hour hospitalization and will be discharge on D2.
- *The Follow-up visit* at D4 (±1 day) is a virtual visit by phone call unless abnormal, clinically significant findings are observed upon discharge or at the investigator's discretion (participants should then be brought back to the clinic for re-evaluation).
- *The Follow-up visit* at D8 (±2 days) is a face-to-face visit. Participant will be asked to fill in a diary and a NRS questionnaire up to Day 29 to record any AE (in particular pain in the target knee) and analgesic medication taken.
- *The End of Study (EoS) visit* at D29 (±2 days) is a virtual visit by phone call unless abnormal, clinically significant findings are observed upon discharge or at the investigator's discretion (participants should then be brought back to the clinic for re-evaluation). Participant will be asked to send back to the Investigator the diary and the NRS questionnaire.

An independent Data and Safety Monitoring Board (DSMB) has been set up for this study and review safety data during the study. The DSMB is composed of 2 physicians specialized, one in rheumatology and one in diabetology. Members review the safety data in sessions on a regular basis during the study, and at any time if any SAE at least possibly related to liraglutide or safety issue occurs.

5.2 Method of Treatment Assignment and Randomization

Participants are enrolled in 4 cohorts; in each cohort participants receive either 4P004 or placebo (6:2).

Randomization has been performed using a pre-established randomization list. This list has been generated by a statistician for the IMPs (4P004 or placebo) based on study design (sequential randomization according to the dose escalation and sentinel patients).

The randomization is requested by the site at visit 2 (on D1) after eligibility confirmation. Participants are assigned their treatment according to the randomization schedule in the order in which they are randomized into the study.

6 Sequence of Planned Analyses

6.1 Interim Analyses

No interim analysis is planned.

6.2 Final Analyses and Reporting

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the study. A data review meeting will be held prior to database lock and completion of the final analyses.

In addition, no database may be locked, or analyses completed until this SAP has been approved.

Key statistics and study results will be made available following database lock and prior to completion of the final clinical study report (CSR).

Any, post-hoc, exploratory analyses completed to support planned study analyses, which are not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.

7 Sample Size Estimation

The sample size was not based on statistical power considerations. The sample size for this study of 8 participants in each cohort (6 active : 2 placebo) is considered to be sufficient for evaluation of safety, tolerability, and PK of each cohort.

8 Analysis Populations

The following analysis populations are defined for the study:

- Safety population: The safety analysis set will consist of all participants who are enrolled and received 1 dose of study drug.
- PK population: The Pharmacokinetics (PK) analysis set will consist of all participants who receive study drug and have at least 1 measurable plasma concentration. Placebo subjects will not be part of the PK population.

Unless otherwise stated, all analyses will be done on the Safety population.

9 General Principles for Statistical Analysis

Data will be summarized using classical descriptive statistics for the following groups:
- pooled placebo (i.e. participants receiving placebo in any cohort),
- each 4P004 dose level,
- unplanned doses if any (see below),
- 4P004 overall

A group "All" (Placebo + 4P004 overall) will be added if explicitly mentioned.

Categorical data will be presented using counts and percentages of subjects, while continuous variables will be presented using the mean, standard deviation, median, minimum, maximum, and number of observations with non-missing values. The coefficient of variation [%CV] will be provided for PK parameters.

The safety evaluation will be based upon the review of the individual values and descriptive statistics. No statistical significance tests will be performed on safety data.

9.1 Analysis Software

Statistical analysis will be performed using SAS version 9.4 for Windows or later.

9.2 Methods for Withdrawals, Missing Data, and Outliers

Missing data will not be replaced. Analyses will be done on the maximum available observed data. If a PK point is missing at time t, an interpolation may be done, depending on data review.

9.3 Planned and Actual Treatment

In cohort 3 [redacted] one participant was underdosed; the Sponsor decided (blinded review) to include one more participant to ensure 6 participants with the right active dose; consequently a ninth participant has been included to receive the same treatment as the underdosed participant. Therefore, at least one subject may have an actual treatment different from the planned one (if the underdosed subject did not receive placebo).

