CLINICAL TRIAL PROTOCOL

Protocol N° JP-2266-101-FIH / OP109219.JEI
EudraCT N° 2020-000239-39

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A Dose-randomized, Double-blind, Placebo-controlled, Single- and Multiple-dose, Dose-escalation, Phase I Clinical Trial to Investigate the Safety, Tolerability, and Pharmacokinetic and Pharmacodynamic Characteristics of JP-2266 after Oral Administration in Healthy Male Caucasian Subjects

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NAMES AND ADRESSES OF PARTICIPANTS

Sponsor:	**JEIL Pharmaceutical Co., Ltd.** 343, Sapyeong-daero, Seocho-gu, Seoul, Republic of Korea Tel.: + 82 2 549 7451 – Fax: + 82 2 542 7451
Represented by:	**Suk-Je Sung** 343, Sapyeong-daero, Seocho-gu, Seoul, Republic of Korea Tel.: + 82 2 549 7451 – Fax: +82 2 542 7451
Represented in EU by:	**EUROFINS OPTIMED LYON** 1, rue des Essarts - 38610 Gières - France Tel: + 33 438 372 740 - Fax: + 33 438 372 741
Principal investigator:	**Yves DONAZZOLO, MD, MSc,** **EUROFINS OPTIMED** **Clinical Pharmacology Unit** 1, rue des Essarts - 38610 Gières - FRANCE Tel: + 33 438 372 747 - Fax: + 33 438 372 741
Investigators:	**Yves DONAZZOLO, MD, MSc,** **EUROFINS OPTIMED** Tel: + 33 438 372 747 - Fax: + 33 438 372 741 **Mathilde LATREILLE, MD** **EUROFINS OPTIMED** Tel: +33 438 374 750 - Fax: +33 438 372 741 **Valentina HODAJ, MD** **EUROFINS OPTIMED** Tel: +33 438 374 752 - Fax: +33 438 372 741
Sponsor's Project manager:	**Hyejin Kim JEIL Pharmaceutical Co., Ltd.** Tel: + 82 2 549 7451 - Fax: + 82 2 542 7451
EUROFINS-Optimed Project manager:	**Sophie CACACE** **EUROFINS OPTIMED** **Clinical Pharmacology Unit** 1, rue des Essarts - 38610 Gières - FRANCE Tel: + 33 438 372 567 - Fax: + 33 438 372 741
Monitor:	**Eurofins Optimed** Tel: + 33 438 372 740 - Fax: + 33 438 372 741
Biological assays:	**Bernard CADOUX, PharmD** Groupe Oriade Noviale 83 Avenue Gabriel Péri 38400 St Martin d'Hères - FRANCE

	Tel: + 33 476 515 307 - Fax: + 33 476515 307
Pharmacokinetics assays:	**EUROFINS – ADME BIOANALYSES** Tel: + 33 466 731 773
Pharmacodynamics assays:	**Bernard CADOUX, PharmD** Groupe Oriade Noviale 83 Avenue Gabriel Péri 38400 St Martin d'Hères - FRANCE Tel: + 33 476 515 307 - Fax: + 33 476515 307
Pharmacovigilance	**AIXIAL** Tel: + 33 146 996 812
Drug distribution center:	**JEIL Pharmaceutical Co., Ltd.** Tel: + 82 31 332 4457
Data Manager:	**EUROFINS OPTIMED** Tel: + 33 438 372 749 - Fax: + 33 438 372 741
Statistician:	**EUROFINS OPTIMED** Tel: + 33 438 372 749 - Fax: + 33 438 372 741

CLINICAL STUDY PROTOCOL AGREEMENT

Protocol N°: JP-2266-101-FIH / OP109219.JEI

Title: A Dose-randomized, Double-blind, Placebo-controlled, Single- and Multiple-dose, Dose-escalation, Phase I Clinical Trial to Investigate the Safety, Tolerability, and Pharmacokinetic and Pharmacodynamic Characteristics of JP-2266 after Oral Administration in Healthy Male Caucasian Subjects

The sponsor and the investigator agree to conduct the study in compliance with the clinical study protocol (and amendments), International Conference on Harmonization (ICH) guidelines for current Good Clinical Practice (cGCP) and applicable regulatory requirements.

Sponsor:

JEIL Pharmaceutical Co., Ltd.
343, Sapyeong-daero, Seocho-gu, Seoul, Republic of Korea

Represented by:

Suk-Je Sung
JEIL Pharmaceutical Co., Ltd.
343, Sapyeong-daero, Seocho-gu, Seoul, Republic of Korea
Tel: +82 2 549 7451 – Fax: +82 2 542 7451

Date: (dd-mmm-yyyy)

Signature :

Principal Investigator:

Yves DONAZZOLO, MD, MSc
EUROFINS OPTIMED
1, rue des Essarts
38610 Gières – France

Date: (dd-mmm-yyyy)

Signature :

SYNOPSIS

Title:	A Dose-randomized, Double-blind, Placebo-controlled, Single- and Multiple-dose, Dose-escalation, Phase I Clinical Trial to Investigate the Safety, Tolerability, and Pharmacokinetic and Pharmacodynamic Characteristics of JP-2266 after Oral Administration in Healthy Male Caucasian Subjects
Study product :	JP-2266
Protocol No.:	JP-2266-101-FIH / OP109219.JEI
Sponsor:	**JEIL Pharmaceutical Co., Ltd.** 343, Sapyeong-daero, Seocho-gu, Seoul, Republic of Korea
Participating Country :	France
Number of study centers :	Single center study
Principal Investigator:	Yves DONAZZOLO, M.D., M.Sc. EUROFINS OPTIMED, GIERES – France
Study Design:	The study will be divided in 2 successive parts : - Study Part A will be a single ascending dose study in healthy male Caucasian volunteers to assess the safety, the tolerability, the pharmacokinetics and the pharmacodynamics of JP-2266 with nested one way cross-over for food effect. All subjects will receive a placebo administration on day-1 in order to determine the placebo effects of the inert material intake (performed in -blind condition) followed by a single administration period of either JP-2266 or placebo on Day 1. Five JP-2266 doses will be studied. One cohort of the SAD study part will be used to assess the safety, the tolerability, the pharmacokinetics and the pharmacodynamics of JP-2266 in fast or fed conditions. Each subject will participate in one treatment period only (fasted), with the exception of subjects of the food effect group who will participate in two treatment periods (fasted / fed), with a washout phase of at least 14 days between the two treatment periods. - Study Part B will be a multiple ascending dose study in healthy male Caucasian volunteers to assess the safety, the tolerability, the pharmacokinetics parameters and the pharmacodynamics of JP-2266. In order to determine the placebo effects of the inert material intake each subject will first receive on Day -1 a JP-2266 placebo administration (performed in blind condition for the subject) followed by a 15 day repeated administration period of either JP-2266 or placebo (from Day 1 to Day 15 included). Four JP-2266 dose levels will be studied. To minimize the risk, the administration of the investigational product in each dose group of the study will be done sequentially within each cohort (Part A and B). In each dose level, the two first subjects will be randomized as one verum and one placebo. The decision to proceed with the administration of the 6 (Part A) or 8 (Part B) remaining subjects will be taken by the investigator on the basis of clinical and biological safety data after 48 hours for Part A and 3 days for Part B. Before each dose escalation, the Study Safety Committee (SSC), consisting of an investigator, a clinical pharmacologist, sponsor representatives and a person responsible of pharmacokinetics analysis, will evaluate the safety and PK data of the cohort(s) already performed and will give an approval for the next dose.
Study Objectives:	**<u>Part A – Single Ascending Dose</u>** <u>Primary Objective</u>: To evaluate the safety and tolerability of JP-2266 after single oral administration at 5 different doses in healthy male Caucasian subjects.

	Secondary Objectives: To evaluate the pharmacokinetics parameters of JP-2266 after single oral administration at 5 different doses in healthy male Caucasian subjects. To evaluate the pharmacodynamics parameters of JP-2266 after single oral administration at 5 different doses in healthy male Caucasian subjects. **Part A – Food Effect cohort** Primary Objective: To evaluate the impact of food intake on pharmacokinetics after an oral administration of JP-2266 in healthy male Caucasian subjects in fast or fed conditions. Secondary Objectives: To evaluate the safety and tolerability of JP-2266 after single oral administration in fast or fed conditions in healthy male Caucasian subjects. To evaluate the impact of food on pharmacodynamics after an oral administration of JP-2266 in healthy male Caucasian subjects in fast or fed conditions. **Part B – Multiple Ascending Dose** Primary Objective: To evaluate the safety and tolerability of JP-2266 after multiple oral administration at 4 different doses in healthy male Caucasian subjects. Secondary Objectives: To evaluate the pharmacokinetics parameters of JP-2266 after multiple oral administration at 4 different doses in healthy male Caucasian subjects. To evaluate the pharmacodynamics parameters of JP-2266 after multiple oral administration at 4 different doses in healthy male Caucasian subjects. **Exploratory Objectives (part A, B)** Identifying JP-2266 metabolites in human blood and urine after JP-2266 oral administration. Identifying genes involved in JP-2266 absorption and metabolism.
Investigational Treatment:	Name of the compound: JP-2266 Pharmaceutical form: Oral capsule (1mg, 5 mg, 40 mg) Dose per administration: SAD – Part A: 5, 10, 20, 40 and 80 mg. Food Effect – Part A: 20 mg. MAD – Part B: 2, 5, 10 and 20 mg. Number of capsules: From 1 to 4 capsules Timing for administration: Oral administrations with 200mL of tap water, in sitting position and in fasting condition for part B and in fast or fed condition for Part A (30 minutes after the beginning of the High Fat Breakfast). SAD – Part A: Single administration on Day 1 at T0h around 8 am. Food Effect – Part A: Single administration on Day 1 at T0h around 8 am of each period MAD – Part B: Repeated administrations from D1 to D15 at T0h around 8 am. Name of the compound: Placebo Pharmaceutical form: Oral capsule (1mg, 5 mg, 40 mg) Dose per administration: SAD – Part A: 5, 10, 20, 40 and 80 mg. Food Effect – Part A: 20 mg. MAD – Part B: 2, 5, 10 and 20 mg.

	Number of capsules: Timing for administration:	From 1 to 4 capsules Oral administrations will take place around 8 am with a 200mL of tap water, in sitting position and in fasting condition for parts A and B. SAD – Part A: Single administration on Day 1 at T0h at around 8 am. Food Effect – Part A: Single administration on Day 1 at T0h around 8 am of each treatment period. MAD – Part B: Repeated administrations from D1 to D15 at T0h around 8 am. A single administration on D-1 morning will be also performed of the same number of capsules than in D1 morning for each subject and for all study parts (Part A for each period, Part B).
Subjects:	Subjects will be healthy male Caucasian volunteers aged between 18 and 50 years. Up to eighty subjects are planned to be enrolled. Part A/ SAD: 5 groups of 8 subjects (6 active / 2 placebo), for a total of 40 subjects Part A/ Food effect: will be tested in period 2 for 1 group of the SAD part (dose 20mg) of 8 subjects (6 active / 2 placebo). Part B/MAD: 4 groups of 10 subjects (8 active / 2 placebo), for a total of 40 subjects.	
Main Evaluation Criteria:	**<u>Part A – Single Ascending Dose</u>** <u>Primary Evaluation Criteria</u>: Assessment of systemic tolerability and safety: - Adverse Events - Vital signs - Physical examination - ECG - Biological analysis: o Blood : Hematology, Coagulation, Biochemistry o Urine : urinalysis, urine electrolyte test <u>Secondary Evaluation Criteria</u>: Pharmacokinetic assessments of JP-2266: In Plasma: C_{max}, C_{min}, t_{max}, AUC_{0-24h}, AUC_{last}, AUC_{inf}, $\%AUC_{extra}$, $t_{1/2}$, Kel, Vd/F, Cl/F In Urine: CL_r, Ae_{last}, Ae_{0-24h}, fe%. Pharmacodynamics assessments of JP-2266 effect: In Plasma: Plasma glucose (AUEC, E_{max}, ΔE_{max}), In Urine: urine glucose excretion (Ae, cumulative at each time point). **<u>Part A – Food Effect Cohort</u>** <u>Primary Evaluation Criteria:</u> Pharmacokinetic assessments of JP-2266: In Plasma: C_{max}, t_{max}, C_{min}, AUC_{0-24h}, AUC_{last}, AUCinf, $\%AUC_{extra}$, $t_{1/2}$, Kel, Vd/F, Cl/F In Urine: CLr, Ae_{last}, Ae_{0-24h}, fe%. The analysis of C_{max}, AUC_{last} and AUC_{inf} will be performed on the log-transformed values using a mixed model analysis of variance (ANOVA) to determine the geometric mean ratio between fed and fasted conditions and its 90% Confidence Interval (CI).	

	Secondary Evaluation Criteria: Assessment of systemic tolerability and safety: - Adverse Events - Vital signs - Physical examination - ECG - Biological analysis: o Blood : Hematology, Coagulation, Biochemistry o Urine : urinalysis, urine electrolyte test Pharmacodynamics assessments of JP-2266 effect: In Plasma: Plasma glucose (AUEC, E_{max}, ΔE_{max}), In Urine: urine glucose excretion (Ae, cumulative at each time point). **Part B – Multiple Ascending Dose** Primary Evaluation Criteria: Assessment of systemic tolerability and safety: - Adverse Events - Vital signs - Physical examination - ECG - Biological analysis: o Blood: Hematology, Coagulation, Biochemistry, phosphorus metabolism (Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D). o Urine: urinalysis, urine electrolyte test, β2-microglobulin, 24-hour urine creatinine level. Secondary Evaluation Criteria: Pharmacokinetic assessments of JP-2266 at Day 1 and at Steady State: In Plasma: C_{max}, C_{min}, t_{max}, AUC_{0-24h}, AUC_{last}, AUC_{inf}, $\%AUC_{extra}$, $t_{1/2}$, Kel, Vd/F, Cl/F In Urine: CL_r, Ae_{last}, Ae_{0-24h}, fe%. Pharmacodynamics assessments of JP-2266 effect: In Plasma: Oral Glucose Tolerance Test (OGTT) (AUEC, E_{max}, ΔE_{max}), Plasma glucose (AUEC, E_{max}, ΔE_{max}), Insulin (AUEC, E_{max}), Body Weight, HbA1c (change from baseline), In Urine: urine glucose excretion (Ae, cumulative at each time point). **Exploratory Criteria (part A, B)** - To determine factors that may affect the safety, pharmacokinetics, and pharmacodynamics, an exploratory analysis of drug metabolites can be performed using samples collected for the pharmacokinetic evaluation of investigational products. If relevant drug metabolites are detected, the correlation between pharmacokinetic parameters, including metabolite-to-parent drug exposure ratios, and pharmacokinetics/pharmacodynamics can be evaluated. - If inter-individual pharmacokinetics results differences are observed, genotyping analysis could be performed to assess the correlation between genetic polymorphism and pharmacokinetic parameters.
Main Inclusion Criteria:	For eligibility into the trial, subjects must meet all the following inclusion criteria : 1- Healthy male Caucasian subject aged 18 to 50 years inclusive; 2- Non-smoker subject (smoking cessation for at least 3 months before the first study treatment administration); 3- Body Mass Index (BMI) between 18 and 27 kg/m^2 inclusive and body weight

	≥ 50 kg at screening; 4- Considered as healthy after a comprehensive clinical assessment (detailed medical history and complete physical examination); 5- Agree to use an adequate contraceptive method from the time of informed consent signature up to 1 month after last IMP administration. Furthermore, it is recommended that subjects with partners of childbearing potential use a highly effective method of birth control defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion; 6- Normal Blood Pressure (BP) and Heart Rate (HR) at the screening visit after 10 minutes in supine position: • 95 mmHg ≤ Systolic Blood Pressure (SBP) ≤ 140 mmHg, • 50 mmHg ≤ Diastolic Blood Pressure (DBP) ≤ 90 mmHg, • 45 bpm ≤ HR ≤ 90 bpm, • Or considered NCS by investigators; 7- Normal ECG recording on a 12-lead ECG at the screening visit: • 120 ms < PR < 210 ms, • QRS < 120 ms, • QTcf≤ 430 ms, • No sign of any relevant trouble of sinusal automatism, • Or considered NCS by investigators; 8- Laboratory parameters within the normal range of the laboratory (hematological, blood chemistry tests, urinalysis). Individual values out of the normal range can be accepted if judged non-clinically significant by the Investigator , except for AST, ALT and creatinine which must be within the normal ranges; 9- Normal dietary habits; 10- Signing a written informed consent prior to selection; 11- Covered by Health Insurance System and / or in compliance with the recommendations of National Law in force relating to biomedical research.
Main Non-Inclusion Criteria:	Subjects meeting any of the following criteria will not be included into the trial : 1- Any history (including family history) or presence of cardiovascular, pulmonary, gastro-intestinal, hepatic, renal, metabolic, haematological, neurologic, psychiatric, systemic or infectious disease; 2- Any history of clinically significant surgeries; 3- Frequent headaches (> twice a month) and / or migraine, recurrent nausea and / or vomiting; 4- Subject with clinically significant infectious and inflammatory findings at screening; 5- Subject with clinically significant atopic syndrome; **6-** Subject with clinically significant gastrointestinal symptoms at screening; 7- Symptomatic hypotension whatever the decrease of blood pressure or asymptomatic postural hypotension defined by a decrease in SBP or DBP equal to or greater than 20 mmHg within two minutes when changing from the supine to the standing position; 8- Blood donation or transfusions (including in the frame of a clinical trial) within 3 months before administration; 9- General anaesthesia within 3 months before administration;

	10- Presence or history of drug hypersensitivity, or allergic disease diagnosed and treated by a physician. A specific attention should be given to SGLT-2 inhibitors, medications containing similar ingredients; 11- Inability to abstain from intensive muscular effort; 12- No possibility of contact in case of emergency; 13- Subject taking any prescribed drug or herbal medicine within 2 weeks prior to the first scheduled drug administration, or taking any OTC health functional food or vitamin within one week (provided that other conditions are appropriate under the investigator's opinion may participate in the clinical trial) or those in whom any OTC drug, functional food, or vitamin use is expected; 14- History or presence of alcohol abuse (alcohol consumption >40 grams / day); 15- Excessive consumption of beverages with xanthine bases (> 4 cups or glasses / day); 16- The subject is not willing or able to refrain from consuming caffeine-containing foods (coffee, tea (black tea and green tea, etc.), carbonated drinks, coffee milk, nourishment drink, etc) during the period from 24 hours prior to the first hospitalization and until the end of study visit; 17- Subject with the following screening test results: • AST or ALT levels out of laboratory standard normal ranges, • Plasma creatinine out of the laboratory standard normal ranges • Repeated demonstration of a QTc interval > 450 ms, • Fasting plasma glucose levels > 6.1 mmol/l or < 3.9 mmol/l, • Serum HbA1c levels > 6.0 % 18- Positive Hepatitis B surface (HBs) antigen or anti Hepatitis C Virus (HCV) antibody, or positive results for Human Immunodeficiency Virus (HIV) 1 or 2 tests at screening; 19- History or positive results of screening for drugs of abuse; 20- Subject who, in the judgment of the Investigator, is likely to be non-compliant or uncooperative during the study, or unable to cooperate because of a language problem, poor mental development; 21- Use of an investigational drug within 3 months (or 90 days) prior to Day1; 22- Administrative or legal supervision; 23- Subject who would receive more than 4500 euros as indemnities for his participation in biomedical research within the 12 last months, including the indemnities for the present study.
Study Duration:	**<u>Part A – Single Ascending Dose</u>** Screening within 21 days prior to the administration; Hospitalization for 7 days (D-2 afternoon to D5 morning); End of Study Visit at D10 (+/- 2 days); Expected duration: approximately 5 weeks for each participating subject. **<u>Food Effect Cohort (Part A)</u>** For one cohort of part A, additional hospitalization for 1 periods of 7 days (D-2 afternoon to D5 morning); with a 14 days washout between periods End of Study Visit at P2D10 (+/- 2 days); Expected duration: approximately 7 weeks for each participating subject (2 periods included). **<u>Part B – Multiple Ascending Dose</u>** Screening within 21 days prior to the first administration; Hospitalization from Day-3 afternoon to D19 morning;

	End of Study Visit at D24 (+/- 2 days); Expected duration: approximately 7 weeks for each participating subject.
Statistics :	**Data analysis/ descriptive and inferential statistical Analysis** 1) Safety/ tolerability - For safety/ tolerability assessment, description of the abnormalities observed in safety evaluation items such as adverse events, vital signs, clinical laboratory results. If appropriate, comparison between cohorts can be performed. - Medical history and adverse events are described in terms of MedDRA (version 22.1 or later). 2) Pharmacokinetic - For each part of the study, pharmacokinetic parameters of JP-2266 will be summarized by mean, standard deviation, coefficient of variation, geometric mean, median, min an,d max for each cohort or group. Descriptive statistics on pharmacokinetic parameters will be calculated with WinNonlin (version 8.1 or latest) - The relationship between C_{max}, AUC and dose will be evaluated by the regression analysis to confirm the pharmacokinetic linearity with increasing dose, and AUC and C_{max}, which is adjusted for dose, will be compared between the dose groups using a parametric or non parametric statistical test. Other parameters such as T_{max}, $t_{1/2}$, and Clr could be compared between the dose groups through a proper method. 3) Pharmacodynamics - For pharmacodynamic parameters, the changes between measured values and baseline values shall be analysed by descriptive statistics, when necessary; comparison among dose groups shall be made using either parametric or non-parametric statistical tests, according to the distribution.

STUDY FLOW CHARTS

Table 1-1: STUDY FLOW CHART for PART A – Single Ascending Dose

Visit/Period	Screening	Inclusion		Treatment period					End of study visit
Day	**D-21 to D-3**	**D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D10 (+/- 2 days)**
Informed consent	X								
Demographics and baseline data	X								
Eligibility criteria	X		X[1]						
Previous Medical / Surgical History	X								
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Physical examinations	X		X	X	X			X	X
Body weight	X								X
Body height	X								
Haematology	X		X[2]	X	X			X	X
Coagulation	X		X[2]	X	X			X	X
Biochemistry	X		X[2]	X	X			X	X
Urinalysis	X		X[2]	X	X			X	X
Urine electrolyte test	X			X	X			X	X
Serology	X								
Urine drug screen including urinary cotinine	X	X							
Alcohol breath test	X	X							
Vital Signs	X[3]		X	X	X	X	X	X	X[3]
12-lead ECG recording	X		X	X	X			X	X
Admission		X							
Discharge								X	
Randomization			X						
Study Drug / Placebo Administration			X[4]	X					
Blood sample for Pharmacokinetics				X	X	X	X		
Blood sample for Pharmacodynamic				X	X	X	X		
Urine collection for Pharmacokinetics				X	X	X			
Urine collection for Pharmacodynamic			X	X	X	X	X		
Blood sample for exploratory genomic				X					
HbA1c measurement	X								
AE collection[5]	←								→

[1] Confirmation of the Inclusion/exclusion criteria prior to randomization number assignment and prior to first study product administration;
[2] At Pre-dose;
[3] Including body temperature;
[4] Placebo administration in blind condition for the subject;
[5] All AEs will be reported.

