CLINICAL TRIAL PROTOCOL

Protocol N° DNDi-6148-01 / OP105718.DND
EudraCT N° 2018-004023-37

Version N°8.0 - Date: 19-NOV-2020

Sponsor:
DRUGS FOR NEGLECTED DISEASES *initiative (DNDi)*,
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Phase: Phase I, First-in Human trial

A Phase 1, blinded, randomized, single centre, parallel-group, single-dose, dose-escalation, placebo-controlled study of the safety, tolerability, and pharmacokinetics of DNDI-6148 after oral dosing in healthy male subjects

SUMMARY OF CHANGES

Version	Modification	Author	Date	Application
1.0	**Initial Version**	**Eurofins Optimed DNDi**	***26-OCT-2018***	**NA**
2.0	***Following ANSM remarks***	**Eurofins Optimed DNDi**	***04-DEC-2018***	**NA**
3.0	**Update on risks section, inclusion criteria, contraception requirements**	**Eurofins Optimed DNDi**	**07-OCT-2019**	**NA**
4.0	**Update following ANSM intermediate answer**	**Eurofins Optimed DNDi**	**15-NOV-2019**	**as of ANSM approval**
5.0	**Update on the unblinding process**	**Eurofins Optimed DNDi**	**17-DEC-2019**	**as of last signature (non-substantial)**
6.0	**Update the project management team and statistician Update Appendix 2**	**Eurofins Optimed DNDi**	**06-APR-2020**	**as of last signature (non-substantial)**
7.0	**Add new preclinical results and diagnostic test of SARS-CoV-2 Update section 1.2.2 Clinical studies Update section 1.3 Summary of potential risks to humans**	**Eurofins Optimed DNDi**	**17-JUN-2020**	**as of ANSM/CPP approval**
8.0	**Add two ambulatory visits and change one PK sampling time point to complete the pharmacokinetic profile**	**Eurofins Optimed DNDi**	**19-NOV-2020**	**as of ANSM/CPP approval**

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CLINICAL STUDY PROTOCOL AGREEMENT

Protocol N°: DNDi-6148-01 / OP105718.DND

Title: A Phase 1, blinded, randomized, single centre, parallel-group, single-dose, dose-escalation, placebo-controlled study of the safety, tolerability, and pharmacokinetics of DNDI-6148 after oral dosing in healthy male 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.

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SYNOPSIS

Title:	A Phase 1, blinded, randomized, single centre, parallel-group, single-dose, dose-escalation, placebo-controlled study of the safety, tolerability, and pharmacokinetics of DNDI-6148 after oral dosing in healthy male subjects
Study product	DNDI-6148
Protocol No.:	DNDi-6148-01/ OP105718.DND
Sponsor:	**DND*i*,** Chemin Louis Dunant, 15 1202 Geneva - Switzerland
Number of study centers	Single center study
Principal Investigator:	Yves DONAZZOLO, M.D., M.Sc. EUROFINS OPTIMED, GIERES – France
Study Design:	Randomized, blinded, placebo-controlled, single centre, single ascending dose study with DNDI-6148 administered as an oral suspension. Bioanalysis (in plasma and urine) will be performed in open conditions. Decision on dose escalation will be taken in blinded conditions, based on safety data review report and DNDI-6148 plasma exposure.
Study Objectives:	**Primary objective** To assess the safety and tolerability of DNDI-6148 after single oral doses administered as oral suspension of DNDI-6148 in healthy male subjects, compared to matching placebo. **Secondary objective** - To determine AUC_{0-24}, AUC_{0-t}, AUC_{0-t}/D, $AUC_{0-\infty}$, $AUC_{0-\infty}/D$, C_{max}, C_{max}/D for DNDI-6148 in plasma after single oral doses, administered as oral suspension in healthy male subjects. - To determine other PK parameters of DNDI-6148 in plasma and urine after single oral doses administered as oral suspension of DNDI-6148 in healthy male subjects. **Exploratory objective** - To determine PD effect on cardiologic parameters after single oral dose administered as oral suspension of DNDI-6148 in healthy male subjects. - To identify DNDI-6148 main metabolites

Investigational Treatment:	Name of the compound:	DNDI-6148
	Pharmaceutical form:	Powder for oral suspension (bottles of pre-weighted powder corresponding to two strenghts of 60 mg and 600 mg free acid equivalent) Vehicle: ORA-Sweet®
	Dose per administration:	10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 260 mg, 380 mg and 500 mg (free acid equivalent)
	Timing for administration:	Single oral dose administration on D1 according to the randomization. The administration will be performed around 8:00 a.m. in sitting position and in fasting conditions. 250ml of tap water to be administered after dosing.
	DNDI-6148 will be pre-weighted in closed bottles and a suspension will be prepared extemporaneously by the pharmacist prior to administration to volunteers. The powder will be suspended in ORA-Sweet® vehicle, a maximum of 24 hours prior to dosing. Volume of suspension to be administered will vary from 4 to 25 ml per subject.	
	Name of the compound:	DNDI-6148 - Placebo
	Pharmaceutical form:	Powder for oral suspension, vehicle: ORA-Sweet®.
	Dose per administration:	NA
	Timing for administration:	Single oral dose administration on D1 according to the randomization. The administration will be performed around 8:00 a.m. in sitting position and in fasting conditions. 250ml of tap water to be administered after dosing.
Subjects:	**Number of Subjects Planned: 64** Subjects will be healthy male volunteers of Caucasian origin aged between 18 and 50 years. Subjects will be randomized 6 active/2 placebo in sequential approach: the 2 first subjects will be randomized as one under active and one placebo (sentinel group). 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 a 24-hour period. 8 cohorts are planned. DNDi, investigators and subjects will be blinded to treatment allocation. Site pharmacist will be unblinded to treatment allocation.	

Main Evaluation Criteria:	**Primary evaluation criteria** Assessment of safety and tolerability of DNDI-6148 by evaluation of following parameters: • Adverse Events, • Physical examination (including body weight), Clinical neurological examination • Vital signs, • 12-lead ECG, • Clinical laboratory (including serum chemistry, hematology, hormonology and urinalysis). Psychological and cognitive examination (evaluated by CSSR-S and Bond & Lader questionnaires). **Secondary evaluation criteria**: *Pharmacokinetic evaluation* For PK **in plasma**, the recording of following parameters will be analyzed: • Main DNDI-6148 PK parameters: ○ $AUC_{0-\infty}$; C_{max} ; • Other DNDI-6148 PK parameters: • AUC_{0-24}, AUC_{0-t}, AUC_{0-t}/D, $AUC_{0-\infty}/D$, C_{max}/D, t_{max}, $t_{1/2}$, MRT, CL/F, Vz/F • ke, %AUCextra; The following parameters will be calculated from **urine** data for DNDI-6148: • **Ae(0-t)** Total amount excreted over 24 h and 72 h (*i.e.* t = 24 or 72). • **Fe** The fraction of the dose excreted in urine over 24 h and 72 h. • **CLr** The renal clearance of DNDI-6148. **Exploratory evaluation criteria** ➢ *Exploratory Pharmacodynamic evaluation* The following cardiologic pharmacodynamics parameters of DNDI-6148 will be analyzed: • RR, HR, PR, QRS, QT, QTcF, QTcB, ΔHR, ΔRR, ΔPR, ΔQRS, ΔQT, ΔQTcF and ΔQTcB. ➢ *Exploratory* identification of DNDI-6148 metabolites

Study Duration:	- For the cohorts 10 mg, 20 mg, 40 mg and 80 mg:Screening within 28 days prior to the first administration; - Hospitalization for 5 days (D-1 morning to D4 morning); - End of study visit: D4. For the cohorts 160 mg, 260 mg, 380 mg and 500 mg: - Screening within 28 days prior to the first administration; - Hospitalization for 5 days (D-1 morning to D4 morning); - Ambulatory visits on D5 and D6; - End of study visit: D6. Expected duration = approximately 35 days for each subject Expected duration of the trial = 15 months
Statistics	**Safety parameters:** **AEs:** AEs will be individually listed per subject number, presenting: assigned dose group, verbatim, MedDRA Primary System Organ Class, MedDRA Preferred Term, treatment-emergence (TEAEs or not), date and time of onset, date and time of the study drug administration before AE, duration, time from onset since last study drug administration, frequency, severity and seriousness, relationship to study drug, the required action taken, outcome. The non-treatment emergent events (or pre-dose events) 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, by dose group and overall for the safety set to describe the evaluation of the number of TEAEs and the number of subjects reporting these TEAEs. **Physical examination, neurological examination, ECGs, vital signs and questionnaires:** Physical examination, neurological examinations, ECGs, vital signs and questionnaires (C-SSRS, Bond and Lader VAS) recorded during the study will be individually listed and quantitative parameters will be summarised by using descriptive statistics. For vital signs and ECG parameters, all values recorded during the study will be individually listed and flagged for abnormalities and for clinical significance (assessed by investigator). In addition, values and abnormalities (not clinically significant and clinically significant) will be described by dose group and overall, at screening, study baseline (D-1, or D1 predose), each evaluation under treatment phase and at the end of the study. Change between the value at baseline and the value at each evaluation under treatment phase and at end of study visit will be described for each parameter by dose group and overall. **Laboratory parameters:** All laboratory values recorded during the study will be individually listed and flagged for values outside reference ranges and for clinical significance (assessed by investigator). Quantitative parameters will be summarized by descriptive statistics. Values, position according to laboratory range and clinical significance assessment will be described at screening, D-1 (baseline) and at D2, D4 and D6 (only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg) by dose group and overall. Change between the value at baseline and the value at post-dose visits will be described for each parameter by dose group and overall. All quantitative and qualitative urinary test results will be listed, sorted dose group, visit and subject. **<u>Pharmacokinetic parameters:</u>** Plasma concentrations will be summarized by dose level and time point. The derived PK parameters will be listed by subject and summarized by dose level. In addition, the hypothesis that AUC and C_{max} are dose proportional will be formally tested using a power model approach. **Pharmacodynamic parameters:** ECG parameters will be summarized by dose level and time points on actual values and changes from baseline. Placebo corrected changes from baseline ($\Delta\Delta$) will be calculated with their 90% CI for each dose level and time points and displayed. Subjects meeting predefined criteria for ECG parameters abnormality and results of the morphological analysis will be summarized by dose level using count and percentage. An optional post hoc concentration-response analysis between ΔQTcF and DNDI-6148 concentrations will be performed on ECG data issued from Holter extraction. $\Delta\Delta$QTcF with their 90% CI will be estimated from the model at each dose C_{max} geometric means.

Table 1 Study Flow Chart

Visit/Period	Screening	Inclusion	Treatment period				Ambulatory visits	
Day	D-28 to D-2	D-1	D1	D2	D3	D4	D5[4]	D6[4]
Informed consent	X							
Eligibility criteria	X	X[2]	X[2]					
Previous Medical / Surgical History	X	X[2]						
Prior/concomitant medications	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X		X		X
Clinical neurological exam	X	X	X[3]			X		X
Body weight	X					X		X
Hematology	X	X		X		X		X
Hemostasis	X	X		X		X		X
Hormonology	X	X				X		X
Biochemistry	X	X		X		X		X
Urinalysis	X	X		X		X		X
Serology	X							
Diagnostic test of SARS-CoV-2		X						
Urine drug screen	X	X						
Alcohol breath test	X	X						
Admission		X						
Discharge						X		
Randomization			X					
Study Drug Administration			X					
Meals		X	X	X	X	X		
Blood pressure / Heart rate / Body temperature	X	X	X	X	X	X	X	X
CSSR-S evaluation – Bond & Lader questionnaire	X	X	X[3]			X		X
12-lead ECG recording	X	X	X	X	X	X	X	X
Holter 24-hours recording			⟷	⟷				
Blood sample for Pharmacokinetics [1]			X	X	X	X	X	X
Urine collection for Pharmacokinetics [1]			X	X	X	X		
AE and pre-dose events collection	⟷							

1 See Detail on details Study Flow Chart 2Recheck only 3 Only around T6h 4 only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg

Visit/Period	**Treatment period**																**Ambulatory visits**	
Day	**D1**													**D2**	**D3**	**D4**	**D5**[3]	**D6**[3]
Theoritical time	**Predose**	**T0h**	**T30min**	**T1h**	**T1h30**	**T2h**	**T2h30**	**T3h**	**T4h**	**T5h**	**T6h**	**T9h**	**T12h**	**T24h**	**T48h**	**T72h**	**T96h**	**T120h**
Prior/concomitant medications	←												→					
Physical examination	X													X		X		X
Clinical Neurological exam											X					X		X
Body weight																X		X
Hematology														X		X		X
Hemostasis														X		X		X
Hormonology																X		X
Biochemistry														X		X		X
Urinalysis														X		X		X
Discharge																X		
Randomization		X																
Study Drug Administration		X																
Meals									X				X	X	X	X		
Blood pressure / Heart rate /body temperature	X			X	X[2]	X	X	X	X	X[3]	X		X	X	X	X	X	X
CSSR-S evaluation – Bond & Lader questionnaire											X					X		X
12-lead ECG recording	X[1]			X		X		X	X		X	X	X	X	X	X	X	X
Holter	←														→			
Blood sample for Pharmacokinetics	X		X	X	X[2]	X	X	X	X	X[3]	X	X	X	X	X	X	X	X
Urine collection for Pharmacokinetics	X	←											→					
AE collection	←															→		

1 triplicate in baseline 2 only for the cohorts 10 mg, 20 mg, 40 mg and 80 mg 3 only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS
(standard Units are not defined in the abbreviation's list)

AE	**:**	Adverse Event
Ae(0-t)	**:**	Total amount excreted over 24 h and 72 h
ALT	**:**	Alanine Leucine Transferase
ANSM	**:**	Agence Nationale de sécurité du médicament et des produits de santé
AST	**:**	Alanine serine transferase
ARS	**:**	Agence Régionale de Santé
AUC_t	:	Area under the plasma concentration curve from administration up to the last quantifiable concentration at time t
$AUC_{0-\infty}$	:	Area under the plasma concentration-time curve from administration up to infinity with extrapolation of the terminal phase
$\%AUC_{extra}$	:	Percentage of extrapolated AUC_{inf}
BMI	**:**	Body Mass Index
BP	**:**	Blood pressure
bpm	**:**	beats per minute
cGCP	**:**	Current Good Clinical Practice
Cl/F	**:**	Clearance
CLr	**:**	Renal clearance
C_{max}	**:**	Observed maximum plasma concentration
CPK	**:**	Creatine phosphokinase
CPP	**:**	Comité de Protection des Personnes
CRF	**:**	Case Report Form
CRO	**:**	Contract Research Organisation
CSP	**:**	Code de la Santé Publique
CQA	**:**	Clinical Quality Assurance
C-SSRS	**:**	Columbia-Suicide Severity Rating Scale
DNDI	**:**	Drugs for Neglected Diseases Initiative
DRF	**:**	Data Resolution Form
EC	**:**	Ethics committee
ECG	**:**	Electrocardiogram
eCRF	**:**	Electronic Case Report Form
EDC	**:**	Electronic Data Capture
Fe	**:**	The fraction of the dose excreted in urine over 24 h and 72 h
GCP	**:**	Good Clinical Practice
GDPR	**:**	General Data Protection Regulation
GGT	**:**	Gamma Glutamyl Transferase
HBs	**:**	Hepatitis B surface antigen
HCV	**:**	Hepatitis C virus
HIV	**:**	Human Immunodeficiency Virus
HR	**:**	Heart Rate
IB	**:**	Investigator's Brochure
ICH	**:**	International Conference on Harmonization
IMP	**:**	Investigational Medicinal Product
IP	**:**	Investigational product
K_{el} (h)	**:**	Elimination rate constant
RTSM	**:**	LifeSphere Randomization and Trial Supply Management

MCH	:	Mean Corpuscular Hemoglobin
MCHC	:	Mean Corpuscular Hemoglobin Concentration
MCV	:	Mean Corpuscular Volume
MedDRA	:	Medical Dictionary for Regulatory Activities
ms	:	Millisecond
MTD	:	Maximum Tolerated Dose
MRT	:	Mean Residence Time
NA	:	Not Available
NCE	:	New Chemical Entity
NCS	:	Non Clinicaly Significant
NTEAE	:	Non-Treatment Emergent Adverse Event
OTC	:	Over The Counter
PBPK	:	Physiologically based Pharmacokinetic
PDR	:	Patient Data Report
PK	:	Pharmacokinetics
PI	:	Principal Investigator
PM	:	Paromomycin
PV	:	Pharmacovigilance
R	:	Accumulation ratio
RBC	:	Red Blood Cells
RT-PCR	:	Reverse Transcriptase Polymerase-Chain-Reaction
SAD	:	Single administration dose
SAE	:	Serious Adverse Event
SAR	:	Serious Adverse Reaction
SARS-CoV-2	:	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	:	Systolic Blood Pressure
SD	:	Standard Deviation
SEM	:	Standard Error of the Mean
SSG	:	Sodium Stibogluconate
SMP	:	Safety Management Plan
SmPC	:	Summary of Product Characteristics
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
ULN	:	Upper limit of normal
VAS	:	Visual Analog Scale
Vd	:	Volume of distribution
VL	:	Visceral Leishmaniasis
WBC	:	White Blood Cells
WHO-DD	:	World Health Organization - Drug Dictionary
WHO-DRL	:	World Health Organization - Drug Reference List

1. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION OF THE RESEARCH

1.1. Introduction and background

Leishmaniasis is generally seen as one of the most neglected tropical diseases and has strong links with poverty. It comprises a complex vector-borne disease, caused by more than 20 species of the protozoan genus *Leishmania* and ranging from localized skin ulcers to lethal systemic disease. Leishmaniasis is endemic in 101 countries/territories, with 350 million people at risk.

Visceral Leishmaniasis (VL), also known as kala-azar, is caused by the protozoan parasites *Leishmania donovani* and *Leishmania infantum*, with a distribution in Asia, East Africa, Latin America and the Mediterranean region. It usually affects remote rural communities with difficult access to health care, and majority of cases are children. The parasites are transmitted through the bite of female phlebotomine sand flies and in the human host are obligate intracellular parasites of the reticuloendothelial system, surviving and multiplying in different macrophage populations. In patients who develop symptoms, presentation is insidious with development of splenomegaly, irregular fevers, anaemia or pancytopenia, weight loss and weakness occurring progressively over a period of weeks or even months and evolves toward death if untreated. Patients need life-saving treatment to be cured. There are important geographical features in VL: different parasites, response to drug treatment which varies between and within regions: higher dose regimens are required to achieve efficacy in the East Africa and Latin America as opposed to South Asia foci. Geographical variation has also been shown within East Africa. The differences in cure rate between Asia and Eastern Africa could be related to differences in parasite, host and/or drug exposure. The *L. donovani* population in Eastern Africa is genetically different from that in India, with high parasite population diversity observed in North region of East Africa. There is also evidence of different PK profiles of miltefosine in adult VL patients in Asia and Africa, with the former having higher drug exposure. Therefore, treatment regimens need to be adapted to the context of the disease in the regions, and clinical trial data cannot be extrapolated between regions.

In the Indian sub-continent, a sharp decrease of number of VL cases occurred recently likely due to the conjunction of a successful elimination campaign, the natural fluctuating trend of incidence, vector control activities and improvement in the living conditions of the local population. It remains a major public health problem in East Africa (Ethiopia, Kenya, Somalia, Sudan, South Sudan and Uganda) and Latin America (mainly Brazil).