Participants who did not receive the planned treatment will be assigned, upon review of their actual treatment, to either of the following actual arm:

- [redacted] if the received treatment is one of the planned ones, or close enough, to the corresponding arm [redacted]
- otherwise, to an arm "4P004 unplanned"

Unless stated otherwise, analyses will be presented by actual arm.

9.4 Derived and Computed Variables

For any variable, the baseline value is defined as the last observation before IMP injection.

The time will be split into 3 periods (epochs):
- before treatment (screening)
- during treatment (from IMP injection to 7 days after IMP injection date)

- after treatment

The following PK parameters will be calculated from measured plasma concentrations for each participant:
- Maximum observed concentration (Cmax)
- Time of maximum observed concentration (Tmax)
- Area under the curve (AUC_{0-t})
- Terminal Half-life ($T_{1/2}$)

10 Study Subjects

10.1 Disposition of Participants and Withdrawals

Table TTT. Participant disposition

	Placebo (pooled)	4P004 [redacted]	4P004 [redacted]	4P004 [redacted]	4P004 [redacted]	4P004 (pooled)	All
Screened Participants							XX
Randomized Subjects[1]	XX	XX	XX	XX	XX	XX	XX
Treated Subjects[2]	XX	XX	XX	XX	XX	XX	XX
Completed Subjects[2]	XX	XX	XX	XX	XX	XX	XX
Withdrawn Subjects[2]	XX	XX	XX	XX	XX	XX	XX
Reason 1	XX	XX	XX	XX	XX	XX	XX
...	XX	XX	XX	XX	XX	XX	XX

[1] by planned treatment
[2] by actual treatment

10.2 Protocol Violations and Deviations

Protocol violations and deviations are not described in the protocol, and will be established by blind review.

Major deviations are defined as follows:
- non respect of inclusion criteria
- underdose
- overdose

All others will be considered as minor deviations.

Table TTT. Deviations by Category

Major, Minor

Major deviations will be listed:

Listing LLL. Major Deviations

Subject Id, Treatment Group, Deviation Text

11 Demographics and Other Baseline Characteristics

All TFL in this section will include the column “All”.

11.1 Demographics

Table TTT. Demographics and Baseline Characteristics

Sex, Age, Weight, BMI, KL Grade, Pain at Visit 2 (mean of the previous 48h)

Table TTT. Other Baseline Characteristics

Height, Race

11.2 Prior Medications

Medication will be coded using the WHO-ATC/DDD Index 2023.

All tables in this section will be sorted by descending percentages in the column “4P004 (pooled)”.

Medications will be flagged with 3 flags:
- pre-treatment: treatment taken during screening

- on-treatment: treatment taken during the treatment period
- post-treatment: treatment taken after the treatment period

In case of uncertainty, a medication will be assigned to all periods during which it might have been taken.

Medications not classified as pain killer vs. other medications will be assigned to one of the two categories for analyses, based on medical review by the Sponsor

Table TTT. Pain killers started and ended before treatment

ATC Level 2	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)	All (N=XX)
Any pain killer	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table TTT. Other medications started and ended before treatment

ATC Level 2	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)	All (N=XX)
Any medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

11.3 Medical History

All tables in this section will be sorted by descending percentages in the column "4P004 (pooled)".

Table TTT. Medical History by SOC

SOC	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)	All (N=XX)
Any Medical History	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SOC term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SOC term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

12 Safety and Tolerability Analyses

12.1 Concomitant Medications

All tables in this section will be sorted by descending percentages in the column "4P004 (pooled)".

Table TTT. Pain killers started before treatment and continuing at IMP injection

ATC Level 2	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)	All (N=XX)
Any pain killer	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 4 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table TTT. Other medications started before treatment and continuing at IMP injection

ATC Level 2 ATC Level 4	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)	All (N=XX)
Any medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 4 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 4 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table TTT. Pain killers started during treatment

ATC Level 2 ATC Level 4	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)
Any pain killer	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 4 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 4 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table TTT. Other medications started during treatment

ATC Level 2 ATC Level 4	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)
Any medication	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 4 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 2 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
ATC 4 term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

12.2 Adverse Events

All tables in this section will be sorted by descending percentages in the column "4P004 (pooled)".