Table 1-2: DETAILED FLOW CHART for PART A – Single Ascending Dose

Visit/Period	**Inclusion**			**Treatment period**																				**EOS**
Day	**D-2**	**D-1**		**D1**															**D2**		**D3**	**D4**	**D5**	**D10**
Theoretical time (h)		**Predose**		**Predose**	**T0**	**T0h15**	**T0h30**	**T0h45**	**T1h**	**T1h30**	**T2h**	**T2h30**	**T3h**	**T3h30**	**T4h**	**T6h**	**T8h**	**T10h**	**T12h**	**T24h**	**T36h**	**T48h**	**T72h**	**T96h**	
Eligibility criteria		X																						
Prior/concomitant medications	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►
Physical examinations		X		X																	X			X	X
Body weight																									X
Haematology		X		X																X				X	X
Coagulation		X		X																X				X	X
Biochemistry		X		X																X				X	X
Urinalysis		X		X																X				X	X
Urine electrolyte tests				X																X				X	X
Urine drug screen including urinary cotinine	X																								
Alcohol breath test	X																								
Vital signs		X		X					X		X				X					X		X	X	X	X[1]
12-lead ECG recording		X									X				X					X				X	X
Admission	X																								
Discharge																								X	
Randomization		X																							
Study Drug / Placebo Administration			X[2]		X																				
Blood sample for Pharmacokinetics				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood sample for Pharmacodynamic				X			X		X	X	X		X		X	X	X		X	X		X	X		
Urine collection for Pharmacokinetics				X	◄	─	─	─	─	─	─	─	─	►	◄	─	►	◄	─	►	◄	─	►	◄	►		
Urine collection for Pharmacodynamic		◄	─	─	►	◄	─	─	─	─	─	─	─	►	◄	─	►	◄	─	►	◄	─	►	◄	►		
Blood sample for exploratory genomic				X																					
HbA1c measurement																									
AE collection	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►

[1] Including body temperature;

[2] Placebo administration in blind condition for the subject.

Table 2-1: STUDY FLOW CHART for Part A – Food Effect Cohort

Visit/Period	Screening	Period 1								Period 2							End of study visit
Day	D-21 to D-3	D-2	D-1	D1	D2	D3	D4	D5		D-2	D-1	D1	D2	D3	D4	D5	P2D10 (+/- 2 days)
Informed consent	X																
Demographics and baseline data	X																
Eligibility criteria	X		X[1]														
Previous Medical / Surgical History	X																
Prior/concomitant medications	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Physical examinations	X		X	X	X			X			X	X	X			X	X
Body weight	X																X
Body height	X																
Haematology	X		X[2]	X	X			X			X[2]	X	X			X	X
Coagulation	X		X[2]	X	X			X			X[2]	X	X			X	X
Biochemistry	X		X[2]	X	X			X			X[2]	X	X			X	X
Urinalysis	X		X[2]	X	X			X			X[2]	X	X			X	X
Urine electrolyte tests	X			X	X			X				X	X			X	X
Serology	X																
Urine drug screen including urinary cotinine	X	X								X							
Alcohol breath test	X	X								X							
Vital Signs	X[3]		X	X	X	X	X	X			X	X	X	X	X	X	X[3]
12-lead ECG recording	X		X	X	X			X			X	X	X			X	X
Admission		X								X							
Discharge								X								X	
Randomization			X														
Study Drug / Placebo Administration			X[4]	X							X[4]	X					
Blood sample for Pharmacokinetics				X	X	X	X					X	X	X	X		
Blood sample for Pharmacodynamic				X	X	X	X					X	X	X	X		
Urine collection for Pharmacokinetics				X	X	X						X	X	X			
Urine collection for Pharmacodynamic			X	X	X	X	X				X	X	X	X	X		
Blood sample for exploratory genomic				X													
HbA1c measurement	X																
AE collection	◄																►

Wash-Out period (at least 14 days between each administration)

[1] Confirmation of the Inclusion/exclusion criteria prior to randomization number assignment and prior to first study product administration;
[2] At Pre-dose;
[3] Including body temperature;
[4] Placebo administration in blind condition for the subject.

Table 2-2: DETAILED STUDY FLOW CHART for Part A – Food Effect Cohort

Visit/Period	**Inclusion**			**Treatment period**																				**Period 2**
Day	**D-2**	**D-1**		**D1**																**D2**		**D3**	**D4**	**D5**	**EOS**
Theoretical time (h)		**Predose**	**T0**	**Predose**	**T0**	**T0h15**	**T0h30**	**T0h45**	**T1h**	**T1h30**	**T2h**	**T2h30**	**T3h**	**T3h30**	**T4h**	**T6h**	**T8h**	**T10h**	**T12h**	**T24h**	**T36h**	**T48h**	**T72h**	**T96h**	**D10 (+/-2 days)**
Eligibility criteria		X																							
Prior/concomitant medications	←																								→
Physical examinations		X		X																	X			X	X
Body weight																									X
Haematology		X		X																X				X	X
Coagulation		X		X																X				X	X
Biochemistry		X		X																X				X	X
Urinalysis		X		X																X				X	X
Urine electrolyte tests				X																X				X	X
Urine drug screen including urinary cotinine	X																								
Alcohol breath test	X																								
Vital signs		X		X					X		X				X					X		X	X	X	X[1]
12-lead ECG recording		X									X				X					X				X	X
Admission	X																								
Discharge																								X	
Randomization[2]		X																							
Study Drug / Placebo Administration			X[3]		X																				
Blood sample for Pharmacokinetics				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood sample for Pharmacodynamic				X			X		X	X	X		X		X	X	X		X	X		X	X		
Urine collection for Pharmacokinetics				X	←										→	←		→	↔	←		↔				
Urine collection for Pharmacodynamic		←		→	←										→	←		→	↔	←		↔	↔			
Blood sample for exploratory genomic[4]				X																					
HbA1c measurement																									
AE collection	←																								→

[1] Including body temperature;

[2] Only on P1D-1;
[3] Placebo administration in blind condition for the subject;
[4] Only on P1.

Table 3-1: STUDY FLOW CHART for Part B – Multiple Ascending Dose

Visit/Period	Screening	Hospitalization																					End of study visit
		Inclusion			Treatment period																		
Day	**D-21 to D-4**	**D-3**	**D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**	**D17**	**D18**	**D19**	**D24 (+/- 2 days)**
Informed consent	X																							
Demographics and baseline data	X																							
Eligibility criteria	X			X[1]																				
Previous Medical / Surgical History	X																							
Prior/concomitant medications	◄																							►
Physical examinations	X			X	X	X			X										X	X			X	X
Body weight	X			X																			X	X
Body height	X																							
Hematology	X			X	X	X			X					X			X		X	X			X	X
Coagulation	X			X	X	X			X					X			X		X	X			X	X
Biochemistry	X			X	X	X			X					X			X		X	X			X	X
Phosphorus metabolism[2]				X					X					X									X	
Urinalysis	X			X[3]	X	X			X		X[4]			X			X		X[3]	X			X	X
Urine electrolyte tests	X				X	X			X					X			X		X	X			X	X
Urine B2-microglobulin				X							X								X					X
Serology	X																							
Urine drug screen including urinary cotinine	X	X																						
Alcohol breath test	X	X																						
Vital Signs	X[5]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[5]
12-lead ECG recording	X			X	X	X			X					X					X	X			X	X
Admission		X																						
Discharge																							X	
Randomization				X																				
Study Drug / Placebo Administration				X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Blood sample for Pharmacokinetics					X	X	X	X			X			X			X		X	X	X	X		
Blood sample for Pharmacodynamics[7]				X	X	X	X	X			X			X			X		X	X	X	X		
HbA1c measurement	X			X																			X	
Oral Glucose Tolerance Test[8]			X															X						
Urine collection for Pharmacokinetics					X	X	X				X			X			X		X	X	X			
Urine collection for Pharmacodynamics				X	X	X	X	X			X			X			X		X	X	X	X		
Blood sample for exploratory genomic					X																			
AE collection	◄																							►

[1] Confirmation of the Inclusion/exclusion criteria prior to randomization number assignment and prior to first study product administration;
[2] Phosphorus metabolism: Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D;
[3] Including 24-hour urine creatinine level (T0-24h);
[4] Only 24-hour urine creatinine level (T0-24h);[5] Including body temperature;
[6] Placebo administration in blind condition for the subject;
[7] Plasma glucose measurement at predose then at T0h30, T1h, T1h30, T2h, T3h, T4h, T6h, T8h, T12h on D1, at pre-dose on D2, at pre-dose on D3, at pre-dose on D4, at pre-dose on D7, at pre-dose on D10, at pre-dose on D13,on D15 at predose and then at T0h30, T1h, T1h30, T2h, T3h, T4h, T6h, T8h, T12h administration, on D16 at T24h, on D17 at T48h and on D18 at 72h; Serum insulin measurement at predose then at T0h30, T1h, T1h30, T2h, T3h, T4h and T6h on D-1, D1 and D15 administration;
[8] Blood sampling for OGTT at predose then at T0h30, T1h, T1h30, T2h, T3h and T4h on D-2 and D14 (after oral glucose administration).

Table 3-2: DETAILED STUDY FLOW CHART for Part B – Multiple Ascending Dose (1/4)

Visit/Period	**Inclusion**																	
Day	**D-3**	**D-2**								**D-1**								
Theoritical time (h)		**Pre dose**	**T0**	**T0h30**	**T1h**	**T1h30**	**T2h**	**T3h**	**T4h**	**Pre dose**	**T0**	**T0h30**	**T1h**	**T1h30**	**T2h**	**T3h**	**T4h**	**T6h**
Eligibility criteria										X[1]								
Prior/concomitant medications	←																	→
Physical examinations										X								
Body weight										X								
Hematology										X								
Coagulation										X								
Biochemistry										X								
Phosphorus metabolism[2]										X								
Urinalysis										X[3]								
Urine electrolyte tests																		
Urine B2-microglobulin										X								
Urine drug screen including urinary cotinine	X																	
Alcohol breath test	X																	
Vital Signs										X					X		X	X
12-lead ECG recording										X					X		X	X
Admission	X																	
Discharge																		
Randomization										X[1]								
Study Drug / Placebo Administration											X[4]							
Blood sample for Pharmacokinetics																		
Blood sample for Pharmacodynamics (plasma glucose)																		
Blood sample for Pharmacodynamics (serum insulin)										X		X	X	X	X	X	X	X
HbA1c measurement										X								
Oral glucose Administration			X															
Oral glucose Tolerance Test (OGTT)		X		X	X	X	X	X	X									
Urine collection for Pharmacokinetics																		
Urine collection for Pharmacodynamics[5]										←								→
Blood sample for exploratory genomic																		
AE collection	←																	→

[1] Confirmation of the Inclusion/exclusion criteria prior to randomization number assignment and prior to first study product administration;
[2] Phosphorus metabolism (Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D);
[3] Including 24-hour urine creatinine level (T0-24h);
[4] Placebo administration in blind condition for the subject;
[5] Urine collection for PD from D-1 predose until D1 predose.

Table 3-3: DETAILED STUDY FLOW CHART for Part B – Multiple Ascending Dose (2/4)

Visit/Period	**Treatment Period**																				
Day	**D1**																**D2**		**D3**	**D4**	**D5**
Theoritical time (h)	**Pre dose**	**T0**	**T0h15**	**T0h30**	**T0h45**	**T1h**	**T1h30**	**T2h**	**T2h30**	**T3h**	**3h30**	**T4h**	**T6h**	**T8h**	**T10h**	**T12h**	**T0**	**T12h**	**T0h**	**T0h**	**T0h**
Eligibility criteria																					
Prior/concomitant medications	←																				→
Physical examinations	X																X[1]				X[1]
Body weight																					
Hematology	X																X[1]				X[1]
Coagulation	X																X[1]				X[1]
Biochemistry	X																X[1]				X[1]
Phposphorus metabolism																					X[1]
Urinalysis	X																X[1]				X[1]
Urine electrolyte tests	X																X[1]				X[1]
Urine B2-microglobulin																					
Urine drug screen including urinary cotinine																					
Alcohol breath test																					
Vital Signs	X					X		X				X					X[1]		X[1]	X[1]	X[1]
12-lead ECG recording								X				X					X[1]				X[1]
Admission																					
Discharge																					
Randomization																					
Study Drug / Placebo Administration		X															X		X	X	X
Blood sample for Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]	X	X[1]	X[1]	
Blood sample for Pharmacodynamics (plasma glucose)	X			X		X	X	X		X		X	X	X		X	X[1]		X[1]	X[1]	
Blood sample for Pharmacodynamics (serum insulin)																					
HbA1c measurement																					
Oral glucose Administration (OGTT)																					
Oral glucose Tolerance Test																					
Urine collection for Pharmacokinetics	X	←									→	↔		↔		↔	↔		↔		
Urine collection for Pharmacodynamics		←									→	↔		↔		↔	↔		↔	↔	
Blood sample for exploratory genomic	X																				
AE collection	←																				→

[1] At pre-dose.

Table 3-4: DETAILED STUDY FLOW CHART for Part B – Multiple Ascending Dose (3/4)

Visit/Period	Treatment Period																		
Day	D6	D7		D8-D9	D10		D11-D12	D13		D14									
Theoritical time (h)		Predose	T0	T0	Predose	T0	T0	Predose	T0	Pre dose	T0	T0h5	T0h35	T1h05	T1h35	T2h05	T3h05	T4h05	T12h
Eligibility criteria																			
Prior/concomitant medications	←																		→
Physical examinations																			
Body weight																			
Hematology					X			X											
Coagulation					X			X											
Biochemistry					X			X											
Phosphorus metabolism					X														
Urinalysis		X[1]			X			X											
Urine electrolyte tests					X			X											
Urine B2-microglobulin		X																	
Urine drug screen including urinary cotinine																			
Alcohol breath test																			
Vital Signs	X[2]	X		X[2]	X		X[2]	X		X									
12-lead ECG recording					X														
Admission																			
Discharge																			
Randomization																			
Study Drug / Placebo Administration	X		X	X		X	X		X		X								
Blood sample for Pharmacokinetics		X			X			X											
Blood sample for Pharmacodynamics (plasma glucose)		X			X			X											
Blood sample for Pharmacodynamics (serum insulin)																			
Oral glucose Administration												X							
Oral glucose Tolerance Test (OGTT)										X			X	X	X	X	X	X	
Urine collection for Pharmacokinetics			X[3]			X[3]			X[3]										
Urine collection for Pharmacodynamics			X[3]			X[3]			X[3]										
HbA1c measurement																			
Blood sample for exploratory genomic																			
AE collection	←																		→

[1] Only 24-hour urine creatinine level (T0-24h);

[2] At Pre-dose;
[3] 24 hours urine collection at D7, D10 and D13.

Table 3-5: DETAILED STUDY FLOW CHART for Part B – Multiple Ascending Dose (4/4)

Visit/Period	Treatment Period																					End of Study
Day	D15																D16		D17	D18	D19	D24 (+/-2 days)
Theoritical time (h)	Pre dose	T0	T0h15	T0h30	T45min	T1h	T1h30	T2h	T2h30	T3h	3h30	T4h	T6h	T8h	T10h	T12h	T24h	T36h	T48h	T72h	T96h	
Eligibility criteria																						
Prior/concomitant medications	→																					
Physical examinations	X																X				X	X
Body weight																					X	X
Hematology	X																X				X	X
Coagulation	X																X				X	X
Biochemistry	X																X				X	X
Phosphorous metabolism																					X	
Urinalysis	X[1]																X				X	X
Urine electrolyte tests	X																X				X	X
Urine B2-microglobulin	X																					X
Urine drug screen including urinary cotinine																						
Alcohol breath test																						
Vital Signs	X					X		X				X					X		X	X	X	X[2]
12-lead ECG recording	X							X				X					X				X	X
Admission																						
Discharge																					X	
Randomization																						
Study Drug / Placebo Administration		X																				
Blood sample for Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood sample for Pharmacodynamics (plasma glucose)	X			X		X	X	X		X		X	X	X		X	X		X	X		
Blood sample for Pharmacodynamics (serum insulin)	X			X		X	X	X		X		X	X									
Oral glucose Administration (OGTT)																						
Oral glucose Tolerance Test																						
Urine collection for Pharmacokinetics	↔	↔	↔	↔																		
Urine collection for Pharmacodynamics	↔	↔	↔	↔	↔																	
HbA1c measurement																					X	
Blood sample for exploratory genomic																						
AE collection	↔																					

[1] Including 24-hour urine creatinine level (T0-24h);
[2] Including body temperature.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

(standard Units are not defined in the abbreviation's list)

ADA	**:**	American Diabetes Association
AE	**:**	Adverse Event
Ae_{0-24h}	:	cumulative amount of drug excreted unchanged in urine between 0 and 24 hours
Ae_{last}	:	amount of drug excreted unchanged in urine between 0 and the last time of collection
ALT	**:**	Alanine Leucine Transferase
ANSM	**:**	Agence Nationale de sécurité du médicament et des produits de santé
APTT	**:**	Activated Partial Thromboplastin Time
AST	**:**	Alanine serine transferase
$\%AUC_{Extra}$	**:**	Percentage of extrapolated AUC0-∞
AUC_t	:	Area under the plasma concentration curve from administration up to the last quantifiable concentration at time t
AUC_{0-24h}	**:**	Area Under the plasma concentration Curve from administration up to the last quantifiable concentration at time 24h
AUC_{last}	**:**	Area Under the plasma concentration Curve from administration up to the last quantifiable concentration at time t
BMI	**:**	Body Mass Index
BP	**:**	Blood pressure
bpm	**:**	beats per minute
BSACF	**:**	Body Surface Area Conversion Factor
BUN	**:**	Blood Urea Nitrogen
cGCP	**:**	Current Good Clinical Practice
Clr	:	Renal Clearance
Cl/F	**:**	Clearance
C_{max}	**:**	Observed maximum plasma concentration
Cmin	:	Observed minimum plasma concentration
CPK	**:**	Creatine phosphokinase
CPP	**:**	Comité de Protection des Personnes
CRF	**:**	Case Report Form
CRO	**:**	Contract Rresearch Organisation
CSP	**:**	Code de la Santé Publique
CQA	**:**	Clinical Quality Assurance
DM	**:**	Diabete Mellitus
DRF	**:**	Data Resolution Form
EC	**:**	Ethics committee
ECG	**:**	Electrocardiogram
eCRF	**:**	Electronic Case Report Form
EMA	**:**	European Medicines Agency
%fe	**:**	fraction of the dose excreted in urine
GCP	**:**	Good Clinical Practice

GDM	:	Gestational Diabete Mellitus
GDPR	:	General Data Protection Regulation
GGT	:	Gamma Glutamyl Transferase
GLP-1	:	Glucagon-Like Peptide 1
HbA1c	:	Hemoglobin A1c
HBs	:	Hepatitis B surface antigen
HBW	:	Human Body Weight
HCV	:	Hepatitis C virus
HIV	:	Human Immunodeficiency Virus
HR	:	Heart Rate
ICH	:	International Conference on Harmonization
IMP	:	Investigational Medicinal Product
INR	:	International Normalised Ratio
IP	:	Investigational product
LDH	:	Lactate Dehydrogenase
MAD	:	Multiple ascending dose
Kel	:	Elimination rate constant
MCH	:	Mean Corpuscular Hemoglobin
MCHC	:	Mean Corpuscular Hemoglobin Concentration
MCV	:	Mean Corpuscular Volume
MedDRA	:	Medical Dictionary for Regulatory Activities
NOAEL	:	No-Observed-Adverse-Effect-Level
MRSD	:	Maximum Recommended Starting Dose
MTD	:	Maximum Tolerated Dose
NTEAE	:	Non-Treatment Emergent Adverse Event
OTC	:	Over The Counter
PI	:	Principal Investigator
PT	:	Prothrombin Time
R	:	Accumulation ratio
RBC	:	Red Blood Cells
SAD	:	Single Ascending dose
SAE	:	Serious Adverse Event
SAR	:	Serious Adverse Reaction
SBP	:	Systolic Blood Pressure
SD	:	Standard Deviation
SEM	:	Standard Error of the Mean
SF	:	Safety Factor
SG	:	Specific Gravity
SGLT	:	Sodium Glucose Linked Transporter
SmPC	:	Summary of Product Characteristics
SSC	:	Study Safety Committee
SUSAR	:	Suspected Unexpected Serious Adverse Reaction
TEAE	:	Treatment Emergent Adverse Event
$t_{1/2}$ (h)	:	Plasma elimination half-life
t_{max} (h)	:	First time to reach Cmax
Vd/F	:	Volum of distribution
WBC	:	White Blood Cells
WHO-DD	:	World Health Organization - Drug Dictionary

1. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE RESEARCH

1.1. Introduction and background

Diabetes mellitus is a metabolic disease resulting from impaired insulin secretion and abnormal insulin action, which is characterized by high blood glucose levels. There are three different types of diabetes, including Type 1, Type 2, and gestational diabetes mellitus.
Type 1 DM is an autoimmune disease and it occurs when the immune system mistakenly attacks and destroys insulin-producing pancreatic beta cells. Patients with Type 1 DM need to receive lifelong insulin injections due to permanent damage of pancreatic beta cells and to maintain blood glucose levels within the normal range through diet therapy and periodic examinations. If these patients do not receive insulin therapy, diabetic ketoacidosis as an acute complication can occur and result in death. Thus, mortality rate is higher in patients with Type 1 DM than in those with Type 2 DM. Type 1 DM mainly occurs in children because of congenital factors and may appear in adults. This accounts for 5-10% of all diabetes cases.
Type 2 DM commonly occurs in adults. Type 2 DM is a condition in which insulin secretion decreases resulting from genetic factors, lifestyle factors (e.g. unhealthy dietary pattern, insufficient exercise, and obesity), and environmental factors, or in which cells in the body do not normally respond to insulin due to increased insulin resistance. Patients with Type 2 DM account for 90-95% of total patients with diabetes mellitus. Blood glucose levels can be controlled through weight loss, healthy diet, and exercise. However, diabetes mellitus is a progressive disease with a gradual deterioration over time, so insulin injections are eventually needed if the duration of diabetes lengthens. Main symptoms of diabetes mellitus include polyuria, polydipsia, lethargy, anorexia, and weight loss resulting from increased blood glucose levels.
Gestational diabetes mellitus (GDM) occurs during pregnancy and appears due to insulin deficiency. GDM occurs in 2-4% of pregnant women. If pregnant women have diabetes mellitus, their babies may be at increased risks of stillbirth, preterm birth, congenital anomaly, fetal macrosomia, hyperbilirubinemia, and respiratory distress. Thus, early diagnosis and appropriate treatment of GDM is very important. In most patients with GDM, diabetes mellitus that first occurred during pregnancy disappears after birth. However, 40-60% of patients with GDM may develop Type 2 DM 5 to 15 years after birth, so continuous monitoring is required.