Existing treatment options, recent advances and unmet needs

Until recently, antimonial monotherapy for 20-30 days was the mainstay of treatment. However, in the last 15 years liposomal amphotericin B (AmBisome®), followed by paromomycin (PM) and miltefosine were developed or made available for use. In Asia, the 1st line treatment is a single dose of AmBisome®, whereas the combination paromomycin/miltefosine is 2nd line treatment, both with high efficacy and good safety profile. In Eastern Africa, Sodium Stibogluconate and paromomycin (SSG&PM) for 17 days has been recommended as a first line treatment by the WHO expert committee (2010). It is an improvement over the 30 days SSG monotherapy, but still requires double painful injections and carrying SSG toxicity. Patients with age above 45 years and with HIV co- infection are not suitable for this treatment, due to lower efficacy and higher mortality rates observed in these groups. Attempts to develop in Eastern Africa short course AmBisome® therapy and combination therapies with AmBisome® have failed due to poor and variable efficacy in the region. In Brazil, the guidelines are under review to replace the toxic meglumine antimoniate with AmBisome® as 1st line therapy.

Despite the improvement and advances in VL therapy in the last decade, the current treatment options have limitations of being still toxic, not adapted to field conditions (most are parenteral drugs, with AmBisome® requiring cold chain), and some require long hospitalizations.

In Africa regional meetings with VL experts, it has been defined as consensus that the ideal treatment for East Africa should be a combination of oral drugs which is efficacious, safe and affordable.

DNDi priority is to eliminate the use of antimonials and develop a safe, effective, oral, short-course VL treatment that can be used at any health care level in all foci of the disease. If possible, DNDi will develop combination therapy based on newly developed NCEs. Innovative oral safe and highly efficacious combination treatments will have an impact in VL control, by delivering a therapy better adapted to the remote settings where VL transmission occurs.

DNDI-6148 is a 6-substituted benzoxaborole, which exhibits *in vitro* and *in vivo* activity against various strains of *Leishmania* parasites, including *L. donovani* and *L. infantum*, the causative agents of VL (see Table 2). DNDI-6148 by oral route is efficacious in mouse and hamster models of both acute and chronic VL infection.

The present trial aims at evaluating the safety, tolerability and the PK parameters of the drug in humans after administration of a single dose by oral route. This will bring crucial information to evaluate if further development of this compound will be possible.

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

As described below in detail, based on safety preclinical data, DNDI-6148 arginine monohydrate was the form selected to be administered orally to healthy volunteers.

1.2.1. Non-clinical studies

1.2.1.1. Primary pharmacodynamic activity

DNDI-6148 exhibits *in vitro* and *in vivo* activity against various strains of *Leishmania* parasites, including *L. donovani* and *L. infantum*, the causative agents of VL (see Table 2), including clinical isolates or resistant strains, as well as against cutaneous leishmaniasis strains.

No direct studies have been performed on the mode of action of DNDI-6148.

Table 2 Summary of In vitro Primary Pharmacodynamic activity of DNDI-6148*:

	Strain ID	Strain origin	DNDI-6148 Free Acid	DNDI-6148 Arginine monohydrate
			IC_{50} values (µM)	
L. donovani	MHOM/IN/80/DD8	India WHO-reference strain	2.46	>10
	MHOM/ET/67/HU3	Ethiopia WHO-reference strain	1.62 ± 1.07	na
	MHOM/SD/62/1SCL2D	Sudan WHO-reference strain	0.15	na
	GR265	Ethiopia, clinical isolated	na	8.36
L. infantum	MHOM/MA/67/ITMAP263	Morocco	2.59 ± 1.66	2.35 ± 0.48
	MHOM/FR/09/LEM4038	France WHO-reference strain	0.51 ± 0.11	na
	MCAN/DZ/2008/ENV48*	Algeria WHO-reference strain	0.04 ± 0.03	na
	MHOM/FR/96/LEM3323 Cl4 PMM^	France WHO-reference strain	0.69 ± 0.15	na

** methodology of experiment, more strains available in the Investigator's Brochure (IB)*

DNDI-6148, administered par oral route as free acid or arginine monohydrate, is effective in both the acute and chronic VL in *in vivo* models and against both L. donovani and L. infantum. The dose of 25 mg/kg

bid was identified as the minimal efficacious dose for DNDI-6148 free acid, leading to >96% reduction of parasite burden in main target organs (liver, spleen when applicable) whatever the model is. Also, an administration of five days at that dose is required in mice infected with L. donovani or L. infantum and in hamsters infected with L. infantum, while 10 days seem to be required in hamsters infected with L. donovani. Table 3 summarizes the dose regimen required for efficacy on both models and the corresponding exposure (AUC).
Pharmacodynamic properties of DNDI-6148 are clearly dose and duration dependent and this information can be used for human dose prediction and adjustment.

Table 3 Summary of Toxicokinetic and Pharmacokinetic parameters for DNDI-6148*

Species	Gender	Type of study	Dose PO (mg/kg/day)	$AUC_{0\text{-}24h}$ at steady state
Mice (acute model *L. infantum*)	F	Efficacy	25 (12.5 bid) /10 days 50 (25 bid) / 5 days i.e. minimal efficacy dose	na
Mice	F	PK	50 (25 bid) /5 days	99.2 h*µg/mL
Hamster (chronic model *L. infantum*)	F	Efficacy	50 (25 bid) / 10 days i.e. minimal efficacy dose	na
Hamster	F	PK	50 (25 bid) / 5 days	32.9 h*µg/mL

** methodology of experiments, more doses and time-points available in the IB*

1.2.1.2. Nonclinical Pharmacokinetics and Human PK Prediction

The pharmacokinetic (PK) behavior of DNDI-6148 has been adequately assessed in several preclinical species including mouse and hamster (used for pharmacodynamics models) as well as rat, dog and monkey (used for PK and TK assessment). DNDI-6148 is a low clearance compound in rat and monkey while low-to-medium in dog. The volume of distribution at steady state (V_{ss}) is relatively low in the range of body water for rat and monkey. Importantly, *in vitro* ADME data suggest that humans likely align with rat and monkey (see below for prediction of human PK). The resulting elimination half-life in relevant species was in the range of 3-4 hours in rats and 4-7 hours in monkeys. Due to the very low clearance, both species demonstrated that DNDI-6148 can achieve essentially complete bioavailability (F >85% in both species) with the only limiting factor being intestinal dissolution (microsuspension of DNDI-6148 arginine monohydrate provided enhanced exposure). DNDI-6148 arginine monohydrate was therefore selected for further development: all safety pre-clinical studies were performed with DNDI-6148 arginine monohydrate, and this is the form that is also intended to be administered orally to healthy volunteers.
All human metabolites detected *in vitro* are also formed in toxicology species used as part of the regulatory preclinical package (rat and monkey).

A brief summary of human PK prediction is given below and is based on modelling work reported in several key publications [2, 3, 4] (for more details see also [1]).

The prediction of clearance was performed via two methods [2], (Obach & et al., 1997), i.e. inter-species allometric scaling using *in vivo* clearance from preclinical species and, independent of this, intra-species scaling using *in vitro* intrinsic clearance in hepatocyte (with and without correction for plasma protein binding) of all available species including human in combination with the PBPK-based well-stirred model which allows scaling to an intact human liver. The latter approach technically predicts “hepatic clearance” only. Importantly, both approaches resulted in similar clearance predictions indicating that indeed liver metabolism appears to be the major driving force behind DNDI-6148 total plasma clearance (human CL_p anticipated to be less than 5% of liver blood flow).

The human V_{ss} was predicted using the proportionality method [2] where human V_{ss} is predicted via single-species animal V_{ss} with correction of plasma f_u, however, both rat and monkey data were used independently due to their similar plasma protein binding compared to human. Both calculations delivered similar predictions for human V_{ss} with an average of ~0.4 L/kg (somewhat lower than volume of body water).

Half-life (t1/2) is a resulting parameter only, i.e. it is a result of CL and V and, most often, prediction also depends on the type of half-life assessed (e.g. terminal half-life or operational half-life at steady state [3]). Predictions were based on either scaling of terminal half-life data from animals via direct species correlation method [2] or via calculation of resulting t1/2 from predicted CL and Vss. The latter approach is more reflective of a true operational t1/2 under steady state conditions [3] . The different methods resulted in an average half-life prediction of ~11 hours for DNDI-6148 in human. However, these results may predict terminal half-life and the data also indicated the possibility that the "operational t1/2 under steady state conditions" could be in the range of ~4 hours for DNDI-6148, i.e. it is possible that plasma concentrations post-Cmax decline with an initial shorter half-life of ~4 hours [3]. In order to account for this possibility, both predicted half-lives were used in the modelling of human dose prediction (see below).

Finally, preclinical data of oral bioavailability (F) allow to predict a category for bioavailability (low, medium, high) [4]. For DNDI-6148 the predicted bioavailability category for humans is "high" (~100% F can be assumed) since simple suspensions of DNDI-6148 arginine monohydrate resulted in >85% F in rat and monkey.

These human predicted PK parameters were used to further calculate potential plasma exposures at steady state (see section 1.4 below).

Using the predicted human PK parameters and animal efficacy data, the human QD dose of DNDI-6148 for efficacy is estimated to be between 16 and 479 mg for a 70 kg human (see section 1.4 below).

1.2.1.3. Safety Pharmacology

There were no major safety concerns regarding the pharmacological effects of DNDI-6148 on respiratory and central nervous system functions assessed in rats up to 25 mg/kg.
The potential effects of DNDI-6148 on QT prolongation were assessed in *in vitro* hERG assays. DNDI-6148 did not significantly inhibit the amplitude of the current mediated by the hERG potassium channel *in vitro*, with IC_{50} value of >30.0 µM (17% inhibition at 30 µM) and up to the highest concentration tested, 45 µM (19% inhibition). As part of a four weeks GLP toxicity study in the conscious Cynomolgus, DNDI-6148 was assessed by telemetry at oral doses up to 15 mg/kg after 7 days. Results did not evidence any effects of DNDI-6148 on QTc nor any changes in the morphology of the ECG.

1.2.1.4. Regulatory toxicology studies

Toxicological safety assessment demonstrated that the toxicity profile of DNDI-6148 as determined in the repeat dose toxicity studies differed to some extent between the rodent and non-rodent species.

Doses of up to 25 mg/kg/day administered for four weeks did not induce any adverse effects in rats and 25 mg/kg/day was thus considered as the NOAEL in that species.

In the Cynomolgus monkey, a sacrifice for ethical reasons of one female treated with the highest dose of 15 mg/kg was required before completion of the 28-day toxicology study, on Day 21. Blood samples were taken prior to necropsy and demonstrated that electrolytes, urea, creatinine and total protein were affected, however no macroscopic nor anatomical changes were observed in that animal. Histopathological evidences considered likely related to stress were observed in the adrenal glands (minimal bilateral increase in eosinophilia in the zona fasciculata) and thymus (slight decrease in size of the paracortex). Non-adverse stress related changes were also noted in the large intestine (minimal acute inflammation in the colon and cecum), kidneys (slight bilateral cortical tubular dilatation) and sciatic nerve

(minimal myelin vacuolation). At this dose level of 15 mg/kg, for all other male and female animals (total of 9 animals), there were no signs of overt toxicity in clinical observations or parameters monitored, including complete clinical pathology panel and histopathology at day 28. Systemic exposure ($AUC_{0\text{-}24h}$) at NOAEL doses was 162 h*µg/mL in males (15mg/kg) and 65 h*µg /mL in females (5mg/kg) at steady state. Considering that a relationship between poor condition in one female that had to be sacrificed for ethical reasons and DNDI-6148 administration cannot be absolutely excluded, the NOAEL in Cynomolgus was established at 5 mg/kg/day for females and 15 mg/kg/day for males.

Following the unexplained poor health status in one animal described above, an additional non-GLP repeated-dose study in the monkey was conducted during 29 days at 15 mg/kg/day and 30 mg/kg/day. The NOAEL was considered as 30 mg/kg/day in this study in both males and females, leading to a mean AUC0-t at steady state of 264 h*µg/mL for males and 210 h*µg/mL for females.

The female NOAEL of 5 mg/kg/day from the GLP study was used as a basis of calculation of the starting dose in the phase I single ascending dose study.

1.2.1.5. Genotoxicity

Standard *in vitro* and *in vivo* genotoxicity testing did not suggest any genotoxic/clastogenic potential on the nuclear genetic material for DNDI-6148. The drug is therefore not expected to pose a genotoxic risk for humans.

1.2.1.6. Reproductive Toxicity Studies

A Segment I fertility study in rats of both sexes has been completed. DNDI-6148 was administered orally at doses of 6.25, 12.5 or 25 mg/kg/day for 64 days in males and 21 days in females.

In males, at 25 mg/kg/day, the following adverse effects related to DNDI-6148 were observed: decreased fertility and fecundity indices, a decrease in sperm motility, sperm count per cauda epididymis, sperm concentration per cauda epididymis, and increased percent of abnormal sperm.
In females, uterine and implantation findings observed at all dose levels included an increase in preimplantation loss and mean number of resorptions. Additionally, at 25 mg/kg/day, female fertility and fecundity indices were lower than controls. No test article-related effect was observed from reproductive performance and fertility indices at 6.25 and 12.5 mg/kg/day.

Based on the results of this study, the no-observed-adverse-effect level (NOAEL) for maternal and paternal toxicity was 25 mg/kg/day, while the NOAEL for fertility and reproductive toxicity was 12.5 mg/kg/day, corresponding to the systemic exposure (AUC0-24h) of 168 h*µg/mL (males) and 162 h*µg/mL (females).

1.2.2. Clinical studies

The recruitment in the present study was interrupted on the 16 March 2020 due to the Covid-19 outbreak in France and following the confinement measures implemented by the French government.

On restart of the trial on the 17th August 2020, Cohort 2 recruitment was completed before proceeding to dose-escalation.

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

There is no known (identified) risks 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.

Some changes may be anticipated in humans and thus will be monitored accordingly during the clinical trial as mentioned in section 7.3.1 of the Investigator's Brochure (IB): potential risk of decrease in

appetite, potential risks of alteration of renal and liver function tests, hematology parameters, and glucose levels, as well as potential risk of Central Nervous System alteration. All details on these risks and overall guidance are described in the IB Section 7 (Summary and Guidance for the Investigator).

DNDI-6148 was shown to have no genotoxicity potential. The fertility and reproductive toxicity data available in rats and generated after 64 days of dosing indicate a potential risk for decreasing male fertility. A potential effect on female reproductive performance cannot be excluded in regard to the increase in preimplantation loss and mean number of resorptions observed in the female rats following 21 days of administration. In the absence of animal data on developmental toxicity, risk of human teratogenicity/fetotoxicity cannot be excluded [6]. Of note, no women of childbearing potential are planned to be included in the present clinical trial and measures to prevent any exposure through seminal fluid are in place.

Decrease in fertility in clinical trial participants is not expected, considering the maximum dose considered and duration of treatment planned in the single dose administration study. Findings in male animals, both related to sperm abnormalities and histopathological changes were reported after 64 days of repeated dosing, while no histopathological change was noted in the 28 days repeated dosing study in the same species. The likeliness of impact of a single dose of DNDI-6148 on human male fertility is thus very low.

Before receiving a single dose of DNDI-6148, male participants to the present clinical study should be informed of this concern on the fertility in rat after a long exposure (64 days) while no concern were identified after 28 days, and at a higher exposure than expected in human.

Information on compound from the same chemical class

Preclinical toxicology findings and side effects observed in clinical trial subjects with a compound from the same oxaborole family were also considered. SCYX-7158 or Acoziborole, a long-lasting compound (t½ 400 h), is being developed for the treatment of human African trypanosomiasis and is currently investigated in a phase II/III clinical trial. The main parameters currently monitored for that compound are thyroid function laboratory tests, liver functions tests and neuropsychiatric disorders. See all details in the Investigator Brochure (section 7.3.1).

Both compounds are crossing the blood-brain barrier. Thus, special attention should be given to the occurrence of neurological events, even of mild intensity in DNDI-6148 studies in healthy volunteers.

Risk associated with the conduct of the trial during Covid-19 pandemia

In the present epidemiological context of SARS-CoV-2/Covid-19 virus circulation in France, special attention is paid to the risk for the volunteers to be exposed to the virus while staying in the Clinical Centre. Current Standard Precautions measures to prevent infection have been put in place at the Centre level.

A Reverse Transcriptase Polymerase-Chain-Reaction (RT-PCR) test SARS-CoV-2 on the day of admission in the facility will be performed to minimize the risk of a healthy volunteer to contaminate any other volunteer and/or facility staff, as well as avoiding the risk for a volunteer already in the incubation phase without symptoms to get exposed to the IMP.

1.4. Description of and justification for the dosage regimen

Rational Starting dose and safety margin:

Based on efficacy results (section 1.2.1.1), DNDI-6148 is considered a promising candidate for clinical development as a new oral treatment for visceral leishmaniasis.

As mentioned above, the starting dose for this dose-escalation study in healthy volunteers has been selected based on the results of the 28-day GLP toxicity studies in the rat and non-human primate, which indicated a NOAEL at 25 mg/kg/day in rats and 5 mg/kg/day in female (most sensitive gender) non-human primates (corresponding to an $AUC_{0\text{-}24}$ of 65 h*µg/mL).

Table 4 Summary of exposure at NOAEL in various species and genders

	Treatment duration	AUC at NOAEL in males	AUC at NOAEL in females
Rat: NOAEL = 25 mg/kg/day	28 Days	353 h*µg/mL	347 h*µg/mL
Rat: Fertility and reproductive toxicity Males NOAEL = 12.5 mg/kg/day Females NOAEL = 12.5 mg/kg/day	64 Days 21 Days	168 h*µg/mL	162 h*µg/mL
Monkey: males NOAEL = 15mg/kg/day females NOAEL = 5mg/kg/day	28 Days 28 Days	162 h*µg/mL	65 h*µg/mL

§ exposure used to define the dose-escalation stopping rule (section 3.5.3)

The Human Equivalent Doses (HED), corresponding to the rat and monkey NOAEL, are 4.03 mg/kg and 1.61 mg/kg respectively according to FDA *Guidance for Industry* (GUIDANC\5541fnlcln1) – July 2005, equivalent to 282 mg and 112 mg per 70 kg subject, respectively. Considering the lowest of these HED values, and a minimum safety margin of 10 as recommended by the FDA guidance above, a starting dose of 0.16 mg/kg (11.2 mg, resulting in the dose of 10 mg per 70 kg subject) has been considered. Exposure at starting dose (10 mg in a 70kg human) has been predicted to provide a C_{max} of 509 ng/ml and an $AUC_{0\text{-}24}$ of 7.68 h*ng/ml. A ~10-fold safety margin at starting dose compared to established stopping criteria is predicted (stopping criteria: C_{max}=7.3 µg/mL and $AUC_{0\text{-}24}$=65 h*µg/mL). The new data on reproductive toxicity do not modify the established stopping criteria.

