A Phase I Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of 4P-004 Versus Placebo Injected in the Target Knee Joint of Patients with Grade 2 to 4 Osteoarthritis on the Kellgren and Lawrence Severity Index.

Protocol Name:	**LASARE**
Compound:	**LIRAGLUTIDE**
Sponsor Name:	**4Moving Biotech**
Legal Registered Address:	**Campus de l'Institut Pasteur de Lille** **1 rue du Professeur Calmette, 59 000 Lille (France)**
Protocol code number:	**4MB-LAS-P**
Scientific Coordinator:	[redacted]
Study CRO:	**ARTIALIS SA.**
EudraCT:	**2022-000703-12**
EU CT:	**2022-500271-31-00**

Date : **17-July-2023**

Version	Date	Author	Summary of Changes
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

			[redacted]

INTERVENTIONAL RESEARCH PROTOCOL

RELATING TO A MEDICINAL PRODUCT FOR HUMAN USE

PROTOCOL SIGNATURE PAGE

Title: A Phase I Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of 4P-004 Versus Placebo Injected in the Target Knee Joint of Patients with Grade 2 to 4 Osteoarthritis on the Kellgren and Lawrence Severity Index (LASARE)

Version	**N° 3.0 of 17/07/2023**
Protocol code number :	**4MB-LAS-P**
EudraCT number:	**2022-000703-12**
EU CT:	2022-500271-31-00

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

Name of Local Principal Investigator:
Address:

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Patients). The conduct of the study will be in accordance with the Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).
I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

Date: Local Principal Investigator's Signature:

[redacted]

4movingbiotech

Table of content

1 STUDY SUMMARY

1.1 Synopsis

Protocol title

A Phase I Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of 4P-004 Versus Placebo Injected in the Target Knee Joint of Patients with Grade 2 to 4 Osteoarthritis on the Kellgren and Lawrence Severity Index (KL 2-4).

Short title

Safety, tolerability and pharmacokinetics of intra-articular (IA) single ascending dose of 4P-004 in patient with Kellgren and Lawrence grade 2 to 4 osteoarthritic (OA) knee.

Acronym

LASARE : safety, tolerabiLity, and phArmacokinetics of Single Ascending doses of 4P-004 versus placebo injected in the taRget knee joint of patients with grade 2 to 4 ostEoarthritic (OA) knee.

Objectives

Primary objectives

- To characterize safety and tolerability of single IA administration of 4P-004 at escalating doses [redacted]) in participants with knee OA.
- To determine the maximum tolerated dose (MTD) defined by occurrence of Dose Limiting Toxicities (DLTs)

Secondary objective

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

Exploratory Objectives

- Collection of biological fluids (blood, urine)

Endpoints

Primary Endpoints

- Number of Adverse Events (AEs), serious AEs (SAEs) (Common Terminology Criteria Adverse Events [CTC-AE]) including target knee pain, and tenderness, erythema, swelling, local pain at injection site.
- Vital signs, ECG: Mean change, number of PCSA (Potentially Clinically Significant Abnormality), Percentage of participants with PCSA.
- Laboratory changes (RBC, WBC, ALT, AST, glycemia, amylasemia, creatinin clearance): Mean changes number of PCSA, Percentage of participants with PCSA.

Secondary Endpoint

- Plasma concentration of liraglutide following a single IA injection. PK samples: pre-injection (T0-4h) and 2, 4, 8, 12, 16 and 24-hours post injection.

Exploratory endpoints

Serum and Urine OA-related biomarkers (exploratory proteomic research of 4P-004 efficacy-related biomarkers).

Overall design

This phase I study is a multicenter, randomized, double-blind, placebo-controlled study to assess the safety and tolerability of single ascending dose of IA 4P-004 [redacted] in participants,

- Between 18 and 80 years of age,
- with target knee OA stage KL 2-4

A total of 32 participants will be enrolled in 4 cohorts, in each cohort participants will receive either 4P-004 or placebo (6:2).

Description of Sites/Facilities Enrolling Participants

Three investigational sites will participate.

Participants will be recruited via investigator's patient register or via advertising.

Description of study intervention

4P-004 [redacted] or placebo IA injection

Data and Safety Monitoring Board (DSMB)

The DSMB will be composed of 2 independent physicians specialized, one in rheumatology and one in diabetology.

After each dose level completion (and at any time if needed), a DSMB evaluation based on a safety data analysis is intended by the sponsor before moving forward to the next higher dose level (or to randomize the next participant).

Study Duration

The total duration of the study is approximately 7 months

Participant Duration

The total duration of the study will be around 5 to 6 weeks for each participant:

- Screening between 4 to 14 days before treatment (D-14 to D-4)
- Treatment period of 1 day (D1)
- Follow-up period of 28 days

1.2 Study flowcharts

1.2.1 Whole study flowchart

Study Period	SCR	RDZ		FU		EoS
Study Day (D)	**D-7 D-14/D-4**	**D1***	**D2**	**D4 ±1d**	**D8** ±2d**	**D29 ±2d**
Visit (V)/ Phone Call (PC) Number	V1	V2		PC1	V3	PC2
Informed consent	x					
Incl/excl criteria	x	x				
ECG	x	x				
Target knee X Ray***	x					
Medical history	x	x				
Prior & conc medication	x	x	x	x	x	x
Demographics	x					
Body Weight	x	x			x	
Hospitalization		<---------				
Inclusion		x				
Randomization		x				
Diary distribution	x					
Diary Verification		x	x	x	x	x
Study treatment						
Knee IA injection		**x**				
Safety assessment						
Physical Exam	x	x	x		x	
Vital Signs	x	x	x		x	
AEs / SAEs / AESI		x	x	x	x	x
Target knee pain	x	x	x	x	x	x
Local reaction		x	x			
Blood PK		x	x			
Clinical safety laboratory tests						
SARS-CoV-2 Rapid Antigen Test		(x)				
Hematology	x				x	
Chemistry / Serology	x				x	
Glycemia / Glucose meter	x	x			x	
Urine Pregnancy test		x				
Exploratory analyses						
Blood Sample		x	x		x	
Urine Sample		x	x		x	

EoS: end-of-study, FU: follow-up, RDZ: randomization, SCR: screening

***D1** is a full day hospital (approximately 24 hours), the participant is discharged on D2.

****D8 Visit:** to be performed at any time (before D8) in case of premature study discontinuation.

*****Target knee X Ray**: to be done locally before D1, but not necessary if performed within the 6 previous months.

Clinical safety laboratory tests:

- Results of SARS-CoV-2 Rapid Antigen Test should be negative on D1 before definitive inclusion and randomization in the study (test to be performed if required according to standard practice on site),
- Urine Pregnancy test for WOCBP should be negative on D1 before definitive inclusion and randomization in the study,
- Results of RBC, Hemoglobin, WBC, Platelets, AST, ALT, Amylasemia, creatinine clearance should be obtained before D1 (sampling within 14 days before D1),
- Tests for Human Immunodeficiency Virus (HIV), hepatitis B virus [Hepatitis B surface Antigen (HBsAg)] and hepatitis C virus [Hepatitis C virus antibodies (HCV-Ab)] can be based on participant-reported medical history, available medical records, and the most recently available laboratory results for the participant (tests performed within the previous 12 months).

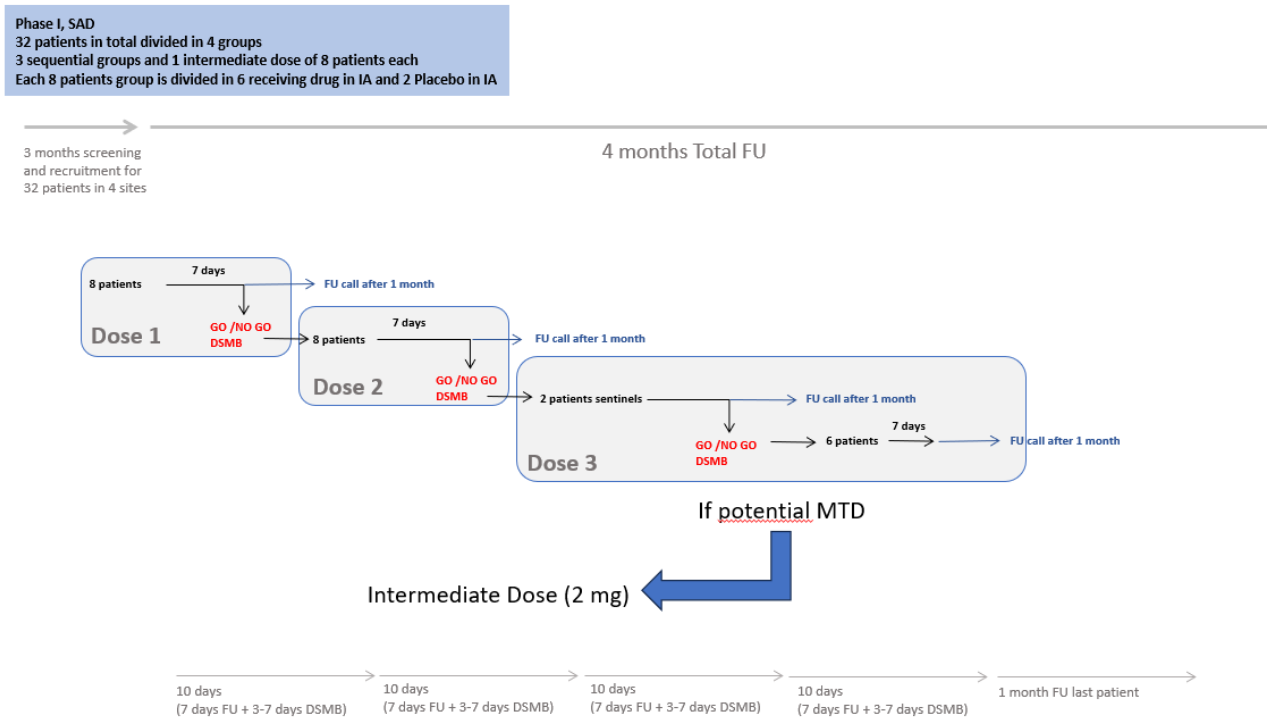
1.2.2 Visit 2 (randomization): D1-D2 study flowchart (24h hospitalization)