The number of patients with diabetes mellitus (DM) has been closed to approximately 420 million people worldwide in 2014. As the mortality rate of patients with DM due to a variety of complications has increased.

Medications used for the treatment of diabetes can be largely divided into two types: insulin and oral hypoglycemic agents. Insulin is commonly used for the treatment of Type 1 DM. For oral hypoglycemic agents, monotherapy or combination therapy with drugs from different classes of hypoglycemic agents is used for the treatment of Type 2 DM. The commonly used antidiabetic drugs include metformin, sulfonylurea, thiazolidinedione, insulin analogue, and glucagon-Like Peptide-1 (GLP-1) receptor agonist.

The American Diabetes Association (ADA) guidelines recommend monotherapy for diabetic patients with HbAlc levels below 9%, combination therapy of two drugs for those with HbAlc levels of 9-10%, and combination therapy with insulin for those with HbAlc levels above 10%, as initial regimen. For combination therapy using two or three drugs, drugs from different classes of antidiabetic drugs, which are suitable for health conditions of individual patients, should be used concurrently.

Approximately 180 g of glucose per day are filtered by the renal glomerulus. In the healthy human body, almost all of the filtered glucose is reabsorbed. Glucose reabsorption is primarily handled by SGLT1 and SGLT2 in the proximal convoluted tubule. To date, six SGLT isoforms distributed in several organs have been identified, but all of their functions have not yet been found. Glucose reabsorption in the proximal convoluted tubule is performed by SGLT2, exclusively expressed in kidney, for approximately 90% of filtered glucose and by SGLT1, mainly expressed in both the intestine and kidney, for the remaining 10%

of filtered glucose. In healthy individuals, filtered glucose is normally reabsorbed until blood glucose levels reach approximately 200 mg/dL, and it begins to be detected in urine if blood glucose level exceeds 200 mg/dL.

SGLT-2 inhibitors are oral antidiabetic drugs commercially available since 2014. These drugs control blood glucose levels by preventing reabsorption of glucose filtered by kidney and by excreting the filtered glucose. Since SGLT-2 inhibitors have the mechanism of insulin-independent blood glucose-lowering action, the absence of hypoglycemic risk is unclear and body weight loss that occurred in using existing antidiabetic drugs.

JP-2266 developped by JEIL Pharmaceutical is an antidiabetic drug which regulates blood glucose levels by inhibiting both SGLT1 (Sodium-Glucose Linked Transporter 1) and SGLT2 and is a small-molecule synthetic compound.

JP-2266 reduces peak post-prandial blood glucose and insulin levels and has an insulin-independent blood glucose-lowering effect. In vitro and in vivo studies using animal models of diabetes mellitus revealed that JP-2266 has potent therapeutic effects.

1.2. Summary of available results of non-clinical studies and clinical studies pertinent to the biomedical research concerned

1.2.1. Non clinical studies

1.2.1.1. Non clinical primary pharmacology

During the course of non-clinical pharmacology investigations, primary pharmacodynamics studies were conducted in vitro and in vivo. In vitro studies focused on the mechanism of action of JP-2266 and the aim of in vivo studies was to assess JP-2266 efficacy in animal models as well as its mechanism of action in these models.

In a STZ-induced T1DM rat model, it was confirmed that combination therapy of oral JP-2266 (3mg/kg) with insulin (2U/day) has advantages of decreasing hypoglycemic episodes, lowering HbA1c levels, and reducing weight gain, compared with intensive insulin monotherapy alone. In the same STZ-T1DM rat model, a 4-week repeated dose of JP-2266 had a superior blood glucose-lowering effect in the dose range of 3-10 mg/kg, compared to 10 mg/kg Sotagliflozin. In this model, the maximum blood glucose-lowering effect of JP-2266 seems to be reached at a dose of 3mg/kg.

Finally, oral administration of JP-2266 (2 mg/kg) seems to exert a better glycemic control effect than Canagliflozin (2mg/kg) or Sotagliflozin (2mg/kg), after 4-week repeated doses in type 2 diabetic (db/db) mice.

1.2.1.2. Toxicology

A single dose toxicity study was conducted with JP-2266 in SD rats and mini-pigs. JP-2266 (100, 300, 1000, and 2000 mg/kg) was orally administered to SD rats (3/sex/group). In SD rats, **MTD** was **300mg/kg** due to dehydration noted at ≥1000mg/kg/day.

Increasing JP-2266 doses (15, 30, 60 and 120 mg/kg) were orally administered to 1 male and 1 female mini-pigs with 3~11 days washout period. No clinical signs were observed up to 120mg/kg. No adverse effects were observed in mini-pigs up to 120 mg/kg. **MTD is 120 mg/kg/day**.
After 1 week of daily JP-2266 oral administration (25, 50, 100 mg.kg/day) to SD rats, body weight of male rats treated with doses ≥ 50mg/kg was significantly decreased. Dose-dependent dehydration as a result

of exaggerated pharmacology to JP-2266 (increase in urine glucose and output) was observed at ≥ 25 mg/kg/day and required fluid treatment in some cases. Additionally, increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were noted in both sexes at ≥25 mg/kg/day.
After 4 weeks of daily JP-2266 oral administration (5, 10, and 25 mg/kg) to male and female **SD rats** (10/sex/group), no death was observed. 10 and 25mg/kg dose groups showed clinical signs, such as soft stool, diarrhea, decreased skin elasticity and abnormal hair. Body weigh was decreased in male SD rats and all dose groups was showed increase in food intake. Microscopic changes in the bone of the sternum and femur consisted of slightly increased amounts of trabecular bone with cartilage cores. These changes were confined to the metaphysis and the adjacent metaphyseal cortex, which was slightly thickened with increased bone and cartilage in animals with mild findings. The physis (growth plate) was normal in all animals. This finding was non-adverse due to the low magnitude of change (only minimal to mild severity), limited involvement of only the metaphyseal region, lack of change in the physis, and absence of bone fractures, bone malformations or other bone macroscopic changes, reduced motility, lameness, limb impairment, or clinical pathology findings suggestive of any potential bone marrow functional impairment. **NOAEL determined at 5 mg/kg/day**.

Hyperostosis in rodent species is attributable to carbohydrate malabsorption (rat-specific) and is observed only in young rats. It is accompanied by a decrease in serum levels of 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D, PTH, and calcitonin and these parameters were used to determine the safety associated with bone changes in a phase 1 clinical study. Hyperostosis reportedly occurs as a drug class effect of SGLT2 inhibitors in rodent species only, but not in humans. Indeed, toxicology studies lead on Canagliflozin, a representative SGLT2 inhibitor, showed that hyperostosis occurred in rodent species, but not in non-rodent species, and histopathological findings observed at the same dose level were not considered adverse effects. Besides, histopathological findings observed at the same dose level were not considered adverse effects. In clinical studies involving Canagliflozin, there was no difference between the Canagliflozin-treated group and the placebo-treated group in term of risk of bone fractures.
Following daily administration at 180 and 240 mg/kg/day (BID) for 7 consecutive days possible non-adverse test article-related effects were noted within clinical pathology in **minipigs**.
After daily oral administrations of JP-2266 (10, 30, and 100 mg/kg) for 4 weeks followed by a 2 week recovery period to mini-pigs (3/sex/group), no death was observed and there were no JP-2266-related changes in clinical signs, body weight gain, food intake, serum biochemistry, bone marrow test, ophthalmoscopy, and macroscopic findings. **NOAEL determined at 100 mg/kg/day**.

In vitro and *in vivo* genotoxicity studies conducted with JP-2266 did not reveal any genotoxic potential.

1.2.1.3. Safety Pharmacology

Four safety pharmacology studies has been conducted.

During safety pharmacology studies conducted with JP-2266, no neurobehavioral effects and no respiratory effects were observed following a single oral dose of 5, 10, or 25 mg/kg of JP-2266 in rats. NOEL is thus 25 mg/kg for both the CNS and the respiratory systems. Additionally, a single oral administration of JP-2266 at a dose up to 100 mg/kg did not affect the cardiovascular parameters in male mini-pigs. NOEL for JP-2266 is thus 100 mg/kg for the cardiovascular system. Finally, JP-2266 was shown to possibly inhibit hERG channel current in vitro with an IC50 higher than 50 µM.

1.2.1.4. Pharmacokinetics

Absorption and distribution

After JP-2266 oral administration to mouse, the Tmax value was 0.5 hours, suggesting a fast oral absorption. Mean half-life was 3.0 hours, and oral bioavailability of JP-2266 was calculated as 84.5%.

After JP-2266 oral administration to rats, Tmax was 1.0 hour, suggesting a fast oral absorption. Mean half-life was 4.1 hours, and oral bioavailability was calculated as 69.3% for males and 91.3% for females. A dose-dependent increase in plasma concentrations was observed at each dose level. Plasma concentration was 2.2 to 3.0 higher in female rats than in male rats. Oral bioavailability of JP-2266 was 1.3-fold higher in females than in males.
Plasma concentration of JP-2266 under non-fasting conditions was 1.7-fold lower than that under fasting conditions.

When JP-2266 (5, 10 and 25 mg/kg) was orally given to male and female rats daily for 4 weeks, T_{max} was between 0.5 and 1 hour on Days 1 and 28. Dose-proportional (linear) increase in systemic exposure to JP-2266 was observed in both genders. Exposure was clearly higher in females than in males regardless the dose and treatment duration. No accumulation of JP-2266 was observed in rat blood.

When JP-2266 5 mg/kg was given IV to dogs, blood clearance was low with an average of 0.09 L/h/kg. Volume of distribution was 0.7 L/kg, indicating that JP-2266 is largely distributed outside the vessel. Half-life was 6.9 hours. When JP-2266 10 mg/kg was given orally to a beagle dogs, T_{max} was 5 hours, suggesting slow oral absorption, and half-life was 7.4 hours. Oral bioavailability of JP-2266 in dog was calculated to be 97.4%.

After single oral administration (15, 60 mg/kg) to male and female mini-pigs, T_{max} was 0.5~24.0 hours. Average half-life was 1.5~5.1 hours. Compared to the 15 mg/kg group, a 3.4-fold increase in male $AUC_{0\text{-}inf}$ and a 44.8-fold increase in female $AUC_{0\text{-}inf}$ were observed in 60 mg/kg group, indicating a dose dependent plasma concentration.

In mini-pig administered orally twice daily for 1 week (180, 240 mg/kg per day), male and female T_{max} values were 1 to 24 hours. In the 180 and 240 mg/kg dose groups, AUC ratio on Day 7 and Day 1 was 5.0~7.8 and 3.6~7.8, respectively, indicating drug accumulation in blood. Besides, there was no dose response in systemic exposure.

In mini-pig administered orally for 4 weeks (10, 30, 100 mg/kg), male and female Tmax were 0.5 to 1 hour and 4 to 24 hours, respectively. Dose-dependent exposure to JP-2266 was observed, and it was similar in both female and male mini-pigs. In the male and female 100 mg/kg dose group, AUC ratio on Day 28 and Day 1 was 2.970 and 6.682, respectively, and drug accumulation was observed only in the 100 mg/kg dose group.

JP-2266 may be a substrate of P-gp in human intestinal Caco-2 cell line.
JP-2266 has been shown to be highly bound to protein in human (95.33%), mouse (91.26%), rat (94.11%), and dog (94.68%) plasma.

Metabolism
Metabolism of JP-2266 is expected to occur at a fast rate and JP-2266 appears to be more stable in dog and human liver microsomes than in mouse, rat, and mini-pig microsomes.

A total of 11 metabolites were identified, categorized into 4 structural classes based on the functional groups introduced during biotransformation reactions: hydroxidation, O-demethylation, oxidation and dehydrogenation. Relative peak intensities of metabolites produced by hydroxylation (mouse, rat, dog, mini-pig and human), O-demethylation (rat) or dehydrogenation (mouse, mini-pig) were much greater than other metabolites, suggesting that these biotransformations are the main metabolism pathways of JP-2266.

Excretion
When JP-2266 5 mg/kg was given IV to mice, average half-life was 2.1 hours. When JP-2266 10 mg/kg was given orally to mice, average half-life was 3.0 hours.

When JP-2266 5 mg/kg was given IV to male and female rats, average half-life was 1.7 and 4.1 hours, respectively. When JP-2266 10 mg/kg was orally given to male and female rats, average half-life was 4.1 in both genders.

When JP-2266 15 and 60 mg/kg was given orally to mini-pig, half-life was around 5.0 hours in male and 1.5-4.3 hours in female.

Pharmacokinetics drug interactions
In vitro, 10 µM JP-2266 did not show inhibitory effect on CYP isoforms 1A2, 2C9, 2C19, 2D6, 3A4, 2B6, 2C8.

In an *in vitro* study with human hepatocytes, JP-2266 did not induce the activities of CYP1A2 and CYP2B6 isoforms at concentrations from 0.1 to 20 µM. However, JP-2266 may induce the mRNA expression and the enzymatic activity of CYP3A4 at concentrations centµM and everµM, respectively.

In vitro, JP-2266 does not inhibit P-glycoprotein, multidrug transporter expressed in various human tissues including gastrointestinal tract.

1.2.2. Clinical studies

No clinical study has been conducted so far. The present one is the First-in-Human study.

1.3. Summary of the known and potential risk and benefits to human subjects

The subjects enrolled in the present study being healthy are not expected to derive any benefit from participating in the present study.
No specific risk was identified as no organ toxicity was observed during regulatory toxicity studies, as mentioned in the Investigator's Brochure.

The only expected risks are those arising from the intake of a drug/product, and from the punction of venous blood through a catheter.

1.4. Description of and justification for the dosage regimen

1.4.1. Rationale for the choice of starting dose in man

The starting dose to be tested in this initial clinical study in man is based on NOAEL in rat and mini-pig after 4 weeks treatment and on the pharmacological activity in mice and rat.

NOAEL:

Based on the NOAEL, the Maximum Recommended Starting Dose (MRSD) is calculated as follows:

MRSD (in mg) =NOAEL (mg/kg) x HBW (kg) x BSACF x SF-1 with:

- NOAEL= 5 mg/kg in rat and 100 mg/kg in mini-pig
- HBW (human body weight) = 60 kg
- BSACF (body surface area conversion factor) = 0.162 for rat and 0.909 for mini-pig

- SF (safety factor) : considering the difference between the NOAEL in rat and mini-pig, a safety factor of 10 is taken for rat and of 20 for mini-pig.

Therefore, a MRSD can be calculated based on these assumptions:

- In rat: 5 x 60 x 0.162 / 10 = 5 mg
- In mini-pig: 100 x 60 x 0.909 / 20 = 273 mg

As rat is the most sensitive species, the lower MRSD of 5 mg is chosen.

Pharmacological activity:

A pharmacological activity has been observed in mice at 10 mg/kg and in rats from 1 mg/kg to 10 mg/kg i.e. HED from 10 mg to 100 mg for 60 kg BW. Therefore these results are in accordance with the calculation based on a NOAEL approach.

Taking into account the results obtained by the methods of estimation, the first dose of JP-2266 to be administered to humans will be 5 mg. This starting dose represents a low dose and a conservative approach.

Finally, since the starting dose obtained from extrapolations made using the NOAEL and the activity approaches provided similar results, it can be concluded that the approach for the selection of the starting dose was robust further decreasing the risk and indicating that the adopted risk mitigation strategy can be considered satisfactory.

Regarding systemic exposure, toxicokinetic studies showed plasma exposures increasing by a dose-dependent trend in rat and mini-pig. The systemic exposure of JP-2266 was higher in female rat than in male rat. In mini-pigs, plasma exposure was unchanged between male and female. There was no drug accumulation (D28/D1) in rat and mini-pig up to 30 mg/kg. Drug accumulation was observed in mini-pig at the highest tolerated dose (100 mg/kg) by 3 in male and 6.7 in female.

Therefore, the accumulation ratio should be evaluated after each repeated dosing in human.

The exposure at the NOAEL was :

1470 ng.h/mL for AUC and 636 ng/mL for Cmax in male rat ;

8800 ng.h/mL for AUC and 1340 ng/mL for Cmax in female rat ;

281 000 ng.h/mL for AUC and 8940 ng/mL for Cmax in mini-pig.

1.4.2. Rationale for the choice of highest dose in man

The highest dose and the highest exposure to be tested in this initial clinical study in man is based on the rat and on the mini-pig studies. The preclinical studies indicated that the pharmacokinetics of JP-2266 is dose-dependent (linear) without drug accumulation in rat up to 25 mg/kg (HED 240 mg for 60kg) and in mini-pig up to 100 mg/kg (HED 5454 mg for 60 kg).
Then the highest proposed dose of 80 mg is considered to be safe. It is 67 times lower than the HED at the NOAEL of mini-pig. This dose is higher than the HED at the NOAEL of rat (48 mg) but it is lower than the HED at 25 mg/kg (240 mg) which was used in safety pharmacology studies without safety concern and without drug accumulation.
In the present study additional risk mitigation come from the fact that dose administration will be conducted using a staggering approach and dose escalation will be continued only after evaluation of all safety and PK data.

1.4.3. Rationale for dose escalation

For the starting dose (see above) and for the dose escalation the ANSM guideline "Estimation of the starting dose, definition of dose progression and protocol administration to volunteers" September 2006) and the revised EMA guideline from 2017 have been taken into account.
Dose escalation steps for the study are provided in Table 1. Dose escalation is 2-fold at eachsteps.
The following single doses are planned to be administered:
Table 1 – Doses for Part A: Single Ascending Dose

Dose group	Dose (mg)	Ratio
1	5	
2	10	2,0
3	20	2,0
4	40	2,0
5	80	2,0

Based on the pharmacokinetics results after single doses, this dose schedule could be revised especially if an unexpected risk of accumulation appears.

1.5. Rationale for the choice of food effect study dose in man

In the SAD group of 20 mg, the subjects will be asked to come to the clinical unit for a second period in order to take the study product in fed condition.
The Dose of 20 mg has been chosen to evaluate the food intake on the pharmacokinetics parameters of JP-2266.
According to non-clinical study in rats, the food intake before the administration of JP-2266 is expected to decrease the blood exposure under fed condition in comparison to fasting condition (1.7 fold decrease of systemic exposure in rat).

1.6. Rationale for dose escalation – Multiple Ascending Dose

Dose escalation steps for the study are provided in Table 2. Dose escalation is 2,5-fold at the first step, and 2-fold at the second step.
The Part B will start only after the completion of a dose in SAD for which the observed tolerated exposure is higher than the exposure expected at tfhe first dose level of Part B. Table 2 below shows dose schedule for multiple ascending doses.

Table 2 – Doses for Part B: Multiple Ascending Doses

Dose group	Dose (mg)	Ratio
1	2	
2	5	2,5
3	10	2,0
4	20	2,0

1.7. Ethical considerations

The study will be carried-out in accordance with the Declaration of Helsinki as modified in Fortaleza (2013), the recommendations on Good Clinical Practice (GCP) (ICH E6 R2) and any applicable local regulatory requirement(s).

The clinical study will start upon receipt of the approval of both the Ethics Committee [“Comité de Protection des Personnes” (CPP)] and the [French Health Authorities [“Agence Nationale de sécurité du médicament et des produits de santé” (ANSM)].

1.8. Description of the population to be studied

Subjects will be healthy male Caucasian volunteers aged between 18 and 50 years. Up to eighty subjects are planned to be enrolled.

Part A/ SAD: 5 groups of 8 subjects (6 active / 2 placebo), for a total of 40 subjects.
Part A/ Food effect: will be tested in period 2 for 1 group (dose 20mg) of 8 subjects (6 active / 2 placebo).
Part B/ MAD: 4 groups of 10 subjects (8 active / 2 placebo), for a total of 40 subjects.

Subjects will be recruited from volunteers’ database of the clinical unit. Newspaper advertisements, radio spots, posters, mailing, specific press inserts, broadcast message or clinical unit recruitment website may be used. Only study-specific recruitment tools approved by EC will be used.

STUDY OBJECTIVES AND PURPOSE

2.1. Principal objective

Part A – Single Ascending Dose
To evaluate the safety and tolerability of JP-2266 after single oral administration at 5 different doses in healthy male Caucasian subjects..

Part A – Food Effect cohort
To evaluate the impact of food intake on pharmacokinetics after an oral administration of JP-2266 in healthy male Caucasian subjects in fast or fed conditions.

Part B – Multiple Ascending Dose
To evaluate the safety and tolerability of JP-2266 after multiple oral administration at 4 different doses in healthy male Caucasian subjects.

2.2. Secondary objectives

Part A – Single Ascending Dose

- To evaluate the pharmacokinetics parameters of JP-2266 after single oral administration at 5 different doses in healthy male Caucasian subjects.
- To evaluate the pharmacodynamics parameters of JP-2266 after single oral administration at 5 different doses in healthy male Caucasian subjects.

Part A – Food Effect cohort

- To evaluate the safety and tolerability of JP-2266 after single oral administration in fast or fed conditions in healthy male Caucasian subjects.
- To evaluate the impact of food on pharmacodynamics after an oral administration of JP-2266 in healthy male Caucasian subjects in fast or fed conditions.

Part B – Multiple Ascending Dose

- To evaluate the pharmacokinetics parameters of JP-2266 after multiple oral administration at 4 different doses in healthy male Caucasian subjects.
- To evaluate the pharmacodynamics parameters of JP-2266 after multiple oral administration at 4 different doses in healthy male Caucasian subjects.

Exploratory Objectives (part A, B)

- Identifying JP-2266 metabolites in human blood and urine after JP-2266 oral administration.
- Identifying genes involved in JP-2266 absorption and metabolism.