Using the overall predicted human PK parameters (described in section 1.2.1.2), with the predicted range of half-life as best (t1/2 ~11 h) and worst (t1/2 ~4 h) case scenarios, in combination with average unbound exposures needed for animal efficacy data from hamster and mouse, the human efficacious QD dose is estimated between 16 and 479 mg for a 70 kg human. The human efficacious dose range was calculated using standard clinical PK equations [5] at assumption of rapid absorption (k_{abs}>>k_{el}) in order to reach average and minimum unbound concentrations which were efficacious in mouse and hamster (for details see [1]).

Dose incrementation:

The proposed dose escalation is initially following a logarithmic scheme, then a progressively decreasing dose increment with dose level increase scheme.

However, pharmacokinetic assessment during the dose escalation will be key in order to establish real exposures of DNDI-6148 during dose escalation. This will ultimately allow to enforce pre-set stopping criteria as well as refinement of the early human PK and exposure predictions described so far.

Rational for the highest dose:

The rationale for the highest scheduled dose of 500 mg in the Single Ascending Dose study is that it is just above the assumed higher human therapeutic dose level prediction derived from preclinical data. If required however, provided that safety stopping criteria are not met and safety and tolerability at previous dose are acceptable, a higher dose may be optionally considered and would be tested after substantial amendment of the protocol.

Prediction of exposure shown in Table 5, based on current knowledge that include both *in vitro* and animal data, show that the PK stopping rules (see § 3.5.3 Dose escalation Stopping criteria between cohorts) are likely to be met before reaching the maximum dose planned in the study if all worse-case scenario hypotheses used for the prediction are met. Because a certain degree of uncertainty on the level of exposure at a given dose remains as no data is available in human, the proposed doses may as well not reach the PK stopping rule defined in the current version of the protocol (due to lower than expected bioavailability, higher elimination rate, shorter half-life, etc.). For this reason, some cohorts have been planned but may actually not be performed. Importantly, at all stages, both actual data providing exposure in humans in the previous cohort and the predictions will be considered for dose-escalation decisions, so that the defined stopping rules are not overpassed, and safety of the subjects is insured.

Moreover, should the PK stopping rules be met at any time but not the safety stopping criteria, the trial will be interrupted and a substantial amendment on the PK stopping rule may be considered, depending on the actual safety data gathered up to that point.

Table 5 Exposure predictions

DNDI-6148	Dose/subject* (mg)	Est. Human C_{max} (ng/mL)	Est. Human AUC_{0-24} (h*µg/mL)
First cohort dose	10	509	7.68
Last cohort dose**	500	18105	100
Lowest Predicted efficacious dose	16	724	8.81
Highest Predicted efficacious dose	479	17351	96.1

* Dose is based on a 70 kg body weight

** Predicted exposures at worst case scenario may reach Cmax and AUC0-24 stopping criteria set to 7.34 µg/mL and 64.8 h*µg/mL based on female monkey 5 mg/kg D28 TK

Acute toxicity with single drug dosing is not anticipated to pose a risk of concerns to volunteers due to expected limited exposure.

The following single doses of DNDI-6148 are planned to be administered:

Table 6 Doses for administration

Dose group	Dose (mg)	Dose (mg/kg*)	Increase from the previous dose
1	10	0.14	
2	20	0.29	+100%
3	40	0.57	+100%
4	80	1.14	+100%
5	160	2.29	+100%
6	260	3.71	+63%
7	380	5.46	+46%
8	500	7.14	+32%

* Assuming a 70-kg person

1.5. 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) dated 09 Nov 2016 (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/National] Health Authorities ["Agence Nationale de sécurité du médicament et des produits de santé" (ANSM)].

1.6. Description of the population to be studied

Sixty-four (64) healthy male volunteers, aged 18 to 50 will be included in the study. They will be recruited from volunteers' database of the clinical unit.

Recruitment has been limited to Caucasian population to avoid possible ethnicity differences in assessments within a cohort.

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.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary objective

To assess the safety and tolerability of DNDI-6148 after single oral doses administered as oral suspension of DNDI-6148 in healthy male subjects, compared to matching placebo.

2.2. Secondary objectives

- To determine $AUC_{0\text{-}24}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}t}/D$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}\infty}/D$, C_{max}, C_{max}/D for DNDI-6148 in plasma after single oral doses, administered as oral suspension in healthy male subjects.
- To determine other PK parameters of DNDI-6148 in plasma and urine after single oral doses administered as oral suspension of DNDI-6148 in healthy male subjects.

2.3. Exploratory objective

- To determine PD effect on cardiologic parameters after single oral dose administered as oral suspension of DNDI-6148 in healthy male subjects.
- To identify DNDI-6148 main metabolites.

3. STUDY DESIGN

3.1. Evaluation criteria

3.1.1. Primary endpoint

Assessment of safety and tolerability of DNDI-6148 by evaluation of following parameters:

- Adverse Events,
- Physical examination (including body weight),
- Clinical neurological examination,
- Vital signs,
- 12-lead ECG,
- Clinical laboratory (including serum chemistry, hematology, hormonology and urinalysis)
- Psychological and cognitive examination (Columbia-Suicide Severity Rating Scale (C-SSRS) and Bond & Lader questionnaires).

3.1.2. Secondary endpoints

➢ *Pharmacokinetic evaluation*

For PK **in plasma**, the recording of following parameters will be analyzed:

- Main DNDI-6148 PK parameters:
  - $AUC_{0-\infty}$; C_{max} (ng/mL);

- Other DNDI-6148 PK parameters:
  - AUC_{0-24}, AUC_{0-t}, AUC_{0-t}/D, $AUC_{0-\infty}/D$, C_{max}/D, t_{max}, $t_{1/2}$, MRT, CL/F, Vz/F
  - ke, %AUCextra;

The following parameters will be calculated from **urine** data for DNDI-6148:

- **Ae(0-t)** Total amount excreted over 24 h and 72 h (*i.e.* t = 24 or 72).
- **Fe** The fraction of the dose excreted in urine over 24 h and 72 h.
- **CLr** The renal clearance of DNDI-6148.

3.1.3. Exploratory endpoints

➢ *Pharmacodynamic evaluation*

The following cardiological pharmacodynamics parameters of DNDI-6148 will be analyzed:

- RR, HR, PR, QRS, QT, QTcF, QTcB, ΔHR, ΔRR, ΔPR, ΔQRS, ΔQT, ΔQTcF and ΔQTcB.

➢ *Identification of metabolites*

- Exploratory identification of DNDI-6148 metabolites.

3.2. Design

This will be a First in Human (FiH) phase I blinded, single ascending dose study with DNDI-6148 administered as an oral suspension in healthy male volunteers. Each cohort will include 8 subjects (6 active/ 2 placebo).

Bioanalysis (in plasma and urine) will be performed in open conditions. Central reading for ECGs will be in blind conditions.

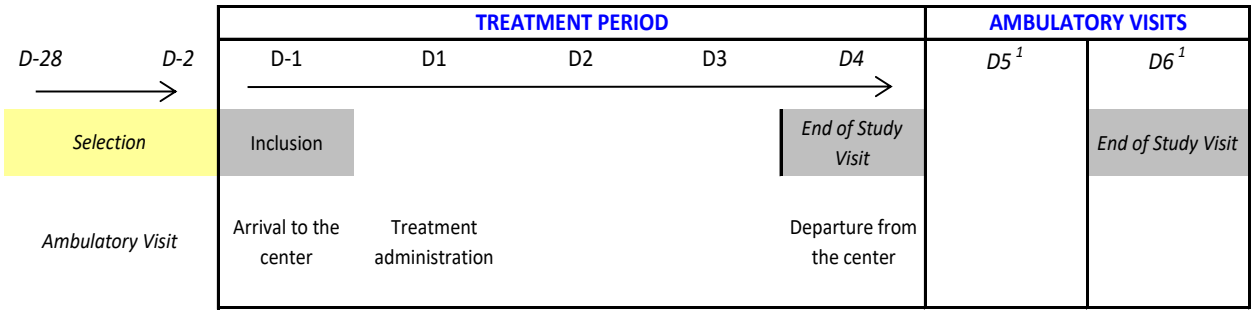
Decision on dose escalation will be taken in blinded conditions, based on safety interim report and DNDI-6148 plasma exposure.

The administered dose will be 10 mg, 20 mg, 40 mg, 80 mg, 160mg, 260 mg, 380 mg and 500 mg. The treatment will be administered as a single dose on Day 1.

The study plan is shown in Figure 1.

Study procedures are detailed in Section 6 and 7.

Figure 1 Study plan



1 only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg

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

3.3.1. Randomization

The randomization list will be provided by Eurofins Optimed. The treatments will be allocated on D1. Treatment arm will be entered into the eCRF by the Pharmacist of the study on randomization day (D1).

3.3.2. Blinding

DNDi, investigators and subjects will be blinded to treatment allocation. Site pharmacist will be open to treatment allocation.

The following measures are taken to avoid bias:

- Double Blind Study,
- Active drug and placebo will be indistinguishable in appearance:
  To be used as a suspension: to be resuspended extemporaneously with ORA-Sweet® (30 mL per bottle), then volume corresponding to the dose to be administered to be measured by the pharmacist at the CRO center using appropriate precision syringes (volume from 4 to 25 ml/subject), opaque to minimize risk of unblinding (DNDI-6148 is not sensitive to light).

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

3.3.3.1. Number of subjects receiving the study drug simultaneously

To minimize the risk to healthy volunteers, the administration of the investigational product in each dose group of the study will be done sequentially within each cohort:

Table 7 Cohorts and treatment doses.

Cohort	Treatment dose (randomization)
1 (8 subjects)	Single oral administration of DNDI-6148, 10 mg on Day 1 or placebo (6/2)
2 (8 subjects)	Single oral administration of DNDI-6148, 20 mg on Day 1 or placebo (6/2)
3 (8 subjects)	Single oral administration of DNDI-6148, 40 mg on Day 1 or placebo (6/2)
4 (8 subjects)	Single oral administration of DNDI-6148, 80 mg on Day 1 or placebo (6/2)
5 (8 subjects)	Single oral administration of DNDI-6148, 160 mg on Day 1 or placebo (6/2)
6 (8 subjects)	Single oral administration of DNDI-6148, 260 mg on Day 1 or placebo (6/2)
7 (8 subjects)	Single oral administration of DNDI-6148, 380 mg on Day 1 or placebo (6/2)
8 (8 subjects)	Single oral administration of DNDI-6148, 500 mg on Day 1 or placebo (6/2)

At each dose level, subjects will be split at least in two sub-cohorts: first sub-cohort will be one subject under active, one subject on placebo (sentinel approach as recommended by EMA[7]). The 6 remaining subjects will be dosed after a minimum of 24 hours of safety surveillance of the first 2 subjects. Decision to proceed with the administration of the 6 remaining subjects will be taken by the investigator on the basis of biology and clinical safety data. The 6 remaining subjects can be divided in multiple subgroups. Any safety data available on previous subjects will be taken into consideration before dosing any new subject. Any concern should be shared with the Sponsor prior to next dosing.

3.3.3.2. 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 planned dose up to the occurrence of relevant events if any.

At the end of each dose level 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.

Starting with the lowest dose, each of the subsequent escalating doses will be administered only if the preceding dose was safe and well tolerated. Decision to escalate the dose will be taken during the meeting of the Safety Review Committee described below after reviewing the following data per cohort:

- Blinded Safety data: all data collected over the 4 days for the cohorts 10 mg, 20 mg, 40 mg and 80 mg, or 6 days for the cohorts 160 mg, 260 mg, 380 mg and 500 mg, following study drug administration, for at least 6 subjects, including:
    - Any adverse events reported;
    - All laboratory parameters outside of ranges;
    - Concomitant therapy;
    - Physical and neurological examination (including VAS and C-SSRS questionnaires);
    - Vital signs;
    - Safety ECG if abnormalities are considered clinically significant by the investigator

  All safety data will be presented in an Interim Safety Report issued by the Investigator.

- Blinded blood PK data:

- Up to H72 timepoint for the dose escalation from 1st to 2nd cohort for the 6 subjects under active;
- Up to H48 preliminary PK analysis for a minimum of 4 subjects under active for cohorts 40 mg and 80mg
- Up to H120 preliminary PK analysis for a minimum of 4 subjects under active for the cohorts 160 mg, 260 mg, 380 mg and 500 mg

- Blinded Central Reading ECG for a minimum of 6 subjects. ECG central reading data will be presented in a cohort report.

The 3-day surveillance period has been defined based on the predicted half-life of the drug (i.e. sufficient time to determine the terminal half-life and maintain the clinical and biological surveillance up to final drug elimination). Following review of interim results of the 3 first cohorts (10 mg, 20 mg and 40 mg), GM half-life of DNDI-6148 was around 20 hours and five half-lives corresponds to 100 hours. All the volunteers will remain under medical surveillance for 72 hours (presence of a medical doctor in the facility 24h/24 during the hospitalisation of volunteers), and for the cohorts 160 mg, 260 mg, 380 mg and 500 mg, the collection of blood PK samples has been extended up to 120 hours

The study will proceed to the next dose level only if the safety results are acceptable, as agreed by the Safety Review Committee (gathering *at least* the Sponsor medical responsible, a pharmacokineticist and the Investigator) and if stopping rules are not met. A minimum of 6 subjects per cohort with complete safety data available will be required for decision to proceed to the next dose level (i.e. minimum of 4 subjects under active). All safety data available at the time of the Safety Review Committee meeting will be taken into account for decision on dose-escalation (including safety data from previous cohorts).

At the end of the Safety Review Committee 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.

One cohort can be duplicated to enlarge the number of subjects in one sub-group in case of need. In case the stopping rules are met, no duplication of the same cohort will be possible.

3.4. Expected duration of subject participation

3.4.1. Description and duration of trial periods

For the cohorts 10 mg, 20 mg, 40 mg and 80 mg:

- Screening within 28 days prior to the first administration;
- Hospitalization for 5 days (D-1 morning to D4 morning);
- End of study visit: D4.

For the cohorts 160 mg, 260 mg, 380 mg and 500 mg:

- Screening within 28 days prior to the first administration;

- Hospitalization for 5 days (D-1 morning to D4 morning);
- Ambulatory visits on D5 and D6;
- End of study visit: D6.

Expected duration = approximately 35 days for each subject
Expected duration of the trial = 15 months

3.4.2. 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. Adverse events (AEs), if any, 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 8.5). In case abnormal laboratory values are obtain following last samples taken during end of study visit, a further follow-up will also be arranged.

3.4.3 End of study

The last visit of the last subject as scheduled in the protocol will be used to determine the end of study (= Day 4 for the cohorts 10 mg, 20 mg, 40 mg and 80 mg or Day 6 for the cohorts 160 mg, 260 mg, 380 mg and 500 mg).
In case an adverse event or an abnormal laboratory result 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 than expected and the event is assessed as “chronic” or “stable”.

3.5. Stopping rules

3.5.1. Trial stopping criteria

The trial will be stopped if either of the following occurs:

- a ‘serious’ adverse reaction (SAR) (i.e. a serious adverse event (SAE) considered at least possibly related to DNDI-6148) in one subject; or
- ‘severe’ non-serious adverse reactions (AR) (i.e. severe non-serious adverse events considered as, at least, possibly related to DNDI-6148) in two subjects in the same cohort, independent of within or not within the same system organ class (SOC).

3.5.2. Stopping criteria 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 dosing in 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. > 5 upper limit of normal value [ULN]) of ALAT.

3.5.3. Dose escalation Stopping criteria between cohorts

The Safety Review Committee will decide to stop the dose escalation as planned per protocol in case of occurrence of:

- 2 subjects of the same cohort experiencing:
    - a significant increase of ALAT > 3ULN,

- simultaneous increases of total bilirubin > 2ULN, ALAT > 2ULN and alkaline phosphatases > 1.5ULN,

- 6 subjects of the same cohort experiencing:
  - study drug related moderate, non-serious AEs (that are considered at least possibly related to the drug effect i.e. moderate, non-serious ARs).

- 1 subject of the cohort presenting:
  - a C_{max} or AUC_{0-24} value above 7.3 µg/mL and 65 h*µg/mL, respectively (based on the NOAEL in Cynomolgus toxicology studies).

- The maximum C_{max} and AUC_{0-24} observed in the cohort leads to believe that, taking into account the dose increase, C_{max} or AUC_{0-24} values of 7.3 µg/mL and 65 h*µg/mL might be overpassed 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 by the investigator or on request of the sponsor, for one or several volunteers, or the Safety Review Committee could request the support of an independent non-blinded external advisor. Regarding laboratory abnormalities described above, if unblinding confirms that at least two subjects presenting these abnormalities received the active drug, the dose escalation will be stopped.

3.5.4. Restarting the trial

If, after consultation of the Safety Review Committee, it is appropriate to restart the trial, a substantial amendment will be submitted to the Health Authorities and Ethics Committee. The trial will not restart until the amendment has been approved by the Health Authorities and Ethics Committee.

3.6. Removal of Subjects from Therapy or Assessment

In accordance with the Declaration of Helsinki, subjects will be free to withdraw from the study at any time if they wish to do so, for any reason, specified or unspecified.

Subjects who withdraw from trial participation before randomization are considered screening failures.

The following reasons will be accepted for study discontinuation:

- Withdrawal of subject consent, or loss to follow-up, or inability to remain under medical observation including post-study examination,
- Non-compliance or major deviation from the protocol,
- Appearance of a serious AE (SAE),
- New significant information (French regulation: “fait nouveau”), any new fact concerning the research or the study product which may jeopardize the participants’ safety, and which leads the Sponsor or Investigator to take appropriate urgent security decision,
- Any other situation where, in the opinion of the Investigator, continuation of the study would not be in the interest of the subject,
- Discontinuation of the study by the Sponsor.

Should any of the subjects be withdrawn from the study, the Sponsor’s representative and Investigator will discuss the possibility of replacement. All subjects withdrawing for reasons unrelated to the investigational product will have to be replaced. The reason for withdrawal will have to be recorded in the e-CRF for all withdrawn subjects.

The e-CRF has to be completed up to the time of drop out. All drop outs after the first intake of investigational product should be given a post-study assessment as appropriate. The premature termination form in the e-CRF must be completed for all drop outs.

All data, including any drug concentrations from any withdrawn subject, have to be included in the final clinical study report. These data will only be evaluated if both the Sponsor and the Investigator agree that it is valid to do so.

Subjects presenting adverse experiences will undergo a physical examination and laboratory tests planned at the subsequent visits. A follow-up of AEs will also be undertaken for all subjects until resolution or stabilisation of the event.

3.7. Blind and procedures for unblinding

This study is a double-blind study.

Randomization will be performed at D1.

3.7.1. Coding list

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

As a pharmaceutical preparation is required, the EUROFINS-OPTIMED pharmacist will receive a sealed coding list which should be kept in a safe place and which will be only accessible to unblinded personnel.

The investigator, CRO staff (except the Pharmacist and pharmacy assistant in charge of the IMP reconstitution and final packaging) and Sponsor's clinical trial team members will not have access to the randomization (treatment) code except under provisions of section 3.7.2 below.

Of note, the bioanalysis department (independent of the trial site and of Sponsor) will receive the coding list that should be kept in a safe place and only accessible to unblinded personnel.

3.7.2. Breaking the blind

The code for any study participant should only be broken by the Investigator or authorised person if it is absolutely necessary to know the treatment allocation to provide the best medical care to the trial subject.

In case of emergency, for a subject in particular, the code may be broken by the Investigator (or a person designated from his team) using sealed envelope. Sponsor must be notified within 24 hours and a full written explanation must be provided.
Two sets of sealed envelopes will be prepared:

- 1 set will remain in the clinical unit under the control of the investigator
- 1 set will be provided to the sponsor PV department.