D1 / D2	T0 - 4h*	T0	1h	2h	3h	4h	5h	6h	8h	10h	12h	16h	24h
Urine Pregnancy Test	x												
SARS-CoV-2 Rapid Antigen Test	(x)												
Definitive inclusion	x												
Randomization**	x												
Physical Exam	x												x
Bodyweight	x												
Veinous line	x	x	x	x	x	x	x	x	x	x	x	x	x
IMP IA injection		x											
Vital signs	x		x	x		x			x		x		x
ECG	x										x***		
AEs / SAEs / AESI	x	x	x	x	x	x	x	x	x	x	x	x	x
Target knee pain	x		x	x	x	x	x	x					x
Local reaction			x	x	x	x	x						x
Glycemia	x			x		x			x		x	x	
Blood glucose meter	x		x					x		x			x
Blood PK sample	x			x		x			x		x	x	x
Blood sample	x								x				x
Urine Sample	x								x				x

***For practical reasons, all procedures planned before T0 (time of administration) can be done within 4 hours before T0.**

****Randomization** will be done before T0once results of the SARS-CoV-2 test (if required according to standard practice on site) and urine pregnancy test (if necessary) are available.
All assessments after T0 must be carried out ± 10 minutes compared to the theoretical time.
*** A time window of ± 2 hours for the ECG planned at T0 +12 is allowed
AEs / SAEs / AESI reporting is continuous during the hospitalization

1.2.3 Global study scheme



2 INTRODUCTION

2.1 Background

Osteoarthritis (OA) has been defined as "*a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness*." (OARSI). The disease occurs when the dynamic equilibrium between the breakdown and repair of joint tissues becomes unbalanced, often in a situation where the mechanical loads applied exceed those that can be tolerated by the joint tissues.

OA is characterized by progressive cartilage loss, subchondral bone-remodeling, osteophyte formation and synovial inflammation, with resultant joint pain and increasing disability. OA can affect single and/or multiple peripheral joints such as knee, hip, and hand.

Globally prevalent cases of osteoarthritis increased (and disability induced by OA) by more than 110% in almost 30 years with 517 million of affected people (GBD et al., 2020; Long et al., 2022).

The current therapeutic arsenal of OA aims at alleviating pain and minimizing loss of physical function. To date, there is no structural-modifying drug to slow or revert the disease. More precisely, standard therapy is patient personalized and includes changes in lifestyle (nutrition, exercise, weight loss, physical therapy) and symptom-modifying medications (paracetamol, topical and/or oral non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, IA injections of corticosteroids, and hyaluronic acid although there is no consensus to consider the latter a standard therapy. Prosthetic replacement surgery is performed when OA symptoms are advanced, and pain is unmanageable.

Liraglutide is a biotechnology-derived peptide for which the mechanism of action relies on the glucagon-like peptide GLP-1 receptor (GLP-1 receptor or GLP-1R) thanks to its GLP-1 analogue structure. GLP-1R is involved in the control of blood sugar level by enhancing insulin secretion. Liraglutide was originally studied as an agent that stimulates insulin release from pancreatic beta cells following oral nutrient ingestion, or postprandially, as well as an agent slowing stomach emptying with an impact on body weight management. These biological activities are the basis of the clinical indications claimed for the marketed product Victoza® (SmPC provided in IB, Appendix I), Saxenda® and Xultophy® (in association with insulin degludec) currently authorized in more than 50 countries including the EU, USA, UK, Canada, Australia.

Considering the following:

(i) Recent studies reporting the impact of the GLP-1 – GLP-1R axis stimulation in chondrocytes (Que et al., 2019; Meurot et al., 2022) and macrophages (Shiraishi et al., 2012),

[redacted]

(iii) The current therapeutic arsenal of osteoarthritis aims at alleviating pain and minimizing loss of physical function without disease modifying action,

the sponsor has investigated the potential of liraglutide to treat OA. [redacted]

Unlike the approved conditions of Victoza® as detailed in the SmPC (i.e., daily subcutaneous bolus administration of maximum 1.8 mg), the investigational medicinal product (IMP) 4P-004 is intended to be administered by IA injection once.

4P-004 is intended to prevent OA associated physiopathological degeneration ("Prevent structural damage" as per CPMP/EWP/784/97 Rev. 1 "Guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis").

In the current Investigator's Brochure (IB), all IMP-related non-clinical and clinical data supporting the safety and efficacy of the following items are provided:

- The new route of administration,
- The dose regimen,
- The indication in OA.

PK Data

In human, after a single subcutaneous (SC) administration (current authorized route of administration) liraglutide is well absorbed from the injection site. Overall bioavailability following SC administration is estimated to be 55% in human. The distribution volume is low and close to plasma volume, which indicates that a high fraction of liraglutide is circulating in plasma. Liraglutide is extensively bound to plasma protein (>98%).

The mean clearance following subcutaneous administration of a single dose liraglutide is approximately 1.2 l/h with an elimination half-life of approximately 13 hours.

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment. There is no therapeutic experience in patients with end-stage renal disease, and Victoza is therefore not recommended for use in these patients.

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment. Victoza is not recommended for use in patients with severe hepatic impairment.

Interaction Data

In vitro, liraglutide has shown very low potential to be involved in pharmacokinetic interactions with other active substances related to cytochrome P450 and plasma protein binding.

The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption and therefore no dose adjustment is required.

Safety pharmacology

Safety pharmacology studies were performed in rats and dogs to evaluate any adverse effects on the central nervous system (CNS), the respiratory system, or the cardiovascular system during initial marketing authorization. A transient and mild increase in glycemia was observed in male and female

rats following anesthesia and IA administration of 300 µg of 4P-004 that was resolved at 24h. This transient and reversible effect on blood glucose was not observed after IA knee joints administration of 0.9 mg of 4P-004 in Beagle dogs.

2.2 Rationale

OA is a slowly degenerative disease that affects the whole joint with impact on the articular cartilage, subchondral bone and the synovial membrane. Identified risks factors for OA include age, sex, obesity, traumatic injuries (post-traumatic OA) and cardiometabolic factors. Dysregulation in glucose, lipid metabolism as well as overall low-grade inflammation are common phenotypes found in OA and metabolic disease, which prompted scientists to suggest that OA was not only a age-related degenerative disease but also a proper component of the metabolic syndrome (metabolic OA) (Kornaat et al.,2009; Courties, et al., 2017).

Glucagon-like peptide-1 (GLP-1) belongs to the incretin family, a group of hormones with glucose-dependent insulin secretion activity. Notably Glucagon-Like Peptide 1(GLP-1) analogues such as liraglutide have been developed and used in humans since 2009 for the treatment of type 2 diabetes mellitus. In recent years, numerous studies have detailed the anti-inflammatory impact of GLP-1 in numerous organs and diseases (Nauck, 2016; Li et al., 2017). Thus, GLP-1 analogues could also prove beneficial for OA treatments.

The non-clinical studies (*in vitro* and *in vivo*) in the literature or conducted by the sponsor with liraglutide provide a mechanistic basis for its primary pharmacological effect for the target indication in OA, whereby liraglutide with its anti-inflammatory, anti-catabolic and anabolic activities acts in concert on the synovial membrane inflammation and the articular cartilage to alleviate OA-related symptoms and structure damages.