2.3. Evaluation criteria

2.3.1. Primary endpoint

Part A – Single Ascending Dose and Food Effect Cohort

Assessment of systemic tolerability and safety:

- Adverse Events
- Vital signs
- Physical examination
- ECG
- Biological analysis:
  - Blood : Hematology, Coagulation, Biochemistry
  - Urine : urinalysis, urine electrolyte test

Part A – Food Effect Cohort

Pharmacokinetic assessments of JP-2266:

In Plasma: C_{max}, t_{max}, C_{min}, $AUC_{0\text{-}24h}$, AUC_{last}, AUC_{inf}, %AUCextra, $t_{1/2}$, Kel, Vd/F, Cl/F

In Urine: CLr, Ae_{last}, $Ae_{0\text{-}24h}$, fe%.

The analysis of C_{max}, AUC_{last} and AUC_{inf} will be performed on the log-transformed values using a mixed model analysis of variance (ANOVA) to determine the geometric mean ratio between fed and fasted conditions and its 90% Confidence Interval (CI).

Part B – Multiple Ascending Dose

Assessment of systemic tolerability and safety:

- Adverse Events
- Vital signs
- Physical examination
- ECG
- Biological analysis:

- Blood : Hematology, Coagulation, Biochemistry, phosphorus metabolism (Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D)
- Urine: urinalysis, urine electrolyte test, β2-microglobulin, 24-hour urine creatinine level.

2.3.2. Secondary endpoints

Part A – Single Ascending Dose

Pharmacokinetic assessments of JP-2266:
In Plasma: C_{max}, C_{min}, t_{max}, AUC_{0-24h}, AUC_{last}, AUC_{inf}, $\%AUC_{extra}$, $t_{1/2}$, Kel, Vd/F, Cl/F
In Urine: CL_r, Ae_{last}, Ae_{0-24h}, fe%.

Pharmacodynamics assessments of JP-2266 effect:
In Plasma: Plasma glucose (AUEC, E_{max}, ΔE_{max}),
In Urine: urine glucose excretion (Ae, cumulative at each time point).

Part A – Food Effect Cohort

Assessment of systemic tolerability and safety:

- Adverse Events
- Vital signs
- Physical examination
- ECG
- Biological analysis:
  - Blood : Hematology, Coagulation, Biochemistry
  - Urine : urinalysis, urine electrolyte test

Pharmacodynamics assessments of JP-2266 effect:
In Plasma: Plasma glucose (AUEC, E_{max}, ΔE_{max}),
In Urine: urine glucose excretion (Ae, cumulative at each time point).

Part B – Multiple Ascending Dose

Pharmacokinetic assessments of JP-2266 at Day 1 and at Steady State:
In Plasma: C_{max}, C_{min}, t_{max}, AUC_{0-24h}, AUC_{last}, AUC_{inf}, $\%AUC_{extra}$, $t_{1/2}$, Kel, Vd/F, Cl/F
In Urine: CLr, Ae_{last}, Ae_{0-24h}, fe%.

Pharmacodynamics assessments of JP-2266 effect:
In Plasma: Oral Glucose Tolerance Test (OGTT) (AUEC, E_{max}, ΔE_{max}), Plasma glucose (AUEC, E_{max}, ΔE_{max}), Insulin (AUEC, E_{max}), Body Weight, HbA1c (change from baseline),
In Urine: urine glucose excretion (Ae, cumulative at each time point).

Exploratory Criteria (part A, B)

- To determine factors that may affect the safety, pharmacokinetics, and pharmacodynamics, an exploratory analysis of drug metabolites can be performed using samples collected for the pharmacokinetic evaluation of investigational products. If relevant drug metabolites are detected, the correlation between pharmacokinetic parameters, including metabolite-to-parent drug exposure ratios, and pharmacokinetics/pharmacodynamics can be evaluated.

- If inter-individual pharmacokinetics results differences are observed, genotyping analysis could be performed to assess the correlation between genetic polymorphism and pharmacokinetic parameters.

3. DESIGN

This will be a phase I, versus placebo versus treatment, single centre, double blind, randomized, parallel study in healthy male volunteers.

The study will be divided in 2 successive parts:

- **Part A - Single Ascending Dose**

This part will be a single ascending dose study in healthy male Caucasian volunteers to assess the safety, the tolerability, the pharmacokinetics and the pharmacodynamics of JP-2266 with nested one way cross-over for food effect. All subjects will receive a placebo administration on day-1 in order to determine the placebo effects of the inert material intake (performed in blind condition for the subject) followed by a single administration period of either JP-2266 or placebo on Day 1. Five JP-2266 doses will be studied.

One cohort of the SAD study part will be used to assess the safety, the tolerability, the pharmacokinetics and the pharmacodynamics of JP-2266 in fast or fed condition.

Part A – Food Effect Cohort

Each subject will participate in one treatment period only (fasted), with the exception of subjects of the food effect group who will participate in two treatment periods (fasted / fed), with a washout phase of at least 14 days between the two treatment periods.

- **Part B - Multiple Ascending Dose**

This part will be a multiple ascending dose study in healthy male Caucasian volunteers to assess the safety, the tolerability, the pharmacokinetics parameters and the pharmacodynamics of JP-2266. In order to determine the placebo effects of the inert material intake each subject will first receive on Day -1 a JP-2266 placebo administration (performed in blind condition for the subject) followed by a 15 day repeated administration period of either JP-2266 or placebo (from Day 1 to Day 15 included). Four JP-2266 dose levels will be studied.

To minimize the risk, the administration of the investigational product in each dose group of the study will be done sequentially within each cohort (Part A and B). In each dose level, the two first subjects will be randomized as one verum and one placebo. The decision to proceed with the administration of the 6 (Part A) or 8 (Part B) remaining subjects will be taken by the investigator on the basis of clinical and biological safety data after 48 hours for Part A and 3 days for Part B. Before each dose escalation, the Study Safety Committee (SSC), consisting of an investigator, a clinical pharmacologist, sponsor representatives and a person responsible of pharmacokinetics analysis, will evaluate the safety and PK data of the cohort(s) already performed and will give an approval for the next dose.

The study plan is shown in Figure 1.
Study procedures are detailed in Section 6 and 7.

Figure1 - Study plan: PART A – Single Ascending Dose

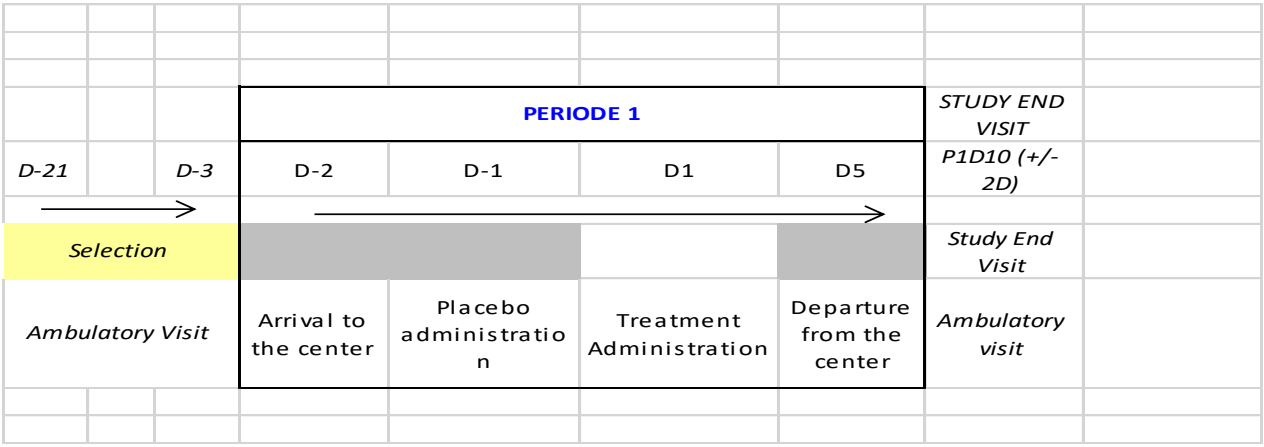


Figure2- Study plan: Part A – Food Effect Cohort

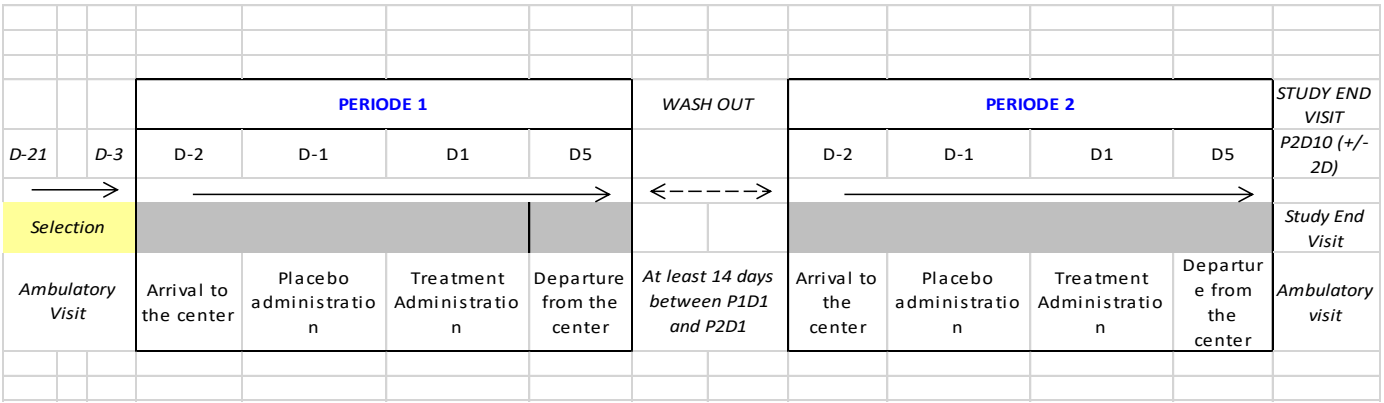
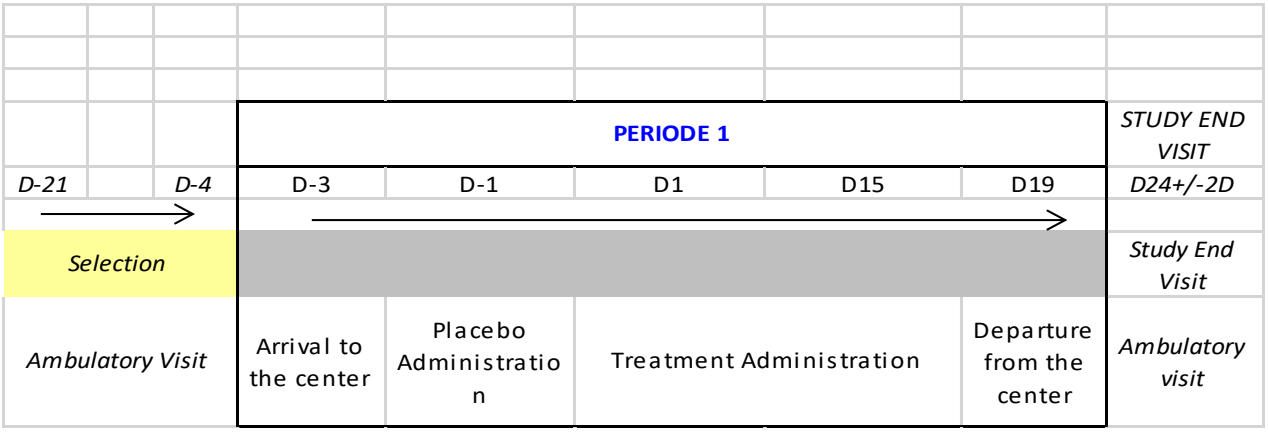


Figure 3 - Study plan: Part B – Multiple Ascending Dose



3.1. Description of the measures taken to minimize and avoid bias

3.1.1. Randomization

The randomization list will be provided by Eurofins Optimed.

PART A – Single Ascending Dose: treatments will be allocated at D1.

PART A – Food effect Cohort: The treatments will be allocated at D1 of each treatment period.
For each part (Part A SAD and Food Effect Cohort), a placebo will be administered on D-1.

PART B – Multiple Ascending Dose: The treatments will be allocated from D1 to D15.
A placebo will be administered on D-1.

3.1.2. Blinding

The following measures are taken to avoid bias:

- Double Blind Study,
- The JP2266 containing active drug and placebo will be indistinguishable in appearance.

For each part, randomization will be performed at D-1.

3.1.3. Risk assessment, study conduct and method of dose escalation

3.1.3.1. Number of subjects receiving the study drug simultaneously

Based on clinical data, no major specific safety issues related to acute toxicity with JP2266 is expected at the doses planned to be tested.

Part A - Single Ascending Dose
To minimize the risk, the administration of the investigational product in each dose group of the study will be done sequentially within each cohort using a sentinel approach. In each dose level, the two first subjects will be randomised as oneverum and one placebo. For each dose level, the decision to proceed with the administration of the 6 remaining subjects will be taken by the investigator on the basis of clinical and biological safety data, after at least 48 hours. The 6 remaining subjects can be divided in multiple subgroups.

Part A – Food Effect Cohort
A single oral dose of 20 mg JP-2266 will be given on two occasions in the food interaction dose level group, in a one way cross-over design , first in the fasted, and after a washout period of at least 14 days in the fed state.
To minimize the risk, the administration of the investigational product will be done sequentially within each group (maximum 6 subjects each day). The decision to proceed with the administration of the remaining subjects will be taken by the investigator on the basis of clinical and biological safety data.

Part B - Multiple Ascending Dose
The Multiple administration part is planned to be conducted as soon as the data from the single administration part are available for a single dose which is at least twice the dose to be tested in multiple administration.
To minimize the risk, the administration of the investigational product in each dose group of the study will be done sequentially within each cohort, on 15 consecutive days. In each dose level, the two first subjects will be randomized as one verum and one placebo. For each dose level, the decision to proceed

with the administration of the 8 remaining subjects will be taken by the investigator on the basis of clinical and biological safety data, after 3 days.

3.1.3.2. Dose Escalation

As the first objective of the study is safety assessment, the dose escalation is designed to progress from the first to the highest dose up to the occurrence of relevant events if any.

At the end of each dose level, an interim safety report will be issued by the Investigator. A dose escalation teleconference meeting will be held between the Investigator and the Sponsor representatives, and the decision on how to proceed (e.g. next higher dose) will be taken on the basis of a blind safety and pharmacokinetic data review.

The following safety parameters will be reviewed until D5, for 8 subjects in Part A and until D19, for 10 subjects in part B:

- Any adverse events reported;
- All laboratory parameters outside of ranges;
- Concomitant therapy;
- Physical examination;
- Vital signs;
- ECG.

During the teleconference meeting, pharmacokinetic data should be available for all subjects of dose level cohort “n”, up to at least 48hrs post-dose.
Identification of non-acceptable risks or significant proportion of AEs with common pathological pattern can justify the modification of the dose escalation design.
After mutual agreement between the Sponsor and the Investigator and if it is considered useful for the selection of the next dose level, the treatment of a specific subject and/or a cohort may be unblinded before the next dose level of JP-2266 is administered.
At the end of the teleconference meeting, the following decisions can be taken:

- Dose escalation will continue as scheduled;
- An intermediate dose between the current dose and the following dose will be administered to the next cohort;
- A lower intermediate dose, between the current dose and the dose administered in the previous cohort will be administered to the next cohort;
- The current dose will be repeated in the next cohort;
- The study will be stopped.

According to the conclusion of this meeting, the formal agreement/disagreement will be signed by both the Sponsor and the Investigator.

3.2. Expected duration of subject participation

3.2.1. Description and duration of trial periods

Part A – Single Ascending Dose

- Screening within 21 days prior to the administration;
- Hospitalization for 7 days (D-2 afternoon to D5 morning);
- End of Study Visit at D10 (+/- 2 days).

Expected duration: approximately 5 weeks for each participating subject.

Part A - Food Effect Cohort

- For one group of the Single Ascending dose: additional hospitalization for 1 period of 7 days (D-2 afternoon to D5 morning);
- Washout period after SAD of at least 14 days between administrations.
- End of Study Visit at P2D10 (+/- 2 days).

Expected duration: approximately 7 weeks for each participating subject.

Part B – Multiple Ascending Dose

- Screening within 21 days prior to the first administration;
- Hospitalization from Day-3 afternoon to D19 morning;
- End of Study Visit at D24 (+/- 2 days).

Expected duration: approximately 7 weeks for each participating subject.

3.2.2. Duration of follow-up

During the last visit, subjects will undergo a complete clinical and biological examination, identical to the examination at the start of the study. (AEs) will be recorded, and if they are on-going a further follow-up will be arranged; follow-up will continue until the event is resolved or the condition is unlikely to change or the subject is lost to follow-up (see section 10.3).

3.2.3. End of study

The last visit of the last subject as scheduled in the protocol will be used to determine the end of study. In case an adverse event is in follow-up phase after this date, the end of study would be considered as the date of the last examination performed (e.g.: clinical examination or biological analysis) or the last date of contact in case the follow up is longer as expected and the event is stabilized.

3.3. Stopping rules

3.3.1. Stopping rule applicable at any time

In case of occurrence of a SAE at least possibly related to the study drug administration, the study will be put on-hold. Unblinding may be required for further evaluation. If the subject was treated by placebo, the study will be continued as planned per protocol. If the subject was receiving verum, the study will be immediately interrupted and depending on the nature and SAE resolution it should be potentially re-started after submission and approval by both CPP and CA of a substantial amendment.

3.3.2. Stopping rule for a subject

During the treatment period, the safety and tolerability will be evaluated on an ongoing basis, the following criteria will apply to stop a subject:

- The subject experiences an AE that prevents him from continuing in the study, including any AE graded ≥ 2 according to CTCAE,
- Significant increase (i.e. > 3N) of ALT or AST (N being the upper limit of the normal value),
- Abnormal laboratory results with simultaneous increases of total bilirubin (> 2 N), ALT or AST(> 2 N) and alkaline phosphatases (> 1.5 N),

- The subject develops a serum creatinine ≥ 2 times the ULN,
- Sustained QTcF value of > 500 msec confirmed by at least one repeat ECG,
- The subject withdraws consent,
- At the request of the Sponsor or at the Investigator's request (for example if the Investigator considers that the subject's health is compromised by remaining in the study or the subject is not sufficiently cooperative).

3.3.3. Stopping rules within a cohort

During the treatment period, the safety and tolerability will be evaluated on an ongoing basis, the following criteria will apply to stop the cohort:

- 2 subjects experiencing severe non serious AEs considered as at least possibly related to the study drug,
- 2 subjects experiencing a significant increase (i.e. > 5N) of ALT or AST (N being the upper limit of the normal value).

3.3.4. Stopping rule for dose escalation

The safety review committee will decide to stop the dose escalation as planned per protocol in case of occurrence of:

- subjects experiencing severe non serious AEs of the same organ class and nature related to the study drug,
- 6 subjects experiencing study drug related moderate non serious AEs (that are considered directly related to the drug effect unless they resolved despite the continuation of the treatment),
- 2 subjects of the group experience a significant increase (i.e. > 3 N) ALT or AST,
- 2 subjects of the group experience simultaneous increases of total bilirubin (> 2 N), ALT or AST (> 2 N) and alkaline phosphatases (> 1.5 N),
- 2 subjects have a sustained QTc value > 500 ms (confirmed by a second ECG under strict resting position),
- One subject presents a Cmax or AUC(0-24h) values respectively above 2500 ng/mL and 10 000 ng/mL*h,
- The mean Cmax and AUC(0-24h) observed lead to believe taking into account the dose increase that Cmax or AUC(0-24h) values of 2500 ng/mL and 10 000 ng/mL*h will be overpass with the following planned higher dose.

In one of the cases listed above, the dose group in progress will be stopped and the blind could be broken. Regarding laboratory and QTc abnormalities described above, if unblinding confirms that at least two subjects presenting these abnormalities were receiving the active drug the dose escalation will be stopped.

3.4. Blind and procedures for unblinding

3.4.1. Coding list

The analytical centre as well as the Investigator, the team and the subject will be in blind conditions.

A randomization list will be generated by Eurofins Optimed and transmitted to a dedicated (unblind) person. For each subject, a coding list containing the identification of the treatment (emergency envelopes) is/are supplied by Eurofins Optimed and kept in a safe place on site during the whole clinical

study period. In addition, this process will be completed by an enrolment via the eCRF to assign treatment arm which will be conducted by the pharmacist after manual randomization in clinical unit.

In the case of a pharmaceutical preparation is required, the pharmacist will have an open access to the decoding system used is a sealed coding list to be given to the EUROFINS-OPTIMED pharmacist. The sealed coding list should be kept in a safe place and accessible to any person authorised to unblind.
The investigator, CRO staff (except the Pharmacist and pharmacy assistant in charge of the IP final packaging) and Sponsor's clinical trial team members will not have access to the randomization (treatment) code except under certain circumstances.

3.4.2. Breaking the blind

The code for any study participant should only be broken by the Investigator or authorised person if it is absolutely necessary.
In case of emergency, for a subject in particular, the code may be broken to ascertain the type of treatment given to study participant concerned. If so, the Investigator (or a person designated from his team) must write his name, signature, date, the number of the participant concerned, the reason for code breaking and the Sponsor must be notified within 24 hours and a full written explanation must be provided. The Investigator has to inform the Study Manager as soon as possible.

The code may also be broken by the Clinical Quality Assurance (CQA) representative if this information has to be provided to the physician in charge of subjects treatments (i.e. at the hospital). In this case, the code will be broken using the sealed coding list if available or sealed envelope. The information resulting from code-breaking (i.e., the subject's group assignment) will not be communicated to either the Investigator or the Sponsor.

A copy of the emergency envelopes will be supplied also to the Sponsor. While the Investigator (PI) will operate under blind conditions until the end of the study, the Sponsor may open the code for a single cohort, but only after the study cohort has been completed and the joint (together with the PI) blinded decision, about whether or not to continue with the planned dose escalation, has been taken.
The randomization envelopes should not be opened by the Investigator at the end of the study.

Unblinding for safety reason can be performed in eCRF by Pharmacovigileance or Principal investigator. Unblind process must be done at subject level, without possibility to unblind all subjects in same time. Login, password and reason of unblinding are required to proceed with unblinding. Once done, treatment arm is visible in pop-up window. Once this window is closed, treatment arm is not visible anymore, except by doing with new unbliding procedure.

In case of Suspected Unexpected Serious Adverse Reaction (SUSAR), the Sponsor should break treatment codes before reporting on an expedited basis the SUSAR to the Competent Authorities and to the Ethics Committee concerned. The blinding code should be broken only for the subject concerned with that SUSAR and it will be maintained for biometrics personnel and staff responsible for data-analysis and interpretation of results at the study conclusion as well as for Investigators.