In case of Suspected Unexpected Serious Adverse Reaction (SUSAR), the Sponsor PV department should get the treatment/product 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 and overall clinical team.

4. STUDY POPULATION

4.1. Subject inclusion criteria

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

1- Healthy Caucasian male subject aged 18 to 50 years inclusive.
2- Non-smoker subject or light smoker of not more than 5 cigarettes a day. No smoking (or use of smoking substitute e.g. nicotine patch) is permitted from screening throughout the study;
3- Body Mass Index (BMI) between 18 and 30.1 kg/m^2 inclusive at screening;
4- Considered as healthy after a comprehensive clinical assessment (detailed medical history and complete physical and neurological examination);
5- 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;
6- Normal ECG recording on a 12-lead ECG at the screening visit:
    - 120 ms ≤ PR ≤ 210 ms,
    - QRS < 120 ms,
    - QTcf ≤ 430 ms for male,
    - No sign of any relevant trouble of sinusal automatism
    - Or considered as non-clinically significant by investigators,
7- Laboratory parameters within the normal range of the laboratory (hematological, hormonology, blood chemistry tests, urinalysis). Individual values out of the normal range can be accepted if judged non-clinically significant by the Investigator; for example, isolated elevated bilirubin is acceptable if judged by the physician without clinical relevance (i.e. Gilbert's syndrome)
8- ALAT, ASAT and Creatinine values strictly within the normal range
9- A negative result for diagnostic test of SARS-CoV-2 at D-1
10- Normal dietary habits;
11- Provision of written informed consent to participate as shown by a signature on the volunteer consent form, after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or his delegate;
12- Able to communicate well with the Investigator and research staff and to comply with the requirements of the entire study;
13- Covered by Health Insurance System and / or in compliance with the recommendations of National Law in force relating to biomedical research;
14- Must agree to adhere to the contraception requirements defined in Section 4.3 : use of condom by the male subject plus an effective method of contraception for the subject or the subject partner of child bearing potential from study drug administration until 90 days post-dosing OR use of a condom for 10 days post-dosing if the partner is known to be pregnant.

4.2. Subject exclusion criteria

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

1- Having previously received DNDI-6148, or who participated in another clinical trial within 3 months prior and during the study, or 5-times the half-life of the drug tested in the previous clinical trial, whichever is longer (time calculated relative to the last dose in the previous clinical trial);
2- Any history (direct questioning) or presence (physical examination) of cardiovascular, pulmonary, gastro-intestinal, hepatic, renal, metabolic, hematological, neurologic, psychiatric, systemic or infectious acute or chronic disease; including known or suspected HIV, HBV or HCV infection;

3- With any clinically significant abnormality following review of pre-study laboratory tests, vital signs, full physical examination and ECG;
4- 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;
5- Who have a history of allergy, intolerance or photosensitivity to any drug,
6- Who have a history of serious allergy, asthma, allergic skin rash or sensitivity to any drug,
7- Who have a history of additional risk factors for "Torsades de Pointe" (e.g., heart failure, hypokalemia, family history of Long QT Syndrome);
8- Current suicide risk or history of suicide risk (CSSRS baseline: "yes" answer to items 4 and/or 5); subjects with a "yes" answer for current suicide risk should be referred for psychiatric evaluation;
9- Subjects with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency,
10- Who used a prescription medicine during the 28 days before the first dose of trial medication or use of an over-the-counter medicine (including antacid drug, with the exception of acetaminophen (paracetamol)), during the 7 days before the first dose of trial medication,
11- History or presence of drug or alcohol abuse (more than 14 units of alcohol per week, one unit = 8 g or about 10 mL of pure alcohol);
12- Excessive consumption of beverages with xanthine bases (more than one liter / day);
13- Who drink more than 8 cups daily of beverage containing caffeine;
14- Who has regular daily consumption of more than 5 cigarettes daily, or use more than 3 grams (1/8 ounce) of tobacco,
15- Who use dietary supplements or herbal remedies (such as St John's Wort) known to interfere with the CYP3A4 and/or P-gp metabolic pathways during the 28 days before the first dose of trial medication;
16- Grapefruit should also be avoided during the 7 days before the first dose of trial medication.
17- 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;
18- Positive results of screening for drugs of abuse (opiates, cocaine, amphetamine, cannabis, benzodiazepines);
19- Blood donation (including in the frame of a clinical trial) within 12 weeks before administration;
20- General anaesthesia within 3 months before trial medication administration;
21- Inability to abstain from intensive muscular effort;
22- Who have any clinical condition or prior therapy which, in the opinion, of the Investigator, made the subject unsuitable for the study,
23- Who had surgery (e.g. stomach bypass) or medical condition that might affect absorption of study drug taken orally,
24- Who had febrile illness within 1 week before the start of the study,
25- 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;
26- No possibility of contact in case of emergency;
27- Exclusion period of a previous study;
28- Administrative or legal supervision;
29- Who are unwilling to give their informed consent,
30- 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. Contraception and Limitation of exposure through sperm

4.3.1. Exposure of study subject Partners During the Study

DNDI-6148 was shown to have no genotoxicity potential. But to date, no developmental toxicity data are available. In the absence of data in animals, a risk of drug exposure through the ejaculate that might be harmful to the sexual partners cannot be excluded, including pregnant partners of male subjects. Therefore, a condom must be used by all study male subjects who are sexually active (even if vasectomised) from dosing up to 10 days post dosing (relative to systemic exposure based on conservative estimate of more than 10 half-lives of DNDI-6148).

This is required independently of the existence of a risk for the partner to become pregnant during the study (applicable to vasectomised males, partner already pregnant, partner of non-child bearing potential, etc…).

4.3.2. Contraception requirements

Subjects who are sexually active must use, with their partner of child-bearing potential, a condom plus an approved method of effective contraception from the time of dosing to 90 days after study discharge. The following methods are acceptable:

- Partner's use of combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal

- Partner's use of progestogen-only hormonal contraception:
  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system

- Partner's use of implantable intrauterine device

- Surgical sterilisation (for example, vasectomy or partner's bilateral tubal occlusion)

Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

4.3.3. Sperm Donation

Subjects should not donate sperm for the duration of the study and for 90 days post dosing.

4.4. Subject Identification

4.4.1. 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.

4.4.2. Inclusion number

The inclusion number will be composed of a total of 6 digits, 3 for the number of centre (001) and 3 for the subject. For example: 001-001. It will be a chronological number.

4.4.3. Randomization number

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

4.5. Subject withdrawal criteria

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

4.5.1.1. 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.

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

4.5.2.1. Decided by the Sponsor

The Sponsor may decide premature discontinuation of the study in the following cases:

- The study is not conducted in accordance with the procedures defined in the approved protocol (i.e. low rate of recruiting - 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;
- Left at the discretion of the Sponsor.

4.5.2.2. 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 in writing the Sponsor of this decision providing the reason thereof.

4.6. Premature discontinuation of subject

4.6.1. 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 electronic Case Report Form (eCRF) page.

If the subject withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data, with the exception of safety data, which should be collected if possible and in accordance with subject consent. The Sponsor may retain and continue to use any data collected before any withdrawal of consent.

The Investigator should inquire about the reason for withdrawal and request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs.

The safety data exams scheduled for the end-of-study visit will be performed if the participant agrees to it.

4.6.2. Methods of replacement

A subject who prematurely ends his study period (for reasons unrelated to the investigational product) after the start of the baseline period and who received product/treatment will be replaced.

The replacement subject will undergo the complete study. He will be given a number corresponding to the number of the subject being replaced plus 100 (i.e. for the subject number 004, the replacement subject will receive the number 104).

Subjects who have been withdrawn from the study during the selection process ("Screening failure") can be re-included in the study. In this case, a new selection procedure will be completed (new selection number, new consent, etc..). The previous selection number must not be re-used.

4.6.3. 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 failed to attend the visit and to determine his health status.
In case of consent withdrawal concomitant to an AEs, 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 8.5).

4.7. 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.

5. STUDY PRODUCT/TREATMENT

5.1. Description of the treatment(s)

5.1.1. Pharmaceutical form

Name of the compound:	DNDI-6148
Pharmaceutical form:	Powder for oral suspension (bottles of pre-weighted powder corresponding to 60 mg and 600 mg DNDI-6148 acid free equivalent) Vehicle: ORA-Sweet®
Dose per administration:	10 mg, 20 mg, 40 mg, 80 mg, 160mg, 260 mg, 380 mg and 500 mg
Timing for administration:	Single oral dose administration on D1 according to the randomization. The administration will be performed around 8:00 a.m. in sitting position and in fasting conditions. 250ml of tap water will be ingested after dosing. The syringe will be first rinsed with the tap water up to the entire capacity of the syringe. Then the subject will drink the rest of the 250 mL tap water.

DNDI-6148 will be pre-weighted in closed bottles (2 strengths) and a suspension will be prepared extemporaneously by the pharmacist prior to administration to volunteers. The powder will be suspended in 30 mL ORA-Sweet® vehicle, a maximum of 24 hours prior to dosing according to stability data available after preparation of the suspension. Volume of suspension to be administered will vary from 4 to 25 ml per subject.
Bottles of pre-weighted powder of DNDI-6148 arginine monohydrate (corresponding to 60 and 600 mg free acid equivalent) and corresponding placebo will be provided to the pharmacy's site.

To be used as a suspension: to be resuspended extemporaneously with ORA-Sweet® (30 mL per bottle), then volume corresponding to the dose to be administered to be measured by the pharmacist at the CRO centre using appropriate precision syringes (volume from 4 to 25 ml/subject), if possible opaque to minimize risk of unblinding (DNDI-6148 is not sensitive to light).

Strengths (mg) of DNDI-6148 in bottle in acid free equivalent	**60**	**600**
Concentration (mg/mL)*	2	20
Dose escalation (mg)	Volume to administer (mL)	
10	**5**	
20	**10**	
40	**20**	
80		**4**
160		**8**
260		**13**
380		**19**
500		**25**

** (30 mL working volume bottles)*

Name of the compound: DNDI-6148 - Placebo

Pharmaceutical form: Powder for oral suspension, Vehicle: ORA-Sweet®

Dose per administration: NA

Timing for administration: Single oral dose administration on D1 according to the randomization.

The administration will be performed around 8:00 a.m. in sitting position and in fasting conditions. 250ml of tap water will be ingested after dosing.
The same procedure as for the active drug will be followed for extemporaneous preparation of placebo.

5.1.2. Unit form, packaging and labelling

Therapeutic units will be manufactured, packaged and labelled in India by Syngene (Bangalore, India). Eurofins Biopharma Product Testing will be the importer and will perform the QP release.

Labelling will be in accordance with local regulatory specifications and requirements (follow Annex 13 European GMP).

The following information will be reported on boxes and bottles, in French language:

- Name, address and telephone number of the sponsor,
- Name of the investigator,
- Trial reference code (Sponsor),
- Packaging batch number,
- Subject's 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"

Label of primary and secondary packaging:

DNDI-6148 60 mg

Médicament expérimental – pour recherche biomédicale uniquement	
DNDI-6148 (60 mg) Poudre pour suspension orale	
Chaque flacon contient DNDI-6148 (60 mg). Voie orale uniquement. Posologie : se référer au protocole clinique. A conserver entre 15 et 25°C. Promoteur : Drugs for Neglected Diseases *initiative* 15 chemin Louis Dunant 1202 Genève, Suisse +41 22 906 9230 Investigateur : Yves Donazzolo Tenir hors de portée des enfants	Numéro de lot : Date de péremption : MM/AAAA Numéro de sujet : _____ Protocole : DNDi-6148-01

DNDI-6148 600 mg

Médicament expérimental – pour recherche biomédicale uniquement	
DNDI-6148 (600 mg) Poudre pour suspension orale	
Chaque flacon contient DNDI-6148 (600 mg). Voie orale uniquement. Posologie : se référer au protocole clinique. A conserver entre 15 et 25°C. Promoteur : Drugs for Neglected Diseases *initiative* 15 chemin Louis Dunant 1202 Genève, Suisse +41 22 906 9230 Investigateur : Yves Donazzolo Tenir hors de portée des enfants	Numéro de lot : Date de péremption : MM/AAAA Numéro de sujet : _____ Protocole : DNDi-6148-01

Placebo

Médicament expérimental – pour recherche biomédicale uniquement	
Placebo pour DNDI-6148 Poudre pour suspension orale	
Chaque flacon contient uniquement du placebo. Voie orale uniquement. Posologie : se référer au protocole clinique. A conserver entre 15 et 25°C. Promoteur : Drugs for Neglected Diseases *initiative* 15 chemin Louis Dunant 1202 Genève, Suisse +41 22 906 9230 Investigateur : Yves Donazzolo Tenir hors de portée des enfants	Numéro de lot : Date de péremption : MM/AAAA Numéro de sujet : _____ Protocole : DNDi-6148-01

Label for oral syringes of DNDI-6148 or Placebo :

Etude DNDi-6148-01 / OP105718.DND
Promoteur : DNDi
Investigateur : Dr Yves DONAZZOLO
Traitement : DNDI-6148 ou Placebo
N° du sujet : 001- _ _ _
Dose : XX mg soit XX mL de suspension
Seringue pour administration orale
A utiliser conformément aux indications du protocole
Prep n° : PREP201_ _ _ _
Date de péremption : _ _/_ _ _ _
Administration D1 : _ _/_ _/_ _ _ _
A conserver entre 15°C et 25°C
Pour recherche sur la personne humaine uniquement

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

DNDI-6148 or matching placebo will be administered orally, at T0h in sitting and in fasting conditions, 250ml of tap water to be ingested after dosing.

Treatments will be administered under the supervision of the Investigator, in the Clinical Pharmacology Unit EUROFINS OPTIMED in Grenoble, France, at around 8 a.m. on day 1.

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 Product 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 OP105718.DNDI”. 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 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 amount of treatment returned supplies will be established and countersigned by the monitoring team.

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 not exceeding 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 eCRF:

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

5.4. Procedures of monitoring subject compliance

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

6. ASSESSMENT OF PHARMACOKINETIC EVALUATION

6.1. Specification of the pharmacokinetic parameters

6.1.1. Plasma

The following pharmacokinetic parameters will be determined from DNDI-6148 concentrations:

- Main DNDI-6148 PK parameters:
  - $AUC_{0-\infty}$ (h*ng/mL): area under the plasma concentration-time curve from administration up to infinity with extrapolation of the terminal phase;
  - C_{max} (ng/mL): observed maximum plasma concentration,
- Other DNDI-6148 PK parameters:
  - AUC_{0-24}: AUC from administration up to 24h
  - AUC_{0-t}: area under the plasma concentration-time curve from administration up to the last quantifiable concentration at time t
  - AUC_{0-t}/D: AUC_{0-t} divided by dose
  - $AUC_{0-\infty}/D$, : $AUC_{0-\infty}$ divided by dose
  - C_{max}/D, : C_{max} divided by dose
  - t_{max} (h): first time to reach C_{max}
  - $t_{1/2}$ (h): plasma elimination half-life
  - MRT (h) : Mean time of drug presence in plasma
  - CL/F (mL/h) : Apparent total clearance of the drug from plasma after oral administration
  - Vz/F (L): Apparent volume of distribution
  - k_e: terminal elimination rate constant
  - %AUCextra: % of AUC extrapolated

6.1.2. Urine

The amount and concentration of DNDI-6148 will be measured. The appropriate specific PK parameters to be calculated will be decided according to concentration.

The following parameters will be calculated from urine data for DNDI-6148:

- **Ae(0-t)** Total amount excreted over 24 h and 72 h (*i.e.* t = 24 or 72).
- **Fe** The fraction of the dose excreted in urine over 24 h and 72 h.
- **CL_r** The renal clearance of DNDI-6148.

6.2. Methods and timing for assessing, recording, and analysing pharmacokinetic parameters

6.2.1. Collection, treatment and storage of blood samples

Blood sampling will be performed for DNDI-6148 concentration measurements at the exact time-points with an authorised time-window described in the Table 8:

Table 8 PK Sampling time

Day	Sampling time	Sample N°	Time window (min)
1	T0 (predose)	P00	+/-1
	T0h30min	P01	+/-1
	T1h00	P02	+/-1
	T1h30min[1]	P03[1]	+/-3
	T2h	P04[1] or P03[2]	+/-3
	T2h30min	P05[1] or P04[2]	+/-5
	T3h	P06[1] or P05[2]	+/-5
	T4h	P07[1] or P06[2]	+/-5
	T5h	P08[1] or P07[2]	+/-5
	T6h	P09[1] or P08[2]	+/-5
	T9h	P10[1] or P09[2]	+/-5
	T12h	P10[2]	+/-5
2	T24h	P11	+/-15
3	T48h	P12	+/-15
4	T72h	P13	+/-15
5[2]	T96h	P14	+/-30
6[2]	T120h	P15	+/-30

1 for the cohorts 10 mg, 20 mg, 40 mg and 80 mg
2 for the cohorts 160 mg, 260 mg, 380 mg and 500 mg

Blood handling procedures: at each time point indicated in the table, a 6 mL blood sample should be drawn into K_2EDTA tube. The blood samplings will be carried out on Day 1 by means of a catheter, and on the other days of the study using a single-use needle.
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 following blood collection, centrifuge each blood sample at 1500 *g* for 10 minutes at 4°C.

Immediately after the end of centrifugation, the top layer of human plasma will be transferred into 2 pre-labelled polypropylene tubes prefilled with phosphoric acid (H_3PO_4) 2% (1/1 v/v). The two tubes will contain 500 µL of plasma each for PK analysis (primary and backup tubes).
Tubes will be capped immediately for each time point and the plasma will be frozen in an upright position at -80°C (+/- 10°C) for storage. In case of temperature deviation, the total time spent above -20°C should not exceed 4 hours.

The remaining plasma (approx. 2 mL) shall be used for metabolite identification: it will be transferred in 2 pre-labelled polypropylene tube with H_3PO_4 2% (1/1 v/v) (twice 500 µL), and 1 pre-labelled polypropylene tube without H_3PO_4 (remaining volume, approx. 1 mL).
Tubes will be capped immediately for each time point and the plasma will be frozen in an upright position at -80°C (+/- 10°C) for storage.

Blood cells should not be transferred. All sample tubes must be clearly and appropriately labelled.

6.2.2. Collection, treatment and storage of urine samples

Urine collection will be performed for DNDI-6148 urine concentration measurements, at the following time points: predose,]D1T0h – D1T12h],]D1T12h – D2T24h],]D2T24h – D3T48h] and]D3T48h – D4T72h].

Urine handling procedures:
Subjects will have to urinate in a polypropylene container. Weight will be measured and recorded for each urination. Within 5 minutes, urine will be transferred in a polypropylene container containing 20 g of citric acid monohydrate. This container will be mixed vigorously to dissolve citric acid. This container will be kept at 4°C for a maximum of 43 hours. During the interval period, each urination will be added in this container. At the end of the interval period, the pool of acidified urine will be vigorously mixed and two aliquots will be prepared each with 1 mL of acidified urine and 1mL of aqueous solution of BSA 50 g/L and NaCl 9 g/L.
The tubes containing the mixture acidified urine/BSA will be capped immediately for each time point and the mixture acidified urine/BSA will be frozen in an upright position at -80°C (+/- 10°C) for storage. In case of temperature deviation, the total time spent above -20°C should not exceed 4 hours.

6.2.3. Transport of samples

Samples will be sent to laboratory SGS Wavre, Belgium, attention to Pegah Maghdooni, for analysis. The shipment will be done in dry ice by a specialized carrier. Temperatures will be monitored using data logger during all transport. The primary samples will be sent separately from the back-up samples. The back-up samples will be shipped with the subsequent cohort samples.

6.3. Analytical methods

A validated internally standardized liquid chromatography tandem mass spectrometry (LC/MS-MS) method will be used for the analysis of DNDI-6148 in acidified K_2EDTA human plasma and acidified human urine.

The Lower limit of quantification (LLOQ) of DNDI-6148 in plasma is 1 ng/ml in plasma and 10 ng/ml in urine.
Bioanalysis will be carried out at SGS Life Sciences, Wavre, Belgium. The bioanalytical procedures of the laboratory are certified according to Good Laboratory Practice (GLP).

7. ASSESSMENT OF PHARMACODYNAMIC EVALUATION

Subjects will be resting in a quiet supervised setting with minimal stimulation (e.g. no television, loud music, computer games, cell phones, handled music player, etc.) and lay in a supine position for 15 min

before each nominal PK time point for the duration of the ECG sampling period. The ECG extraction window will precede any PK blood draw (within 10 minutes prior to PK sampling). All other exams should be done after the ECG extraction period.

Holter recordings will be archived. Analyses will be conducted at the end of the trial by Banook Groupe, Nancy, France if decision to progress to Multiple Ascending Dose (MAD) study is taken or after MAD in order to pool data from SAD and MAD studies. Subjects will be in resting position from -70 to -15 minutes prior to dosing in order to insure proper quality of the recording for ECG extraction pre-dose at T-60 min, T-40min and T-20min. Windows of ECG extractions for each timepoint are defined in the Banook Groupe Scope of Work document.

The Holter data collected in this trial will not be part of the trial's clinical data base.

In case the Holter extracted data are analysed, the following analyses are planned and will be reported in a separate report:

For each selected post-dose PK time-point, Triplicate ECG with at least a 1 min interval will be extracted from the Holter recording at the cardiac core laboratory at the following time points:
On D1 and on D1 to D2 : T0 (pre-dose 3 times triplicate ECG as described above), T0h30min, T1h, T1h30 (only for the cohorts 10 mg, 20 mg, 40 mg, 80 mg), T2h, T2h30, T3h, T4h, T5h (only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg), T6h, T9h, T12h, T24h. T0h corresponds to the administration time reference at which subjects will receive the study drug throughout the study (around 8:00 am).

The Holter-extracted triplicate parameters (RR, HR, PR, QRS, and QT) would be averaged to obtain one single value per time point. On Day 1, three pre-dose triplicates will be extracted and averaged to establish the baseline value.

Changes from baseline with the recorded Holter (Day 1) will be calculated for each parameter:

- Categorical analysis for QT, QTcF, QTcB, ΔQTcF and ΔQTcB according to the thresholds defined below.
- ECG morphological analysis.

The pre-defined thresholds for the categorical analysis for maximum actual values will be:

- QTc interval > 450 ms
- QTc interval > 480 ms
- QT/QTc interval > 500 ms

and for maximum changes from baseline:

- ΔQTc interval > 30 ms
- ΔQTc interval > 60 ms

All parameters and their changes from baseline will be summarized by dose regimen and time-point (including ΔHR, ΔRR, ΔPR, ΔQRS, ΔQT). Placebo group extracts will be used for the double-delta analysis of QT.

QT interval calculation would be manually checked by a cardiologist.
A concentration-response analysis between ΔQTcF and DNDI-6148 concentrations will be performed on ECG data issued from Holter extraction. ΔΔQTcF with their 90% CI will be estimated from the model at each dose Cmax geometric means.

8. ASSESSMENT OF SAFETY

8.1. Specification of safety parameters

8.1.1. Clinical parameters

8.1.1.1. Blood pressure and heart rate

Vital signs consist of body temperature measurement, systolic (SBP) and diastolic (DBP) blood pressures and heart rate.
The measurements for blood pressure and heart rate 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 pre-dose). In case of Holter recording, vital sign will be measured after PK sampling.

8.1.1.2. Physical and neurological 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. A complete neurological examination will be performed at screening, D-1, D1 (around T6h), D4 and for the cohorts 160 mg, 260 mg, 380 mg and 500 mg at D6.
Weight will be only measured at screening, D4 and for the cohorts 160 mg, 260 mg, 380 mg and 500 mg at D6.

8.1.1.3. Electrocardiogram (ECG)

Single 12-lead ECGs will be recorded after at least 10 minutes in supine position using a Cartouch Cardionics® Device (in case of abnormality, a retest is allowed at a minimum of one-minute interval between 2 subsequent ECG). Baseline assessment will be conducted in triplicate, at a minimum 1-minute interval between 2 subsequent ECG.

ECGs should always be recorded before the PK sampling (if any), except pre-dose and holter recording.

Each ECG consists of a minimum 10 second recording of the 12 leads simultaneously, leading to a 12-lead ECG (25 mm/s, 10mm/mV) print-out with morphology, HR, PR, QRS, QT, QTc automatic correction evaluation QTcB, QTcF, including date, time, year of birth 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.

Electronic recordings will be transferred to the ECG central reading facility at the end of each day. Safety cohort reports will be prepared at the end of each cohort, to be provided to the Safety Review Committee for dose-escalation decision. Central reading values will be transferred into the clinical database at the end of the study and will prevail on the automatic values for the final ECG analysis.

8.1.2. Biological parameters

8.1.2.1. Routine laboratory observations

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 full biological test comprises:

- Hematology:
  Hemoglobin, hematocrit, Red Blood Cells (RBC), White Blood Cells (WBC), differential count, platelet count, reticulocytes count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC);
- Hemostasis:
  Haptoglobin, International normalized ratio (INR), Prothrombin time (PT), activated partial thromboplastin time (aPTT),

- Hormonology:
  TSH, free T3,
- Biochemistry:
  Creatinine, fasting blood glucose, total proteins, electrolytes (sodium, potassium, chloride), alanine serine transferase (ASAT), alanine leucine transferase (ALAT), Gamma Glutamyl Transferase (GGT), alkaline phosphatases (ALP), creatine phosphokinase (CPK), total bilirubin and urea, total cholesterol;

8.1.2.2. Urinalysis

The urinalysis tests will be performed by Eurofins-Optimed.

Semi-quantitative ("dipstick") analysis will be performed for the following parameters: pH, ketone bodies, proteins, glucose, occult blood, leukocytes, density. If “dipstick” shows a positive result for protein, glucose, blood and leukocytes, a quantitative result will be performed by the Groupe Oriade Noviale , Mr Bernard CADOUX, 83 Avenue Gabriel Péri, 38400 St Martin d’Héres.

8.1.2.3. Drug of abuse screening tests

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

8.1.2.4. Serologies

It will consist of the determination of: HBs antigen (hepatitis B antigen), anti HCV antibody, anti HIV1/HIV2 and antibodies.

8.1.2.5. Diagnostic test of SARS-CoV-2

In order to detect the COVID-19 infection, the diagnostic test of SARS-CoV-2 will be performed by the Groupe Oriade Noviale, Mr Bernard CADOUX, 83 Avenue Gabriel Péri, 38400 St Martin d’Héres, using a validated RT-PCR method, on nasopharyngeal samples.

8.1.2.6. Cognitive evaluation

Bond and Lader Visual Analog Scale (VAS) questionnaire (see appendix IV).
The Bond and Lader VAS [36] is a measure of subjective feelings using 16 bipolar pairs of adjectives such as alert-drowsy or calm-excited on a 100 mm VAS. This is an auto-questionnaire.

8.1.2.7. Columbia-Suicide severity rating scale (C-SSRS)

C-SSRS evaluation (see appendix V).
A Columbia-Suicide severity rating scale (C-SSRS) evaluation will be done.

8.1.3. Other parameters

8.1.3.1. Alcohol breath test

An alcohol breath test will be performed at the centre, at screening and D-1. The test will be performed using the alcohol breath device ref 7410 plus Drager.

8.1.4. Abnormal safety parameters

Before the subject is allowed to enter the study a full clinical evaluation, ECG and full biological test will be obtained and the absence of clinically significant abnormalities confirmed by the Investigator.

In case of abnormality of any safety parameters (clinical, biological and ECG parameters) during the conduct of the study, an assessment on clinical significance of the abnormality will be made and a comment will be recorded in the eCRF; If an abnormality is judged clinically significant, an AE will be recorded.

8.2. Study Procedure

8.2.1. Screening procedures

Screening procedures occur within 4 weeks (D-28 to D-1) before starting study medication.

Subject enrolment – Screening visit

Subjects will be screened within subject's panel of Eurofins Optimed 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 undergo a complete medical history and a physical examination including blood pressure and heart rate measurements. 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);
- A complete neurological examination
- 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;
- Body temperature
- Safety ECG,
- C-SSRS evaluation – Bond & Lader questionnaire,
- A biological screening test, including:
    - Serology test: HBsAg, anti-HCV antibody, anti-HIV 1 and 2 antibodies,
    - Urine drug screen: amphetamines, benzodiazepines, cannabis, cocaine and opiates,
    - Hematology,
    - Hemostasis,
    - Hormonology,
    - Biochemistry,
    - Urinalysis (qualitative).

8.2.2. Description by type of visit

D-1

- Subject admission;
- Diagnostic test of SARS-CoV-2;
- Alcohol breath test;
- Urine drug screen;
- Physical examination
- Complete neurological examination;
- AE/Concomitant medication check;
- Laboratory safety (hematology, biochemistry, hemostasis, hormonology and urinalysis) will be performed in order to have the results before the Day 1 morning drug administration);
- Blood pressure, heart rate and body temperature;
- ECG
- C-SSRS evaluation – Bond & Lader questionnaire.

D1

- *Before administration*
  - Physical examination;
  - ECG in triplicate before the T0 dosing time
  - Blood pressure, heart rate and body temperature at T0h;
  - AE/Concomitant medication check;
  - Blood sampling (Pre-dose);
  - Predose urine sample;
  - Start of Holter recording 70 minutes before dosing;
  - Randomization.

- *oral administration in fasting condition.*

  - AE/Concomitant medication check (any time)
  - Complete neurological examination around T6h;
  - Blood pressure, heart rate and body temperature at T1h, T1h30 (only for the cohorts 10 mg, 20 mg, 40 mg and 80 mg), T2h, T2h30, T3h, T4h, T5h (only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg), T6h, T12;
  - ECG in single at T1h, T2h, T3h, T4h, T6h, T9h, T12h;
  - C-SSRS evaluation – Bond & Lader questionnaire around T6h;
  - Holter 24h-hours recording;
  - Blood sampling (T30min, T1h, T1h30min (only for the cohorts 10 mg, 20 mg, 40 mg and 80 mg), T2h, T2h30min, T3h, T4h, T5h (only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg), T6h, T9h, T12h);
  - Urine collection:]T0-T12h],]T12h-T24h].

D2

- Physical examination;
- Laboratory safety (hematology, biochemistry, hemostasis and urinalysis);
- Blood pressure, heart rate and body temperature
- End of 24h Holter recording (after blood sampling T24h);
- AE/Concomitant medication check (any time);
- Blood sampling (T24h);
- ECG in single;
- Urine collection]T24h-T48h].

D3

- Blood pressure and heart rate and body temperature;
- ECG in single;
- Blood sampling (T48h);
- AE/Concomitant medication check.
- Urine collection]T48h- T72h].

D4: (end of study visit for the cohorts 10 mg, 20 mg, 40 mg and 80 mg**)**

- Physical examination (including weight);
- Complete neurological examination,
- Laboratory safety (hematology, biochemistry, hemostasis, hormonology and urinalysis);
- Blood pressure, heart rate and body temperature;
- ECG in single;
- C-SSRS evaluation – Bond & Lader questionnaire;
- Blood sampling (T72h);
- AE/Concomitant medication check;
- Discharge.

D5, only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg

- Blood pressure and heart rate and body temperature;
- ECG in single;
- Blood sampling (T96h);
- AE/Concomitant medication check.

D6: end of study visit only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg

- Physical examination (including weight);
- Complete neurological examination,
- Laboratory safety (hematology, biochemistry, hemostasis, hormonology and urinalysis);
- Blood pressure, heart rate and body temperature;
- ECG in single;
- C-SSRS evaluation – Bond & Lader questionnaire;
- Blood sampling (T120h);
- AE/Concomitant medication check.

8.2.3. Diet and Study restriction(s)

On the Day 1, the subjects will be allowed to eat at the following times relative to drug administration:

- T4h standardized lunch;
- T12h standardized dinner.

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

On the other hospitalization days, a standard breakfast will be served. 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 Day-1 but will be stopped at least 24 h before Day-1 and throughout the study duration.

The consumption of grapefruit and grapefruit-containing products will be stopped at least 7 days before Day-1 and throughout the study duration.

8.2.4. Sampled blood volume

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

Biology:.....	60 mL
Pharmacokinetic.....	96 mL
Total volume:	**156 mL**

8.3. Adverse Event and Reporting

8.3.1. Definitions

By the following is understood:

Adverse Event (AE), any untoward medical occurrence in a patient or clinical trial subject administered an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

It can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Definition of an AE includes worsening (in severity and frequency) of pre-existing conditions ("Medical history") before first Investigational Medicinal Product (IMP) administration and abnormalities of procedures (i.e. ECG, X-ray…) or laboratory results which are assessed as "clinically significant".

Clinically Significant Laboratory/Procedures Abnormalities:

For every laboratory assessment, the investigator will evaluate if the laboratory test is normal or abnormal. If abnormal (after repeat test as required), the investigator will assess if this finding is clinically significant or not. If a laboratory parameter is abnormal and clinically significant, it should be reported as an AE.

An abnormal laboratory/procedure result must be compared with the previous value taking into account normal values in the studied population/country.

An AE is a new fact after the administration of the first dose of the study drug or a worsening in the condition; in the case of abnormal laboratory/procedure tests results, it is an increase in severity (clinical intensity) of the abnormality which is judged clinically significant by the investigator.

Laboratory/procedures (i.e. ECG...) abnormalities should be assessed as "clinically significant" (and therefore have to be reported as an AE) if they meet at least one of the following conditions:

- The abnormality suggests a disease and/or organ toxicity AND this abnormality was not present at the screening visit or is assessed as having evolved since the screening visit
- The abnormality requires medical intervention or concomitant therapy

Furthermore, laboratory abnormalities associated with clinical signs and symptoms will also be considered clinically significant.

When reporting an abnormal laboratory result as an AE, a clinical diagnosis should be recorded rather than the abnormal value itself, if available. However, in these cases, the AE should be recorded as the syndromic clinical diagnosis (e.g., acute pancreatitis instead of each finding separately: high levels of amylase, high levels of lipase, abdominal pain and vomiting; e.g. "hypokalemia" rather than "decreased potassium levels").

Adverse Drug Reaction (ADR),
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 possibility of a causal relationship with the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship between the event and the IMP (see definition of causality in 8.3.5.).

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): in this context refers to an AE in which the patient was at risk of death at the time of the AE; it does not refer to an AE that hypothetically might have caused death if more severe;
- Requires in patient hospitalization or prolongation of existing hospitalization: i.e. the AE requires at least an overnight admission or prolongs a hospitalisation beyond the expected length of stay;
- Results in persistent or significant disability or incapacity: i.e. the AE resulted in a substantial disruption of the subject's ability to conduct normal activities;
- Is a congenital anomaly or birth defect i.e. an AE outcome in a child or foetus of a subject exposed to the IMP before conception or during pregnancy;
- Is an important medical event: i.e., AE is medically significant: medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events/reactions, such as important medical event 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.
  In addition, any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event/reaction.

Unexpected adverse reaction, an unexpected adverse reaction is an adverse reaction, whose nature, severity or outcome is not consistent with the applicable product safety reference information on the IMP 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.

Suspected Unexpected Serious Adverse Reaction (SUSAR), a suspected AE related to an investigational medicinal product that is both unexpected and serious.

8.3.2. 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 (IB) currently in force at the time of SAE occurrence.

The reference document for ORA-Sweet® is attached in appendix III.

8.3.3. Recording of events

Any AE (including laboratory test/procedures "clinically significant" abnormalities, intercurrent illnesses or injuries, and/or study procedures related AE) reported spontaneously by the subjects, or observed by the Investigator, after IMP administration, will be recorded according to the procedures in force at EUROFINS OPTIMED.
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" (not considered an adverse event *per se*) and will be recorded according to the procedures in force at EUROFINS OPTIMED.

Any untoward medical event which occurs after the completion of the clinical trial and that is possibly reported by the Investigator to EUROFINS OPTIMED will be classified as a "post-study event" and will be recorded according to the procedures in force at EUROFINS OPTIMED.

8.3.4. Analysis of events

8.3.4.1. By the investigator

Each AE is to be classified by the investigator (in this order):

- For severity
- For causality
- As serious or non- serious

8.3.4.1.1. Grading of Adverse Event severity

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

Mild:	The subject is aware of the event or symptom, but the event or symptom is easily tolerated (e.g. no reduction in daily activities is required).
Moderate:	The subject experiences sufficient discomfort to interfere with or reduces his or her usual level of activity.
Severe:	Significant impairment of functioning: the subject is unable to carry out usual activities and/or the subject's life is at risk from the event.
Life-Threatening:	The subject is at significant risk of life; it does not refer to an event which hypothetically might have caused death if it were more severe (life-threatening consequences, urgent intervention required).
Death:	Death related to an event.

When the intensity of an AE changes over time, each change in intensity will be recorded in the source documents until the event resolves. However, only one AE and the maximum intensity will be recorded in the eCRF for each separate event. If the AE resolves but then recurs, each will be recorded as a separate AE, with the appropriate start and stop times.

8.3.4.1.2. Adverse Event causality assessment

The Investigator will evaluate the possible relationship between the AE and the study drug, i.e. to determine whether there exists a reasonable possibility that the trial drug(s) caused or contributed to the AE(s) and will transmit the result of this evaluation to the Sponsor.

The possible relationship between the AE and the study drug will be quoted as following:

Not related:	There is no reasonable possibility of causal relationship.
Related:	There is at least a reasonable possibility of a causal relationship between an adverse event and an investigational medicinal product. This means that there are facts (evidence) or arguments to suggest a causal relationship.

To help investigators with the decision binary tree yes/no (i.e. Related/Not related) in the evaluation of causality, the Council for International Organizations of Medical Sciences (CIOMS VI) group recommends that investigators be asked to consider the following before reaching a decision:

- Medical history (including presence of risk factors)
- Lack of efficacy/worsening of existing condition
- Study medications
- Other medications (concomitant or previous)
- Withdrawal of study medication, especially following trial discontinuation / end of study medication
- Erroneous treatment with study medication (or concomitant)
- Protocol related procedure

8.3.4.1.3. Adverse Event seriousness assessment

The Investigator will evaluate the seriousness of any event as per the definition (§ 8.3.1).

8.3.4.2. By the Sponsor

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.

The Sponsor is responsible for determining the expectedness of the serious adverse event, using the IMP reference safety information (see §8.3.2 above). Each SAE has to be classified by the sponsor as expected or unexpected for the IMP.