12.2.1 Definitions

Adverse events will be classified in one of three categories:
- pre-treament: events that certainly started during screening
- post-treatment: events that certainly started after the treatment period
- treatment-emergent (TEAE): all other events

12.2.2 Overview of TEAEs

This table will also show the number of AEs, as depicted below.

Table TTT. Overview of TEAEs

	Placebo (pooled) (N=XX)		4P004 [redacted] (N=XX)		4P004 [redacted] (N=XX)		4P004 [redacted] (N=XX)		4P004 [redacted] (N=XX)		4P004 (pooled) (N=XX)	
	Subjects	#[1]	Subjects	#[1]	Subjects	#[1]	Subjects	#[1]	Subjects	#[1]	Subjects	#[1]
Any TEAE	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
AESI	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
SAEs	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
by Toxicity Grade												
1 Mild	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
2 Moderate	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
by Relationship to Study Drug												
Not Related	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
Unlikely	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
(…)	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
by Outcome												
Recovered	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
Recovering	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX
(…)	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX	XX (X.X%)	XX

[1] Numbers of adverse events

12.2.3 All TEAEs

Table TTT. TEAEs by SOC and PT

SOC PT	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)
Any TEAE	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SOC term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
PT term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SOC term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
PT term	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)

Table TTT. TEAEs by SOC, PT and Toxicity Grade

SOC PT	Toxicity Grade	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)
Any TEAE	1 Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2 Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
SOC term	1 Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2 Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
PT term	1 Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2 Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)							
SOC term	1 Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2 Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
PT term	1 Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2 Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	(…)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)							

With the same template, the TEAEs will be presented by Relationship to study drug, grouped as:
- Not related: No/Unlikely
- Related: Possible, Probable, Definite

Table TTT. TEAEs by SOC, PT and Relationship to Study Drug

12.2.4 AESI

AESI defined in the protocol are:
- Pregnancy of the participant or of his partner
- Symptomatic overdose
- Anaphylaxis
- Severe IMP injection site reactions
- Hypoglycemia
- Severe gastro-intestinal disorder

All tables in the section “All TEAEs” will be reproduced for TEAEs of SI, except by relationship to study drug. All tables will also show the number of adverse events, as in the Overview of Adverse Events.

Table TTT. Treatment-Emergent AESIs by SOC and PT

Table TTT. Treatment-Emergent AESIs by SOC, PT and Toxicity Grade

A listing of all treatment-emergent AESI will also be provided.

Listing LLL. Treatment-Emergent AESIs

12.2.5 Local tolerability

The AE details in case of severe IMP injection site reaction will be presented as follows:

Table TTT. Injection Site Reactions

Kind of Reaction	Maximum Toxicity Grade	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)
Any Kind	Any Grade	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1 Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2 Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	(…)						
Tenderness	Any Grade	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1 Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2 Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	(…)						
Erythema	Any Grade	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	1 Mild	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	2 Moderate	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
	(…)						
(…)							

12.2.6 Serious adverse events

A listing of all SAEs will be provided.

Listing LLL. Serious Adverse Events

12.2.7 Deaths

If any subject dies during the study, relevant information will be supplied in a data listing, and appropriate SAE narratives.

Listing LLL. Deaths

12.3 Target knee pain

The target knee pain, evaluated on a 0-10 scale, is measured as follows:

Visit	Timepoint	Table
Screening	(mean of the last 48 hours)	-
Visit 2	(mean of the last 48 hours)	2,3
	Pre-Dose	1
	1h Post-Dose	1
	2h Post-Dose	1
	3h Post-Dose	1
	4h Post-Dose	1
	5h Post-Dose	1
	6h Post-Dose	1
	24h Post-Dose (mean of the last 24 hours)	1,2,3
Visit 3	(mean of the last 24 hours)	2,3
	Day 3 (mean of the last 24 hours)	3
	Day 4 (mean of the last 24 hours)	3
	Day 5 (mean of the last 24 hours)	3
	Day 6 (mean of the last 24 hours)	3
	Day 7 (mean of the last 24 hours)	3
	Day 8 (mean of the last 24 hours)	3
Phone Call 2	Day 15 (mean of last 48 hours)	2
	Day 22 (mean of last 48 hours)	2
	Day 29 (mean of last 48 hours)	2

In the tables of this section, in addition to the values, the change from Baseline will be added, with the standard summary statistics and the number of subjects with an aggravation since the Baseline.