STUDY POPULATION

4.1. Subject inclusion criteria

For eligibility into the trial, subjects must meet all the following inclusion criteria :

1- Healthy male Caucasian subject aged 18 to 50 years inclusive;

2- Non-smoker subject (smoking cessation for at least 3 months before the first study treatment administration);
3- Body Mass Index (BMI) between 18 and 27 kg/m2 inclusive and body weight ≥ 50 kg at screening;
4- Considered as healthy after a comprehensive clinical assessment (detailed medical history and complete physical examination);
5- Agree to use an adequate contraceptive method from the time of informed consent signature up to 1 month after last IMP administration. Furthermore, it is recommended that subjects with partners of childbearing potential use a highly effective method of birth control defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion;

6- Normal Blood Pressure (BP) and Heart Rate (HR) at the screening visit after 10 minutes in supine position:
   - 95 mmHg ≤ Systolic Blood Pressure (SBP) ≤ 140 mmHg,
   - 50 mmHg ≤ Diastolic Blood Pressure (DBP) ≤ 90 mmHg,
   - 45 bpm ≤ HR ≤ 90 bpm,
   - Or considered NCS by investigators;
7- Normal ECG recording on a 12-lead ECG at the screening visit:
   - 120 ms < PR < 210 ms,
   - QRS < 120 ms,
   - QTcf≤ 430 ms,
   - No sign of any relevant trouble of sinusal automatism,
   - Or considered NCS by investigators;
8- Laboratory parameters within the normal range of the laboratory (hematological, blood chemistry tests, urinalysis). Individual values out of the normal range can be accepted if judged non-clinically significant by the Investigator , except for AST, ALT and creatinine which must be within the normal ranges;
9- Normal dietary habits;
10- Signing a written informed consent prior to selection;
11- Covered by Health Insurance System and / or in compliance with the recommendations of National Law in force relating to biomedical research.

4.2. Subject non-inclusion criteria

Subjects meeting any of the following criteria will not be included into the trial :

1- Any history (including family history) or presence of cardiovascular, pulmonary, gastro-intestinal, hepatic, renal, metabolic, haematological, neurologic, psychiatric, systemic or infectious disease;
2- Any history of clinically significant surgeries
3- Frequent headaches (> twice a month) and / or migraine, recurrent nausea and / or vomiting;
4- Subject with clinically significant infectious and inflammatory findings at screening;
5- Subject with clinically significant atopic syndrome;
6- Subject with clinically significant gastrointestinal symptoms at screening;
7- Symptomatic hypotension whatever the decrease of blood pressure or asymptomatic postural hypotension defined by a decrease in SBP or DBP equal to or greater than 20 mmHg within two minutes when changing from the supine to the standing position;
8- Blood donation or transfusions (including in the frame of a clinical trial) within 3 months before administration;

9- General anaesthesia within 3 months before administration;
10- Presence or history of drug hypersensitivity, or allergic disease diagnosed and treated by a physician. A specific attention should be given to SGLT-2 inhibitors, medications containing similar ingredients;
11- Inability to abstain from intensive muscular effort;
12- No possibility of contact in case of emergency;
13- Subject taking any prescribed drug or herbal medicine within 2 weeks prior to the first scheduled drug administration, or taking any OTC health functional food or vitamin within one week (provided that other conditions are appropriate under the investigator's opinion may participate in the clinical trial) or those in whom any OTC drug, functional food, or vitamin use is expected;
14- History or presence of alcohol abuse (alcohol consumption >40 grams / day);
15- Excessive consumption of beverages with xanthine bases (> 4 cups or glasses / day);
16- The subject is not willing or able to refrain from consuming caffeine-containing foods (coffee, tea (black tea and green tea, etc.), carbonated drinks, coffee milk, nourishment drink, etc) during the period from 24 hours prior to the first hospitalization and until the end of study visit;
17- Subject with the following screening test results:
    - AST or ALT levels out of laboratory standard normal ranges,
    - Plasma creatinine out of the laboratory standard normal range,
    - Repeated demonstration of a QTc interval > 450 ms,
    - Fasting plasma glucose levels > 6.1 mmol/l or < 3.9 mmol/l,
    - Serum HbA1c levels > 6.0 %
18- Positive Hepatitis B surface (HBs) antigen or anti Hepatitis C Virus (HCV) antibody, or positive results for Human Immunodeficiency Virus (HIV) 1 or 2 tests at screening;
19- History or positive results of screening for drugs of abuse;
20- Subject who, in the judgment of the Investigator, is likely to be non-compliant or uncooperative during the study, or unable to cooperate because of a language problem, poor mental development;
21- Use of an investigational drug within 3 months (or 90 days) prior to Day1;
22- Administrative or legal supervision;
23- Subject who would receive more than 4500 euros as indemnities for his participation in biomedical research within the 12 last months, including the indemnities for the present study.

4.3. Subject Identification

4.3.1. Site identification

The sites will be identified using the following code: YYY, where YYY is the specific site number in the country, starting from 001.

4.3.2. Screening number

The screening number will be S and 3 digits, for example: S003. It will be a chronological number. The screening number will be used throughout the study.

4.3.3. Inclusion number

The inclusion number will be composed of 7 digits, 3 for the number of centre (001) and 4 for the inclusion number (the first digit of the inclusion number represents the cohort number). For example: 001- 1001. It will be a chronological number.

4.3.4. Randomization number

The randomization number will be the same as the inclusion number.

4.4. Subject withdrawal criteria

4.4.1. Definitive or temporary stop of a person's participation in the research

4.4.1.1. List of withdrawal criteria

The criteria of withdrawal could be serious adverse events (SAE) or AEs.

4.4.1.2. Reasons for withdrawal

The subjects may withdraw from the study if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision.

4.4.2. Suspension, definitive or temporary stop of a part or the totality of the research

4.4.2.1. Decided by the Sponsor

The Sponsor may decide to discontinue the study prematurely in the following cases:

- The study is not conducted in accordance with the procedures defined in the approved protocol (i.e. low rate of recruitment - protocol deviations - failure to ensure the quality of the data collected);
- Information on the Investigational Medicinal Product (IMP)/Study Product that might change the current benefit-risk profile of the IMP or that would be sufficient to require changes in the IMP administration or in the overall conduct of the trial;
- At the discretion of the Sponsor.

4.4.2.2. Decided by the Investigator

The Investigator may suspend or stop the research if in his judgment the participating subjects are exposed to risks that are not ethically or scientifically justifiable and must notify the Sponsor of this decision in writing providing the reason therefor.
If the research is suspended for safety reasons, the Health Authorities must be immediately notified of the suspension. In this case, the study can resume after an amendment is approved by the Health Authorities.
If the study is stopped, the Ethics Committee and Health Authorities should be informed by Eurofins Optimed, in the 15 days after the decision is taken.
The information of the EC and HA is a Sponsor's responsibility. In the frame of the current study, it is delegated to Eurofins Optimed.

4.5. Premature discontinuation of subject

4.5.1. Data to be collected, and time of recording of these data

Each participant is free to discontinue from the study at any time, for any reason. If a participant discontinues from the study (regardless of the reason for a participant's discontinuation and regardless of the participant's status as evaluable or not evaluable), the Investigator will indicate the reason for discontinuation on the appropriate eCRF page. A follow-up visit will be planned by the Investigator. The exams scheduled for the end-of-study visit will be performed.

In case of premature discontinuation due to AEs, the Investigator will indicate that on the AE Form of the eCRF and in the SAE Form, if appropriate. Participants will be monitored until resolution (see section 3.2.2 and 10.3).

4.5.2. Methods of replacement

In case of study discontinuation due to AE, the replacement will be discussed between the Investigator and the Sponsor.
A subject who prematurely ends his study period after the start of the baseline period and who received treatment will be replaced.
The replacement subject will undergo the complete study. He will be assign the same randomization number corresponding to the number of the subject being replaced with suffix "-R1" (i.e. for the subject number 1004, the replacement subject will receive the number 1004-R1).

Subjects who have been withdrawn from the study cannot be re-included in the study, whatever the step when he/she withdrew. Their selection, inclusion and product/treatment number must not be re-used.

4.5.3. Methods of follow-up of premature discontinuations

For subjects considered lost to follow-up, the eCRF must be filled in up to the last visit.
The Investigator should make every effort to contact the subject and to identify the reason why he/she failed to attend the visit and to determine his/her health status.
In case of premature discontinuation due to AEs/SAEs, follow-up will continue until the event is resolved or the condition is unlikely to change or the subject is lost to follow-up (see section 8.4).

4.6. Exclusion period

The subjects included in this study will be prohibited from participating simultaneously in other research. The principal objective of this study being safety parameters, the exclusion period planned at the end of the research will be 3 months.

4.7. Implementation of health measures related to the COVID pandemic

Since September 1st 2020, it is required by the health protocol written by the Authorities, to wear a protective mask when remaining in professional environment.
Hence, all subjects coming to the Clinical Unit for any visit will be requested to wear a protective mask. During selection and ambulatory visits, the subjects will keep the mask on during their whole stay in the premises.
During hospitalization, subjects will come on the day of hospitalization with a protective mask. At arrival, they will undergo a nasopharyngeal sample with a swab, for COVID status determination (PCR).
Sample will be taken by trained staff at Eurofins Optimed.
Samples collected will be analyzed by Eurofins Labazur (Eurofins Biologie Médicale Labazur Rhone Alpes 333 avenue d'Annecy 73000 Chambéry) or Oriade Noviale, 83 avenue Gabriel Péri, 38330 Saint-Martin-d'Hères, using standard kits dedicated to this analysis.
Subjects will be requested to keep the mask on during the hospitalization, until the result of the test is known.
In case of positive results, subjects will immediately leave the Clinical Unit and will revert to their General Practitioner for the follow-up of the disease Covid-19.
In case of negative results, subjects will be allowed to take the mask off during all their stay in the Clinical Unit, for meals and during the night. They will keep the mask on for all other activities.

For Part A, Single Ascending Dose, and Part B, test will be performed on the first day (or the day before) of hospitalization.
For Part A, Food Effect Cohort, test will be repeated for each hospitalization, on the first day (or the day before) for both period 1 and 2.
These measures will be maintained as long as those specific national recommendations apply. They will be no more used if the national health protocol does not require wearing the mask in professional environment anymore.
The COVID-19 tests will only be performed to the subjects that are eligible to enter the trial.

5. STUDY PRODUCT/TREATMENT

5.1. Description of the treatment(s)

5.1.1. Pharmaceutical form

SAD – Part A

Name of the compound:	JP-2266
Pharmaceutical formulation:	Oral capsule (1 mg, 5 mg, 40mg)
Dose per administration:	5, 10, 20, 40 and 80 mg
Number of capsules per administration:	From 1 to 4 capsules
Timing for administration:	Oral administrations with 200mL of tap water, in sitting position in fast condition. Single administration on Day 1 at T0h around 8 a.m.

Name of the compound:	Placebo
Pharmaceutical formulation:	Oral capsule (1mg, 5 mg, 40mg)
Dose per administration:	**SAD – Part A:** 5, 10, 20, 40and 80 mg **Food Effect Cohort – Part A:** 20mg
Number of capsules per administration:	From 1 to 4 capsules
Timing for administration:	Oral administrations with 200mL of tap water, in sitting position in fasted condition. Single administration on Day 1 at T0h around 8 am. A single administration on D-1 morning will be also performed of the same number of capsules than in D1 morning for each subject.

Food Effect Cohort – Part A

Name of the compound:	JP-2266
Pharmaceutical formulation:	Oral capsule (1 mg, 5 mg, 40mg)
Dose per administration:	20 mg
Number of capsules per administration:	4 capsules
Timing for administration:	Oral administrations with 200mL of tap water, in sitting position in fasted condition for period 1 and in fed condition (30 minutes after the beginning of the High Fat Breakfast) for period 2 Single administration on Day 1 at T0h around 8 am of each period.

MAD – Part B

Name of the compound:	JP-2266
Pharmaceutical formulation:	Oral capsule (1mg, 5 mg)
Dose per administration:	2, 5, 10 and 20 mg.
Number of capsules per administration:	From 1 to 4 capsules
Timing for administration:	Oral administrations with 200mL of tap water, in sitting position in fasted condition. Repeated administrations from D1 to D15 at T0h (around 8 am).

Name of the compound:	Placebo
Pharmaceutical formulation:	Oral capsule (1 mg, 5 mg)
Dose per administration:	2, 5, 10 and 20 mg
Number of capsules per administration:	From 1 to 4 capsules
Timing for administration:	Oral administrations with 200mL of tap water, in sitting position in fasted condition. Repeated administrations from D1 to D15 at T0h. A single administration on D-1 morning will be also performed of the same number of capsules than in D1 morning for each subject.

5.1.2. Unit form, packaging and labelling

Labelling will be in accordance with local regulatory specifications and requirements.
The following information will be reported on boxes, cases and vials, in French language:

- Name, address and telephone number of sponsor,
- Name of the investigator,
- Trial reference code (Sponsor),
- Packaging batch number ,
- Treatment number,
- Expiry date, in month/year format,
- Pharmaceutical dosage form, route of administration, quantity of dosage units, and name/identifier and strength/potency,
- Directions for use ,
- The storage conditions,
- The mention “Drug for clinical use only”.

Blister JP-2266 labels will bear the following information's:

JP-2266-101-FIH / OP109219.JEI
EudraCT N°2020-000239-39
Sponsor: Jeil Pharmaceutical Co., Ltd.
343, Sapyeong-daero, Seocho-gu, Seoul, Republic of Korea
Tel.: + 82 2 549 7451 **Fax:** + 82 2 542 7451
Legal representative in EU: Eurofins Optimed Lyon
Investigator: Dr Yves Donazzolo
Eurofins Optimed Clinical Research
1 rue des Essarts – 38610 Gières France
Treatment: JP-2266 – capsules of 1, 5 or 40 mg
XX blisters of 10 capsules each
Batch n°:
Expiry Date: _ _/_ _/_ _ _ _
Administration: oral route
To be used in accordance with protocol instructions
To be kept between +01 and +30°C
Drug for Clinical Use Only

Blister JP-2266-Placebo labels will bear the following information's:

JP-2266-101-FIH / OP109219.JEI
EudraCT N°2020-000239-39
Sponsor: Jeil Pharmaceutical Co., Ltd.
343, Sapyeong-daero, Seocho-gu, Seoul, Republic of Korea
Tel.: + 82 2 549 7451 **Fax:** + 82 2 542 7451
Legal representative in EU: Eurofins Optimed Lyon
Investigator: Dr Yves Donazzolo
Eurofins Optimed Clinical Research
1 rue des Essarts – 38610 Gières France
Treatment: JP-2266 placebo– capsules of 1, 5 or 40 mg
XX blisters of 10 capsules each
Batch n°:
Expiry Date: _ _/_ _/_ _ _ _
Administration: oral route
To be used in accordance with protocol instructions
To be kept between +01 and +30°C
Drug for Clinical Use Only

Unitary dose labels will bear the following information's:

JP-2266-101-FIH / OP109219.JEI **EudraCT N°2020-000239-39** **Sponsor:** Jeil Pharmaceutical Co., Ltd. **Dr Yves Donazzolo** Treatment: JP-2266 or Placebo Pharmaceutical form: Oral capsule Inclusion N°: 001-_ _ _ _ Dose: XX mg (XX capsules of XX mg) Administration: oral route, in sitting position with 200ml of tap water, in fasted/fed* condition To be used in accordance with protocol instructions Batch n°: PREP202_ _ _ _ Expiry Date: _ _/_ _/_ _ _ _ Administration of **PX**DX :** _ _/_ _/_ _ _ _ To be kept between +01 and +30°C **Drug for Clinical Use Only**

* To be adapted for each administration

** Only for Part A – Food Effect Cohort

The address and telephone number of the main contact for information on the product, clinical trial and for emergency contact will be displayed on study cards that subjects will have been instructed to keep in their possession at all times.

5.1.3. Route and mode of administration

Part A: Singe Ascending Dose

JP-2266 or placebo will be administered orally, at T0h in sitting position, in fasted conditions, with 200 ml of water.
Subject will receive once the study treatment.

A single dose of Placebo will be administered orally on D-1, at T-24h, in sitting position, in fasting condition, with 200 ml of tap water.
Subject will receive once Placebo as a single dose on D-1 morning around 8 a.m. The same number of capsules as in D1 morning will be given in blind condition for subjects.

Treatments will be administered under the supervision of the Investigator, in the Clinical Pharmacology Unit EUROFINS OPTIMED, around 8 a.m.
The actual time of drug administration will be documented in the individual eCRF.

Part A: Food effect Cohort

Treatment will be administered orally, at T0h in sitting position, in fed conditions, with 200 ml of water.
Subject will receive twice the study treatment.

A single dose of Placebo will be administered orally on D-1 of each period, at T-24h, in sitting position, in fasting condition, with 200 ml of tap water, by 8 a.m.
The same number of capsules as in D1 morning will be given in blind condition for subjects.

Treatments will be administered under the supervision of the Investigator, in the Clinical Pharmacology Unit EUROFINS OPTIMED, by 8 a.m.
The actual time of drug administration will be documented in the individual eCRF.

Part B: Multiple Ascending Dose

Treatment will be administered orally, at T0h in sitting position, in fasted conditions, with 200 ml of water. Subject will receive 15 times the study treatment (from D1 to D15).
Repeated administrations will be performed at the same times with an authorised window of ±5 minutes.

A single dose of Placebo will be administered orally on D-1, at T-24h, in sitting position, in fasting condition, with 200 ml of tap water, by 8 a.m.
The same number of capsules as in D1 morning will be given in blind condition for subjects.

Treatments and placebo will be administered under the supervision of the Investigator, in the Clinical Pharmacology Unit EUROFINS OPTIMED, by 8 a.m.
The actual time of drug administration will be documented in the individual eCRF.

5.2. Accountability procedures for the investigational product(s)

5.2.1. Responsibilities

The Investigator, the pharmacist or other personnel allowed to store and dispense IMP will be responsible for ensuring that the Investigational Treatment used in the study is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.
The IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained.

5.2.2. Accountability

Details of the quantities of each medication dispensed will be entered onto the accountability form. At the end of the study, the amount of each product retained (if required) in the Clinical Unit and the remaining amount (if any) to be returned to the Sponsor will also be entered. A copy of the form will then be sent to the Sponsor, together with any remaining medication (see section 5.2.3).

Specific procedures for the IMP preparation, dispensation, storage and destruction when required will be detailed in the “pharmacy manual for study JP-2266-101-FIH / OP109219.JEI”. This document will be supplied by the pharmacist of Eurofins Optimed and approved by the sponsor, apart from the study protocol.

5.2.3. Return and /or destruction of IMP

Investigational medicinal product reconciliation must be performed at the site by the Investigator (or the pharmacist) and the monitoring team using the appropriate form countersigned by the Investigator (or the pharmacist) and the monitoring team.

All partially used or unused treatments will be returned to the Sponsor. A detailed of the accounting of treatment returned supplies will be established with the Investigator (or the pharmacist) and countersigned by the Investigator (or the pharmacist) and the Monitoring Team.

A written authorization for destruction will be given by the clinical trial team once the investigational medicinal product reconciliation is achieved. This destruction will be performed by the pharmacist or delegated person and a certificate of destruction will provided.

5.3. Medication(s)/treatment(s) permitted and no permitted before and/or during the trial

No concomitant therapy (prescribed or non-prescribed drug included OTC) will be allowed during the study, except paracetamol to 3g/day. However, in case of intercurrent illness or emergency, the investigator is allowed to use any needed medication.
This must be done with a particular attention to the available pharmacological knowledge of the given medication and possible interaction(s) with the study drug. In case of intake of any concomitant medication during the study, the following information must be noted in the relevant section of the CRF:

- Name of the treatment and its form,
- Reasons for prescription,
- Date and time of start,
- Route of administration,
- Daily dose,
- Duration of treatment.

The decision to withdraw the subject may be made by mutual agreement between the Investigator and the sponsor.

5.4. Procedures of monitoring subject compliance

Administration will be performed under medical supervision. A mouth control will be performed immediately after the administration.

STUDY PROCEDURES

6.1. Screening procedures

Screening procedures occur within 3 weeks (D-21 to D-3 for Part A (SAD/Food Effect Cohort); and D-21 to D-4 for Part B) before starting study medication.

Subject enrolment – Screening visit
Subjects will be selected from Eurofins Optimed's pool of volunteers or recruited via advertisements if necessary (in this case, the advertisement has to be submitted to the Ethics Committee for approval before use).
Dedicated recruitment officers will propose subjects to participate in this study. They will be first informed verbally about the study. Then an appointment will be scheduled at the clinical centre (selection visit).
Before any screening assessment is performed, complete and detailed information about the aim, the consequences and the constraints of the trial will be given by a physician, both verbally and by reviewing the information leaflet and consent form. If subject agrees to perform the study, he will sign the Informed Consent form and a copy of the information leaflet and consent form will be given to subjects.

At the screening visit, each subject will be questioned about his medical history and a physical examination including blood pressure and heart rate measurements will be performed. The subject will undergo the following tests and procedures:

- A medical examination including age, ethnic origin, alcohol, caffeine and nicotine consumptions, previous medication usage, surgical and medical history;
- A complete physical examination including height (cm), weight (kg) and BMI (kg/m²);;
- Body temperature measurement;
- An alcohol breath test;
- Blood pressure (SBP and DBP) and heart rate in both supine position (after at least 10 minutes rest) and standing position (after 2 minutes), using an automatic sphygmomanometer;
- ECG;
- HbA1c measurement;
- Biological screening test, including:
    - Serology test: HBsAg, anti-HCV antibody, anti-HIV 1 and 2 antibodies.
    - Urine drug screen: amphetamines/metamphetamines, benzodiazepines, cannabis, cocaine, opiates and barbiturates.
    - Urinary cotinine
    - Hematology: Haemoglobin, haematocrit, Red Blood Cell count (RBC), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin Concentration (MCHC), White Blood Cell count (WBC) with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelets.
    - Coagulation: APTT, PT, INR.
    - Blood Biochemistry: Fasting glucose, Total protein, Urea, Alanine Serine Transferase (AST), Alanine Leucine Transferase (ALT), Sodium, Alkaline phosphatase, Potassium, Gamma Glutamyl Transferase (GGT), Chloride, Creatinine Phosphokinase (CPK), Triglycerides, Total bilirubin, conjugated and free, total cholesterol, creatinine, creatinine clearance, Blood Urea Nitrogen (BUN), calcium, phosphorus, Lactate Dehydrogenase (LDH), Lipase.
    - Urinalysis: ketones, proteins, glucose, pH (qualitative), specific gravity, bilirubin, urobilinogen, nitrites, occult blood, WBC(s). Microscopy (Urine RBC, Urine WBC, Urine Epithelial Cell, Urine Crystals, Urine casts, Urine bacteria, Urine Epithelial Renal Cell).
    - Urine: electrolytes test (Sodium, Potassium, Chloride, Calcium, Phosphorus).