8.4. Procedures in place for the recording and notification of serious adverse events

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

The Investigator must:

- **note** in the participant's medical file the date on which he become aware of the SAE (at a follow-up visit or a telephone contact with the participant or a third person, etc);
- **immediately inform** (within 24 h of awareness of SAE by the Investigator) **by telephone** the Sponsor Medical responsible, and the Sponsor Clinical Project Manager, and confirmed by an email to pharmacovigilance@dndi.org (copy SAE_DNDI6148@dndi.org)
- complete the SAE form and send it by email to pharmacovigilance@dndi.org (copy SAE_DNDI6148@dndi.org), immediately after of being informed of this event, without waiting for the results of the clinical outcome or of additional investigations, and in any case within 24 h of knowledge by the investigator; this form includes a description of the event, onset date and seriousness criteria, duration, severity, causal relationship to study drug, outcome, measures taken and all other relevant clinical and laboratory data;
- provide the persons designated above, as they become available, additional information (follow-up SAE form) 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; any follow-up reports should be submitted as soon as possible, and if possible within 2 working days of knowledge, 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;

The Investigator must also report all SAEs/SARs in the eCRF by filling in the AE form. Where the same data are collected in the eCRF and in the SAE form, the two forms must be completed in a consistent manner, and the same medical terminology should be used.

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 and the Sponsor Medical Responsible and Sponsor Clinical Project Manager will be informed immediately (within 24 h of the investigator becoming aware of the event) by telephone and email.

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;

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.

The Sponsor is responsible for all declarations to Ethics Committee and Health Authorities. The Sponsor will answer to any request from the Competent Authority or Ethics Committee concerning such reactions.

The Sponsor will notify all Suspected Unexpected Serious Adverse Reaction (SUSAR) to the European Medicines Agency (EMA), the Competent Authorities (the “Agence Nationale de Sécurité du Médicament et des Produits de Santé” (ANSM)), and the Ethics Committee (CPP), the two latter having given their approval for the research to take place, in compliance with the applicable safety reporting requirements (see appendix II).

In addition, as this is a first-in-Human study, the Sponsor will notify all SAE (including SUSARs, expected SARs and unrelated serious events) immediately to 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), EUROFINS OPTIMED will declare it to ANSM and CPP within 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.

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

All subjects experiencing an AE, independent of whether considered associated with the use of the IMP or not, have to be monitored until symptoms subside or normalize, until a satisfactory explanation of the observed changes is found or until the investigator considers it medically justifiable to terminate follow-up.

This may also last until after end of the clinical trial.

Resolution of such events is to be documented on the eCRF AE and SAE form.

If a follow-up is necessary, the investigator will decide if the subject has to be hospitalized in the phase I center or if ambulant control examinations are sufficient. For this purpose, control appointments are agreed with the subject. Should it turn out after his release that a follow-up examination is necessary, the subject is called by the investigator or a qualified representative. If the subject is not reached although several calls were made, a written information will be sent out. If the subject does not answer after a reasonable period of time, its duration depending among others on the nature of the finding, he will be considered "lost to follow-up". The sponsor is informed about the outcome of the follow-up.

Information on the results of the follow-up examinations are forwarded to the monitor and sponsor as soon as they are available.

8.6. 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 facts 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 fact" and treated as such (see section 8.4).

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 facts relating to the conduct of the trial or the development of the IMP where the new fact 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 facts 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 facts, 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 serious adverse events and serious adverse reactions, as per current regulations.

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

The declaration to ANSM follows the requirements.
CPP and ARS, if applicable, are informed by email and receive the same documents as requested by ANSM (see appendix II).
All details on roles, responsibilities, processes for safety reporting to Authorities (ANSM, CPP, ARS) and relevant contact details will be identified in the study Safety Management Plan prior to study start.

8.8. Procedure in case of a pregnancy in a trial subject´s partner

In the unlikely event that any trial subject´s partner becomes or is found to be pregnant while trial subject is receiving the study treatment or within 10 days after last administration of the IMP, the investigator must submit the event in writing, on a "Pregnancy Surveillance form", to the Sponsor in an expedited manner, i.e. within 24 hours, with the same procedure and timelines as for SAEs (see paragraph 8.5). This must be done irrespective of whether an AE has occurred.

Subjects will be instructed that if their partner becomes pregnant during the study, this should be reported to the Investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study.

The subject should try to convince his partner to come to the Clinical Unit and meet the Investigator. Consent will be sought from the partner by the Investigator.

Pregnancies that have been caused by the subject are recorded and tracked, if the partner has consented. The information submitted should include the anticipated date of delivery. The Investigator will evaluate the date of pregnancy start (1st day of last menstruation period) so that a potential exposure during pregnancy based on product's half-life could be evaluated.

The investigator will follow the trial subject´s partner (once consent obtained from female partner) until completion of the pregnancy or until pregnancy termination (i.e., induced / spontaneous abortion). The investigator will provide pregnancy outcome information on a "Pregnancy Surveillance Form".

A pregnancy is not an SAE.

In the case of a live birth, a medically qualified person should assess the infant at the time of birth and submit a Child Surveillance form. An SAE should be declared in the case of unfavorable pregnancy outcome (abortion, still birth) or congenital abnormality (in addition to the Child Surveillance Form).

In case of in utero exposure, the parents will be proposed a follow-up of the new born up to the age of 2 years old.

In the case the consent of the partner would not be obtained, the pregnancy shall only be declared to the Sponsor without any information on the partner.

9. DATA MANAGEMENT

9.1. 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.

9.2. Source document requirements

According to the guidelines on GCP, the Monitoring Team must check the eCRF entries against the source documents, except for the pre-identified source, data directly recorded in 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.

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

9.3.1. 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, a validated Electronic Records/Electronic Signature-compliant (21 CFR Part 11) application of Aris Global.

Should a correction be made, the corrected information will be entered in the eCRF and the initial information will be tracked in the audit trail.

ECG Central reading data will be transferred in the study database prior to database freeze.

9.3.2. Responsibilities

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

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.

9.3.3. 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.

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. A CD-ROM of PDRs will be kept at site and another one will be sent to the sponsor for archiving.

10. 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. Monitoring activities have been delegated by the Sponsor to Eurofins-Optimed which will appoint 2 monitors (one blinded monitor and one unblinded monitor who will specifically proceed to monitoring activities at pharmacy level). Co-monitoring visits with the Sponsor representative are possible only on blinded data.

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.

11. STATISTICS

11.1. Description of the statistical methods

The statistical analysis will consist of individual data listings and descriptive statistics performed by EUROFINS OPTIMED (baseline characteristics, safety and study conduct), using the SAS® computer program (release 9.4).

The pharmacokinetic and pharmacodynamic data will be analysed by PhinC Development.

All individual data for all included subjects will be presented in data listings, sorted by subject within dose group.
Demographic and baseline characteristics data will be summarized by dose group and overall. On-product/treatment data will be summarized by dose group and overall.
For safety parameters with evaluation before dosing and in case of rechecked value(s) for one 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.

11.1.1. 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, and descriptive statistics for qualitative parameters will be provided using frequencies (n) and percent frequencies (%).

11.1.1.1. Subject demographic characteristics, medical history and diagnoses

Continuous variables (age, height, weight, BMI and qualitative variables will be summarized in descriptive statistics for all distinct study populations.
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)). Abnormal physical findings at baseline will be listed.

11.1.1.2. 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.

11.1.1.3. Baseline safety parameters

Individual safety data (clinical laboratory, vital signs, ECG, questionnaires) 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).

11.1.1.4. 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; most recent version at the time of study start). 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 treatment group and overall subjects, presenting the frequency of subjects (n) taking a given medication and the number of occurrences of each medication.

11.1.2. Analysis of principal criteria

11.1.2.1. Adverse event

AEs will be coded according to the most recent version at the time of study start of the Medical Dictionary for Regulatory Activity (MedDRA). They 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”).

An AE occurring during the follow-up will be related to the last day of treatment administration received. AEs will be individually listed per subject number, presenting: assigned dose group, verbatim, MedDRA Primary System Organ Class, MedDRA Preferred Term, treatment-emergence (TEAEs or not=NTEAEs) date and time of onset, date and time of last study drug administration before AE, duration, time from onset since last study drug administration, frequency, severity and seriousness, relationship to study drug (with justification is assessed related), the required action taken (e.g. corrective treatment, hospitalisation) outcome and if it is a reason for drop-out.
The non-treatment emergent AEs will be summarised by System Organ Class and Preferred Term for the safety set.
The treatment emergent AEs will be summarised by Primary System Organ Class, Preferred Term and dose group for the safety set. It will consist in the evaluation of the number of AEs and the number of subjects reporting these AEs.

11.1.2.2. Physical examination, neurological examination, ECG, vital signs and questionnaires

Physical examination, neurological examinations, ECGs, vital signs and questionnaires (C-SSRS, Bond and Lader VAS) recorded during the study will be individually listed and quantitative parameters will be summarised by using descriptive statistics.
For vital signs and ECG parameters, values and abnormalities (not clinically significant and clinically significant) will be described by dose group and overall , at screening, study baseline (D-1 or D1 pre-dose), , each evaluation under treatment phase and at the end of the study.
Change between the value at baseline and the value at each evaluation under treatment phase and at end of study visit will be described for each parameter by dose group and overall.

11.1.2.3. Laboratory parameters

All laboratory values recorded during the study will be individually listed and flagged for values outside reference ranges and for clinical significance (assessed by investigator). Quantitative and qualitative parameters will be summarised by descriptive statistics.
Values, position according to laboratory range and clinical assessment will be described at screening, D-1 (baseline), at D2, D4 and D6 (only for the cohorts 160 mg, 260 mg, 380 mg and 500 mg) by dose group and overall.
Change between the value at baseline and the value at post-dose visits will be described for each parameter by dose group and overall.

11.1.3. Analysis of secondary criteria

Pharmacokinetic

A detailed SAP will be prepared by PhinC Development. This SAP should be validated by the Sponsor prior to unblinding.

The summary tables and data listings will be produced by PhinC Development.

Concentrations will be presented by dose level and time point. Descriptive statistics for the concentrations will be presented as mean, SD, and will be calculated if at least 2/3 of the values per time-point are above LOQ. For descriptive statistics calculations, plasma concentrations below the limit of quantification will be set to zero (0) before the first concentration equal or above LOQ and considered as missing after.

No descriptive statistics will be done on urine concentrations.

Individual PK parameters will be presented by dose level. Descriptive statistics of the PK parameters will be presented as mean, SD, coefficient of variation (CV%), median, geometric mean (GM), Min, and Max and will be calculated if at least 2/3 of the reliable PK parameters are available.

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.

The individual AUC and Cmax values will be presented graphically by dose level.

Dose proportionality

The hypothesis that AUC and C_{max} are dose proportional will be formally tested using a power model approach. AUC and C_{max} values, for all dose levels, will be analyzed for dose proportionality using analysis of variance (ANOVA) techniques.

Data will be fitted to the following model:

$$\log(\text{AUC or } C_{max}) = \mu + [\beta \times \log(\text{Dose})]$$

This is usually referred to as a power model because after exponentiation:

$$\text{AUC or } C_{max} = \alpha \times \text{Dose}^{\beta}$$

Prior to the analysis, the assumption of a linear relationship between the log AUC (C_{max}) and log-dose will be tested using ANOVA by partitioning the sums of squares for treatments into those for linearity and departures from linearity. If the departures from linearity are significant then the hypothesis of dose proportionality is rejected and the power model analysis will not be performed.

In case, $AUC_{0-\infty}$ could not be considered as reliable in a majority of subjects (*e.g.* too large percentage of extrapolation, poor quality of k_e determination), dose proportionality assessment will be performed on AUC_{0-t} values.

The estimate obtained for β is a measure of dose proportionality. The estimate of β together with its 90% CI (β_l, β_u) will be presented to quantify the degree of non-proportionality.

The dose proportionality will be confirmed if the 90% CI of β (β_l, β_u) is contained completely within the following critical region:

$$[\Theta_L ; \Theta_H] = \left[1 + \frac{\log(0.8)}{\log(r)} ; 1 + \frac{\log(1.25)}{\log(r)}\right]$$

where *r*, defined as the dose ratio, is equal to h/l , *h* being the highest dose and *l* the lowest dose.

In this decision rule, the dose proportionality will be analyzed as an equivalence problem. If the 90% CI is excluded completely from the critical region $[\Theta_L ; \Theta_H]$ defined here above, the hypothesis of dose proportionality is rejected. If the 90% CI of β includes the lower or the upper bound of the critical region, no conclusion can be done on dose proportionality. The proportionality will be tested at a 5% significance level.

The calculation of the increase in AUC and C_{max} for a two-fold increase in dose will be performed by substituting the value of β in the equation 2^{β}. CI for this ratio will be obtained by substituting β_l and β_u in the equation 2^{β}.

Assessment of the dose proportionality will be performed on the complete dose range. In case of departures from linearity or of negative conclusion of dose proportionality on the complete dose range, further investigation using the same methodology might be done on a restrained dose range.

The statistical package SAS® v.9.4 will be used to perform all statistical analyses.

Pharmacodynamic

In case the Holter data are analysed, the following analyses will be reported in a separate report:

All ECG parameters for PD analysis will be extracted in triplicate from 24-hours Holter recording. Extraction will be matched to PK sampling time and triplicate values will be averaged in order to obtain one single value per time point. Individual data listings and descriptive statistics by dose level and time point will be performed.

All parameters will be presented descriptively and graphically on raw data and changes from baseline by dose level and time points.

Categorical analysis consisting in counts and percentages of abnormal values per dose level will be performed for HR, QTc, PR and QRS according to regulatory thresholds for raw data and changes from baseline.

Treatment emergent morphological findings will be summarized as counts and percentage of subjects presenting at least one finding by dose level.

Concentration-response relationship will be investigated between change from baseline in QTcF and DNDI-6148 concentrations. First, graphics of change from baseline in QTcF and concentrations of DNDI-6148 will be generated in order to visualize the overall pattern of each relationship. Modelling of each of these graphics will then be performed by means of linear or nonlinear mixed model.

For each compound, a model will be selected according to the overall precision of the model towards observed data and diagnostic plots. Using these models, predictions of changes from baseline at concentrations of interest (e.g. Cmax) will be obtained from the concentration-response models with their 90%CI.

11.2. Sample size

No formal calculation was performed. It has been decided to include 8 subjects (6 active and 2 placebo) within each treatment group, which, given the exploratory nature of the trial, is considered as a sufficient number of subjects.

11.3. 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.

11.4. Interim Analysis

Interim PK calculations will be performed at the end of each dose group based on blinded data.

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

Missing data values will not be replaced. Reason for missing data should be provided.

11.6. 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.

11.7. Selection of subjects to be included in the analyses

In case of incorrect treatment assigned, subjects will be analysed in the treatment group they actually were included and the treatment they received.

12. QUALITY CONTROL AND ASSURANCE

12.1. Quality Assurance

The study will be carried out in conformity with legal conditions and French regulations, and with respect to GCP (ICH E6 (R2)) guideline. 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.

12.2. 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.

12.3. 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 to verify that 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 these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.
The confidentiality of the data and the anonymity of the subjects should be respected during these inspections.

13. ETHICS

13.1. 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 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.

13.2. 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 and of the Competent Authorities.

13.3. Protocol amendments

Any protocol amendment must be approved and signed by the sponsor and the Principal investigator and is to be submitted to the appropriate IEC for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval by IEC (and Regulatory Authority, if applicable) must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial.

The protocol amendment can be initiated by either sponsor or by any Principal investigator.

The investigator will provide in writing the reasons for the proposed amendment and will discuss with the medical responsible and the sponsor.
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.

13.4. Protocol deviations

The Principal investigator will ensure that the study protocol is strictly adhered to throughout, and that all data are collected and recorded correctly on the CRF.

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). Critical deviations should be communicated to the Sponsor on timely manner.

13.5. 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. They should address their request in writing to the Investigator, and will obtain a response within 8 working days.

14. DATA HANDLING AND RECORD KEEPING

14.1. 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 twenty-five 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.

14.2. 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 MR-001 and the European Regulation N°2016/679 on General Data Protection Regulation (GDPR).

14.3. 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.

15. 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 and to the CPP.

16. 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.

17. REFERENCES AND REGULATORY GUIDELINES

[1] Investigator Brochure of DNDI-6148, current version.
[2] Obach et al., JPET 283(1997)46. The Prediction of Human Pharmacokinetic Parameters from Preclinical and In Vitro Metabolism Data.
[3] Sahin and Benet, Pharm. Res. 25(2008)2869. The Operational Multiple Dosing Half-life: A Key to Defining Drug Accumulation in Patients and to Designing Extended Release Dosage Forms.
[4] Musther et al., Eur. J. Pharm. Sci. 57(2014)280. Animal versus human oral drug bioavailability: Do they correlate?
[5] Clinical Pharmacokinetics (Chapter 1), Ed. Soraya Dhillon, Andrzej Kostrzewsk, Pharmaceutical Press (2006), London.
[6] CTFG (2014) Recommendations related to contraception and pregnancy testing in clinical trials.
[7] Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1), 20 July 2017.

And

- 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.
- ANSM guidelines "Données de vigilance : Obligations de déclarations immédiates du promoteur" Version 3 Mai 2017.

18. LIST OF APPENDICES

APPENDIX I DECLARATION OF HELSINKI

APPENDIX II ANSM GUIDELINE FOR SAE, SAR, SUSAR, NEW FACTS DECLARATION

APPENDIX III ORASWEET® PRODUCT INFORMATION

APPENDIX IV Visual Analog Scale (VAS) Bond and Lader questionnaire

APPENDIX V Columbia-Suicide severity rating scale

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.

APPENDIX II
ANSM GUIDELINE FOR SAE, SAR, SUSAR, NEW FACTS DECLARATION Extract from "H-919_FR_Tome II. Vigilance of Clinical Trials_Notice to Sponsors of Clinical Trials of Drugs Including Advanced Therapy Drugs_local language_2020"

ANNEXE 2	OBLIGATIONS DE DECLARATION IMMEDIATE DU PROMOTEUR (EN DEHORS DU RAPPORT ANNUEL DE SECURITE)

1. Pour tous les EC, qu'ils soient menés chez des volontaires malades (VM) ou chez des volontaires sains (VS), le promoteur doit notifier :

Les suspicions d'effet indésirable grave inattendu (EIGI ou SUSAR) survenues en France et en dehors du territoire national :

- au cours de l'EC concerné ;

- liées à la même substance active, survenues au cours d'un autre EC (mené dans un autre Etat membre ou hors UE) promu par le même promoteur ou un autre promoteur appartenant à la même société mère ou lié par un accord.

<table>
<tr><th rowspan="2">A qui déclarer ?
(paragraphe 3.3.1.3.)</th><th rowspan="2">Quand ?
(paragraphe 3.3.1.4.)</th><th colspan="2">Comment ? (paragraphe 3.3.1.5.)</th></tr>
<tr><th>Moyen</th><th>Format</th></tr>
<tr><td rowspan="2">ANSM</td><td>Décès ou mise en danger de la vie du participant :

sans délai
+
rapport de suivi dans les 8 j. suivants</td><td rowspan="2">e-mail : declarationsusars@ansm.sante.fr

Modalités :

cf. Note explicative « Déclaration des SUSARs, effets indésirables graves attendus et évènements indésirables graves » disponible sur le site internet de l'ANSM à la rubrique dédiée aux essais cliniques de médicaments</td><td rowspan="2">Fiche CIOMS I

ou

Fiche ICSR (R3)

(format PDF)</td></tr>
<tr><td>Autres situations :

au plus tard dans un délai de 15 j.
ou sans délai pour les EIGI/SUSARs survenus en France dans un essai mené chez des VS

+ rapport de suivi dans les 8 j. suivants</td></tr>
<tr><td>Eudravigilance module EC (EVCTM)</td><td colspan="3">Cf. l'indication détaillée CT-3 et le site https://eudravigilance.ema.europa.eu</td></tr>
</table>

2. En outre, pour les EC menés chez des volontaires sains (VS), le promoteur doit notifier :

Les effets indésirables graves attendus et tous les autres événements indésirables graves survenus chez le volontaire sain en France au cours de l'EC concerné (en sus des déclarations des EIGI/SUSAR)

A qui déclarer ? *(paragraphe 3.3.1.3.)*	Quand ? *(paragraphe 3.3.1.4.)*	Comment ? *(paragraphe 3.3.1.5.)*	
		Moyen	**Format**
ANSM	Sans délai	e-mail : declarationsusars@ansm.sante.fr Modalités : cf. **Note explicative** « Déclaration des SUSARs, effets indésirables graves attendus et évènements indésirables graves » disponible sur le site internet de l'ANSM à la rubrique dédiée aux essais cliniques de médicaments	Fiche CIOMS ou Fiche ICSR (R3) (Format PDF)

3. Pour tous les EC qu'ils soient menés chez des VS ou des VM, le promoteur doit notifier :

Les faits nouveaux avec ou sans mesure(s) urgente(s) de sécurité

Dans le cas d'un EC portant sur un médicament, il s'agit de toute nouvelle donnée pouvant conduire à une réévaluation du rapport des bénéfices et des risques de la recherche, à des modifications dans l'administration du ME/IMP, dans la conduite de la recherche, ou des documents relatifs à la recherche, ou à suspendre ou interrompre ou modifier le protocole de la recherche ou des recherches similaires.

Pour les EC portant sur la première administration d'un médicament chez des volontaires sains (VS) :

- tout effet indésirable grave est constitutif d'un fait nouveau
- en sus de la déclaration du fait nouveau, le promoteur doit :
  - suspendre l'administration du médicament expérimental dans l'attente de l'adoption de mesures définitives
  - mettre en place des mesures urgentes de sécurité (MUS) appropriées

<table>
<tr><th>A qui déclarer ?

(paragraphe 3.3.1.3.)</th><th rowspan="2">Quand ?

(paragraphe 3.3.1.4.)</th><th colspan="2">Comment ? (paragraphe 3.3.1.5.)</th></tr>
<tr><th>Moyen</th><th>Format</th></tr>
<tr><td>ANSM

(essais VM et VS)</td><td rowspan="2">Sans délai

(+ informations complémentaires pertinentes dans les 8 jours)</td><td>e-mail :

vig-essaiscliniques@ansm.sante.fr

Modalités : cf. Note explicative « Déclaration des faits nouveaux, mesures urgentes de sécurité » disponible sur le site internet de l'ANSM à la rubrique dédiée aux essais cliniques de médicaments

/!\ Modalités spécifiques pour tous les essais de 1ère administration d'un médicament expérimental menés chez des VS</td><td rowspan="2">Formulaire de déclaration d'un fait nouveau / MUS disponible sur le site internet de l'ANSM à la rubrique dédiée aux essais cliniques de médicaments (Accueil > Activités > Médicaments et... > Avis aux promoteurs – Formulaires)</td></tr>
<tr><td>ARS des lieux de recherche concernés

(essais VS)</td><td>Cf. ARS concernée(s)</td></tr>
</table>

APPENDIX III
ORASWEET PRODUCT INFORMATION

Look to Paddock for All of Your Compounding Needs

TOPICALS
INJECTABLES
ORAL LIQUIDS
ORAL SOLIDS
SUPPOSITORIES
COMPOUNDING

ORA-SWEET®

Flavored Syrup Vehicle

ORA-SWEET®

Paddock ORA-SWEET

Size	NDC
473 ML (One Pint)	0574-0304-16

Ora-Sweet is a syrup vehicle used to simplify the process of flavoring and sweetening extemporaneous compounded oral preparations. Ora-Sweet allows the pharmacist to formulate elegant, sweetened products with minimum time and maximum dependability. Ora-Sweet is the modern version of simple syrup flavored with a citrus-berry blend for a highly palatable taste.

Applications

Ora-Sweet may be used alone or in combination with other agents. Ora-Sweet will retain its flavoring properties when diluted up to 50% with water or suspending agents. Its versatility makes it ideal for the flavoring of:

- Pediatric preparations
- Geriatric preparations

How to Use

Ora-Sweet is the ideal flavoring and sweetening agent for many suspensions, but it is specially formulated to complement Paddock's suspending vehicle Ora-Plus. Ora-Sweet and Ora-Plus can be combined in a 50/50 ratio to produce a pleasant tasting elegant suspension.

Properties

Ora-Sweet contains sucrose which acts as a sweetening agent. Small amounts of glycerin and sorbitol are added to prevent "cap lock" problems common to most syrups. Its flavoring agents help increase palatability. Ora-Sweet is buffered to a slightly acidic pH to help diminish degradation of medicinal agents through oxidation.

Ingredients

Purified water, sucrose, glycerin, sorbitol, and flavoring. Buffered with citric acid and sodium phosphate. Preserved with methylparaben and potassium sorbate.

Specifications

Appearance: Clear liquid with a slight tint

pH: Approximately 4.2

Taste: Sweet citrus-berry flavor

Osmolality: 3240 mOsm/Kg

Order through your wholesaler. For additional information please contact Paddock Laboratories at 1-800-328-5113 or www.paddocklabs.com

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ORA-SWEET Formulating and Compounding Examples

CHLOROQUINE PHOSPHATE 15 mg/mL, 100 mL[2]

Chloroquine Phosphate 500 mg/tablet	3 tablets
Ora-Plus	50 mL
Ora-Sweet*	q.s. 100 mL

- Expiration 60 days
- Protect from light
- Shake well before using

METOLAZONE 1 mg/mL, 120 mL[1]

Metolazone 10 mg/tablet	12 tablets
Ora-Plus	60 mL
Ora-Sweet*	q.s. 120 mL

- Expiration 60 days
- Protect from light
- Shake well before using

PROCAINAMIDE HCl 50 mg/mL, 120 mL[1]

Procainamide HCl 250 mg/capsule	24 capsules
Ora-Plus	60 mL
Ora-Sweet*	q.s. 120 mL

- Expiration 60 days
- Protect from light
- Shake well before using

KETOCONAZOLE 20 mg/mL, 120 mL[1]

Ketoconazole 200 mg/tablet	12 tablets
Ora-Plus	60 mL
Ora-Sweet*	q.s. 120 mL

- Expiration 60 days
- Protect from light
- Shake well before using

METRONIDAZOLE 50 mg/mL, 120 mL[1]

Metronidazole powder	6 grams
Ora-Plus	60 mL
Ora-Sweet*	q.s. 120 mL

- Expiration 60 days
- Protect from light
- Shake well before using

SPIRONOLACTONE 25 mg/mL, 120 mL[1]

Spironolactone 25 mg/tablet	120 tablets
Ora-Plus	60 mL
Ora-Sweet*	q.s. 120 mL

- Expiration 60 days
- Protect from light
- Shake well before using

General Directions For Compounding ORA-SWEET*/ORA-PLUS Suspensions

ORA-SWEET and ORA-PLUS should be combined in a 50/50 ratio to achieve optimal formulation.

- Calculate the total amount of active ingredient and volume of solution needed to create a suspension of the proper concentration. (Calculations are provided in the examples above.) *It may be wise to add approximately 10% overage for compounding losses.*
- Crush tablets with a mortar and pestle to a fine powder. If the compound is already in the powder form, use the mortar and pestle to smooth out the powder.
- Add a small amount of **Ora-Plus** and triturate to a thick, smooth paste. Add the remainder of **Ora-Plus** by geometric dilution. *The amount of Ora-Plus should be 50% of the total solution.*
- Bring the suspension to a final volume using **Ora-Sweet***. Mix briefly with a mortar and pestle until a uniform suspension is formed.
- Dispense in a tight, light resistant amber bottle with appropriate labeling.
- Label with an expiration date. *If the stability of the medication in an oral suspension or syrup is unknown, conservative dating is suggested.*
- Depending on the medicinal agent used, label containers "Shake Well Before Using," "Protect From Light," and "Keep Refrigerated."

*Ora-Sweet may be substituted with Ora-Sweet SF. Both products may be used in a 1:1 ratio with Ora-Plus.

[1]American Journal of Health-System Pharmacists 1996; 53:2073-8.
[2]American Journal of Health-System Pharmacists 1998; 55:1915-20.

Contraindications

Ora-Sweet is contraindicated in persons who have shown hypersensitivity to any of the listed ingredients.

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APPENDIX IV
VISUAL ANALOG SCALE BOND AND LADER QUESTIONNAIRE (FRENCH VERSION)

ÉCHELLE VISUELLE ANALOGIQUE (BOND ET LADER)

Indiquez sur l'échelle visuelle analogique ci-dessous votre humeur actuelle par rapport aux deux états situés aux extrémités de chaque ligne.

Résumé de l'échelle visuelle analogique (Bond et Lader)			**Résultat** (mm)
1. Éveillé(e)**.**	_____	Somnolent(e)	
2. Calme)**.**	_____	Excité(e)	
3. Fort(e)	_____	Faible	
4. Confus(e)	_____	Lucide	
5. Adroit(e)	_____	Maladroit(e)	
6. Nonchalant(e	_____	Énergique	
7. Content(e)	_____	Mécontent(e)	
8. Inquiet(e)	_____	Tranquille	
9. Lent(e) d'esprit	_____	Vif(ve) d'esprit	
10. Tendu(e)	_____	Détendu(e)	
11. Attentif(ve)	_____	Rêveur(se)	
12. Incapable	_____	Capable	
13. Heureux(se)	_____	Malheureux(se)	
14. Antipathique	_____	Amical(e)	
15. Intéressé(e)	_____	Ennuyé(e)	
16. Renfermé(e)	_____	Sociable	

APPENDIX V
COLUMBIA-SUICIDE SEVERITY RATING SCALE (FRENCH VERSION)

Baseline Version, French

ÉCHELLE D'ÉVALUATION DE COLUMBIA SUR LA GRAVITÉ DU RISQUE SUICIDAIRE (C-SSRS)

Évaluation initiale

Version du 14/01/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Avertissement :

Cette échelle est destinée à être utilisée par des cliniciens qualifiés. Les questions contenues dans l'Échelle d'évaluation de Columbia sur la gravité du risque suicidaire (C-SSRS) sont des suggestions à titre indicatif. La présence de risque suicidaire dépend de l'estimation clinique finale.

*Les définitions des comportements suicidaires de ce questionnaire sont basées sur celles utilisées dans **The Columbia Suicide History Form**, développé par John Mann, MD, et Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. Dans M.B. First [Ed.] Standardized Evaluation in Clinical Practice, p. 103 -130, 2003.)*

Pour obtenir des copies du C-SSRS veuillez contacter Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032 ; pour toute question et besoins en matière de formation, écrire à : posnerk@nyspi.columbia.edu

C-SSRS Baseline - France/French – Mapi.
ID61171/ C-SSRS-Baseline_AU5.1_fra-FR.doc

IDÉATION SUICIDAIRE	
Posez les questions 1 et 2. Si les deux réponses sont négatives, passez à la section « Comportement suicidaire ». Si la réponse à la question 2 est « oui », posez les questions 3, 4 et 5. Si la réponse à la question 1 et/ou 2 est « oui », complétez la section « Intensité de l'idéation » ci-dessous.	Depuis la naissance : moment où il/elle s'est senti(e) le plus suicidaire
1. Désir d'être mort(e) Le sujet souscrit à des pensées concernant le désir de mourir ou de ne plus être en vie, ou le désir de s'endormir et de ne pas se réveiller. ***Avez-vous souhaité être mort(e) ou vous endormir et ne jamais vous réveiller ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐
2. Pensées suicidaires actives non spécifiques Pensées d'ordre général non spécifiques autour de la volonté de mettre fin à ses jours/se suicider (par ex. *« J'ai pensé à me suicider »*), non associées à des pensées sur les manières permettant de se suicider/méthodes associées, ni à une intention ou à un scénario. ***Avez-vous réellement pensé à vous suicider ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐
3. Idéation suicidaire active avec définition de méthodes (sans scénario), sans intention de passage à l'acte Le sujet pense au suicide et a envisagé au moins une méthode pour y parvenir au cours de la période d'évaluation. Il ne s'agit pas ici de l'élaboration d'un scénario spécifique comprenant le moment, le lieu ou la méthode (par ex. le sujet a pensé à une méthode pour se suicider, mais ne dispose pas d'un scénario précis). Il s'agit par exemple d'une personne déclarant : *« J'ai pensé à avaler des médicaments, mais je n'ai pas de scénario précis sur le moment, le lieu ou la manière dont je le ferais... et je n'irais jamais jusque là ».* ***Avez-vous pensé à la manière dont vous vous y prendriez ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐
4. Idéation suicidaire active avec intention de passage à l'acte, sans scénario précis Pensées suicidaires actives, le sujet exprime une intention plus ou moins forte de passer à l'acte et ne se contente pas de déclarer : *« J'ai des pensées suicidaires, mais je ne ferai jamais rien pour les mettre en œuvre ».* ***Avez-vous eu des pensées de ce genre et l'intention de passer à l'acte ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐
5. Idéation suicidaire active avec scénario précis et intention de passage à l'acte Pensées suicidaires associées à l'élaboration complète ou partielle d'un scénario détaillé ; le sujet exprime une intention plus ou moins forte de mettre ce scénario à exécution. ***Avez-vous commencé ou fini d'élaborer un scénario détaillé sur la manière dont vous voulez vous suicider ? Avez-vous l'intention de mettre ce scénario à exécution ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐
INTENSITÉ DE L'IDÉATION	
Les aspects suivants doivent être évalués en fonction du type d'idéation le plus grave (c.-à-d. idéations 1 à 5 ci-dessus, 1 étant la moins grave et 5 la plus grave). La question portera sur le moment où il/elle s'est senti(e) le plus suicidaire. ***Idéation la plus grave:*** _____ (***N° du type (1 à 5)***) _____ (***Description de l'idéation***)	Idéation la plus grave
Fréquence ***Combien de fois avez-vous eu ces pensées ?*** (1) Moins d'une fois par semaine (2) Une fois par semaine (3) 2 à 5 fois par semaine (4) Tous les jours ou presque (5) Plusieurs fois par jour	
Durée ***Lorsque vous avez ces pensées, combien de temps durent-elles ?*** (1) Quelques instants : quelques secondes ou quelques minutes (2) Moins d'une heure/un certain temps (3) 1 à 4 heures/longtemps (4) 4 à 8 heures/une grande partie de la journée (5) Plus de 8 heures/en permanence ou tout le temps	
Maîtrise des pensées suicidaires ***Pourriez-vous/pouvez-vous arrêter de penser au suicide ou à votre envie de mourir si vous le voul(i)ez ?*** (1) Maîtrise facilement ses pensées. (2) Capable de maîtriser ses pensées avec de légères difficultés. (3) Capable de maîtriser ses pensées avec quelques difficultés. (4) Capable de maîtriser ses pensées avec de grandes difficultés. (5) Incapable de maîtriser ses pensées. (0) N'essaie pas de maîtriser ses pensées.	
Éléments dissuasifs ***Y a-t-il quelque chose ou quelqu'un (par ex. votre famille, votre religion ou la douleur au moment de la mort) qui vous a dissuadé de vouloir mourir ou de mettre à exécution vos pensées suicidaires ?*** (1) Des éléments dissuasifs vous ont véritablement empêché(e) de tenter de vous suicider. (2) Des éléments dissuasifs vous ont probablement arrêté(e). (3) Vous ne savez pas si des éléments dissuasifs vous ont arrêté(e). (4) Vous n'avez très probablement été arrêté(e) par aucun élément dissuasif. (5) Les éléments dissuasifs ne vous ont pas du tout arrêté(e). (0) Sans objet	
Causes de l'idéation ***Quelles sont les raisons pour lesquelles vous avez souhaité mourir ou vous suicider ? Était-ce pour faire cesser la douleur ou bien pour ne plus ressentir votre mal-être (en d'autres termes, vous ne pouviez pas continuer à vivre avec cette douleur ou ce mal-être), ou bien pour attirer l'attention, vous venger ou faire réagir les autres ? Ou tout cela à la fois ?*** (1) Uniquement pour attirer l'attention, vous venger ou faire réagir les autres. (2) Principalement pour attirer l'attention, vous venger ou faire réagir les autres. (3) Autant pour attirer l'attention, vous venger ou faire réagir les autres que pour faire cesser la douleur. (4) Principalement pour faire cesser la douleur (vous ne pouviez pas continuer à vivre avec cette douleur ou ce mal-être). (5) Uniquement pour faire cesser la douleur (vous ne pouviez pas continuer à vivre avec cette douleur ou ce mal-être). (0) Sans objet	

 C-SSRS—Baseline (Version du 1/14/09)

COMPORTEMENT SUICIDAIRE *(Cochez toutes les cases correspondant à des événements distincts ; le sujet devra être interrogé sur tous les types de comportements)*	**Depuis la naissance**
Tentative avérée : Acte potentiellement auto-agressif commis avec l'intention plus ou moins forte de mourir *suite à cet acte*. Ce comportement a été en partie envisagé comme moyen de se suicider. L'intention suicidaire n'est pas nécessairement de 100 %. Si une intention/volonté ***quelconque*** de mourir est associée à l'acte, celui-ci pourra être qualifié de tentative de suicide avérée. ***La présence de blessures ou de lésions n'est pas obligatoire***, mais seulement potentielle. Si la personne appuie sur la gâchette d'une arme à feu placée dans sa bouche, mais que cette arme ne fonctionne pas et qu'aucune blessure n'est engendrée, cet acte sera considéré comme une tentative. Intention présumée : même si la personne nie son intention/sa volonté de mourir, on peut supposer d'un point de vue clinique l'existence de cette intention/volonté d'après le comportement ou les circonstances. Par exemple, un acte pouvant entraîner une mort certaine et ne relevant clairement pas d'un accident, de sorte qu'il ne peut être assimilé qu'à une tentative de suicide (par ex. balle tirée dans la tête, défenestration d'un étage élevé). On peut également présumer une intention de mourir lorsqu'une personne nie son intention de mourir, tout en indiquant qu'elle pensait que ce qu'elle faisait pouvait être mortel. ***Avez-vous fait une tentative de suicide ?*** ***Avez-vous cherché à vous faire du mal ?*** ***Avez-vous fait quelque chose de dangereux qui aurait pu entraîner votre mort ?*** ***Qu'avez-vous fait ?*** ***Avez-vous _____ dans le but de mettre fin à vos jours ?*** ***Vouliez-vous mourir (même un peu) quand vous _____ ?*** ***Avez-vous tenté de mettre fin à vos jours quand vous _____ ?*** ***Ou avez-vous pensé que vous pouviez mourir en _____ ?*** ***Ou l'avez-vous fait uniquement pour d'autres raisons/sans AUCUNE intention de vous suicider (par exemple pour être moins stressé(e), vous sentir mieux, obtenir de la compassion ou pour que quelque chose d'autre arrive) ?*** (Comportement auto-agressif sans intention de suicide) Si oui, décrivez :	**Oui** ☐ **Non** ☐ Nombre total de tentatives
Le sujet a-t-il eu un comportement auto-agressif non suicidaire ?	**Oui** ☐ **Non** ☐
Tentative interrompue : Interruption (par des facteurs extérieurs) de la mise en œuvre par la personne d'un acte potentiellement auto-agressif *(sinon, une tentative avérée aurait eu lieu)*. Surdosage : la personne a des comprimés dans la main, mais quelqu'un l'empêche de les avaler. Si elle ingère un ou plusieurs comprimés, il s'agit d'une tentative avérée plutôt que d'une tentative interrompue. Arme à feu : la personne pointe une arme vers elle, mais l'arme lui est reprise par quelqu'un ou quelque chose l'empêche d'appuyer sur la gâchette. Si elle appuie sur la gâchette et même si le coup ne part pas, il s'agit d'une tentative avérée. Saut dans le vide : la personne s'apprête à sauter, mais quelqu'un la retient et l'éloigne du bord. Pendaison : la personne a une corde autour du cou mais ne s'est pas encore pendue car quelqu'un l'en empêche. ***Vous est-il arrivé de commencer à faire quelque chose pour tenter de mettre fin à vos jours, mais d'en être empêché(e) par quelqu'un ou quelque chose avant de véritablement passer à l'acte ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐ Nombre total de tentatives interrompues
Tentative avortée : La personne se prépare à se suicider, mais s'interrompt d'elle-même avant d'avoir réellement eu un comportement autodestructeur. Les exemples sont similaires à ceux illustrant une tentative interrompue, si ce n'est qu'ici la personne interrompt d'elle-même sa tentative au lieu d'être interrompue par un facteur extérieur. ***Vous est-il arrivé de commencer à faire quelque chose pour tenter de mettre fin à vos jours, mais de vous arrêter de vous-même avant de véritablement passer à l'acte ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐ Nombre total de tentatives avortées
Préparatifs Actes ou préparatifs en vue d'une tentative de suicide imminente. Il peut s'agir de tout ce qui dépasse le stade de la verbalisation ou de la pensée, comme l'élaboration d'une méthode spécifique (par ex. se procurer des comprimés ou une arme à feu) ou la prise de dispositions en vue de son suicide (par ex. dons d'objets, rédaction d'une lettre d'adieu). ***Avez-vous pris certaines mesures pour faire une tentative de suicide ou pour préparer votre suicide (par ex. rassembler des comprimés, vous procurer une arme à feu, donner vos objets de valeur ou écrire une lettre d'adieu) ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐
Comportement suicidaire : Un comportement suicidaire a-t-il été observé au cours de la période d'évaluation ?	**Oui** ☐ **Non** ☐

Répondre en tenant compte des tentatives avérées uniquement	Tentative la plus récente Date:	Tentative la plus létale Date:	Première tentative Date:
Létalité/lésions médicales observées : 0. Aucune atteinte physique ou atteinte physique très légère (par ex. égratignures). 1. Atteinte physique légère (par ex. élocution ralentie, brûlures au premier degré, légers saignements, entorses). 2. Atteinte physique modérée nécessitant une prise en charge médicale (par ex. personne consciente mais somnolente, altération de la réactivité, brûlures au deuxième degré, saignement d'un vaisseau important). 3. Atteinte physique grave, hospitalisation nécessaire et soins intensifs probablement nécessaires (par ex. état comateux avec réflexes intacts, brûlures au troisième degré sur moins de 20 % de la surface corporelle, hémorragie importante mais sans risque vital, fractures importantes). 4. Atteinte physique très grave, hospitalisation et soins intensifs nécessaires (par ex. état comateux avec absence de réflexes, brûlures au troisième degré sur plus de 20 % de la surface corporelle, hémorragie importante associée à une instabilité des signes vitaux, atteinte majeure d'un organe vital). 5. Décès	*Inscrire le code correspondant*	*Inscrire le code correspondant*	*Inscrire le code correspondant*
Létalité potentielle : ne répondre que si la létalité observée = 0 Létalité probable d'une tentative avérée en l'absence de lésions médicales (exemples de tentatives n'ayant entraîné aucune lésion médicale, mais pouvant potentiellement présenter un degré très élevé de létalité : la personne place le canon d'une arme à feu dans sa bouche, appuie sur la gâchette, mais le coup ne part pas et aucune lésion médicale n'est engendrée ; la personne s'allonge sur les rails à l'approche d'un train mais est relevée par quelqu'un avant d'être écrasée). 0 = Comportement peu enclin à engendrer des blessures 1 = Comportement susceptible d'engendrer des blessures mais ne pouvant causer la mort 2 = Comportement susceptible de causer la mort malgré des soins médicaux disponibles	*Inscrire le code correspondant*	*Inscrire le code correspondant*	*Inscrire le code correspondant*

 C-SSRS—Baseline (Version du 1/14/09) Page 3 de 3

"Since Last Visit" Version, French

ÉCHELLE D'ÉVALUATION DE COLUMBIA SUR LA GRAVITÉ DU RISQUE SUICIDAIRE (C-SSRS)

Depuis la dernière visite

Version du 14/01/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Avertissement :

Cette échelle est destinée à être utilisée par des personnes ayant été formées à son administration. Les questions contenues dans l'Échelle d'évaluation de Columbia sur la gravité du risque suicidaire (C-SSRS) sont des suggestions à titre indicatif. Au final, la détermination de l'existence d'une idéation ou de comportements suicidaires repose sur l'appréciation de la personne qui administre l'échelle.

Les définitions des comportements suicidaires de ce questionnaire sont basées sur celles utilisées dans ***The Columbia Suicide History Form****, développé par John Mann, MD, et Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. Dans M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *p. 103 -130, 2003.)*

Pour obtenir des copies du C-SSRS veuillez contacter Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032 ; pour toute question et besoins en matière de formation, écrire à : posnerk@nyspi.columbia.edu

C-SSRS-SinceLastVisit - France/French - Version of 07 Apr 14 - Mapi.
ID7651 / C-SSRS-SinceLastVisit_AU51_fra-FR.doc

IDÉATION SUICIDAIRE

Posez les questions 1 et 2. Si les deux réponses sont négatives, passez à la section « Comportement suicidaire ». Si la réponse à la question 2 est « oui », posez les questions 3, 4 et 5. Si la réponse à la question 1 et/ou 2 est « oui », complétez la section « Intensité de l'idéation » ci-dessous.

Depuis la dernière visite

1. Désir d'être mort(e)
Le sujet souscrit à des pensées concernant le désir de mourir ou de ne plus être en vie, ou le désir de s'endormir et de ne pas se réveiller.
Avez-vous souhaité être mort(e) ou vous endormir et ne jamais vous réveiller ?
Si oui, décrivez :
Oui ☐ **Non** ☐

2. Pensées suicidaires actives non spécifiques
Pensées d'ordre général non spécifiques autour de la volonté de mettre fin à ses jours/se suicider (par ex. *« J'ai pensé à me suicider »*), non associées à des pensées sur les manières permettant de se suicider/méthodes associées, ni à une intention ou à un scénario, au cours de la période d'évaluation.
Avez-vous réellement pensé à vous suicider ?
Si oui, décrivez :
Oui ☐ **Non** ☐

3. Idéation suicidaire active avec définition de méthodes (sans scénario), sans intention de passage à l'acte
Le sujet pense au suicide et a envisagé au moins une méthode pour y parvenir au cours de la période d'évaluation. Il ne s'agit pas ici de l'élaboration d'un scénario spécifique comprenant le moment, le lieu ou la méthode (par ex. le sujet a pensé à une méthode pour se suicider, mais ne dispose pas d'un scénario précis). Il s'agit par exemple d'une personne déclarant : *« J'ai pensé à avaler des médicaments, mais je n'ai pas de scénario précis sur le moment, le lieu ou la manière dont je le ferais... et je n'irais jamais jusque là »*.
Avez-vous pensé à la manière dont vous vous y prendriez ?
Si oui, décrivez :
Oui ☐ **Non** ☐

4. Idéation suicidaire active avec intention de passage à l'acte, sans scénario précis
Pensées suicidaires actives, le sujet exprime une intention plus ou moins forte de passer à l'acte et ne se contente pas de déclarer : *« J'ai des pensées suicidaires, mais je ne ferai jamais rien pour les mettre en œuvre »*.
Avez-vous eu des pensées de ce genre et l'intention de passer à l'acte ?
Si oui, décrivez :
Oui ☐ **Non** ☐

5. Idéation suicidaire active avec scénario précis et intention de passage à l'acte
Pensées suicidaires associées à l'élaboration complète ou partielle d'un scénario détaillé ; le sujet exprime une intention plus ou moins forte de mettre ce scénario à exécution.
Avez-vous commencé ou fini d'élaborer un scénario détaillé sur la manière dont vous voulez vous suicider ? Avez-vous l'intention de mettre ce scénario à exécution ?
Si oui, décrivez :
Oui ☐ **Non** ☐

INTENSITÉ DE L'IDÉATION

Les aspects suivants doivent être évalués en fonction du type d'idéation le plus grave (c.-à-d. idéations 1 à 5 ci-dessus, 1 étant la moins grave et 5 la plus grave).

Idéation la plus grave

Idéation la plus grave : _____ _____
N° du type (1 à 5) ***Description de l'idéation***

Fréquence ____
Combien de fois avez-vous eu ces pensées ?
(1) Moins d'une fois par semaine (2) Une fois par semaine (3) 2 à 5 fois par semaine (4) Tous les jours ou presque (5) Plusieurs fois par jour

Durée ____
Lorsque vous avez ces pensées, combien de temps durent-elles ?
(1) Quelques instants : quelques secondes ou quelques minutes
(2) Moins d'une heure/un certain temps
(3) 1 à 4 heures/longtemps
(4) 4 à 8 heures/une grande partie de la journée
(5) Plus de 8 heures/en permanence ou tout le temps

Maîtrise des pensées suicidaires ____
Pourriez-vous/pouvez-vous arrêter de penser au suicide ou à votre envie de mourir si vous le voul(i)ez ?
(1) Maîtrise facilement ses pensées.
(2) Capable de maîtriser ses pensées avec de légères difficultés.
(3) Capable de maîtriser ses pensées avec quelques difficultés.
(4) Capable de maîtriser ses pensées avec de grandes difficultés.
(5) Incapable de maîtriser ses pensées.
(0) N'essaie pas de maîtriser ses pensées.

Éléments dissuasifs ____
Y a-t-il quelque chose ou quelqu'un (par ex. votre famille, votre religion ou la douleur au moment de la mort) qui vous a dissuadé(e) de vouloir mourir ou de mettre à exécution vos pensées suicidaires ?
(1) Des éléments dissuasifs vous ont véritablement empêché(e) de tenter de vous suicider.
(2) Des éléments dissuasifs vous ont probablement arrêté(e).
(3) Vous ne savez pas si des éléments dissuasifs vous ont arrêté(e).
(4) Vous n'avez très probablement été arrêté(e) par aucun élément dissuasif.
(5) Les éléments dissuasifs ne vous ont pas du tout arrêté(e).
(0) Sans objet

Causes de l'idéation ____
Quelles sont les raisons pour lesquelles vous avez souhaité mourir ou vous suicider ? Était-ce pour faire cesser la douleur ou bien pour ne plus ressentir votre mal-être (en d'autres termes, vous ne pouviez pas continuer à vivre avec cette douleur ou ce mal-être), ou bien pour attirer l'attention, vous venger ou faire réagir les autres ? Ou tout cela à la fois ?
(1) Uniquement pour attirer l'attention, vous venger ou faire réagir les autres.
(2) Principalement pour attirer l'attention, vous venger ou faire réagir les autres.
(3) Autant pour attirer l'attention, vous venger ou faire réagir les autres que pour faire cesser la douleur.
(4) Principalement pour faire cesser la douleur (vous ne pouviez pas continuer à vivre avec cette douleur ou ce mal-être).
(5) Uniquement pour faire cesser la douleur (vous ne pouviez pas continuer à vivre avec cette douleur ou ce mal-être).
(0) Sans objet

COMPORTEMENT SUICIDAIRE *(Cochez toutes les cases correspondant à des événements distincts ; le sujet devra être interrogé sur tous les types de comportements)*	**Depuis la dernière visite**
Tentative avérée : Acte potentiellement auto-agressif commis avec l'intention plus ou moins forte de mourir *suite à cet acte*. Ce comportement a été en partie envisagé comme moyen de se suicider. L'intention suicidaire n'est pas nécessairement de 100 %. Si une intention/volonté ***quelconque*** de mourir est associée à l'acte, celui-ci pourra être qualifié de tentative de suicide avérée. ***La présence de blessures ou de lésions n'est pas obligatoire,*** mais seulement potentielle. Si la personne appuie sur la gâchette d'une arme à feu placée dans sa bouche, mais que cette arme ne fonctionne pas et qu'aucune blessure n'est engendrée, cet acte sera considéré comme une tentative. Intention présumée : même si la personne nie son intention/sa volonté de mourir, on peut supposer d'un point de vue clinique l'existence de cette intention/volonté d'après le comportement ou les circonstances. Par exemple, un acte pouvant entraîner une mort certaine et ne relevant clairement pas d'un accident, de sorte qu'il ne peut être assimilé qu'à une tentative de suicide (par ex. balle tirée dans la tête, défenestration d'un étage élevé). On peut également présumer une intention de mourir lorsqu'une personne nie son intention de mourir, tout en indiquant qu'elle pensait que ce qu'elle faisait pouvait être mortel. ***Avez-vous fait une tentative de suicide ?*** ***Avez-vous cherché à vous faire du mal ?*** ***Avez-vous fait quelque chose de dangereux qui aurait pu entraîner votre mort ?*** ***Qu'avez-vous fait ?*** ***Avez-vous _____ dans le but de mettre fin à vos jours ?*** ***Vouliez-vous mourir (même un peu) quand vous _____ ?*** ***Avez-vous tenté de mettre fin à vos jours quand vous _____ ?*** ***Ou avez-vous pensé que vous pouviez mourir en _____ ?*** ***Ou l'avez-vous fait uniquement pour d'autres raisons/sans AUCUNE intention de vous suicider (par exemple pour être moins stressé(e), vous sentir mieux, obtenir de la compassion ou pour que quelque chose d'autre arrive) ?*** (Comportement auto-agressif sans intention de suicide) Si oui, décrivez :	**Oui** ☐ **Non** ☐ Nombre total de tentatives _____
Le sujet a-t-il eu un comportement auto-agressif non suicidaire ?	**Oui** ☐ **Non** ☐
Tentative interrompue : Interruption (par des facteurs extérieurs) de la mise en œuvre par la personne d'un acte potentiellement auto-agressif *(sinon, une tentative avérée aurait eu lieu)*. Surdosage : la personne a des comprimés dans la main, mais quelqu'un l'empêche de les avaler. Si elle ingère un ou plusieurs comprimés, il s'agit d'une tentative avérée plutôt que d'une tentative interrompue. Arme à feu : la personne pointe une arme vers elle, mais l'arme lui est reprise par quelqu'un ou quelque chose l'empêche d'appuyer sur la gâchette. Si elle appuie sur la gâchette et même si le coup ne part pas, il s'agit d'une tentative avérée. Saut dans le vide : la personne s'apprête à sauter, mais quelqu'un la retient et l'éloigne du bord. Pendaison : la personne a une corde autour du cou mais ne s'est pas encore pendue car quelqu'un l'en empêche. ***Vous est-il arrivé de commencer à faire quelque chose pour tenter de mettre fin à vos jours, mais d'en être empêché(e) par quelqu'un ou quelque chose avant de véritablement passer à l'acte ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐ Nombre total de tentatives interrompues _____
Tentative avortée : La personne se prépare à se suicider, mais s'interrompt d'elle-même avant d'avoir réellement eu un comportement autodestructeur. Les exemples sont similaires à ceux illustrant une tentative interrompue, si ce n'est qu'ici la personne interrompt d'elle-même sa tentative au lieu d'être interrompue par un facteur extérieur. ***Vous est-il arrivé de commencer à faire quelque chose pour tenter de mettre fin à vos jours, mais de vous arrêter de vous-même avant de véritablement passer à l'acte ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐ Nombre total de tentatives avortées _____
Préparatifs : Actes ou préparatifs en vue d'une tentative de suicide imminente. Il peut s'agir de tout ce qui dépasse le stade de la verbalisation ou de la pensée, comme l'élaboration d'une méthode spécifique (par ex. se procurer des comprimés ou une arme à feu) ou la prise de dispositions en vue de son suicide (par ex. dons d'objets, rédaction d'une lettre d'adieu). ***Avez-vous pris certaines mesures pour faire une tentative de suicide ou pour préparer votre suicide (par ex. rassembler des comprimés, vous procurer une arme à feu, donner vos objets de valeur ou écrire une lettre d'adieu) ?*** Si oui, décrivez :	**Oui** ☐ **Non** ☐
Comportement suicidaire : Un comportement suicidaire a-t-il été observé au cours de la période d'évaluation ?	**Oui** ☐ **Non** ☐
Suicide réussi :	**Oui** ☐ **Non** ☐
Répondre en tenant compte des tentatives avérées uniquement	Tentative la plus létale Date:
Létalité/lésions médicales observées : 0. Aucune atteinte physique ou atteinte physique très légère (par ex. égratignures). 1. Atteinte physique légère (par ex. élocution ralentie, brûlures au premier degré, légers saignements, entorses). 2. Atteinte physique modérée nécessitant une prise en charge médicale (par ex. personne consciente mais somnolente, altération de la réactivité, brûlures au deuxième degré, saignement d'un vaisseau important). 3. Atteinte physique grave, hospitalisation nécessaire et soins intensifs probablement nécessaires (par ex. état comateux avec réflexes intacts, brûlures au troisième degré sur moins de 20 % de la surface corporelle, hémorragie importante mais sans risque vital, fractures importantes). 4. Atteinte physique très grave, hospitalisation et soins intensifs nécessaires (par ex. état comateux avec absence de réflexes, brûlures au troisième degré sur plus de 20 % de la surface corporelle, hémorragie importante associée à une instabilité des signes vitaux, atteinte majeure d'un organe vital). 5. Décès	*Inscrire le code correspondant* _____
Létalité potentielle : ne répondre que si la létalité observée = 0 Létalité probable d'une tentative avérée en l'absence de lésions médicales (exemples de tentatives n'ayant entraîné aucune lésion médicale, mais pouvant potentiellement présenter un degré très élevé de létalité : la personne place le canon d'une arme à feu dans sa bouche, appuie sur la gâchette, mais le coup ne part pas et aucune lésion médicale n'est engendrée ; la personne s'allonge sur les rails à l'approche d'un train mais est relevée par quelqu'un avant d'être écrasée). 0 = Comportement peu enclin à engendrer des blessures 1 = Comportement susceptible d'engendrer des blessures mais ne pouvant causer la mort 2 = Comportement susceptible de causer la mort malgré des soins médicaux disponibles	*Inscrire le code correspondant* _____