In case of two different measures on the same day, the value of the diary will prevail.

The pain will be presented in three summary tables:

Table TTT. Target Knee Pain from Pre-Dose to 24h Post-Dose

(timepoints marked « table 1 » in the list above)

Table TTT. Target Knee Pain from Visit 2 to End of Study

(timepoints marked « table 2 » in the list above)
For this table, the baseline will be the mean of the last 48 hours collected at Visit 2 or, if not available, the Screening value.

Table TTT. Target Knee Pain from Visit 2 to Day 8

(timepoints marked « table 3 » in the list above)
This table will be presented by actual day of pain, whatever scheduled day the measure has been assigned to.

12.4 Weight

Weight will be presented at Baseline and at Visit 3, with the change from Baseline.

Table TTT. Weight over Time

12.5 Vital Signs

The vital signs are systolic blood pressure, diastolic blood pressure and heart rate. They are measured as follows:

Visit	**Timepoint**
Screening	-
Visit 2	Pre-Dose
	1h Post-Dose
	2h Post-Dose
	4h Post-Dose
	8h Post-Dose
	12h Post-Dose
	24h Post-Dose
Visit 3	-

The following will be presented for each vital sign:
- value (mean, SD, etc.)
- absolute change from baseline (mean, SD, etc.)
- PCSA (frequencies and percentages)

Table TTT. Systolic Blood Pressure over Time

mmHg	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)
Baseline						
Value						
n	XX	XX	XX	XX	XX	XX
mean (SD)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)
(…)						
1h Post-Dose						
Value						
n	XX	XX	XX	XX	XX	XX
mean (SD)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)
(…)						
Change from BL						
n	XX	XX	XX	XX	XX	XX
mean (SD)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)
(…)						
PCSA						
≤ 95 + decrease from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
≥ 160 + increase from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No PCSA	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)						

Table TTT. Diastolic Blood Pressure over Time

Table TTT. Heart Rate Pressure over Time

12.6 Electrocardiograms (ECG)

The 12-lead ECG parameters are Heart Rate, PR, QRS and QT. They are measured at the following times: Screening (D-7), D1 (T0-15min and T0+12h).

They will be presented with the same layout as Vital Signs, at Baseline and 12 hours post-baseline. The relative change from baseline will be added.

Table TTT. ECG: Hear Rate over Time

Table TTT. ECG: PR over Time

Table TTT. ECG: QRS over Time

Table TTT. ECG: QT over Time

12.7 Clinical safety laboratory assessment

The Hematology and Chemistry parameters are collected at Screening and Visit 3.

They are:

Hematology:
- Erythrocytes
- Hemoglobin
- Hematocrit
- Leukocytes
- Monocytes
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Platelets

Chemistry:
- Creatinine Clearance
- Potassium
- Chloride
- Sodium
- Calcium
- Alanine Aminotransferase
- Aspartate Aminotransferase
- Amylase
- Glucose (at Screening and Visit 3)

They will be presented like Vital Signs, but with one table for Hematology, one for Chemistry.

Table TTT. Hematology over Time

	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)
Erythrocytes (tera/L)						
Baseline						
Value						
n	XX	XX	XX	XX	XX	XX
mean (SD)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)
(…)						
PCSA						
≤ 95 + decrease from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
≥ 160 + increase from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No PCSA	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 3						
Value						
n	XX	XX	XX	XX	XX	XX
mean (SD)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)
(…)						
Change from BL						
n	XX	XX	XX	XX	XX	XX
mean (SD)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)	XX (XX)
(…)						
PCSA						
≤ 95 + decrease from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
≥ 160 + increase from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No PCSA	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)						

For parameters with defined PCSA, a table with PCSA only will be produced:

Table TTT. Hematology PCSA over Time

	Placebo (pooled) (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 [redacted] (N=XX)	4P004 (pooled) (N=XX)
Erythrocytes (tera/L)						
Baseline						
≤ 95 + decrease from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
≥ 160 + increase from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No PCSA	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
Visit 3						
≤ 95 + decrease from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
≥ 160 + increase from baseline ≥ 20	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
No PCSA	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)
(…)						

Table TTT. Chemistry over Time

Table TTT. Chemistry PCSA over Time

Glycemia is measured as follows:

Visit	**Timepoint**	**Method**
Screening	-	Blood
Visit 2	Pre-Dose	Blood & Glucometer
Visit 2	1h Post-Dose	Glucometer
Visit 2	2h Post-Dose	Blood
Visit 2	4h Post-Dose	Blood
Visit 2	6h Post-Dose	Glucometer
Visit 2	8h Post-Dose	Blood
Visit 2	10h Post-Dose	Glucometer
Visit 2	12h Post-Dose	Blood
Visit 2	16h Post-Dose	Blood
Visit 2	24h Post-Dose	Glucometer
Visit 3	-	Blood & Glucometer

In order to obtain one value per scheduled timepoint:

- The baseline value will be selected as the last measure before IMP injection. If there are such two measures (same time, different method), then Blood will be selected.
- Post-baseline, if there are two measures for a scheduled timepoint, Blood will be selected.
- Additional samples vs. scheduled samples will not be analyzed, unless they are the baseline.

The values will be reported over time (Baseline, 1h Post-Dose to 24h Post-Dose) with the same template as Vital Signs.

Table TTT. Glycemia over Time

13 Pharmacokinetics Analyses

Pharmacokinetics analysis will be done on the PK population.

Blood samples for placebo will not be analyzed by the bioanalytical laboratory except for 2 samples per participant receiving placebo, 1 pre-dose and the other at 12h post-dose, to confirm that these participants did not receive liraglutide. These results will be listed in section 16.2 of the CSR.

The placebo group will not be presented in the TFL of this section. In summary tables, only the columns corresponding to the doses will be presented (no “pooled” column).

In this section only, the treatment groups will show the real dose administered, in case the real dose is not one of the scheduled ones.

13.1 Endpoints

The endpoints are:

- Plasma concentration of Liraglutide following a single IA injection at D1 (pre-injection T0-15 min), and 2, 4, 8, 12, 16 and 24 hours post-injection.
- The PK parameters Cmax, Tmax, AUC0-t and T1/2.

13.2 Plasma Concentration of Liraglutide

A summary table will be produced by timepoint:

Table TTT. Plasma Concentrations over Time

The plasma concentrations over time will be plotted for each subject, on both arithmetic and logarithmic scales. There will be one series of figures for all subjects at a given dose.

Figure FFF. Plasma Concentrations over Time by Subject - Dose [redacted]

Figure FFF. Plasma Concentrations over Time by Subject - Dose [redacted]

Figure FFF. Plasma Concentrations over Time by Subject - Dose [redacted]

Figure FFF. Plasma Concentrations over Time by Subject - Dose [redacted]

13.3 Computation of PK Parameters

In case of missing concentration, the individual figure of PK concentrations of the subject will be reviewed, and a decision will be made:
- interpolate the concentration or not
- possibly invalidate some PK parameters (set them to missing)

Concentrations BLOQ will be set to zero if measured at baseline, to LLOQ/2 otherwise.

The parameters will be derived as follows:

- Cmax – Maximum concentration achieved
  computed as max(C0-C6)
- Tmax – Time to reach maximum concentration
  computed as first time Ti where Concentration = Cmax

- AUC0-t – The area under the concentration vs. Time curve
  computed as follows:
  - Tlast = last time where Clast > BLOQ
  - AUC0-t = sum of AUCs using linear trapezoidal summation from time 0 to Tlast
- λz – terminal elimination rate constant
  computed as follows:
  - select the timepoints t1 = T0+16h and t2 = T0+24h, with respective concentrations C1 and C2
  - if either concentration is missing, λz is missing
  - otherwise, compute the slope of the line ln(C1) to ln(C2)
  - if the slope is negative, λz = -slope
  - otherwise λz is missing
- T1/2 = ln(2) / λz

The dose-normalized parameters Cmax and AUC0-t will also be computed (Cmax/Dose and AUC0-t/Dose).

13.4 Reporting of PK Parameters

The PK parameters will be summarized. In addition to standard univariate statistics, the coefficient of variation, geometric mean and geometric standard deviation will be added.

Table TTT. PK Parameters

14 Exploratory Analyses

Exploratory analysis will be done on the Safety set.

14.1 Endpoints

The endpoints are:

Serum and urine OA-related biomarkers (exploratory proteomic research of 4P004 efficacy related biomarkers) at D1 (T0-15min, 8h, 24h) and D8.

The exploratory endpoint will be analyzed separately, and the related data will not be included in the SDTM/ADaM datasets.

15 Reporting Conventions

The following reporting conventions will be adopted for the SAP. These conventions will enhance the review process and help to standardize presentation with common notations.

15.1 General Reporting Conventions

Legends will be used for figures with more than one variable or item displayed.

All date values will be presented as YYYY-MM-DD (*e.g.*, 2001-08-29) format.

As a general rule, percentages will be presented with one decimal digit, but can be presented with no decimal digit for table width requirements.

15.2 Population Summary Conventions

The biomarker concentration in serum determined at each sampling time point should be presented on the original scale for each subject participating in the study.

Population(s) identified in all TFL titles as “All Subjects”, “Safety Population” or “PK Population”.

16 References

ICH Guidance Topic E9 “Statistical Principles for Clinical Trials”

17 Tables, Figures & Listings in CSR Section 14

The following tables will be included in the report either in the text or in a dedicated chapter reporting all tables but not included in the text.

Type	Number	Title	Population
Table	1.1	Participant disposition	All
Table	1.2	Deviations by Category	Safety
Listing	1.2.1	Major Deviations	Safety
Table	1.3	Demographics and Baseline Characteristics	Safety
Table	1.4	Other Baseline Characteristics	Safety
Table	1.5.1	Pain killers started and ended before treatment	Safety
Table	1.5.2	Other medications started and ended before treatment	Safety
Table	1.6	Medical History by SOC	Safety
Table	2.1	Pain killers started before treatment and continuing at IMP injection	Safety
Table	2.2	Pain killers started during treatment	Safety
Table	2.3	Other medications started before treatment and continuing at IMP injection	Safety
Table	2.4	Other medications during treatment	Safety
Table	3.1	Overview of TEAEs	Safety
Table	3.1.1	TEAEs by SOC and PT	Safety
Table	3.1.2	TEAEs by SOC, PT and Toxicity Grade	Safety
Table	3.1.3	TEAEs by SOC, PT and Relationship to Study Drug	Safety
Table	3.2	Treatment-Emergent AESIs by SOC and PT	Safety
Table	3.2.1	Treatment-Emergent AESIs by SOC, PT and Toxicity Grade	Safety
Listing	3.2.2	Treatment-Emergent AESIs	Safety
Table	3.3	Injection Site Reactions	Safety
Listing	3.4	Serious Adverse Events	Safety
Listing	3.5	Deaths	Safety
Table	4.1	Target Knee Pain from Pre-Dose to 24h Post-Dose	Safety
Table	4.2	Target Knee Pain from Visit 2 to End of Study	Safety
Table	4.3	Target Knee Pain from Visit 2 to Day 8	Safety
Table	5.0	Weight over Time	Safety
Table	5.1	Systolic Blood Pressure over Time	Safety
Table	5.2	Diastolic Blood Pressure over Time	Safety
Table	5.3	Heart Rate over Time	Safety
Table	6.1	ECG: Heart Rate over Time	Safety
Table	6.2	ECG: PR over Time	Safety
Table	6.3	ECG: QRS over Time	Safety
Table	6.4	ECG: QT over Time	Safety
Table	7.1	Hematology over Time	Safety
Table	7.1.1	Hematology PCSA over Time	Safety
Table	7.2	Chemistry over Time	Safety
Table	7.2.1	Chemistry PCSA over Time	Safety
Table	7.3	Glycemia over Time	Safety
Table	8.1	Plasma Concentrations over Time	PK
Figure	8.1.0.3	Plasma Concentrations over Time by Subject - [redacted]	PK
Figure	8.1.1	Plasma Concentrations over Time by Subject - [redacted]	PK
Figure	8.1.2	Plasma Concentrations over Time by Subject - [redacted]	PK
Figure	8.1.3	Plasma Concentrations over Time by Subject - [redacted]	PK
Table	8.2	PK Parameters	PK

18 Listings in CSR Section 16.2

The following listings will be included in section 16.2 of the CSR.

Type	Number	Title	Population
Listing	16.2.1	Demographics and Disposition	Safety
Listing	16.2.2	Prior and Concomitant Medications	Safety
Listing	16.2.3	Medical History	Safety
Listing	16.2.4	Serology	Safety
Listing	16.2.5	Knee X-Ray and Kellgren-Lawrence Grade	Safety
Listing	16.2.6	Failed Inclusion/Exclusion Criteria	Safety
Listing	16.2.7	IMP Injection	Safety
Listing	16.2.8	Deviations	Safety
Listing	16.2.9	Adverse Events	Safety
Listing	16.2.10	Knee Pain Assessments	Safety
Listing	16.2.11	Height, Weight and BMI	Safety
Listing	16.2.12	Vital Signs	Safety
Listing	16.2.13	ECG	Safety
Listing	16.2.14	Hematology	Safety
Listing	16.2.15	Chemistry	Safety
Listing	16.2.16	Glycemia	Safety
Listing	16.2.17	Exploratory Sample Collection	Safety
Listing	16.2.18	Plasma Concentrations	Safety
Listing	16.2.19	PK Parameters	Safety
Listing	16.2.20	Visits	Safety

19 Potentially Clinically Significant Abnormalities

Potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor, according to predefined criteria/thresholds based on literature reviews and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG parameters.

When possible, PCSA will be computed at baseline or before.

Parameter	PCSA	Comments
Chemistry		
AST or ALT	> 3 ULN	Guidance for Industry Drug-Induced Liver Injury FDA, 2009
Potassium	< 3 mmol/L or ≥ 5.5 mmol/L	
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft Gault equation)	< 15 (end stage renal disease) ≥ 15 - < 30 (severe decrease in GFR) ≥ 30 - < 60 (moderate decrease in GFR)	FDA draft Guidance 2020 Pharmacokinetics in Patients with Impaired Renal Function Study Design, Data Analysis, and Impact on Dosing
Amylasemia	≥ 1.5 ULN	
Glycemia	< 70 mg/dL	DSMB
Hematology		
RBC	≥ 6 Tera/L	
Hb	≤ 115 g/L (Male); ≤ 95 g/L (Female) ≥ 185 g/L (Male); ≥ 165 g/L (Female) Decrease from Baseline ≥ 20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value.
WBC	< 3.0 Giga/L (Non-Black) < 2.0 Giga/L (Black) ≥ 16.0 Giga/L	
Lymphocytes	> 4.0 Giga/L	
Neutrophils	< 1.5 Giga/L (Non-Black); < 1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	> 0.7 Giga/L	
Basophils	> 0.1 Giga/L	
Eosinophils	> 0.5 Giga/L	Harrison- Principles of internal Medicine 17th Ed., 2008
Platelets	< 100 Giga/L ≥ 700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Vital Signs		
HR (bpm)	≤ 50 + decrease from baseline ≥ 20 ≥ 120 + increase from baseline ≥ 20	
SBP (mmHg)	≤ 95 + decrease from baseline ≥ 20 ≥ 160 + increase from baseline ≥ 20	
DBP (mmHg)	≤ 45 + decrease from baseline ≥ 10 ≥ 110 + increase from baseline ≥ 10	
ECG		
HR (bpm)	< 50 < 50 + decrease from baseline ≥ 20 > 100 > 100 + increase from baseline ≥ 20	
PR (ms)	> 200 > 200 + increase from baseline ≥ 25%	
QRS (ms)	> 110 > 110 + increase from baseline ≥ 25%	
QT (ms)	> 500	