6.2. Description by type of visit

Part A – Single Ascending Dose

D-2

- Subject admission;
- Alcohol breath test and urine drug screen including urinary cotinine;
- AE/Concomitant medication check;

D-1

- Eligibility criteria;
- Physical examination;
- AE/Concomitant medication check;
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis) (Pre-dose);
- Blood pressure and heart rate at pre-dose;
- ECG at pre-dose;
- Randomization;
- Placebo administration;
- Urine collection for pharmacodynamic (from D-1 pre-dose to D1 T0h).

D1

- *Before administration*

  - Blood pressure and heart rate;
  - Physical examination;
  - Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests);
  - AE/Concomitant medication check;
  - Blood sampling for pharmacokinetic (Pre-dose);
  - Blood sampling for pharmacodynamic (Pre-dose);
  - Urine collection for pharmacokinetic (Pre-dose);
  - Blood sampling for exploratory genomic ((Pre-dose).

- *Oral administration in fasting condition.*

  - Blood pressure and heart rate at T1h, T2h and T4h;
  - AE/Concomitant medication check;
  - ECG at T2h and T4H;
  - Blood sampling for pharmacokinetic (T0h15, T0h30, T0h45, T1h, T1h30, T2h, T2h30, T3h, T3h30, T4h, T6h, T8h, T10h and T12h);
  - Blood sampling for pharmacodynamic (T0h30, T1h, T1h30, T2h, T3h, T4h, T6h, T8h, T12h);
  - Urine collection for pharmacokinetic (0-4h; 4-8h; 8-12h; 12-24h);
  - Urine collection for pharmacodynamic (0-4h; 4-8h; 8-12h; 12-24h).

D2

- Physical examination at T36h;
- Blood pressure and heart rate (T24h);
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests) at T24h;
- AE/Concomitant medication check (any time);
- ECG (T24h);
- Blood sampling for pharmacokinetic (T24h and T36h);
- Blood sampling for pharmacodynamic (T24h);
- Urine collection for pharmacokinetic (24-48h);
- Urine collection for pharmacodynamic (24-48h).

D3

- Blood pressure and heart rate (T48h);
- AE/Cconcomitant medication check (any time);
- Blood sampling for pharmacokinetic (T48h);
- Blood sampling for pharmacodynamic (T48h);
- Urine collection for pharmacokinetic (48-72h);
- Urine collection for pharmacodynamic (48-72h).

D4

- Blood pressure and heart rate (T72h);
- AE/Concomitant medication check (any time);
- Blood sampling for pharmacokinetic (T72h);
- Blood sampling for pharmacodynamic (T72h);
- Urine collection for pharmacodynamic (72-96h).

D5

- Physical examination at T96h;
- Blood pressure and heart rate (T96h);
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests) at T96h;
- AE/Concomitant medication check (any time);
- ECG (T96h);
- Discharge.

D10 (±2): end of study visit

- Physical examination including body weight;
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests);
- Blood pressure,heart rate and body temperature;
- ECG;
- AE/Concomitant medication check.

Part A – Food Effect Cohort

Period 1 and 2

D-2

- Subject admission;
- Alcohol breath test and urine drug screen including urinary cotinine;
- AE/Concomitant medication check.

D-1

- Eligibility criteria *(only in Period 1)*;
- Physical examination;
- AE/Concomitant medication check;
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis) (Pre-dose);
- Blood pressure and heart rate at pre-dose;
- ECG at pre-dose;
- Randomization *(only in Period 1)*;
- Placebo administration;
- Urine collection for pharmacodynamic (from D-1 pre-dose to D1 T0h).

D1

- *Before administration*

- Blood pressure and heart rate;
- Physical examination;
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests);
- AE/Concomitant medication check;
- Blood sampling for pharmacokinetic (Pre-dose);
- Blood sampling for pharmacodynamic (Pre-dose);
- Urine collection for pharmacokinetic (Pre-dose);
- Blood sampling for exploratory genomic (Pre-dose);

- High fat breakfast *(Period 2 only)*.

- *Oral administration in fast (Period 1) or fed (Period 2) condition.*

  - Blood pressure and heart rate at T1h, T2h and T4h;
  - AE/Concomitant medication check;
  - ECG at T2h and T4H;
  - Blood sampling for pharmacokinetic (T0h15, T0h30, T0h45, T1h, T1h30, T2h, T2h30, T3h, T3h30, T4h, T6h, T8h, T10h and T12h);
  - Blood sampling for pharmacodynamic (T0h30, T1h, T1h30, T2h, T3h, T4h, T6h, T8h, T12h);
  - Urine collection for pharmacokinetic (0-4h; 4-8h; 8-12h; 12-24h);
  - Urine collection for pharmacodynamic (0-4h; 4-8h; 8-12h; 12-24h).

D2

- Physical examination at T36h;
- Blood pressure and heart rate (T24h);
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests) at T24h;
- AE/Concomitant medication check (any time);
- ECG (T24h);
- Blood sampling for pharmacokinetic (T24h and T36h);
- Blood sampling for pharmacodynamic (T24h);
- Urine collection for pharmacokinetic (24-48h);
- Urine collection for pharmacodynamic (24-48h).

D3

- Blood pressure and heart rate (T48h);
- AE/Concomitant medication check (any time);
- Blood sampling for pharmacokinetic (T48h);
- Blood sampling for pharmacodynamic (T48h);
- Urine collection for pharmacokinetic (48-72h);
- Urine collection for pharmacodynamic (48-72h).

D4

- Blood pressure and heart rate (T72h);
- AE/Concomitant medication check (any time);
- Blood sampling for pharmacokinetic (T72h);
- Blood sampling for pharmacodynamic (T72h);
- Urine collection for pharmacodynamic (72-96h).

D5

- Physical examination at T96h;
- Blood pressure and heart rate (T96h);
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests) at T96h;
- AE/Concomitant medication check (any time);
- ECG (T96h);
- Discharge.

D10 (±2): end of study visit

- Physical examination including body weight;
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests);
- Blood pressure, heart rate and body temperature;
- ECG;
- AE/Concomitant medication check.

Part B – Multiple Ascending Dose

D-3

- Subject admission;
- Alcohol breath test and urine drug screen including urinary cotinine;
- AE/Concomitant medication check.

D-2

- AE/Concomitant medication check;
- Oral Glucose Tolerance Test (pre-dose);

- *Oral glucose administration*
  - Oral Glucose Tolerance Test (T0h30; T1h, T1h30, T2h, T3h, T4h).

D-1

- *Before administration*
  - Eligibility criteria;
  - Physical examination (including body weight);
  - AE/Concomitant medication check;
  - Laboratory safety (haematology, coagulation, biochemistry, urinalysis);
  - HbA1c measurement;
  - Phosphorus metabolism (Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D);
  - Urine β2-microglobulin;
  - Blood pressure and heart rate at pre-dose;
  - ECG at pre-dose;
  - Randomization;
  - Blood sampling for pharmacodynamic (insulin) (Pre-dose);

- *Placebo oral administration*

  - AE/Concomitant medication check;
  - Blood pressure and heart rate (T2h, T4h and T6h);
  - ECG (T2h, T4h and T6h);
  - Blood sampling for pharmacodynamics (insulin), (T0h30, T1h, T1h30, T2h, T3h, T4h and T6h);
  - Urine collection for pharmacodynamic (from D-1 pre-dose until D1 pre-dose);
  - 24-hour-urine creatinine level (T0-T24h).

D1

- *Before administration*

  - Blood pressure and heart rate;
  - Physical examination;

- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolytes);
- AE/Concomitant medication check;
- Blood sampling for pharmacokinetic (Pre-dose);
- Blood sampling for pharmacodynamic (glucose), (Pre-dose);
- Urine collection for pharmacokinetic (Pre-dose);
- Blood sampling for exploratory genomic (Pre-dose).

- *Treatment oral administration in fasted condition.*

- Blood pressure and heart rate at T1h, T2h and T4h;
- AE/Concomitant medication check;
- ECG (T2h and T4H);
- Blood sampling for pharmacokinetic (T0h15, T0h30, T0h45, T1h, T1h30, T2h, T2h30, T3h, T3h30, T4h, T6h, T8h, T10h and T12h);
- Blood sampling for pharmacodynamic (plasma glucose), (T0h30, T1h, T1h30, T2h, T3h, T4h, T6h, T8h, T12h);
- Urine collection for pharmacokinetic (0-4h; 4-8h; 8-12h; 12- D2 pre-dose);
- Urine collection for pharmacodynamic (0-4h; 4-8h; 8-12h; 12- D2 pre-dose).

D2

- Physical examination (Pre-dose);
- Blood pressure and heart rate (Pre-dose;
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests) at Pre-dose;
- AE/Concomitant medication check (any time);
- ECG (Pre-dose);
- Study drug administration (T0h);
- Blood sampling for pharmacokinetic (Pre-dose and T12h);
- Blood sampling for pharmacodynamics (plasma glucose) (Pre-dose);
- Urine collection for pharmacokinetic (from D2 pre-dose to D3 pre-dose);
- Urine collection for pharmacodynamic (from D2 pre-dose to D3 pre-dose).

D3

- Blood pressure and heart rate (Pre-dose);
- AE/Concomitant medication check (any time);
- Study drug administration (T0h);
- Blood sampling for pharmacokinetic (Pre-dose);
- Blood sampling for pharmacodynamics (plasma glucose), (Pre-dose);
- Urine collection for pharmacokinetic (from D3 pre-dose to D4 pre-dose);
- Urine collection for pharmacodynamic (D3 pre-dose to D4 pre-dose).

D4

- Blood pressure and heart rate (Pre-dose);
- AE/Concomitant medication check (any time);
- Study drug administration (T0h);
- Blood sampling for pharmacokinetic (Pre-dose);
- Blood sampling for pharmacodynamic (plasma glucose), (Pre-dose);
- Urine collection for pharmacodynamic (from D4 pre-dose to D5 pre-dose).

D5

- Physical examination at Pre-dose;

- Blood pressure and heart rate (Pre-dose);
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolyte tests) at Pre-dose;
- Phosphorus metabolism (Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D) (Pre-dose);
- AE/Concomitant medication check (any time);
- Study drug administration (T0h);
- ECG (Pre-dose).

D6

- Blood pressure and heart rate (Pre-dose);
- AE/Cconcomitant medication check (any time);
- Study drug administration (T0h).

D7

- *Before administration*
  - Blood pressure and heart rate (Pre-dose);
  - AE/Concomitant medication check (any time);
  - Blood sampling for pharmacodynamic (plasma glucose), (Pre-dose);
  - Urine β2-microglobulin (Predose);
  - 24-hour urine creatinine (T0-24h);
  - Blood sampling for pharmacokinetic (Pre-dose);

- *Treatment oral administration in fasted condition.*
  - Urine collection for pharmacokinetic (24h urine collection);
  - Urine collection for pharmacodynamic (24h urine collection).

D8

- Blood pressure and heart rate (Pre-dose);
- AE/Concomitant medication check (any time);
- Study drug administration (T0h).

D9

- Blood pressure and heart rate (Pre-dose);
- AE/Concomitant medication check (any time);
- Study drug administration (T0h).

D10

- *Before administration*
  - Blood pressure and heart rate (Pre-dose);
  - Laboratory safety (haematology, coagulation, biochemistry, urinalysis, and urine electrolyte tests) at Pre-dose;
  - Phosphorus metabolism (Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D) (Pre-dose);
  - AE/Concomitant medication check (any time);
  - ECG (Pre-dose);
  - Blood sampling for pharmacodynamic (plasma glucose), (Pre-dose);
  - Blood sampling for pharmacokinetic (Pre-dose).

- *Treatment oral administration in fasted condition.*
  - Urine collection for pharmacokinetic (24h urine collection);
  - Urine collection for pharmacodynamic (24h urine collection).

D11

- Blood pressure and heart rate (Pre-dose);
- AE/Concomitant medication check (any time);
- Study drug administration (T0h).

D12

- Blood pressure and heart rate (Pre-dose);
- AE/Concomitant medication check (any time);
- Study drug administration (T0h).

D13

- Blood pressure and heart rate (Pre-dose);
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolytes) at Pre-dose;
- AE/Concomitant medication check (any time);
- Blood sampling for pharmacodynamic (plasma glucose), (Pre-dose);
- Study drug administration (T0h);
- Blood sampling for pharmacokinetic (Pre-dose);
- Urine collection for pharmacokinetic (24h urine collection);
- Urine collection for pharmacodynamic (24h urine collection).

D14

- *Before administration*

  - Blood pressure and heart rate;
  - AE/Concomitant medication check;
  - Oral Glucose Tolerance(Pre-dose).

- *Treatment oral administration in fasted condition.*

  - Oral glucose administration (T0h5);
  - Oral Glucose Tolerance Test (T0h35, T1h05, T1h35, T2h05, T3h05, T4h05);
  - AE/Concomitant medication check.

D15

- *Before administration*

  - Blood pressure and heart rate;
  - Physical examination;
  - Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolytes);
  - Urine β2-microglobulin;
  - 24-hour urine creatinine (T0-24h);
  - AE/Concomitant medication check;
  - ECG (pre-dose);
  - Blood sampling for pharmacokinetic (Pre-dose);
  - Blood sampling for pharmacodynamic (plasma glucose and insulin), (Pre-dose);
  - Urine collection for pharmacokinetic (Pre-dose);

- *Treatment oral administration in fasted condition.*

- Blood pressure and heart rate (T1h, T2h and T4h);
- AE/Concomitant medication check;
- ECG (T2h and T4h);
- Blood sampling for pharmacokinetic (T0h15, T0h30, T0h45, T1h, T1h30, T2h, T2h30, T3h, T3h30, T4h, T6h, T8h, T10h and T12h);
- Blood sampling for pharmacodynamic (plasma glucose), (T0h30, T1h, T1h30, T2h, T3h, T4h, T6h, T8h, T12h);
- Blood sampling for pharmacodynamic (serum insulin), (T0h30, T1h, T1h30, T2h, T3h, T4h, T6h);
- Urine collection for pharmacokinetic (0-4h; 4-8h; 8-12h; 12-24h);
- Urine collection for pharmacodynamic (0-4h; 4-8h; 8-12h; 12-24h).

D16

- Physical examination (T24h);
- Blood pressure and heart rate (T24h);
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolytes) at T24h;
- AE/Concomitant medication check (any time);
- ECG (T24h);
- Blood sampling for pharmacokinetic (T24h and T36h);
- Blood sampling for pharmacodynamics (plasma glucose), (T24h);
- Urine collection for pharmacokinetic (24-48h);
- Urine collection for pharmacodynamic (24-48h).

D17

- Blood pressure and heart rate (T48h);
- AE/Concomitant medication check (any time);
- Blood sampling for pharmacokinetic (T48h);
- Blood sampling for pharmacodynamics (plasma glucose), (T48h);
- Urine collection for pharmacokinetic (48-72h);
- Urine collection for pharmacodynamic (48-72h).

D18

- Blood pressure and heart rate (T72h);
- AE/Concomitant medication check (any time);
- Blood sampling for pharmacokinetic (T72h);
- Blood sampling for pharmacodynamics (plasma glucose), (T72h);
- Urine collection for pharmacodynamic (72-96h).

D19

- Physical examination including weight (T96h);
- Blood pressure and heart rate (T96h);
- Laboratory safety (haematology, coagulation, biochemistry, urinalysis and urine electrolytes) at T96h;
- HbA1c measurement;
- Phosphorus metabolism (Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D) (T96h);
- AE/Concomitant medication check (any time);
- ECG (T96h);
- Discharge.

D24 (±2): end of study visit

- Physical examination including weight and body temperature;
- Laboratory safety (haematology, coagulation, biochemistry urinalysis and urine electrolytes);
- Urine β2-microglobulin;
- Blood pressure and heart rate;
- ECG;
- AE/Concomitant medication check.

6.3. Diet and Study restriction(s)

On the administration days, the subjects will be allowed to eat at the following times relative to drug administration:

Part A (SAD and Food Effect Cohort Period 1 only)
- T2 standardized breakfast only on D2 to D5;
- T4h standardized lunch;
- T12h standardized dinner.

Part B from D-1 to D15
- T2h standardized breakfast on D2 to D13, and D16 to D18;
- T4h standardized lunch on D-2, D-1, D1, D14 and D15 and T5h standardized lunch on the other days;
- T12h standardized dinner.

Meals should always be taken after the PK sampling, in case both coincide.

IP administration for both Part A/SAD and Part B/MAD will be performed in fasting condition for at least 4 hours when full PK/PDy samples are performed, and for at least 2 hours when only one PK or PDy sample is performed.
SAD:
- Fasting condition for at least 4 hours on Day 1.
- Fasting condition for at least 2 hours on Days 2 to 5.

MAD:
- Fasting condition for at least 4 hours on Days -2, -1, 1, 14 and 15.
- Fasting condition for at least 2 hours on Days 2 to 13 and 16 to 18.

For Part A/Food Effect Cohort, a high fat breakfast will be taken 30 min before drug administration on P2D1. The high fat breakfast ingredients are described in annexe (regulatory FDA breakfast for food-effect studies).

For all parts, during IP administrations, water will not be allowed between 1hour before the administration and 2 hours after the administration.
On the other hospitalization days, water supply will be between 1.5 and 2L for each 24-hour period.

During the hospitalization, the subject will be restricted to indoor activities (no exercise), rest and will not leave the Clinical Pharmacology Unit.
Apart from the hospitalization times, the subject will be requested to follow a stable lifestyle throughout the duration of the trial with no sport activity.
Throughout the duration of the study, the consumption of nicotine will be completely prohibited.
The consumption of alcohol and xanthine bases-containing beverages will be allowed between screening and 24 hours before the first hospitalization but will be stopped at least 24 h before the first hospitalization and throughout the study duration.

The consumption of caffeine-containing foods (coffee, tea (black tea and green tea, etc.), carbonated drinks, coffee milk, nourishment drink, etc.) will be stopped during the period from 24 hours prior to the first hospitalization to the last discharge.
The consumption of grapefruit and grapefruit-containing products will be stopped at least 24 hours before the first hospitalization and throughout the study duration.

Subjects participating in the study should use an adequate contraceptive method from the time of informed consent signature up to 1 month after last IMP administration. Furthermore, it is recommended that subjects with partners of childbearing potential use a highly effective method of birth control defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion.

6.4. Sampled blood volume

The total amount of blood collected during the study will be approximately:

	SAD Part	Food Effect Cohort	MAD Part
Biology	60 mL	85 mL	107 mL
Pharmacokinetic	76 mL	152 mL	168 mL
Pharmacodynamic	34 mL	64 mL	94 mL
Pharmacogenetic	5 mL	5 mL	5 mL
Total Volume	175 mL	306 mL	374 mL

7. ASSESSMENT OF PHARMACOKINETIC OR EFFICACY EVALUATION

7.1. Specification of the pharmacokinetic/efficacy parameters

The following pharmacokinetic parameters will be determined from plasma concentrations:

- C_{max} (ng/mL): observed maximum plasma concentration;
- C_{min} (ng/mL): observed minimum plasma concentration;
- t_{max} (h): first time to reach Cmax;
- $t_{1/2}$ (h): plasma elimination half-life;
- $AUC_{0\text{-}24h}$ (ng/mL*h): area under the plasma concentration curve from administration up to the last quantifiable concentration at time 24h;
- $\%AUC_{extra}$: Percentage of extrapolated AUC0-∞
- AUC_{last} (ng/mL*h): area under the plasma concentration curve from administration up to the last quantifiable concentration at time t;
- AUC_{inf} (ng/mL*h): area under the plasma concentration-time curve from administration up to infinity with extrapolation of the terminal phase;
- Cl/F: Clearance;
- Kel (h): elimination rate constant;

- F_{rel}: The relative bioavailability in fed condition compared to that in fasting condition will be obtained by the ratio of individual AUC_{inf} values obtained after administration in each condition (fasting condition being the reference formulation) (For food effect cohort – Part A only);
- R: accumulation ratio (for Part B only);
- Vd/F: volume of distribution.

The following pharmacokinetic parameters will be determined from urine concentrations:

- - Clr : renal clearance;
- - %fe : fraction of the dose excreted in urine.
- $Ae_{0\text{-}24h}$: cumulative amount of drug excreted unchanged in urine between 0 and 24 hours.
- Ae_{last}: amount of drug excreted unchanged in urine between 0 and the last time of collection.