GLP-1 binds to the Glucagon-like-peptide-1 receptor (GLP-1 receptor or GLP-1R). In cartilage, GLP-1 receptor is expressed in OA human chondrocytes (Meurot et al., 2022), and the agonist activity of liraglutide on this receptor increases rat chondrocytes viability through increased resistance against cell-stress and apoptosis (Chen et al., 2018). Furthermore, liraglutide dose-dependently decreases the secretion and gene expression of metalloproteinases (MMP-3, MMP-13) and aggrecanases (ADAMTS-4, ADAMTS-5), while increasing the gene expression of Sox9, a transcription factor crucial for chondrocytes differentiation, collagen 2 and aggrecan, thus liraglutide possesses anti-catabolic activity and anabolic activities in murine chondrocytes (Meurot et al., 2022). In the destabilization of medial meniscus (DMM) model, a surgically induced OA model in rat, repeated IA injections of liraglutide 60µg for 6 weeks decreases proteoglycan loss resulting in significantly less cartilage degeneration width model of OA (sponsor, see IB), the benefits of liraglutide on cartilage structure is also confirmed in the literature (Chen et al., 2018).

Liraglutide presents strong anti-inflammatory activity and decreases in a dose-dependent manner the secretion of NO, PGE2, IL-6 by murine macrophages and chondrocytes in vitro (with an average IC50 value of 50 nM). In the monoiodoacetate (MIA) rat model of inflammatory OA and pain, a single IA administration of liraglutide dose-dependently decreases pain during von Frey test (mechanically induced pain assessment), with a long-lasting effect of 4 weeks (sponsor). Furthermore, in the MIA-induced OA mouse, single administration of Liraglutide decreases

mechanically induced pain as well as synovial membrane inflammation score (liraglutide 20 µg, p = 0.0099, compared to vehicle-treated group) (Meurot et al., 2022).
Additionally, it has been demonstrated that liraglutide GLP-1R agonist does not exhibit cytotoxic effects on chondrocytes, prevents from interleukin-mediated cytotoxicity (Chen et al, 2018) and shows an anti-inflammatory activity through the PKA/CREB pathway activation (Que et al, 2019).

Pharmacokinetic exploration of liraglutide distribution demonstrates that subcutaneous administration does not allow liraglutide passage within synovial fluid of animals while intra-articular administration would provide a synovial exposition. In addition, IA administration of liraglutide leads to systemic level comparable with those observed upon subcutaneous administration. Thus, the intra-articular route of administration is necessary to obtain a local action on OA tissues.

Therefore, and in contrast with the current standard of care in OA, these mechanisms of action allow to prevent structural damages during the evolution of the disease (cartilage protection) and alleviate symptoms with a long-lasting analgesic effect. Thus, IA administration of 4P-004 is expected to act as a disease-modifying OA drug (DMOAD) upon IA administration.

2.3 Risk / Benefit Assessment

The safety profile of 4P-004 is well known when administered subcutaneously (for long-term use) but no human data is available regarding the safety profile after IA injection.

As part of its preclinical data package, the sponsor intends to rely on previously published and assessed data of liraglutide containing authorized medicinal products (Victoza®, Saxenda®) to address systemic safety and toxicology of liraglutide. PK studies performed in dogs have shown very reproducibly that there is no more liraglutide after 24h in the articulation after IA injection in the knee-joint (see IB). A GLP extended single dose toxicity study of knee IA administration 4P-004 has been performed in rats. The product was well tolerated, no adverse signs of toxicity were observed up to the higher tested dose of 300 µg, which was determined as the No Observed Adverse Effect Level (NOAEL) dose of the study. Detailed presentation of the GLP-Toxicity study is available in the current IB.

<u>Liraglutide adverse events</u>

The most frequently reported adverse reactions during clinical trials were gastrointestinal disorders (repeated subcutaneous administration):

- nausea and diarrhea were very common (≥1/10),
- vomiting, constipation, abdominal pain, and dyspepsia were common (≥1/100 to <1/10).

Headache and nasopharyngitis were also common.

Hypoglycemia was common, and very common when liraglutide is used in combination with a sulfonylurea in patients with type 2 diabetes mellitus (Victoza®).

In clinical trials in overweight or obese patients without type 2 diabetes mellitus treated with Saxenda®, no severe hypoglycemic events (requiring third party assistance) were reported. Symptoms of hypoglycemic events were reported by 1.6 % of patients treated with Saxenda® and 1.1% of

patients treated with placebo; however, these events were not confirmed by blood glucose measurements. The majority of events were mild.

Allergic reactions including urticaria, rash and pruritus have been reported from marketed use of liraglutide. Few cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnea, and oedema have been reported with marketed use of Victoza. Few cases (0.05%) of angioedema have been reported during all long-term clinical trials with Victoza.

Liraglutide overdose

From clinical trials and marketed use, overdoses have been reported of up to 40 times (72 mg) the recommended maintenance dose (Nakanishi et al., 2012). Events reported included severe nausea, vomiting, diarrhea and severe hypoglycemia.

In the event of overdose, appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms. The participant should be observed for clinical signs of dehydration and blood glucose should be monitored.

Additional details regarding risks for participants in this clinical study may be found in the SmPC/IB and informed consent documents.

Blind review by the Sponsor of ongoing clinical safety data in Cohort 3 (as of 17 July 2023):

After blinded review of clinical safety data in cohort 3 (dose = [redacted], the Sponsor decided that, taking into consideration the benefit/risk for patients and the potential issues of performing a future double-blind study, the Maximum Tolerated Dose may have been reached based on adverse event "nausea" for 5 participants and "vomiting" for 4 of them. Consequently, the Sponsor decided to test an intermediate dose [redacted] in cohort 4 to obtain clinical safety information with this dose. Higher 4P-004 doses than [redacted] will not be tested in this study.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objectives

- To characterize safety and tolerability of single IA administration of 4P-004 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.

3.1.2 Secondary objective

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

3.1.3 Exploratory objectives

- Collection of biological fluids (blood, urine).

3.2 Endpoints

3.2.1 Primary endpoints

- Number of Adverse events (AEs), serious AEs (SAEs) (Common Terminology Criteria Adverse Events [CTC-AE]) from ICF signature to D29, including target knee pain and tenderness, erythema, swelling, local pain at injection site.
- Vital signs from D-7 to D8, ECG from D-7 to D1: Mean change, number of Potentially Clinically Significant Abnormality (PCSA), Percentage of participants with PCSA
- Laboratory changes (Red Blood Cells (RBC), White Blood Cells (WBC), Hemoglobin (Hb), platelets, alanine transaminase (ALT), aspartate transaminase (AST), glycemia, amylasemia, creatinin clearance) from D-7 to D8: Mean changes number of PCSA, Percentage of participants with PCSA.

3.2.2 Secondary endpoint

- Plasma concentration of liraglutide following a single IA injection. PK samples: D1 pre-injection (T0-4h) and 2, 4, 8, 12, 16 and 24 hours post injection.
  Plasma concentrations will be performed by [redacted]

3.2.3 Exploratory endpoints

- Serum and urine OA-related biomarkers (exploratory proteomic research of 4P-004 efficacy-related biomarkers) at D1 (T0-4h, T0+8h), D2 (T0+24h) and D8.

  Human blood serum and urine samples will be collected and shipped to AO Research Institute Davos for liquid biomarker identification.

4 STUDY DESIGN AND DESCRIPTION

4.1 Overall design

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 4P-004 in participants with target knee OA KL 2-4.
Participants will be enrolled in 4 cohorts; in each cohort participants will receive either 4P-004 or placebo (6:2). 4P-004 dose will increase with cohort 1 to 4.
For the highest dose cohort [redacted] a sentinel dosing will be implemented (see section 4.2).

Recruitment of participants

Participants will be recruited via investigators' patient registry or via advertising. More information is provided in Patient Recruitment Procedure.

A Screening visit at D-7 (D-14 to D-4) will be 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 around 7 days before the randomization day (D-14 to D-4). During this visit, the eligibility of the participant will be evaluated.

The Randomization visit (Day 1 to Day 2) will be performed at study site and the participant will be 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 veinous infusion line has been set up (see Investigator & Pharmacy manuals and sections 1.2 and 6.2.2). Participant will be monitored during the 24-hour hospitalization and will be discharge on D2.

The Follow-up visit at D4 (±1 day) will be 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) will be 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) will be 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) will be set up for this study (see DSMB Charter) and will review safety data during the study. The DSMB will be composed of 2 physicians specialized, one in rheumatology and one in diabetology.

Members will 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 (see section 11.1.5 and DSMB Charter).

4.2 Scientific rationale for study design

This phase 1 study is randomized, double-blinded, and placebo-controlled in order to avoid subjective bias in the assessment of the safety and tolerability of 4P-004.

To mitigate risks associated with 4P-004, first IA injection in human, hypoglycemic properties and other potential risks based on preclinical and clinical data:

- Participants are enrolled in 4 cohorts with IMP dose increasing from cohort 1 to 3;
- Study-specific eligibility criteria have been added to the standard criteria to ensure that participants at increased risk of hypoglycemia are excluded (see section 5.2);
- A DSMB is set up;
- Two sentinel participants are included for the highest tested dose [redacted] all data up to D8 evaluation (including lab safety but not PK data) of these sentinel participants will be reviewed by the DSMB before randomization of the next participant;
- [redacted].

4.3 Justification for route of administration

Pharmacokinetic studies have been performed with liraglutide in dogs (Study report 4P004-027-PK see IB). This study demonstrates that:

- subcutaneous administration (authorized route of administration) of liraglutide does not allow diffusion into the synovial fluid,
- upon IA administration, liraglutide exhibit similar systemic blood exposure as upon subcutaneous administration.

Thus, to expose the diseased tissue, local IA administration is necessary.

4.4 Justification for dose

As part of this phase I trial, four different dose levels of 4P-004 will be investigated: [redacted]. These dose levels have been selected considering the results of pharmacological data (efficacy) and toxicological data (safety) (see IB for detailed justification on dose selection).

Dose 1 (starting dose; [redacted]):

[redacted] is the human starting dose considered for the clinical trial. [redacted] is the Minimum anticipated biological level dose (MABEL). It is assumed that both safety and potential clinical benefit for the patient are ensured with this first dose of [redacted], which is in line with EMEA/CHMP/SWP/28367/07 Rev. 1 considerations.

Dose 2 [redacted]

[redacted] in human is around the effective dose leading to an optimal analgesia effect of 4P-004 in induced osteoarthritis rat model following human equivalent dose (HED) conversion.

Dose 3 [redacted]

[redacted] Sentinel participants will be included for this dose-cohort during the clinical study.

[redacted]

4.5 End of study definition

The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (i.e., the participant is unable to be contacted by the investigator).

4.6 Early study termination

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

The clinical study may be terminated early if new information or other evaluation regarding the safety or efficacy of the study drug that indicates a significant change in the known risk/benefit profile for the drug, such that the risk is no longer acceptable for participants participating in the study.

4.6.1 Clinical criteria for early study termination

It is agreed that for reasonable cause, either the investigator or the Sponsor may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination; if by the investigator notice is to be submitted to the sponsor and if by the Sponsor, notice will be provided to each investigator.

Stopping rules

The study will be immediately suspended, and no additional IMP administered pending review and discussion of all appropriate study data by the DSMB if 1 or more participants develop any of the following adverse events deemed to be possibly, probably, or definitely related to the IMP by the Investigator and/or Medical Monitor, based upon close temporal relationship or other factors:

- Severe local reaction within 7 days after injection
- Clinical manifestations of hypoglycemia
- Severe gastro-intestinal adverse event
- Potentially clinically significant ECG abnormalities.
- Any serious adverse event considered reasonably related to the IMP (SAR) by the Principal Investigator.

The study will not be restarted until all parties have agreed to the course of action to be taken and the EC has been notified.

Dose limiting toxicity (DLT) describes side effects of a drug that are serious enough to prevent an increase in dose or level of that treatment.

When more than 1 DLT occurs in a dosing cohort, dose escalation must be stopped and this dose level will be identified as the non-tolerated dose.

DLT is based on:

- Expert‘s opinion
- Any related SAE

In this study, with liraglutide, DLT will be established if any of the following occurs:

- Anaphylaxis (angioedema, hypotension, shock, bronchospasm, hypoxia, or respiratory distress),
- Hypoglycemia (blood glucose level ≤ 2.5 mmol/L) within 2 days after injection,
- Amylasemia ≥ 3ULN within 7 days after injection,
- Serious gastro-intestinal adverse event within 7 days after injection.

4.6.2 Criteria for premature termination or suspension of investigational sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

Discontinuation of specific sites or of the study as a whole are handled as part of section 11.1.8.

5 STUDY POPULATION

5.1 Inclusion criteria

I1. Participants who have the capacity to give informed consent and who are willing to comply with all study related procedures and assessments (consent via legally authorized representative will not be accepted),

I2. Ambulatory participants, agreeing a 24-hour hospitalization,

I3. Participants between 18 and 80 years of age,

I4. Female participant of childbearing potential (WOCBP), must use contraceptive consistent with local regulations regarding the methods of contraception for those participating in clinical studies (see section 11.4) for at least 5 days following IMP injection, and must have a negative urine pregnancy test done within 24h before randomization,

I5. Male participants (whose partners are of childbearing potential) must consent to use methods of contraception consistent with local regulations regarding the methods of contraception for those participating in clinical studies (see section 11.4), for at least 90 days following IMP injection,

I6. Participants with knee osteoarthritis, KL 2-4 of their target knee (defined at screening as the knee with greater pain based on the participant's evaluation and the investigator's clinical judgment),

I7. X-ray of the target knee within 6 months (if not, to be performed before randomization),

I8. ECG within normal range,

I9. WBC (white blood cell count) > 3500/µL,

I10. Hemoglobin > 12 g/dL,

I11. Platelets > 100,000/ µL,

I12. Creatinine clearance (CrCl) > 60 mL/min,

I13. Glycemia within normal range,

I14. AST, ALT < 1.5 upper limit of normal (ULN),

I15. Amylasemia < 1ULN,

I16. Negative tests for COVID-19 (if required by the standard practice on site), HIV, HbsAg and hepatitis C Ab (Determination of HIV and hepatitis status can be based on participant-reported medical history, available medical records, and the most recently available laboratory results for the participant [tests performed within the previous 12 months]).

5.2 Exclusion criteria

E1. Breastfeeding women,

E2. Treatment with systemic glucocorticoids greater than 10 mg prednisone or the equivalent per day within 4 weeks prior to screening,
E3. Any treatment with glucosamine or chondroitin sulfate in the previous 3 months,
E4. Any glucagon-like peptide 1 analogue hormones,
E5. Anticoagulant treatment (current or within the last 10 days),
E6. Treatment of the target knee with any IA injection (steroids, hyaluronic acid derivatives, PRP ….) within 3 months,
E7. Knee surgery (of the target knee) performed within the previous 12 months or planned within the next 6 months,
E8. Any partial knee replacement of the target knee,
E9. Any known active infections or increased predisposition for the development of infections
E10. Clinical signs and symptoms of active joint crystal disease, or any inflammatory joint disease,
E11. Diabetes type I or II,
E12. Congestive Heart Failure stage III or IV of NYHA classification,
E13. Inflammatory bowel disease,
E14. Any other chronic condition that has not been well controlled for a minimum of 3 months,
E15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer) within the last 5 years,
E16. Any condition, including laboratory findings, that in the opinion of the investigator constitutes a risk or contraindication for participation in the study or that could interfere with the study objectives, conduct or evaluation, (for example, any abnormal reaction to previous IA injection),
E17. Hypersensitivity to the active substance liraglutide or to any of the excipients: Disodium phosphate dihydrate, Propylene glycol, Phenol,
E18. Participation in an interventional clinical research trial within 12 weeks prior.

5.3 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to the IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAEs.

Participant numbers assigned to subjects who fail screening should not be reused. If a participant fails screening but is later successfully rescreened (Individuals who are defined as screen failures may be rescreened once), the data for the participant will be entered as if these were 2 separate participants.

Therefore, the data should be entered as follows:

- The screen failure data should be entered as a screen failure participant.

- Rescreened participant should be assigned a new participant number and treated as a stand-alone participant.

6 STUDY INTERVENTION

6.1 Study intervention administered

A complete description of the IMP and its proper handling will be provided in the Pharmacy manual available to the clinical site.

6.1.1 Liraglutide

Liraglutide will be provided at 6 mg per mL in a clear and colourless or almost colourless, isotonic solution, pH=8.15. Solution also contains disodium phosphate dihydrate, propylene glycol, phenol and water.

6.1.2 Placebo

NaCl 0.9% sterile solution will be used as placebo.

NaCl 0.9% solution is commonly used in biological research.

6.2 Preparation / Handling / Storage /Accountability

A complete description of the Investigational Medicinal Product (IMP) preparation, handling, storage and accountability will be provided in the Pharmacy manual available to the clinical site.

The product should be stored in a refrigerator (2°C–8°C), away from the freezer compartment. It should not be freeze. Sites are requested to maintain a temperature log according to their SOP to ensure storage temperature remains within acceptable limits.

The pharmacist who will be responsible for IMP preparation in an unblinded condition will be responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

The used pen will be kept by the Pharmacist in a secure location up to the full documented reconciliations performed with the Sponsor at the end of the study. The Pharmacist should wait for the written approval form from the Sponsor before proceeding to their destruction. Any annotation on the box containing the pen should be considered as source documents until the time of pen destruction.

6.2.1 IMP preparation, administration and handlings

Dilution will be made according to the dose to get a total volume [redacted] to be injected intraarticularly. Details are provided in the Pharmacy manual.

6.2.2 IA injection

The IMP will be administered by IA injection. A complete and detailed description can be found in the Investigator manual. It is recommended, but not mandatory, to do the IA injection with ultrasound guide.

Use of local anesthetic agent (lidocaine or other) or X-ray contrast agent are not allowed to avoid any interference with the IMP.

The skin is cleansed and sterilized.
The sterile needle 0.8 x 50mm (type Becton Dickinson Microlance™ 3 Aiguilles 21G 2RB green is inserted in the knee IA joint space.
The injection itself (with a second syringe prepared with [redacted] IMP, see Investigator manual) is possibly preceded by an aspiration phase of the synovial fluid, if any, to

- i) free the knee from the tension linked to the excess volume of synovial fluid in the knee,
- ii) make laboratory assessment of the synovial fluid as per standard practice.

6.3 Measures to minimize bias: randomization and blinding

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures. Screening numbers must not be re-used for different participants.

Participants can be rescreened once.

Randomization

Randomization will be performed using a pre-established randomization list. This list will be generated by a statistician for the IMPs (4P-004 or placebo) based on study design (sequential randomization according to the dose escalation and sentinel patients).

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

Product code lists (4P-004 or placebo) will be generated and managed by the unblinded responsible person delegated by the sponsor.

The unblinded responsible person will communicate the result of the randomization (arm 4P-004 or placebo) and the associated product code to the pharmacy of PI site.

Except for the unblinded pharmacist who will prepare the IMP, the Investigator and the whole study team will remain blinded for the study IMP.
Complete instructions will be provided to the site in the randomization and code break procedure.
In case a participant needs to be replaced, the replacement participant should receive the same treatment that the participant being replaced would have received. The unblinded responsible person will attribute the replacement code to the next patient.

Unblinding

In case of an emergency, the Investigator has the sole responsibility for determining if the unblinding of a participant's intervention assignment is warranted (e.g., in case of an AE, the code must only be broken in circumstances when the knowledge of the IMP is required for treating the participant). Participant safety must always be the first consideration when making such a decision. If the Investigator decides that the unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment, unless this could delay emergency treatment of the participant. Code breaking can be performed at any time by using the sealed envelope handled by the Investigator. If a participant's intervention assignment is unblinded, the Sponsor must be notified immediately and maximum 24 hours after breaking the blind (details are given in the code break procedure). The date, time of the day, and reason that the blind

was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable. If the code is broken by the Investigator, the participant must be withdrawn from the study treatment.

Methods of blinding

This is a double-blind study but the Pharmacist who will prepare the IMP material to be injected will not be blinded. Only the Pharmacist who has not any contact with the participant will be unblinded. The DSMB will have access to unblinded data if deemed necessary by the DSMB. No unblinding information will be shared by the DSMB with the study team excepted the unblinded responsible person who will provide tables for the DSMB open/closed sessions. Details about the distribution of unblinding data to the DSMB while protecting the blind are described in the DSMB charter.

6.4 Changes in IMP cohort dosing

[redacted]

6.5 Concomitant therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of randomization or receives during the study must be recorded along with:

- Reason for use,
- Dates of administration including start and end dates,
- Dosage information including dose and frequency.

Oral analgesics (paracetamol, non-Steroidal anti-inflammatory drug [NSAID], tramadol, opioids) or topical NSAID if needed are allowed during the study, all treatments taken for pain relief will be recorded in the eCRF (via participant's diary).

Other treatments not listed in exclusion criteria initiated before the study start can be pursued during the whole study and will be recorded in the CRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of study intervention

NA

7.2 Participant discontinuation / Withdrawal from the study

A participant may withdraw from the study at any time at his/her own request or may withdraw at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. In these situations, if possible, the D8 visit should be performed if discontinuation is before.

Clarification should be made with the participant if

- he/she does not want to come back to next scheduled or

- he/she does not want anymore his/her data to be analyzed for the purpose of the study

The Investigator should make every effort to perform the EoS Visit.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested (e.g., archival samples for future use), and the Investigator must document this in the site study records. The site should document any case of withdrawal of consent.

Should participant withdraw from the study between D1 and D8, or at any later time, participants replacement will be evaluated on a case-by-case basis.

7.3 Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, several telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

The Statistical Analysis Plan (SAP) will specify how these participants lost to follow-up for their primary endpoints will be considered.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Study Flowcharts (section 1.2).

Adherence to the study design requirements, including those specified in the Study Flowchart is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the informed consent form (ICF) may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Study Flowchart and/or in inclusion or exclusion criteria (see sections 1.2, 5.1, 5.2).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 100 mL(the exact assessment specific volumes are described in section 11.2) within approximately 14 days. Repeated or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Safety assessments

Planned time points for all safety assessments are provided in the Study Flowchart.

8.1.1 Physical examination

A physical examination will be conducted at screening, D1, D2 and D8 visits. A symptom-based physical examination will include organ systems, which are deemed, at the discretion of the Investigator, necessary to be evaluated.

Height (at screening only) and weight will also be measured at screening, D1 and D8 and recorded (Body mass index will be calculated automatically).

8.1.2 Vital signs

Vital signs will be measured at screening and D1, D2 and D8 as outlined in the Study flowcharts (see Section 1.2). They will be measured in a sitting position after 5 minutes of rest and will include systolic and diastolic blood pressure, and pulse. Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.1.3 Electrocardiograms

Three 12-lead ECG will be obtained at screening and D1 as outlined in the Study flowcharts (see section 1.2).

Electrocardiogram parameters will be based upon the automatic reading of the device. These ECG parameters and morphology need to be reviewed by the Investigator. If the device does not provide automatic reading, then the ECG parameters will need to be determined and interpreted by the Investigator.

8.1.4 Clinical safety laboratory assessment

See section 11.2 for the list of clinical safety laboratory tests to be performed and section 1.2 (Study flowcharts) for the timing and frequency.

- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of IMP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - ✓ If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - ✓ All protocol-required laboratory assessments, as defined in section 11.2, must be conducted in accordance with the Laboratory manual and the Study flowcharts (see section 1.2).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE, AE, or dose modification), then the results must be recorded in the eCRF.

8.1.5 Local safety

The evaluation of IA injection site reaction following IMP administration will be performed by the Investigator or designees as outlined in section 1.2.2. Findings at the site of injection such as, but not limited to tenderness, erythema, and swelling, will be recorded in the eCRF in 3 different grades (mild/moderate/severe).

8.1.6 Target knee pain

The participants will also assess target knee pain using a numerical rating scale (NRS), 11 points (0-10) to assess pain of the target knee as outlined in section 1.2:

- At screening (as a mean of the previous 2 days)
- At D1: T0-4h as - a mean of the previous 2 days and - currently and every hour after T0 up to T0+6h
- At D2 before hospital discharge: assessment from IA injection to hospital discharge
- From D3 to D8 Visit: daily, assessment from the previous 24 hours
- From D15 to D29: weekly assessment based on pain during the previous 2 days.

A pre-paid and pre-printed envelope will be given to the participant on D8 visit for mailing these records to the Investigator.

8.2 Adverse events and serious adverse events

All AEs will be coded and graded according to the Division of AIDS, table for grading the severity of Adult and Pediatric Adverse Events (DAIDS, Corrected Version 2.1 July 2017).
The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that caused the participant to discontinue the study.

The definitions of an AE, SAE and suspected unexpected serious adverse reactions (SUSAR), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures

for completing and transmitting AE, SAE, SUSAR and other reportable safety event reports can be found in Appendix 3.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.2.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.2.1 Time period and frequency for collecting AE, AESI and SAE

All AEs and SAEs will be collected from the signing of the ICF until the end of study at the time points specified in the study flowcharts (section 1.2).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning event, as indicated in section 11.3.

The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

8.2.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in section 11.3.

8.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end date, all SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is provided in section 11.3.

8.2.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor or designee of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committees (IEC), and Investigators.
- Adverse events that are considered expected will be specified in the reference safety information (see IB).
- SUSARs are reported to regulatory authorities, Investigators, and IECs as follows:
    - For SUSARs that are life-threatening or result in death, reporting is no later than 7 days after first knowledge by the Sponsor, with all relevant follow-up information subsequently reported within an additional 8 days.

- For SUSARs, other than those that are life-threatening or result in death, reporting is no later than 15 days after first knowledge by the Sponsor.

- An Investigator who receives an Investigator safety report describing a SAE, SUSAR, or any other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.2.5 Pregnancy

If a pregnancy is reported, the Investigator should inform the Sponsor or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in section 11.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.2.6 Adverse event of special interest (AESI)

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor or designee is required.

All reported AESIs will be reviewed by an independent DSMB.

For AESIs, the Sponsor is to be informed immediately (i.e., within 24 hours), as per SAE notification guidelines described in section 11.3, even if a seriousness criterion is not met, using the corresponding pages of the case report form (to be sent) or screens in the eCRF:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see section 11.3). Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see section 11.4).
- Symptomatic overdose (serious or non-serious) with IMP. Any adverse event(s) associated with ("results from") an overdose of IMP will be reported as a serious adverse event, even if no other seriousness criteria are met.

Other project specific AESI:

- Anaphylaxis,
- Severe IMP injection site reactions (severe tenderness, erythema, swelling…),
- Hypoglycemia,
- Severe Gastro-intestinal disorder.

8.3 Treatment of overdose

All doses upper than the planned dose will be considered as an overdose. If needed, the participant should be observed for clinical signs of dehydration and blood glucose should be monitored.

In the event of an overdose, the Investigator/treating physician should:

- Contact the Monitor (CRA) immediately.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities at least for 7 days. Special attention should be paid to glycemia levels in the 24 hours,
- Document appropriately in the eCRF.

8.4 Pharmacokinetics

8.4.1 Pharmacokinetic sample collection

Blood samples (one 3 mL sample per scheduled time) will be collected for the determination of concentrations of 4P-004 as planned in the study flowcharts (section 1.2). The actual time of sample collection will be recorded on the source document and eCRF.

Instructions for collecting, processing, and shipping of samples are provided in the laboratory manual.

8.4.2 Bioanalytical methods

The analyses will be performed by high performance liquid chromatography (HPLC) coupled with mass spectrometry (MS) and ultraviolet-visible spectroscopy (UV).

The development and validation of the analytical method as well as the dosing of PK samples will be performed by Nuvisan GmbH (Am Feld 32, 85567 Grafing, Germany) in accordance with the company's standard operating procedures and following international guidelines.

8.4.3 Pharmacokinetic parameters

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})
Half-life ($T_{1/2}$)

8.5 Visits requirements

8.5.1 Screening visit, D-7 (D-14 to D-4)

The screening visit can be performed 4 to 14 days before the IMP administration.

During this visit the Investigator will:

- explain and answer all questions the participant has,
- if the participant agrees, obtain the written informed consent,
- review all inclusion / exclusion criteria, demographics, medical history and medication history,
- notify all pain killer medication taken in the past month,
- do a physical examination, including vital signs, weight and height,
- do an ECG,
- ask the participant to rate his/her pain of the target knee pain (as a mean of the previous 2 days) with the NRS
- take blood samples for clinical safety lab,

- give the participant diary to collect medical events and treatments taken up to next visit,
- give the appointment for the inclusion visit (day of IMP administration) with 24-hour hospitalization and other follow-up visits.

8.5.2 Inclusion visit, D1, full day hospitalization

During this visit (24 hours hospitalization), the Investigator will:

- review inclusion / exclusion criteria, concomitant medication (from screening),
- do physical exams, ECGs, measure vital signs as per D1-D2 Study Flowchart (section 1.2.2),
- record any AE since screening,
- put a veinous line,
- remind the participant to fill in the NRS (before any study intervention on D1) for assessing target knee pain in the previous 2 days and during the hospitalization as outlined in section 1.2.2,
- randomize the participant (performed by the pharmacist)
- take blood / urine samples for glycemia, PK and OA-related biomarkers samples as per D1-D2 Study Flowchart (section 1.2.2),
- do the IA injection (modalities given in section 6.2.2 and in the Investigator manual) of the IMP extemporaneously prepared in a vial by the pharmacist (procedure for preparation is detailed in the Pharmacy manual),
- record AEs as per D1-D2 Study Flowchart (section 1.2.2),
- monitor the participant during the coming 24 hours:
    - on local reaction as per D1-D2 Study Flowchart (section 1.2.2)
    - on blood sugar level (veinous / capillary measures):
        - after IMP injection, glycemia will be systematically monitored (capillary measures via glucose meter and/or veinous measures) as per D1-D2 Study Flowchart (section 1.2.2),
        - when planned measurement indicates glycemia is ≤ 70 mg/dL without clinical symptom repeat the test each 30 min up to obtaining threshold value >70 mg/dL,
        - at any time if occurrence of one or more symptoms of hypoglycemia (common presenting symptoms include nausea, confusion, tremor, sweating, palpitations, or hunger), sugar will be given to the participant and a blood glycemia test should be immediately performed and closely monitored.

8.5.3 Hospital discharge, D2

Before participant discharge from the hospital, the investigator or delegate will

- perform a physical exam and record vital signs,
- remind the participant
    - to assess target knee pain [NRS] (based on the previous 24 hours) on a daily basis from D3 to the next visit date (D8),

    - to fill in the diary from D2 (after hospital discharge) up to the next visit (D8) to self-report adverse events and pain killer medication,
- give appointment for a virtual visit (phone call) at D4 ± 1d and for a face-to-face visit on D8 ± 2 days.

No specific physical limitation is recommended from the day after the injection.

In case of safety concerns after hospital discharge, the participant will be asked to call the investigator / to return to the hospital for an unscheduled safety control visit according to the investigator judgement.

8.5.4 Phone call (Virtual visit), D4 ± 1d

At D4 (±1 day), follow-up -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) will be a virtual visit by phone.

During this phone call, the Investigator or delegate will:

- review the diary with the participant,
- record adverse events if any,
- remind the participant
    - to assess target knee pain (NRS) on a daily basis up to the next visit
    - to self-report adverse events and pain killer medication up to the next visit,
- confirm the appointment for D8 visit.

In case of safety concerns, the participant will be asked to return to the hospital for a safety control visit.

8.5.5 Follow-up visit, D8 ± 2d

During this visit, the Investigator or delegate will:

- review the diary with the participant,
- record adverse events if any,
- take a blood sample for routine tests and OA exploratory biomarkers,
- take a urine sample for exploratory biomarkers,
- remind the participant
    - to assess target knee pain [NRS] (based on the previous 48 hours) at D15, D22 and D29,
    - to fill in the diary for the 3 coming weeks (up to D29) to self-report adverse events and pain killer medication
- give the participant a pre-paid and pre-printed envelope for mailing back the diaries and the NRS questionnaire to the Investigator after the D29 phone call (end of study visit/virtual visit).

8.5.6 EoS visit: Phone call (Virtual visit), D29 ± 2d

The Investigator or delegate call the participant by phone and will ensure that the participant completed the diary (AE, target knee pain, pain killer intake, concomitant medications) and will remind the participant to send the diary and the NRS questionnaire as planned.

The investigator will also inquire for any ongoing AEs or SAEs, worsening of AEs or SAEs, or development of new AEs or SAEs.

In case of safety concerns, the participant will be asked to return to the hospital for a safety control visit.

8.6 Participant compensation

For the purpose of the study, the participant will have to go 3 times to the investigational site including a day of hospitalization (day of study drug administration) for around 24 hours, during which several blood samples for PK study will be drawn. Details of compensation given to the participant are provided in the ICF.

9 DATA MANAGEMENT

The sponsor or designated representative (e.g., contract research organization) will perform the data management activities in accordance with the data management plan (DMP). The DMP will outline the systems and procedures to be used in the study.

9.1 Data Capture

Data will be entered from the source document in an electronic CRF (eCRF, web database) by the Investigator or his/her designee. At the end of the study, each eCRF must be signed electronically by the Investigator.

9.2 Access Rights

Designated personnel (Sponsor, Investigator or designee) will be provided with a personal username and password to access the eCRF database. This username/password pair may be used by a single individual only; passwords must not be shared with any other person.

9.3 Audit Trail

The EDC systems developed for this study comply with the Good Clinical Practices (GCP) predicate rule requirements, laws and regulations (General Data Protection Regulation - GDPR) and allows an audit of actions performed by users. Thus, all data modifications will be documented in an audit trail file. After the last verification, the relevant data will be locked into the database. The system is also compliant with the e-signature laws (particularly the Title 21 CFR Part 11 of the Code of Federal Regulations); in that saving the data is equivalent to a handwritten signature.

9.4 Data Sources

For this study, the following data sources are identified:

9.4.1 Investigator's site data

These data will be directly entered into eCRF by the Investigator or his/her designee. The exhaustive list of clinical data collected at each visit will be described in the Source Data Verification List. This form will be completed and approved by the Investigator or his/her designee during Initiation visit.

9.4.2 Participant reported outcome

These data are reported by the participant himself and will be entered in the eCRF. This section describes the questionnaires, note book that will be used in this study and how data will be managed (entered in eCRF or filled as paper source document).

Data to be entered in eCRF:

- NRS Questionnaire,
- Diary, including AEs/SAEs and concomitant treatments reported by the participant.

9.5 Data Validation

All data entered into the eCRF will be validated by the DM. All computerized edit checks programmed to validate the data, at least on primary outcome data are described in the Data Validation Plan document, written by the DM.

Data discrepancies will trigger automatic queries, directly displayed on the screen when data entered are saved. If necessary, manual queries will be sent to the Investigator for clarification. All these discrepancies/queries have to be answered or confirmed by the site.

9.6 Coding

TYPE OF DATA	DATASET	DICTIONARY
Adverse Events	AE	MedDRA, most up-to-date version
Serious Adverse Events	SAE	MedDRA, most up-to-date version
Medical History	MH	MedDRA, most up-to-date version
Concomitant Medications	CM	ATC/DDD Index, most up-to-date version

9.7 Data Lock

Clinical database will be locked after review, query resolution, signatures of the eCRF and determination that clinical database is ready for analysis.

Once the Trial is finished and database is locked, the DM should follow the database unlock/relock process to document any further change.

10 STATISTICAL METHODS

10.1 Statistical and analytical plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

10.1.1 Analysis sets

Safety set

The safety analysis set will consist of all participants who are enrolled and received 1 dose of study drug. Participants in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK Set

The PK set will consist of all participants who receive study drug and have at least 1 measurable plasma concentration.

Blood samples for placebo will not be analyzed by the bioanalytical laboratory except for 2 samples per participant receiving placebo, 1 predose and the other around the expected time at which Cmax occurred (as emerging from the actual measurement of the samples of the first dose group) to ensure from a safety perspective that no additional participants could have been on active treatment.

10.1.2 Analysis of demographics and other baseline characteristics

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, and BMI) for pooled placebo, each 4P-004 dose level, 4P-004 overall and overall total. The number and percentage of participants in each class of the categorical demographic variables and baseline characteristics variables (sex, ethnicity, and race) will be tabulated for pooled placebo group, each 4P-004 dose level, 4P-004 overall and overall total. Pooled placebo corresponds to participants receiving placebo in the 4 pooled cohorts.

Demographic variables will be summarized overall for participants who are screened, but not enrolled in the study. Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

10.1.3 Pharmacokinetic analysis

Concentrations in plasma

The plasma concentration of 4P-004 will be summarized by dose level over each scheduled sampling time using descriptive statistics. Individual plasma concentration data vs time will be presented in a data listing.

PK parameters

Descriptive statistics (N, arithmetic mean, SD, median, minimum, maximum and percent coefficient of variation [%CV]) will be used to summarize the plasma PK parameters for 4P-004 by, dose level.

10.1.4 Safety analysis

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, figures) and, if needed, on statistical analysis (appropriate estimations, confidence intervals). No statistical significance tests will be performed on safety data.

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.

All safety data will be presented in listings and will be summarized by placebo, each 4P-004 dose level, 4P-004 overall, and overall total.

AEs

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Clinical judgment should be used to determine the severity of AEs as described in Section 11.3.4.

TEAEs with onset occurring within 7 days (onset date – date of dose + 1 ≤ 7) after study drug administration will be listed and included in the summary tables. TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs not-related), severity of AEs and related AEs. AEs leading to study drug discontinuation and SAEs will be listed. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

Local tolerability

The number (%) of participants with injection site reactions will be summarized overall and by maximum severity by treatment group. The incidence of AEs related to local tolerability findings will be summarized over time.

Target knee pain

Results of the NRS will be summarized by visit, maximum value with corresponding visit and will be presented per participant and treatment group.

Clinical safety laboratory evaluation

Individual results of laboratory tests from hematology, and chemistry that meet PCSA criteria to be defined in the SAP will be listed and summarized. Baseline, post-dose, and change from Baseline to post-dose laboratory data will be summarized. All clinical laboratory data will be listed.

Vital signs

Individual results of vital signs that meet PCSA criteria to be defined in the SAP will be listed and summarized. Observed values and changes from Baseline in vital sign measurements (systolic and diastolic blood pressure and heart rate,) will be summarized. All vital signs data will be provided in the data listings.

ECG

ECGs will be summarized by changes from baseline values at each dose level using descriptive statistics.

10.1.5 Surrogate efficacy markers analysis

These parameters are exploratory, and analysis will be described in the SAP.

10.2 Sample size determination

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. The sample size was not based on statistical power considerations.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Appendix 1: Regulatory, ethical, and study oversight considerations

11.1.1 Regulatory and ethical consideration

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines,
- Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR).

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g advertisements) must be submitted to an IEC by the Investigator and reviewed and approved by the IEC before the study is initiated.

Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
- Determining whether an incidental finding should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so, designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, e.g., the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
    - In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (i.e., changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

11.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are 1 year responsible for providing information on financial interests during the study and for after completion of the study.

11.1.3 Informed Consent Process

For the ICF and the optional future use of sample ICF, the following applies:

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study, in language and terms they are able to understand.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IIEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed and dated ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

11.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR.

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party. To comply with the applicable rules on the protection of personal data, specifically regarding the implementation of the organizational and technical arrangements aiming to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and processed personal data, the Sponsor has implemented and maintains the following measures:

- restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel and approved visitors;
- ensuring appropriate and restricted user access relevant to the function and type of activity performed in relation to the clinical trial; implementing the pseudonymisation and encryption of personal data, as appropriate;
- implementing the ability to ensure the ongoing confidentiality, integrity, availability and resilience of processing systems and services;
- implementing network, application, database security by means of firewalls and antivirus/anti-malware; ensuring detection of malware purposed for unauthorized deletion, blocking, copying of information, disabling security measures and response to such attacks;
- means to restore the availability and access to personal information in a timely manner in the event of a physical or technical incident;
- logging of security events/incidents in information systems;
- implementing procedures that cover reporting, analysis, monitoring and resolution of security incidents;
- ensuring that information systems, computers and software involved in the performance of the services provided in the Study are backed up;
- a process for regularly testing, assessing and evaluating the effectiveness of technical and organisational measures for ensuring the security of the processing;
- implementing procedures to capture within reasonable time-manner any personal data breach occurred; Indeed, the Sponsor has put in place a functional process of reporting of any data breach occurring at Sponsor's or its sub-contractor's facilities and premises. In case of the occurrence of any data breach, Sponsor will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery etc… Any data breach presenting risks to the rights and freedoms of data

subjects will be reported to the relevant supervisory data protection authority within 72 hours of Sponsor becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, data subjects will be informed by the Sponsor (via clinical Study site).
- implementing procedures and practices for securing destruction of paper documents containing personal data;
- implementing business continuity procedures ensuring that the Sponsor can continue to provide services through operational interruption
- All locations, personnel and information systems that are used to perform services for the Study will be covered;

- Participant data are intended to be used for the whole drug development program from collection to reimbursement.

11.1.5 Data and Safety Monitoring Board

A DSMB will be charged with monitoring the safety of participants in this study. It will also be responsible for providing recommendations for protecting the safety and ensuring the welfare of these participants to the Sponsor during the study. Two independent physicians, one rheumatologist and one endocrinologist will be part of this board.

The members of the DSMB must not be involved with the study in any other way (e.g., they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DSMB responsibilities and the data review processes are fully described in the DSMB charter.

In the above capacities, the DSMB is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DSMB in terms of study continuation with or without alterations or of potential study termination.

11.1.6 Data quality assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the electronic case report form (eCRF).
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. The Sponsor assumes accountability for actions delegated to other individuals (e.g Contract Research Organizations).
- Study monitors will perform ongoing source data verification (SDV) to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

11.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study reference manual.
- If no monitoring visit can take place on site (due to the pandemic status) and where permitted, a remote Data Source Verification (SDV) can be done.

11.1.8 Study and site start and closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

- Note: in case of investigational site closure or complete regional or national lock-down due to a local epidemic or international pandemic, the study may be suspended regionally or nationally at the affected sites. Every effort will be made to continue the follow-up of already recruited participants as close to the SoE as possible.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
    - Information on the product leading to doubt regarding the benefit/risk ratio,
    - Discontinuation of further study intervention development.
- For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines,
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator,
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs, the regulatory authorities, and any Contract Research Organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.2 Appendix 2: Clinical safety laboratory tests

The tests detailed in Table 1 will be performed by local laboratories

Additionally, if laboratory results not specifically required by the study protocol are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

The investigator (or medically qualified designee) must document their review of each laboratory safety report (e.g., hematology, chemistry, pregnancy).

Table 1 - Protocol-required laboratory assessments

Laboratory assessments	**Parameters**
Serology	• HIV • HbsAg • Hepatitis C Ab
Hematology	• Red blood cell (RBC) count • Hemoglobin

	• Hematocrit • Platelet count • White blood cell (WBC) count with differential: neutrophils, lymphocytes, monocytes, eosinophils and basophils
Clinical chemistry	• Creatinine (including glomerular filtration rate calculation); • Serum electrolytes: potassium, chloride, sodium, calcium; • Liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT); • Amylasemia • Glycemia
Urinalysis Pregnancy test	• β-human chorionic gonadotropin (HCG) for women of childbearing potential (only at screening for WOCBP)
Other test	• Rapid Antigen test for SARS-CoV-2 (if required by standard practice of site)
Exploratory Research	• Blood proteomics • Urine proteomics

Table 2 Approximate Whole Blood Volume (mL)

Study day	Screening	D1/D2	D8
Hematology	4	0	4
Chemistry	4	0	4
Glycemia	2	14	2
Serology	7	0	0
PK samples	0	35	0
Biomarkers	0	15	5
Total per visit	17	64	15
Total per participant			**96 mL**

On D1/D2 (as per Flowcharts in sections 1.2.1 & 1.2.2):

- PK samples: 7 X 3 mL + 7 X 2 mL (discarded)
- Glycemia: 9 X 2 mL
- Biomarkers: 4 X 5 mL

11.3 Appendix 3: Adverse events Definitions, Recording and Reporting

11.3.1 Definition of AE

AE definition (as per International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice (GCP) Guidelines definition):

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen in severity and/or frequency from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

Events NOT meeting the AE definition

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

11.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one of the following conditions:

a. Results in death.

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.)

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Congenital anomaly or birth defect in the offspring of a study participant.

f. Other important medical events.

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediate life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

11.3.3 Definition of SUSAR

A Suspected Unexpected serious Adverse Reaction (SUSAR) is a serious adverse reaction for which the nature and severity is not consistent with the information set out in the reference Safety Information (see IB).

11.3.4 Recording and follow-up of AE and/or SAE

AE and SAE recording

When an AE/SAE occurs, either spontaneously revealed by the patient or observed by the Investigator, and whether believed by the Investigator to be related or unrelated to the study drug, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The Investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE eCRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- As far as possible, each AE/SAE is described by: duration (start and end dates), event verbatim, solicited/unsolicited, frequency (relationship to the study treatment), intensity grade, seriousness, action taken and outcome.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) by recording the grade according to the Table for Grading the Severity of Adult and Pediatric Adverse Events (NIH DAIDS version 2.1, 2017). Any AE which changes DAIDS grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

- Grade 1 Mild event: Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
- Grade 2 Moderate event: Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
- Grade 3 Severe event: Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
- Grade 4 Potentially life-threatening event: Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.
- Grade 5 Death: Deaths related to an AE.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

The relationship of each AE to study intervention will be assessed using the following categories:

- Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
- Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

Category	Criteria	Final reporting of relationship to study drug (interpretation used for regulatory reporting purpose)
Definitely (must have all the mentioned criteria)	• Follows a reasonable temporal sequence from administration of the drug • Cannot be reasonably explained by the known characteristics of the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient • Disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if re-challenge occurs) • Follows a known pattern of response to the drug	Related
Probable (must have the first three)	• Follows a reasonable temporal sequence from administration of the drug • Cannot be reasonably explained by the known characteristics of the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient • Disappears or decreases on cessation or reduction in dose • Follows a known patter of response to the drug • Reappears on re-challenge	
Possible (must have the first two)	• Follows a reasonable temporal sequence from administration of the drug • May have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient • Follows a known pattern of response to the suspected drug	
Unlikely (must have the first two)	• Does not follow a reasonable temporal sequence from administration of the drug • May readily have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient • Does not reappear or worsen when the drug is re-administered	Not related
Unrelated	• Is clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) • Do not meet the criteria for drug relationship listed under Unlikely, Possible, Probable or Definitely	

Assessment of AE Outcome

The investigator will assess the outcome of all unsolicited AEs (including SAEs) recorded during the study, as:

- Resolved
- Resolving
- Not resolved
- Resolved with sequelae
- Fatal (for SAEs only)

Follow-up of AE and SAE

- If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and submit it to the monitor/Pharmacovigilance immediately within 24 hours of receipt.
- All SAEs will be followed up until satisfactory resolution or until the Investigator deems the event to be chronic or the patient to be stable.

11.3.5 Reporting of SAEs, and Other Reportable Safety Events to the Medical monitor

- Any event considered to be serious should be recorded on the SAE reporting form. All SAEs, regardless of relationship, and pregnancies must be reported via eCRF within 24 hours of the Investigator becoming aware of the event. Other supporting documentation may be requested by the Sponsor and should be provided as soon as possible.
- The primary mechanism for reporting an SAE to the medical monitor and pharmacovigilance will be the electronic data collection tool.
    - If the electronic system is unavailable, then the site will use the paper SAE form in order to report the event within 24 hours.
    - The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Medical Monitor by phone. Contacts for SAE reporting can be found in the Investigator site file.
- Following notification from the Investigator, Sponsor's Monitor (or designee) will report events that are serious, unexpected and are considered to be causally related to the study products (SUSARs) to the competent authorities (CA) within the required timelines: fatal and life-threatening events within 7 calendar days and all other SAEs within 15 calendar days.
- The Investigator (or designee) will be responsible for reporting the SUSAR to ethics committees.

11.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

11.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.
Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following
    - Documented hysterectomy,
    - Documented bilateral salpingectomy,
    - Documented bilateral oophorectomy,

For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>ULN as defined by central laboratory readout) is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study randomization.

11.4.2 Contraceptive guidance

Mandatory use of contraception must cover the study drug administration period plus 5 times the half-life of liraglutide (half-life around 13 hours) i.e. 5 days (in order to cover extreme values).
Contraceptives allowed during the study include[a]:

Highly Effective Methods[b] That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Vasectomized partner

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. (Spermatogenesis cycle is approximately 90 days.)

Highly Effective Methods[b] That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- oral
- intravaginal
- transdermal
- injectable

- Progestogen-only hormone contraception associated with inhibition of ovulation
  - oral
  - injectable
- Sexual abstinence

(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal [coitus interruptus]), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

11.4.3 Collection of pregnancy information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive the investigational medicinal product.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy.
- Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- The Investigator should assess if there was any relationship between the outcome and the exposure to study drug.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy (i.e., healthy birth, spontaneous or voluntary abortion, presence or absence of any birth defects, congenital abnormality, or complications for the mother and/or newborn). The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.
- The Investigator should assess if there was any relationship between the outcome and the exposure to study drug.

11.5 Appendix 5: Exploratory tests

Exploratory tests will be described in a separate document.

11.6 Appendix 6: Abbreviations

ADAMTS: a disintegrin and metalloproteinase with thrombospondin motifs
AE: adverse event
AESI: adverse event of special interest
ALT: alanine aminotransferase
AST: aspartate aminotransferase
ATC: anatomical therapeutic chemical
AUC: area under the curve
CA: competent authority
CFR: Code of Federal Regulations
CIOMS: Council for International Organizations of Medical Sciences
CrCl: creatinine clearance
Cmax: maximum concentration

CNS: central nervous system
CONSORT: consolidated standards of reporting trials
COVID-19: coronavirus infectious disease due to SARS-CoV-2
CREB: cAMP response element binding protein
CRF: case report form
CSR: clinical study report
CTC AE: common terminology for adverse events
DDD: defined daily dose
DMM: destabilization of the medial meniscus
DMOAD; disease-modifying osteoarthritis drug
DMP: Data management plan
DSMB: data and safety monitoring board
EC: ethics committee
ECG: electrocardiogram
eCRF: electronic case report form
EMA: european medical agency
EoS: End of Study
EoT: End of Treatment
FDA: food and drug administration
FIM: first-in-man
GCP: Good Clinical Practice
GDPR: General Data Protection Regulation
GLP: good laboratory practice
GLP-1(R): glucagon-like peptide 1 (receptor)
HBsAg: hepatitis B surface antigen
HCG: human chorionic gonadotropin
HCV-Ab: hepatitis C virus antibody
HED: human equivalent dose
HIV: human immunodeficiency virus
hMSC: human mesenchymal stem cells
HPLC: high performance liquid chromatography
HRT: hormonal replacement therapy
IB: investigator's brochure
ICF: informed consent form
ICH: international council for harmonisation
IA: intra-articular
IC50: half maximal inhibitory concentration
IEC: Independent Ethics Committee
Ig: immunoglobulin
IL-6: interleukin 6
IMP: investigational medicinal product
IV: intravenous(ly)
KL: Kellgren and Lawrence classification

MABEL: minimum anticipated biological effect level
MIA: mono-iodo-acetate
MedDRA: medical dictionary for regulatory activities
MMP: matrix metalloproteinase
NO: nitric oxyde
NOAEL: no observed adverse effect level
NRS: numerical rating scale
NSAID: nonsteroidal anti-inflammatory drug
OA: osteoarthritis
OARSI: osteoarthritis research society international
PCSA: potentially clinically significant abnormality
PD: pharmacodynamic(s)
PGE2: prostaglandin 2
PK: pharmacokinetic(s)
PKA: protein kinase A
SAE: serious adverse event
SAP: statistical analysis plan
SC: subcutaneous(ly)
SD: standard deviation
Sox9: SRY-Box Transcription Factor 9
SUSAR: suspected unexpected serious adverse reaction
t1/2: elimination half-life
TEAE: treatment-emergent adverse event
Tmax: time to maximum concentration
ULN: upper limit of normal
WOCBP: women of childbearing potential

11.7 Appendix 7: References

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