7.2. Methods and timing for assessing, recording, and analysing pharmacokinetic/efficacy parameters

7.2.1. Collection, treatment and storage of blood samples

Blood sampling will be performed for plasma concentration measurements at the exact time-points with an authorised time-window described in the table below:

Part A - SAD

Day	Sampling time	Sample N°	Time window(min)
1	T0 (predose)	P00	within 60 min before administration
	T0h15min	P01	+/-1
	T0h30min	P02	+/-1
	T0h45min	P03	+/-1
	T1h00	P04	+/-5
	T1h30min	P05	+/-5
	T2h	P06	+/-5
	T2h30min	P07	+/-5
	T3h	P08	+/-5
	T3h30	P09	+/-5
	T4h	P10	+/-5
	T6h	P11	+/-5
	T8h	P12	+/-5
	T10h	P13	+/-5
	T12h	P14	+/-5
2	T24h	P15	+/-15
	T36h	P16	+/-15
3	T48h	P17	+/-15
4	T72h	P18	+/-15

Part A – Food Effect Cohort

Day Period 1	Sampling time	Sample N°	Time window(min)
1	T0 (predose)	P00	within 60 min before administration
	T0h15min	P01	+/-1
	T0h30min	P02	+/-1
	T0h45min	P03	+/-1
	T1h00	P04	+/-5
	T1h30min	P05	+/-5
	T2h	P06	+/-5
	T2h30min	P07	+/-5
	T3h	P08	+/-5
	T3h30	P09	+/-5
	T4h	P10	+/-5
	T6h	P11	+/-5
	T8h	P12	+/-5
	T10h	P13	+/-5
	T12h	P14	+/-5
2	T24h	P15	+/-15
	T36h	P16	+/-15
3	T48h	P17	+/-15
4	T72h	P18	+/-15

Day Period 2	Sampling time	Sample N°	Time window(min)
1	T0 (predose)	P19	within 60 min before administration
	T0h15min	P20	+/-1
	T0h30min	P21	+/-1
	T0h45min	P22	+/-1
	T1h00	P23	+/-5
	T1h30min	P24	+/-5
	T2h	P25	+/-5
	T2h30min	P26	+/-5
	T3h	P27	+/-5
	T3h30	P28	+/-5
	T4h	P29	+/-5
	T6h	P30	+/-5
	T8h	P31	+/-5
	T10h	P32	+/-5
	T12h	P33	+/-5
2	T24h	P34	+/-15
	T36h	P35	+/-15
3	T48h	P36	+/-15
4	T72h	P37	+/-15

Part B – MAD

Day	Sampling time	Sample N°	Time window(min)
1	T0 (predose)	P00	within 60 min before administration
	T0h15min	P01	+/-1
	T0h30min	P02	+/-1
	T0h45min	P03	+/-1
	T1h00	P04	+/-5
	T1h30min	P05	+/-5
	T2h	P06	+/-5
	T2h30min	P07	+/-5
	T3h	P08	+/-5
	T3h30	P09	+/-5
	T4h	P10	+/-5
	T6h	P11	+/-5
	T8h	P12	+/-5
	T10h	P13	+/-5
	T12h	P14	+/-5
2	T0 (predose)	P15	+/-15
	T12h	P16	+/-15
3	T0 (predose)	P17	+/-15
4	T0 (predose)	P18	+/-15
7	T0 (predose)	P19	within 60 min before administration
10	T0 (predose)	P20	within 60 min before administration
13	T0 (predose)	P21	within 60 min before administration
15	T0 (predose)	P22	within 60 min before administration
	T0h15min	P23	+/-1
	T0h30min	P24	+/-1
	T0h45min	P25	+/-1
	T1h00	P26	+/-5
	T1h30min	P27	+/-5
	T2h	P28	+/-5
	T2h30min	P29	+/-5
	T3h	P30	+/-5
	T3h30	P31	+/-5
	T4h	P32	+/-5
	T6h	P33	+/-5
	T8h	P34	+/-5
	T10h	P35	+/-5
	T12h	P36	+/-5
16	T24h	P37	+/-15
	T36h	P38	+/-15
17	T48h	P39	+/-15
18	T72h	P40	+/-15

Blood handling procedures: at each time point indicated in the table, at least 4 mL blood sample should be drawn into K_2EDTAVacutainer® tube. The blood samples will be gently inverted a few times for

complete mixing with the anticoagulant. The exact time of sample collection will be recorded on the eCRF. Within 30 minutes after blood collection, each blood sample will be centrifuged at 2500 *g* for 10 minutes at 4°C.
Within 15 minutes after the centrifugation, the top layer of human plasma will be transferred into 2 pre-labelled polypropylene tubes. Each tube will contain approximately 800µL of plasma.
Blood cells should not be transferred. All sample tubes must be clearly and appropriately labelled. Tubes will be capped immediately after each time point and the plasma will be frozen within 15 minutes in an upright position at –80+/-10°C for storage.

Blood handling procedures will be confirmed following the validation of the method and will be described in a Laboratory Manual before the inclusion of the first subject.

Blood Samples Transport:
Samples will be sent to laboratory Eurofins ADME Bioanalyses for analysis. The shipment will be done in a dry ice by a specialized carrier. Temperatures will be monitored using data logger during all transport. The 2 sets will be sent frozen separately.

7.2.2. Collection, treatment and storage of urine samples

Part A – SAD and Food Effect Cohort

Urine collection will be performed for JP-2266 urine concentration measurements, at the following time points: D1Predose,]D1T0h – D1T4h],]D1T4h – D1T8h],]D1T8h – D1T12h],]D1T12h – D2T24h],]D2T24h – D3T48h],]D3T48h – D4T72h]. A 30-minutes time frame is allowed at each time window.

Part B – MAD

Urine collection will be performed for JP-2266 urine concentration measurements, at the following time points:

- D1Predose,]D1T0h – D1T4h],]D1T4h – D1T8h],]D1T8h – D1T12h],]D1T12h – D2 pre-dose],]D2 pre-dose – D3 pre-dose],]D3 pre-dose – D4 pre-dose].

- 24-hour urine collection on: D7, D10 and 13.

- D15Predose,]D15T0h – D15T4h],]D15T4h – D15T8h],]D15T8h – D15T12h],]D15T12h – D16T24h],]D16T24h – D17T48h],]D17T48h – D18T72h].

A 30-minutes time frame is allowed at each time window.

Urine handling procedures:

The collected urine volume of each collection time period will be carefully measured by weight and recorded in the eCRF, as well as the exact start and stop time of the collection interval. Each fraction of collected urine will be homogenized and 2 aliquots of 3 mL per interval will be kept and stored at -80+/-10°C.

Urine handling procedures will be confirmed following the validation of the method and will be described in a Laboratory Manual before the inclusion of the first subject

Urine Samples Transport:
Samples will be sent to laboratory Eurofins ADME Bioanalyses for analysis. The shipment will be done in a dry ice by a specialized carrier. Temperatures will be monitored using data logger during all transport. The 2 sets will be sent frozen separately.

7.3. Analytical method

JP-2266 concentrations will be determined in plasma and urine by a validated Liquid Chromatography MS/MS methods referenced PKH/MOA/1239 and PKH/MOA/1240 at EUROFINS ADME BIOANALYSES. Concentrations will be expressed in ng/mL.

The pharmacokinetic parts for JP-2266 will be described in a bioanalytical and pharmacokinetic protocols referenced 19-893b and 19-893c at EUROFINS ADME BIOANALYSES.

8. ASSESSMENT OF PHARMACODYNAMIC EVALUATION

8.1. Specification of the pharmacodynamic parameters

The following pharmacodynamic parameters will be determined from plasma concentrations:

- AUEC;
- E_{max}: maximum response;
- ΔE_{max}

The following pharmacodynamic parameters will be determined from urine concentrations:

- AE, cumulative at each time point

8.2. Methods and timing for assessing, recording, and analysing pharmacodynamic parameters

8.2.1. Collection, treatment and storage of blood samples

Blood sampling will be performed for glucose and insulin concentration measurements at the exact time-points with an authorised time-window described in the table below:

Part A – SAD

Pharmacodynamic for plasma glucose:

Day	Sampling time	Sample N°	Time window(min)
1	T0 (predose) T0h30min T1h00 T1h30min T2h T3h T4h T6h T8h T12h	G00 G01 G02 G03 G04 G05 G06 G07 G08 G09	within 60 before administration +/-1 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5
2	T24h	G10	+/-15
3	T48h	G11	+/-15
4	T72h	G12	+/-15

Part A – Food Effect Cohort
Pharmacodynamic for plasma glucose:

Day Period 1	Sampling time	Sample N°	Time window(min)
1	T0 (predose)	G00	within 60 before administration
	T0h30min	G01	+/-1
	T1h00	G02	+/-5
	T1h30min	G03	+/-5
	T2h	G04	+/-5
	T3h	G05	+/-5
	T4h	G06	+/-5
	T6h	G07	+/-5
	T8h	G08	+/-5
	T12h	G09	+/-5
2	T24h	G10	+/-15
3	T48h	G11	+/-15
4	T72h	G12	+/-15

Day Period 2	Sampling time	Sample N°	Time window(min)
1	T0 (predose)	G13	within 60 before administration
	T0h30min	G14	+/-1
	T1h00	G15	+/-5
	T1h30min	G16	+/-5
	T2h	G17	+/-5
	T3h	G18	+/-5
	T4h	G19	+/-5
	T6h	G20	+/-5
	T8h	G21	+/-5
	T12h	G22	+/-5
2	T24h	G23	+/-15
3	T48h	G24	+/-15
4	T72h	G25	+/-15

Part B – MAD

Pharmacodynamic for plasma glucose:

Day	Sampling time	Sample N°	Time window(min)
1	T0 (predose) T0h30min T1h00 T1h30min T2h T3h T4h T6h T8h T12h	G00 G01 G02 G03 G04 G05 G06 G07 G08 G09	within 60 before administration +/-1 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5
2	T0 (predose)	G10	+/-15
3	T0 (predose)	G11	+/-15
4	T0 (predose)	G12	+/-15
7	T0 (predose)	G13	within 60 before administration
10	T0 (predose)	G14	within 60 before administration
13	T0 (predose)	G15	within 60 before administration
15	T0 (predose) T0h30min T1h00 T1h30min T2h T3h T4h T6h T8h T12h	G16 G17 G18 G19 G20 G21 G22 G23 G24 G25	within 60 before administration +/-1 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5 +/-5
16	T24h	G26	+/-15
17	T48h	G27	+/-15
18	T72h	G28	+/-15

Pharmacodynamic for serum insulin:

Day	Sampling time	Sample N°	Time window(min)
-1	T0 (predose)	I00	within 60 before administration
	T0h30min	I01	+/-1
	T1h00	I02	+/-5
	T1h30min	I03	+/-5
	T2h	I04	+/-5
	T3h	I05	+/-5
	T4h	I06	+/-5
	T6h	I07	+/-5
15	T0 (predose)	I08	within 60 before administration
	T0h30min	I09	+/-1
	T1h00	I10	+/-3
	T1h30min	I11	+/-3
	T2h	I12	+/-5
	T3h	I13	+/-5
	T4h	I14	+/-5
	T6h	I15	+/-5

Blood handling procedures will be described in the laboratory manual established between Oriade Noviale and Eurofins Optimed before the first inclusion.

The pharmacodynamics assessment for serum insulin and plasma glucose will be performed by the Groupe Oriade Noviale, Mr Bernard CADOUX, 83 Avenue Gabriel Péri, 38400 St Martin d'Hères, FRANCE.

Part B – MAD - Oral Glucose Tolerance Test

The following pharmacodynamic parameters will be determined from glucose plasma concentrations following OGTT:

- AUEC;
- E_{max}: maximum response;
- ΔE_{max}.

Blood sampling will be done at predose, T0h30, T1h, T1h30, T2h, T3h and T4h on D-2 and D14 (after oral glucose administration).

The pharmacodynamics assessment of glucose plasma concentration will be performed by the Groupe Oriade Noviale, Mr Bernard CADOUX, 83 Avenue Gabriel Péri, 38400 St Martin d'Hères, FRANCE.

8.2.2. Collection, treatment and storage of urine samples

Part A – SAD and Food Effect Cohort

Urine collection will be performed for urine glucose excretion measurements, at the following time points: from D-1 predose to D1 predose,]D1T0h – D1T4h],]D1T4h – D1T8h],]D1T8h – D1T12h],]D1T12h –

D2T24h],]D2T24h – D3T48h],]D3T48h – D4T72h],]D4T72h – D5T96h]. A 30-minutes time frame is allowed at each time window.

Part B – MAD

Urine collection will be performed for urine glucose excretion measurements, at the following time points:

- from D-1 predose to D1 predose,]D1T0h – D1T4h],]D1T4h – D1T8h],]D1T8h – D1T12h],]D1T12h – D2 pre-dose],]D2 pre-dose – D3 pre-dose],]D3 pre-dose – D4 pre-dose],]D4 pre-dose – D5 pre-dose].

- 24-hour urine collection on: D7, D10 and 13.

-]D15T0h – D15T4h],]D15T4h – D15T8h],]D15T8h – D15T12h],]D15T12h – D16T24h],]D16T24h – D17T48h],]D17T48h – D18T72h],]D18T72h – D19T96h].

A 30-minutes time frame is allowed at each time window.

Urine handling procedures:

The collected urine volume of each collection time period will be carefully measured by weight and recorded in the eCRF, as well as the exact start and stop time of the collection interval. Each fraction of collected urine will be homogenized and 1 aliquot of 5 mL per interval will be kept and stored between 2 and 8°C until the shipment to Oriade Noviale.

Urine Samples Transport:

Samples will be sent to laboratory Oriade Noviale for analysis.

8.3. Analytical methods

The pharmacodynamics analytical methods will be described in a bioanalytical protocol at Oriade Noviale.

9. ASSESSMENT OF SAFETY

9.1. Specification of safety parameters

9.1.1. Clinical parameters

9.1.1.1. Blood pressure and heart rate

Vital signs consist of systolic (SBP) and diastolic (DBP) blood pressures and heart rate.
The measurements should be made after at least 10 minutes rest in the supine position and after 2 minutes in the standing position, before venepuncture when times of each coincide (except predose).

9.1.1.2. Physical examination

A physical examination including weight and evaluation of main body systems/regions, including: skin and mucous, ears/nose/throat, pulmonary, cardiac, gastro-intestinal and neurological systems.

In case of abnormality, a comment will be recorded in the eCRF.

9.1.1.3. Electrocardiogram (ECG)

Twelve-lead ECGs will be recorded after at least 10 minutes in supine position using a Cartouch Cardionics® Device.
ECGs should always be recorded before the PK sampling (if any), except predose.
Each ECG consists of a 10 second recording of the 12 leads simultaneously, leading to a12-lead ECG (25 mm/s, 10mm/mV) print-out with HR, PR, QRS, QT, QTc automatic correction evaluation, including date, time, initials and number of the subject, signature of the research physician, and at least 3 complexes for each lead. The Investigator medical opinion and automatic values will be recorded in the eCRF. This print-out will be retained at the site level.

9.1.2. Biological parameters

9.1.2.1. Routine laboratory observations

Before the subject is allowed to enter the study a complete biological test will be obtained and the absence of clinically significant abnormalities confirmed by the Investigator.
The biological tests will be performed by the Groupe Oriade Noviale, Mr Bernard CADOUX, 83 Avenue Gabriel Péri, 38400 St Martin d'Hères, FRANCE.

The complete biological test comprises:

- Hematology:
  Hemoglobin, hematocrit, Red Blood Cells (RBC), White Blood Cells (WBC), differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC);
- Coagulation:
  INR, PT, aPTT;
- HbA1c measurement;

- Biochemistry:
  - Blood Biochemistry: Fasting glucose, Total protein, Urea, Alanine Serine Transferase (AST), Alanine Leucine Transferase (ALT), Sodium, Alkaline phosphatase, Potassium, Gamma Glutamyl Transferase (GGT), Chloride, Creatinine Phosphokinase (CPK), Triglycerides, Total bilirubin, conjugated and free, total cholesterol, creatinine, creatinine clearance, Blood Urea Nitrogen (BUN), calcium, phosphorus, Lactate Dehydrogenase (LDH), lipase.
- Phosphorus metabolism (Part B only):
  Parathyroid hormone, 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D.

9.1.2.2. Oral Glucose Tolerance Test

Glucose determination at predose and T0.5, T1, T1.5, T2, T3 and T4h after 75g oral glucose intake.

9.1.2.3. Urinalysis

The urinalysis qualitative tests will be performed by Eurofins-Optimed.

Urinalysis:

- ketones, proteins, glucose, pH (qualitative), specific gravity, bilirubin, urobilinogen, nitrites, occult blood, WBC(s).

Quantitative result will be performed by the Groupe Oriade Noviale, Mr Bernard CADOUX, 83 Avenue Gabriel Péri, 38400 St Martin d'Hères.

- The following tests will be performed by Oriade Noviale:Electrolytes (Sodium, Potassium, Chloride, Calcium, Phosphorus).
- 24-hour urine creatinine level.
- microscopy (Urine RBC, Urine WBC, Urine Epithelial Cell, Urine Crystals, Urine casts, Urine bacteria, Urine Epithelial Renal Cell).
- β2 mincroglobulin.

9.1.2.4. Drug of abuse screening tests

Drug of abuse screening tests will be performed, at Eurofins Optimed, on urine samples.
Screened drugs are amphetamines/metamphetamines, barbiturates, benzodiazepines, cannabis, cocaine, opiates. Urinary cotinine will also be performed.

9.1.2.5. Serologies

It will consist of the determination of: HBs antigen (hepatitis B antigen), anti HCV antibody, anti HIV 1 and 2 antibodies.

9.1.3. Other parameters

9.1.3.1. Alcohol breath test

An alcohol breath test will be performed at the centre, at screening and for the Part A/SAD at D-2, at D-2 of each period for Part A/Food Effect Cohort and at D-3 for the Part B. The test will be performed using the alcohol breath device ref 7410 plus Drager.

10. ADVERSE EVENT AND REPORTING

10.1.1. Definitions

By the following is understood:
Adverse Event, any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment/product.
Adverse Drug Reaction, all untoward and unintended responses to an IMP related to any dose administered i.e. any AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship with the IMP. The expression “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event or Reaction, a Serious Adverse Event (SAE) or Reaction (SAR) is any untoward medical occurrence or effect that at any dose:

- Results in death;
- Is life-threatening (at the time of the event);
- Requires in patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important medical event: important medical reactions that may not be immediately life-threatening or results in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the above definition should also usually be considered as serious.

Unexpected adverse reaction, an unexpected adverse reaction is an adverse reaction, whose nature, severity or outcome is not consistent with the applicable medicinal product information i.e. the

Investigator's Brochure for an unauthorized IMP or the Summary of Product Characteristics (SmPC) for an authorized product which is being used according to the terms and conditions of the marketing authorization.

The occurrence of a pregnancy of a partner of a trial subject discovered within 1 week after last administration of the IMP, is to be communicated to the Sponsor in an expedited manner with the same procedure and timelines as for SAEs (see paragraph 10.2), independently from the occurrence of an AE.

Suspected Unexpected Serious Adverse Event, a new event related to the conduct of a trial or the development of an IMP likely to affect the safety of subject, such as:

- A SAE which could be associated with the trial procedures and which could modify the conduct of the trial,
- A significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
- A major safety finding from a newly completed animal study
- A temporary half of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor

New events:
New events are defined as new data which might alter the current benefit-risk assessment of the IMP or the trial; modify the use of the IMP, the conduct of the study, or documents related to the trial; or suspend, terminate or modify the clinical trial protocol.

10.1.2. Adverse Event of Special Interest

According to the safety data obtained in pre-clinicla study, no AESI will be specifically evaluated.

10.1.3. Reference documents for expectedness assessment

The reference document for expectedness assessment of SAE related to study product for the present study is the Investigator Brochure currently in force at the time of SAE occurrence.

10.1.4. Recording of events

Any AE (including laboratory test abnormalities, intercurrent illnesses or injuries, and/or study procedures related AE) reported spontaneously by the subjects, or observed by the Investigator, will be recorded according to the procedures in force at EUROFINS OPTIMED / SPONSOR.
Any untoward medical event, which occurs from the time of signed Informed Consent to the time of IMP administration, will be classified as “pre-dose event”. Any untoward medical event which occurs after the completion of the clinical trial and that is possibly reported by the Investigator to EUROFINS OPTIMED / SPONSOR will be classified as a “post-study event”.
Laboratory, vital signs or ECG abnormalities are to be recorded as AE only if:

- Symptomatic, and/or
- Requiring either corrective treatment or clinically significant , and/or
- Leading to IMP/non IMP discontinuation or modification of dosing, and/or
- Fulfilling a serious criterion.

10.1.5. Analysis of events

The Investigator will evaluate the seriousness of any reported event.

The Investigator will also evaluate each event with regard to its severity. The severity of the AEs will be determined in the following manner:

- mild: no interference with the subject's daily activities and does not require mandatory corrective/symptomatic treatment
- moderate: moderate interference with the subject's daily activities and/or requires minimal medical intervention or corrective treatment required
- severe: major and unacceptable interference with the subject's daily activities and requires mandatory corrective/symptomatic treatment, possible hospitalization.

The Investigator will also evaluate the causality of the study treatment/product and any other treatments for each AE, and will transmit the result of this evaluation to the Sponsor. The possible relationship between the AE and the study product/treatment will be quoted as following:

1. probable: good reasons and sufficient documentation to assume a causal relationship;
2. possible: a causal relationship cannot be excluded and remains likely;
3. unlikely: the event is most likely related to another etiology than the trial drug;
4. unrelated;
5. not assessable: impossible to assess, because of insufficient evidence, conflicting data or poor documentation.

The Sponsor will also evaluate the seriousness of all events which are reported to him by the Investigator, and the causality of the study drug and any other treatments for each AE.
AEs for which the Investigator or the Sponsor consider that a causal link with the study product could reasonably be envisaged will be considered to be suspected adverse effects. Should the evaluations of the Sponsor and the Investigator differ with regard to causality, then both will be reported in the declaration of suspected adverse effect.

10.2. Procedures in place for the recording and notification of serious adverse events and intercurrent pathologies

The Investigator will notify the Sponsor without delay on the day of discovery of all SAEs.

The Investigator must:

- **note** in the participant's medical file the date on which he/she become aware of the event (at a follow-up visit or a telephone contact with the participant or a third person, etc);**Immediately inform** by 1) email (with acknowledgement of receipt), or, in case no answer is given, 2) fax or 3)telephone, the persons responsible of Pharmacovigilance:
    - at SPONSOR: PVassociate,
        - email : pvsafety@jeilpharm.co.kr
        - Phone : + 82 2 549 7451
        - Fax: +82 2 542 7451
    - at AIXIAL : Laurène Jaubert
        - email: vigilance@aixial.com
        - Phone:+33 (0) 146 996 812
        - Fax: +33 (0) 146 990 217,

- complete the SAE form and send it by fax or email to the persons responsible designated above, immediately after of being informed of this event, without waiting for the results of the clinical outcome or of additional investigations;
- provide the persons designated above, as they become available, with all relevant information (together with translation into English language) that could contribute to the clarification of the SAE and to the assessment of potential risk for the study subjects and with anonymised copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis (where possible, the results from pre-treatment assessments should be appended for comparison with the results obtained under treatment), or the autopsy report, if autopsy is performed;
- inform the persons designated above of the outcome, if not previously reported, and other relevant follow up information of the SAE as soon as possible;
- fulfil his/her regulatory obligations to the Regulatory Authorities and/or to the Ethics Committee, in accordance with local regulations.

The Investigator must also report all SAEs/SARs in the eCRF by filling in the AE form.
If the SAE is the reason of subject drop-out from the study, the Investigator will detail the reason for such a statement in the comment section of the form.

The minimum criteria to be reported are as follows:
- a suspected investigational medicinal product;
- an identifiable subject (at least study subject identification code number but no subject initials);
- an AE assessed as serious;
- an identifiable reporting source;
- an unique clinical trial identification;
- the opinion of the Investigator about the causal relationship between the event and the IMP.

The outcome of the SAE shall be classified as following:
- recovered/resolved;
- recovering/resolving;
- recovered/resolved with sequelae;
- not recovered/not resolved;
- fatal;
- unknown.

Details should be given for the latter four categories.

Would any SAR occur, the Sponsor will notify immediately the Health Authorities (ANSM), the Ethics Committee (CPP) and the regional Health Agency (ARS). All product administrations will then be stopped for all subjects, and the necessary immediate procedures will be implemented to ensure subject's safety. In this case, the Sponsor will add a complementary report to all 3 authorities within 8 days. If the study is definitively stopped (anticipated cessation), the Sponsor will declare it to ANSM and CPP in the 15 days after the decision is taken. In case the decision is taken to continue the study, then an amendment must be submitted and agreed before the study is continued.
The Sponsor is responsible for all declarations to Ethics Committee and Health Authorities. In the context of the present study, this responsibility is delegated to Eurofins Optimed.

10.3. Type and duration of the follow-up of subjects after adverse events

All AEs will be monitored by the Investigator until a satisfactory outcome is obtained (i.e. the event is resolved or the condition is unlikely to change or the subject is lost to follow-up). All clinical and biological examinations judged necessary by the Investigator will be continued until return to normal. The

Investigator will provide the Sponsor with copies of all examination results and treatments linked to the follow-up of AEs.

10.4. Other safety issues not falling within the definition of SUSAR and Urgent Safety measures

Events may occur during a clinical trial which do not fall within the definition of Suspect Unexpected Serious Adverse Reaction (SUSAR) and thus are not subject to the reporting requirements for SUSARs, even though they may be relevant in terms of subject safety. These events/observations are not to be reported as SUSARs, but they might require other action, such as urgent safety measures, substantial amendments, or early termination of the trial. Examples of *Safety issues other than SUSAR* are:

- new events related to the conduct of a trial or the development of an IMP likely to affect the safety of subjects, such as:
  - a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
  - a significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease,
  - a major safety finding from a newly completed animal study (such as carcinogenicity),
  - a temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor,
- recommendations of the Data Safety Monitoring Board (DSMB), if any, where relevant for the safety of subjects,
- in the case of advanced therapy investigational medicinal products, relevant safety information regarding the procurement or the donor.

For this study in healthy subjects, any SAR will be considered as a new event and treated as such.
The Sponsor will inform with no delay the concerned Competent Authority and the Ethics Committee of safety issues which might materially alter the current benefit-risk assessment of the IMP while not falling within the actions listed above.
In case of occurrence of any new events relating to the conduct of the trial or the development of the IMP where the new event is likely to affect the safety of the subjects, the Sponsor and the Investigator shall take appropriate *urgent safety measures* to protect the subjects against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time.
Urgent safety measures may be taken without prior notification to the national competent authority. However, the Sponsor must inform *ex post* the national competent authority and the Ethics Committee of the Member State concerned of the new events, the measures taken and the plan for further action as soon as possible. The *ex post* notification of urgent safety measures is independent of the obligation to: notify substantial amendments, notify early termination of the trial, and notify adverse events and serious adverse reactions, as per current regulations.

10.5. Modalities for declarations to Authorities (ANSM, CPP, ARS)

The modalities of declaration to ANSM are presented in Appendix II.
CPP and ARS, if applicable, are informed by email and receive the same documents as requested by ANSM.

DATA MANAGEMENT

11.1. Definition of source data

All evaluations that are reported in the eCRF must be supported by appropriately signed identified source documentation related to but not limited to:

- Subject identification, last participation to a clinical trial, medical history, previous and concomitant medication;

- Physical examination, blood pressure and heart rate, body weight, BMI, subject habits;
- Dates and times of study drug administration;
- Pharmacokinetic time points;
- Laboratory assessments, meals;
- AEs.

11.2. Source document requirements

According to the guidelines on GCP, the Monitoring Team must check the CRF / eCRF entries against the source documents, except for the pre-identified source, data directly recorded/enclosed in/to the Case Report Form. The Informed Consent Form will include a statement by which the subject allows the Sponsor's duly authorized personnel and the regulatory authorities to have direct access to source data which supports the data on the Case Report Forms (e.g. subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

11.3. Use and completion of Case Report Forms (CRFs) and additional request

11.3.1.1. Data collection

All clinical data will be reported electronically by the Investigator or authorised designee on a web-based electronic Case Report Form (eCRF). This eCRF is specifically designed for the study and developed by the Data Management Department of Eurofins Optimed using LifeSphere EDC® 5.2 or higher, a validated Electronic Records/Electronic Signature-compliant (21 CFR Part 11) application developed by Aris Global LLC, USA.

Should a correction be made, the corrected information will be entered in the eCRF and the initial information as weel as user who updated the information will be tracked in the audit trail.

11.3.1.2. Responsibilities

The Investigator or authorised designee is responsible for the timeliness, completeness, and accuracy of all observations and other data pertinent to the clinical investigation in the eCRFs.

The Investigator will ensure that all data are entered promptly (within 2 days) after the evaluation has occurred, in accordance with source documents and specific instructions accompanying the eCRFs, designed specifically for the study.
The Data Management Department of Eurofins Optimed will provide all tools, instructions, and training necessary to complete the eCRF, and each user will be issued a unique username and password.
The data management of Eurofins Optimed will be responsible for data processing, in accordance with the CRO data management procedures.

11.3.1.3. Data Management

During the study, through regular data collection and monitoring, clinical data reported in the eCRFs will be integrated into the clinical database. Computerised logic and/or consistency checks will be systematically applied in order to detect errors or omissions. Queries will be generated and submitted through the electronic data capture (EDC) system to the investigator sites for resolution (queries should be answered within 7 days).
Correction will be made either automatically from the immediate completion or following the review of the data during the Eurofins Optimed monitoring. An audit trail, which will be initiated at the time of the first data entry, allows tracking all modifications.
The Data Management Department of Eurofins Optimed may generate additional requests to which the Investigator must respond electronically by confirming or modifying the data questioned. The requests with their responses will be implemented to the eCRFs.

Each step of this process will be monitored through the implementation of individual passwords and regular backups to maintain appropriate database access and to ensure database integrity.
When eCRFs are complete and all queries have been answered, the Investigator has to sign the eCRFs . Then eCRFs are locked and no modification is possible anymore.

After integration of all corrections in the complete set of data, the database will be locked and saved before being released for statistical analysis.
External data provided at the end of the study, eg Pharmacokinetic data, will be handled with SAS® software and data saved with those exported from EDC.

After database lock, a Patient Data Report (PDR) that consists of the printing out an entire casebook for a subject will be generated for each subject in .pdf format. PDR are kept on site's server (or sent by CD-ROM for external sites) and shared to sponsor via secure exchange platform.

12. STUDY MONITORING

EUROFINS OPTIMED will perform the study in accordance with this protocol, GCP and the applicable regulatory requirements and the contract with the Sponsor.
The Investigator is required to ensure compliance with the Investigational Product schedule, visit schedule and procedures required by the protocol. The Investigator agrees to provide all information requested in the Case Report Form in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents to Sponsor representatives.
The Sponsor is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.
Should repeated breaches to the protocol, the GCP or the current regulation in force occur, which the Investigator would not take in account for improvement, then the Monitor would inform the Sponsor of these breaches. The Sponsor will notify these deliberate and repeated breaches to National Health Authorities.

STATISTICS

13.1. Description of the statistical methods

The statistical analysis will consist in individual data listings and descriptive statistics performed by EUROFINS OPTIMED, using the SAS® computer program (release 9.4). Statistics will be provided for each part separately.

Statistical pharmacokinetic analysis will be performed by EUROFINS ADME Bioanalyses using Phoenix WinNonlin® version 8.1 or latest.

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All individual data for all included subjects will be presented in data listings, sorted by subject within dose group for each study part.
Demographic and baseline characteristics data will be summarized by dose group and totaled over all subjects of each study part. On-treatment data will be summarized by dose group or condition group (fasted/fed state for food effect part) and visit.
For parameters with evaluation before dosing and in case of rechecked value(s) for any subject, only the last observation will be used in descriptive statistics and derivations of other parameter values. After dosing, only observations planned in the protocol will be used in descriptive statistics.

13.2. Descriptive statistics

Descriptive statistics for quantitative parameters will be provided using mean, standard deviation (SD), standard error of the mean (SEM), minimum, median, maximum and number of observations. Descriptive statistics for qualitative parameters will be provided using absolute (n) and relative (%) frequencies.

13.3. Subject demographic characteristics, medical history and diagnoses

For Demography, continuous variables (age, height, weight, BMI) and qualitative variables (race) will be summarized in descriptive statistics on each distinct population.
Results of laboratory screen (drug abuse), serology and alcohol breath test will be summarized by visit.
Medical history will be listed and summarized by system organ class and preferred term (Medical Dictionary for Regulatory Activity (MedDRA)), if relevant. Abnormal physical findings at baseline will be listed.

13.4. Previous medications

Previous medications will be coded according to the World Health Organization-Drug Dictionary (WHO-DD). Subjects who took medications that were stopped before the first study drug dosing will be listed.

13.5. Baseline safety parameters

Individual safety data (clinical laboratory, vital signs) measured before the first drug administration will be checked for validity of entrance criteria, and abnormalities will be documented. Individual abnormalities before dosing will be flagged in data listings and presented along with post-dose measurements in the statistical appendices.

13.6. Study drug and concomitant therapy

Drug dispensing information and details of drug dosing (actual products/treatment received, actual dose received, date and time of drug intake) for each subject will be listed by dose group.
Concomitant treatments will be coded according to the World Health Organization-Drug Dictionary (WHO-DD). Subjects who received concomitant treatments along with the study drug will be listed by dose group and subject. If relevant, concomitant medications will also be summarized by anatomic class and therapeutic class for each dose group and totalled over all subjects, presenting the frequency of subjects (n) taking a given medication and the number of occurrence of each medication.

13.7. Pharmacokinetic analysis

Individual JP-2266 plasma concentrations will be presented by dose level and day (if applicable). Descriptive statistics for the plasma concentrations will be presented as mean, SD,Min, and Max, and will be calculated if at least 2/3 of the plasma values per time-point are nonmissing.

For descriptive statistics calculations, concentrations below the limit of quantification will be set to zero (0) before the first concentration equal or above limit of quantification (LOQ) and missing after.

No descriptive statistics will be done on urine JP-2266 concentrations.

Individual PK parameters will be presented by dose level and day (if applicable). Descriptive statistics of the PK parameters will be presented as mean, SD, coefficient of variation (CV%), median, geometric mean (GM), Min, and Max.

In the tables of individual PK parameters, all the deviations from planned analysis will be mentioned by flagging the abnormal results (e.g., percentage of extrapolated AUC > 20%).

A measured plasma drug concentration vs. actual time curve will be produced in graphic for each subject on both linear/linear and log/linear scales. Mean plasma drug concentration vs.time curves will also be produced for each dose level, separately.

Food effect will be investigated through analysis of Cmax , AUCt and AUCinf by mixed ANOVA modes on the logarithmically transformed data including fixed factor for treatment (conditions fasted/fed), period and sequence. A random effect for the subject will be included in the model.

The 90% standard CI limits for relative treatment differences will be calculated by geometric means based on logarithmic transformation of the intra-individual ratios of Cmax , AUCt and AUCinf.

13.8. Pharmacodynamic analysis

Pharmacodynamic parameter value and change will be statistically described by dose group (or condition group for food effect part) and totaled over all subjects for each part. When necessary, comparison among dose groups could be made using either parametric or non-parametric statistical tests.

13.9. Safety analysis

13.9.2 **Adverse event**

AEs will be coded according to the Medical Dictionary for Regulatory Activity (MedDRA), using the most recent available version. This requires that Sponsor has the appropriate license.
AEs will be classified into pre-defined standard categories according to chronological criteria:

- Treatment emergent AEs (TEAE): AEs that occurs for the first time or if present before worsened during an exposure to drug(s).
- Non-treatment emergent AEs (NTEAE): AEs that occurs before the study drug administration (also called “pre-dose event”).

AEs will be individually listed per subject number, presenting: assigned treatment group (or treatment received), verbatim, MedDRA Primary System Organ Class, MedDRA Preferred Term, emergent (yes or no), date and time of onset and disappearance, date and time of last study drug administration before AE, duration, time between last study drug administration and AE onset, frequency, severity and seriousness, relationship to study drug, the required action taken (e.g. corrective treatment, hospitalisation), outcome and if it is a reason for drop-out.
The non-treatment emergent AEs (NTEAEs) will be summarised by System Organ Class and Preferred Term for the safety set. The treatment emergent AEs (TEAEs) will be summarised by Primary System Organ Class, Preferred Term and dose group (or condition group for food effect part) for the safety set. It will consist in the evaluation of the number of AEs and the number and percentage of subjects reporting these AEs by dose group (or condition group) and for all subjects of each part.

13.9.3 Physical examination, ECG and vital signs

Physical examination, ECGs and vital signs recorded during the study will be individually listed and quantitative parameters will be summarised by using descriptive statistics.
For vital signs and ECGs, values and clinically potentially significant abnormalities will be described by dose group and totaled over all subjects.
Change between the value at study baseline and the value at each day(time) point under treatment will be described for each parameter by dose group.
For food effect part, descriptive statistics will be presented by condition group for period data and by sequence group otherwise (detailed method will be provided in the statistical analysis plan).

13.9.4 Laboratory parameters

All laboratory values recorded during the study will be individually listed and flagged for values outside laboratory ranges and for clinical relevance (assessed by investigator). Quantitative parameters will be summarised by descriptive statistics.
Values, position according to laboratory range and clinical assessment will be described at baseline, each scheduled assessment during the treatment phase and at the end of the study for each parameter by dose group and overall. .
Change between the value at study baseline and the value at each scheduled assessment during the treatment phase and at the end of study visit will be described for each parameter by dose group and overall.
For food effect part, descriptive statistics will be presented by condition group for period data and by sequence group otherwise (detailed method will be provided in the statistical analysis plan).

All quantitative and qualitative urinary test results will be listed, sorted by dose group or condition (food effect part).

13.10. Exploratory analysis

Exploratory parameters will be statistically described by dose group (or condition group for food effect part) and totaled over all subjects for each part.

13.11. Sample size

Sample size for this study was based upon empirical considerations corresponding to usual practices in this type of studies. No formal calculation was performed.

13.12. Level of significance to be used

The level of significance will be fixed at 0.05.
Tests will be two-tailed with no multiplicity adjustment.

13.13. Interim Analysis

NA

13.14. Procedure for accounting, for missing, unused, and spurious data

Missing data values will not be replaced.

13.15. Procedures for reporting any deviation(s) from original statistical plan

This plan may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data collection that could affect planned analyses. These revisions will be based on review of the data, and a final plan will be issued prior to database lock, if applicable.

13.16. Selection of subjects to be included in the analyses

In case of incorrect treatment assigned, subjects will be analyzed in the treatment group they actually received.

QUALITY CONTROL AND ASSURANCE

14.1. Quality Assurance

The study will be carried out in conformity with legal conditions and French regulations, and with respect to GCP (ICH E6 R2). The Quality Assurance system in force at EUROFINS OPTIMED will apply, except for any specific clauses added to the protocol or specified in writing by the Sponsor before the start of the study.

14.2. Quality Control

The main study stages (coherence between source and CRF for: eligibility criteria, main evaluation criteria, AEs) will be submitted to a quality control process.

14.3. Sponsor audits and inspections by regulatory agencies

The study may be subjected to on-site audit visit by the Sponsor and inspection by applicable Regulatory Authorities in order to verify the study is conducted in compliance with the principles of GCP and with the study protocol. The auditor/inspectors will have direct access to medical records, source documents, and all documents and facilities relevant to the clinical trial.
The Investigator agrees to allow the auditors/inspectors to have direct access to study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.
The confidentiality of the data verified and the anonymity of the subjects should be respected during these inspections.

ETHICS

15.1. Informed consent form

The persons participating in the study will be selected during a screening visit. During this meeting, the study objectives and methodology will be explained.
The volunteer subjects will receive a synthesis document explaining the requirements of research, the title and the objectives of the study, the detailed research protocol and the risks and constraints of the research.
Before being included in the study, each participant must give his/her written consent. The text of the consent is to be signed and dated and initialled on each page by the subject and dated and signed by the Investigator.

15.2. Ethics Committee and Competent Authorities

The study will be carried out in conformity with the principles of the Declaration of Helsinki as modified in Fortaleza (2013), and National Regulation.
This study will be undertaken after approval by the Ethics Committee (CPP) and of the Competent Authorities (ANSM).

15.3. Protocol amendments

Neither the Investigator nor the Sponsor can modify the protocol without agreement from the other party.
Any protocol modifications must be the topic/matter of an amendment which will be dated and signed by the two parties and must be included as an addendum to the protocol.
Depending on the importance of the changes to the study conditions, the amendment may be sent to the Ethics Committee and/or Health Competent Authorities either for approval or for information.

15.4. Protocol deviations

No deviations are systematically tolerated. Any protocol deviations will be notified to the Monitor/Sponsor on an ongoing basis, and no later than the date of the blind review, and will give rise to a discussion to define their status (minor – major).

15.5. Access to data by the subjects

In conformity with the law, any subjects who so wish may access any data concerning them, at the end of the research. As stated by regulation on data protection, subjects can ask for access, modification, erasement of all their personal data. Such request should be transmitted in writing to DPO ADDRESS, which will reply within 4 weeks.

16. DATA HANDLING AND RECORD KEEPING

16.1. Archival

All documents related to the study must be kept by the Investigator in appropriate files. The archives of the subjects, original informed consent forms, source documents, case report forms, inventory of study products, correspondence with the Sponsor and Ethics committee related to the study, must be filed.
The Investigator authorises direct access to the source documents for monitoring, audits and inspections.
The Investigator keeps a list identifying the subject names (with addresses and/or medical file numbers), their respective code number and the dates of entry into the study and end of study, in order to be able to verify the concordance between the data contained in the case report forms and those in the source documents .

These documents must be kept on the Investigator site until at least fifteen years. Even at the end of this period, no destruction can be achieved unless authorized in writing by a duly mandated Sponsor's representative.
If the Investigator/Institution is no longer able to be responsible for essential documents the Sponsor must be notified in writing of this change and informed as to whom the responsibility has been transferred.

16.2. Confidentiality

All information obtained during the study (except the informed consent form data) will be input onto computer by EUROFINS OPTIMED, subcontracted by the Sponsor in conformity with the "Information Technology and Liberty Law" (Article 40 of 6 January 1978) which respects the European Regulation n°2016/679 on General Data Protection ("GDPR") and its French application MR-001.

16.3. Ownership of results

The Sponsor is the sole owner of the data and research results. He reserves the right to use them in any form whatsoever, to submit them to the Health Authorities of any country.
Should the study generate results likely to be patented, then only the Sponsor will be authorised to depose such a patent, in his name and at his costs.

17. FINANCING AND INSURANCE

The Sponsor certifies that it has taken out a liability insurance policy which covers the current research in accordance with local laws and requirements.
An insurance certificate will be provided to the Investigator in countries requiring this document.

18. PUBLICATION

All information issuing from the study will be considered to be confidential, and must not be divulged without the Sponsor's prior agreement.
The study results may be published or presented by the Investigator or analysis experts, in collaboration with the Sponsor, with the sponsor's written permission. The Sponsor may use the study results for any publication or communication, with the written agreement of the Investigator or the analysis experts if they are cited.

19. REFERENCES

- Investigator Brochure v1.0 dated on 30 January 2020;
- Directive 2001/20/EC of the European Parliament and of the Council on the approximation of laws regulations and administrative provisions of the members states relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use;
- Declaration of Helsinki, 18th World Medical Assembly, Helsinki, Finland 1964, as modified in Fortaleza (2013);
- Code de la Santé Publique (CSP) ;
- ANSM guidelines "Estimation of the starting dose, definition of dose progression and protocol administration to volunteers" September 2006).

LIST OF APPENDICES

APPENDIX I
DECLARATION OF HELSINKI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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APPENDIX II
MODALITIES OF DECLARATION OF VIGILANCE DATA

ansm
Agence nationale de sécurité du médicament et des produits de santé

Explanatory note

Clinical Trial on medicinal products - Vigilance Data Reporting (SUSARs, expected serious adverse reactions and other serious adverse events)

Naming rules of the CIOMS form

- **Suspected unexpected serious adverse reaction (SUSAR)**

> Each SUSAR must be reported in an individual email message.

> It should be sent to: declarationsusars@ansm.sante.fr

> The subject line should be written as follows:

SUSAR_yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT

Ex: SUSAR_20140115_SUBSTANCE_123456789_CT

Particular case:

SUSARs regarding a clinical trial on medicinal products involving healthy volunteers (whatever the clinical trial phase):

> The subject line should be written as follows:

EC-VS-SUSAR_yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT

> The following document should be attached to the message:

- CIOMS form (PDF format) / File name labelled as follows:

yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT_C

Ex: 20140115_SUBSTANCE_123456789_CT_C

> An acknowledgement of receipt will be automatically sent by return email.

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- **Expected serious adverse reaction or other serious adverse event (clinical trials on a medicinal product involving healthy volunteers)**

Expected serious adverse reaction which occured in France :

> Each notification must be reported in an individual email message.

> It should be sent to: declarationsusars@ansm.sante.fr

> The subject line should be written as follows:

EC-VS-EIGA yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT

> The following document should be attached to the message:

- CIOMS form (PDF format) / File name labelled as follows :

yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT_C

> An acknowledgement of receipt will be automatically sent by return email.

Other serious adverse event which occured in France :

> Each notification must be reported in an individual email message.

> It should be sent to: declarationsusars@ansm.sante.fr

> The subject line should be written as follows:

EC-VS-EVIG yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT

> The following document should be attached to the message:

- CIOMS form (PDF format) / File name labelled as follows :

yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT_C

> An acknowledgement of receipt will be automatically sent by return email.

APPENDIX III
FDA RECOMMANDATIONS FOR FOOD-EFFECT STUDIES

Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies
U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER)
December 2002

[…]

D. Test Meal

We recommend that food-effect BA and fed BE studies be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.[4] The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of the meal is significantly different from the one described above, the Sponsor should provide a scientific rationale for this difference. In NDAs, it is recognized that a Sponsor can choose to conduct food-effect BA studies using meals with different combinations of fats, carbohydrates, and proteins for exploratory or label purposes. However, one of the meals for the food-effect BA studies should be the high-fat, high-calorie test meal described above.

E. Administration

Fasted Treatments:

Following an overnight fast of at least 10 hours, subjects should be administered the drug product with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Fed Treatments: Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 hours post-dose. Water can be allowed as desired except for one hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

[4] An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity.