CLINICAL TRIAL PROTOCOL

A single ascending dose trial investigating the safety, tolerability and pharmacokinetics of orally administered BDM-2 in healthy male subjects.

Version: **3.0** **Date: 25 Apr 2018** **Status: Final**

Clinical Trial Number: BDM-2-C001 (Site Trial Number: QCL118184)

EudraCT No. 2017-004329-34

Clinical Phase: 1

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GCP STATEMENT

This trial will be conducted in compliance with this protocol, Good Clinical Practices and applicable regulatory requirements.

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by law. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply to all future information supplied to you which is indicated as privileged or confidential.

PROTOCOL VERSIONS

Protocol Version	Issue Date
Protocol Version 1.0, original protocol	28 Feb 2018
Protocol Version 2.0	29 Mar 2018
Protocol Version 3.0, this document	25 Apr 2018

Protocol version details below are listed beginning with the most recent version.

Protocol Version 3.0 (this document)

The changes in Protocol Version 3.0 are considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the trial.

The overall reason for Protocol Version 3.0:
This protocol version is written to describe the reduced total amount of blood taken from an individual subject during the trial following completion of the bioanalytical validation activities.

It was confirmed that for the determination of BDM-2 in plasma samples, 20 µL of plasma is required. Therefore, 2.5 mL of blood per pharmacokinetic (PK) sample is sufficient (instead of the 6.5 mL described in Version 2.0 of the protocol) and the total amount of blood taken from an individual subject during the trial is reduced. As a result, the total amount of blood collected from an individual subject in the trial is expected to be maximally 325 mL and will not exceed 550 mL in any 4-week period.

The table below gives an overview of the rationale for each change and all applicable sections

Rationale: the amount of blood taken for bioanalysis is 2.5 mL per sample, instead of 6.5 mL and it is highlighted that 0.5 mL is the discard taken via cannula prior to taking the PK sample in Table 2.

Applicable Sections:
1.1 Summary
1.2 Flow Chart
5.2 Trial Design
5.5.1 Procedure Related Risks
8.4.1 Sample Collection and Handling

Rationale: there is no need for a separate sample for serology, this can be analysed in the sample taken for biochemistry.

Applicable Section:
5.5.1 Procedure Related Risks

Rationale: Trial medication will be prepared from drug substance directly for each individual subject separately, bulk medication will not be prepared and reference to bulk medication has been removed from the text.

Applicable Sections:
7.3 Packaging and Labelling
7.8 Storage

Protocol Version 2.0

Protocol Version 2.0 was written based on questions raised by the MHRA on the originally submitted protocol prior to approval. In summary, the following items were updated:

- Section 6.6.1: Withdrawal criteria were updated and in case that alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentrations are equal or more than 3x the upper limit of the normal range (ULN), the study drug must be discontinued (instead of 5x ULN in Protocol Version 1.0).
- Section 6.7:
  - Updated with the addition of the stopping criterion of an anticipated individual area under the plasma concentration - time curve from time 0 to 24 hours postdose (AUC_{0-24h}) higher than 255 µg.h/mL to Section 6.8;
  - Removal of reference to the Maximum Tolerated Dose (MTD).
- Section 6.8, Update of Dose Escalation Stopping (DES) Criteria:
  - A DES criterion of an anticipated AUC_{0-24h} higher than 255 µg.h/mL was added (previous Section 6.8.1);
  - If any of the DES criteria is met, dosing will be stopped, and the trial will be put on hold (previous Section 6.8.2 allowed one DES);
  - Removal of the MTD (previous Section 6.8.2).

1. SUMMARY AND FLOW CHART

1.1 Summary

Clinical Phase	1
Clinical Trial No.	BDM-2-C001 (site trial number: QCL118184)
EudraCT No.	2017-004329-34
Trial Objectives	The objectives of the trial are: Primary • To investigate the safety and tolerability of BDM-2 following single-dose oral administration in healthy male subjects. Secondary: • To investigate the pharmacokinetics (PK) of BDM-2 in plasma following single-dose oral administration in healthy male subjects; • To investigate the effect of food on the PK of BDM-2 following single-dose oral administration in healthy male subjects. Exploratory: • To collect blood samples from healthy male subjects who received BDM-2 to bank deoxyribonucleic acid (DNA) for future association studies of genotype with the PK and safety characteristics obtained in this trial.
Trial Design	This is a first-in-human (FIH), double-blind, placebo-controlled, randomized trial in healthy adult male subjects, to evaluate the safety, tolerability and PK of single ascending oral doses of BDM-2. The effect of food on the PK of a single dose of BDM-2 will also be evaluated. In Sessions I to VI, 6 single, orally administered ascending doses of BDM-2 or placebo will be investigated, alternately dosed in 2 cohorts of 8 healthy male subjects each (Cohorts A and B). For each dose, 6 subjects will receive active treatment and 2 subjects will receive placebo. Subjects will be randomized in such a way that for each dose different subjects receive placebo. In Sessions I to VI, doses are planned to be administered under fasted conditions. Dose escalation to the next dose level will be done after a blinded interim evaluation meeting of the safety (at least up to 48 hours) and the PK results (at least up to 24 hours) of the previous dose(s) by the investigator, the sponsor and Venn Life Sciences (Venn). Based on these results, decisions will be made on the next dose and the blood sampling scheme. The total amount of blood collected from an individual subject in the trial will not exceed 550 mL in any 4-week period. An intermediate dose may be administered or de-escalation may be performed. It will also be decided whether trial medication intake in the next session will take place under fasted or fed conditions. For dose escalation to proceed, data must be available from a minimum of 6 subjects who have completed the planned safety assessments up to 48 hours after trial medication intake and the planned PK assessments up to 24 hours after trial medication intake to ensure at least 4 subjects had received active treatment. If there are incomplete datasets for PK data, the principal investigator can decide to proceed with dose escalation/de-escalation based on the safety data. To investigate the food effect, it is anticipated that in Session VII trial medication will be administered in the fed state, however administration with food may take place in earlier sessions, depending on emerging data from the interim data evaluations. If Session VII goes ahead as planned, one of the doses administered in a previous fasted session will be administered following

the intake of a standardized breakfast to the same subjects (Cohort A or B), i.e., subjects who received BDM-2 will receive BDM-2 again and subjects who received placebo will receive placebo again in Session VII, respectively.

In total, BDM-2 is planned to be administered as a single dose in up to 7 occasions. For the first 2 sessions (Session I for Cohort A and Session II for Cohort B), a sentinel approach will be followed. The choice of the sentinel approach in these 2 sessions is to reduce the risks associated with exposing all subjects in a session simultaneously for the first trial medication intake in each cohort and not because of any known preclinical safety concerns. The staggered design will be spread over 2 days: the first sub-group (2 subjects) will receive trial medication (1 on active treatment, 1 on placebo) at least 24 hours prior to the second sub-group (6 subjects; 5 on active treatment, 1 on placebo). After interim evaluation meetings of the first 2 sessions it will be decided whether a sentinel approach will be followed in the next session(s).

The washout period between consecutive BDM-2/placebo administrations in each individual subject will be at least 7 days. The day of trial medication intake (Day 1) is the first day of the washout period.

In all sessions, BDM-2 and placebo will be administered as an oral suspension.

Full PK profiles of BDM-2 will be determined up to 48 hours after trial medication intake, unless data from previous sessions suggest using a different sampling schedule.

A mandatory blood sample to bank DNA for future association studies of genotype with the PK and safety characteristics obtained in this trial will be taken once for all subjects.

Safety and tolerability will be assessed throughout the trial from signing of the informed consent form (ICF) until the subject's last trial-related activity.

The total trial duration is expected to be approximately 18 weeks for the cohort participating in Session VII and approximately 14 weeks for the other cohort, including screening and follow-up.

Below the planned design of the trial is presented.

		Week											
Cohort	**≤28 days before Day 1 of first session**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
A (n=8)	screening	D1 fasted SI	Wash out + interim evaluation			D3 fasted SIII	Wash out + interim evaluation			D5 fasted SV	Wash out (or FU) + interim evaluation		
B (n=8)	screening			D2 fasted SII	Wash out + interim evaluation			D4 fasted SIV	Wash out + interim evaluation			D6 fasted SVI	Wash out (or FU) + interim evaluation

	Week	
Cohort	**11 or 13**	**12 or 14**
A or B (n=8)	Dx* fed SVII	FU

D = Dose; fasted = intake under fasted conditions; fed = intake under fed conditions; S = Session; * to be determined; FU = follow-up visit; Washout = the washout period between consecutive BDM-2/placebo administrations in each individual subject (and between the last trial medication intake and the follow-up visit) will be at least 7 days; Interim evaluation: a blinded interim evaluation of the safety (at least up to 48 hours) and PK data (at least up to 24 hours) of the previous dose(s) will be performed via a meeting. Based on the results, decisions will be made on sentinel approach (only after evaluation of the first 2 sessions), dose, PK blood sampling scheme and food status in the next session.

Subject Population	Healthy adult male subjects
Trial Site	Quotient Sciences Ltd
Trial Medication, Dosage, and Route of Administration	<u>Active BDM-2</u> BDM-2 in Bottle (50 mg – 3600 mg); oral suspension. The tentative trial medication intake schedule is as follows: the first single dose will be an oral dose of 50 mg, followed by the tentative single oral doses of 150, 450, 900, 1800 and 3600 mg. <u>Placebo BDM-2</u> Placebo for BDM-2 in Bottle (50 mg – 3600 mg); matching placebo oral suspension (same appearance as active suspension). BDM-2 in bottle or matching placebo will be reconstituted with a 100 mL vehicle (0.2% sodium dodecyl sulfate [SDS] and water) to achieve a suspension for oral administration. Although referred to as a suspension, at low dose levels the trial medication may present a solution-like appearance.
Trial Duration for Each Subject:	The total trial duration is expected to be approximately 18 weeks for the cohort participating in Session VII and approximately 14 weeks for the other cohort, including screening and follow-up.

Total Number of Subjects, Statistical Rationale Provided	16 subjects, equally divided over Cohort A (n=8) and Cohort B (n=8) By experience, the number of subjects to be enrolled in this trial is considered sufficient to achieve the objectives of the trial. Therefore, given the stage of development and the nature of these exploratory investigations, no formal sample size calculations have been performed. Subjects who do not complete all sessions and assessments may be replaced.
Safety Assessments	• Adverse Events (AEs) observed, mentioned upon general questioning or spontaneously reported will be documented • Laboratory safety (haematology, coagulation, biochemistry, serology, urinalysis) • Vital signs (blood pressure, pulse rate) and tympanic body temperature • 12-lead electrocardiogram (ECG) recordings • Respiratory rate • Physical examination
Pharmacokinetic Parameters	Blood samples will be taken for determination of BDM-2 concentrations in plasma up to 48 hours after trial medication intake (unless data from previous sessions suggest using a different sampling schedule). Single-dose PK parameters of BDM-2 will be calculated.
Pharmacogenetics:	A mandatory blood sample to bank DNA will be taken for future association studies of genotype with the PK and safety characteristics obtained in this trial.
Planned Clinical Trial Period	Q1 – Q3 2018

1.2 Flow Chart

Flow Chart of Subject Assessments for all Sessions

Assessment	Screening ≤28 days before Day 1 of first session	Session (days)					Follow-up[2]
		Day -1	Predose on Day 1[1]	1	2	3	
Signing ICF[3]	•						
Check in- and exclusion criteria	•	•					
Physical examination[4]	•	•	•		•	•	•
Medical history/ Medical review[5]	•	•					
Urine drug test	•	•					
Alcohol breath test	•	•					
Urine cotinine dipstick test	•	•					
Hepatitis A/B/C/HIV-1 and 2	•						
Check clinical status		•					
Randomization[7]			•				
Vital signs including tympanic body temperature[6,8]	•		•	•	•	•	•
Respiratory rate[6,9]	•		•	•	•	•	•
12-lead ECG[6,8]	•		•	•	•	•	•
Haematology/Coagulation/ Biochemistry/Urinalysis[6,10]	•	•			•		•
Confinement to trial site[11]		•					
Standardized breakfast (if applicable)[12]			•				
BDM-2/placebo intake[13]				•			
Ambulant visit	•						•
Plasma PK sample[6,14]			•	•	•	•	
Adverse Events	•						
Pretreatment and Concomitant Medication	•						
Pharmacogenetics[6,7]			•				

1 Predose assessments will be performed within 2 hours before trial medication intake.

2 Follow-up visit will take place 7 days after trial medication intake in the last session, or 7 days after dropout/withdrawal (a window of ±2 days is allowed). In case of dropout due to an adverse event (AE), follow-up visit will take place at the moment of dropout or as soon as possible within 7 days after discontinuation.

3 Signing of the ICF needs to be done before the first trial-related activity.

4 Complete physical examination, including height (only at screening) and body weight measurement, will be done at screening, on Day -1 of each session, and at the follow-up visit. Symptom directed physical examination will be done in each session predose on Day 1 and at 24 and 48 hours postdose: general appearance, cardiovascular system, respiratory system, and abdomen, including symptom-driven physical examination.

5 Only at screening and on Day -1 in the first session.

6 If multiple assessments are scheduled for the same time point, procedures should preferably be performed in the following order: ECG, vital signs, respiratory rate, (PK) blood sampling.

7 Only in subject's first session.

8 Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate) will be recorded at screening, in each session predose and at 0.25, 0.5, 1, 2, 4, 8, 12, 24 and 48 hours postdose, and at the follow-up visit. ECG recordings will be done at screening, in each session predose and at 0.5, 2, 4, 8, 24 and 48 hours postdose, and at the follow-up visit. Predose in each session, triplicate ECG recording will be done (in a 5-minute window). Postdose vital signs and ECG recordings will be performed within 15 minutes before PK sampling. All vital sign and ECG measures will be taken supine after at least 5 minutes rest in supine position.

9 Respiratory rate measurements will be done at screening, in each session predose and at 0.5, 2, 4, 8, 24 and 48 hours postdose, and at the follow-up visit. Postdose respiratory rate measurements will be performed within 15 minutes before PK sampling.

10 Sampling for haematology, coagulation, biochemistry and urinalysis will be performed at screening, in each session on Day -1 and Day 2 (about 24 hours postdose) in the morning, and at the follow-up visit,

11 Confinement to trial site: subjects need to be in-house from approximately 24 hours prior to trial medication intake (in the morning of Day -1) until the first 48 hours after trial medication intake in each session (morning of Day 3).

12 In the morning of Day 1 of Session VII, subjects will receive a standardized breakfast. Subjects must ingest this meal completely within 25 minutes and trial medication intake will take place 30 minutes after intake of the breakfast has been started.

13 A washout period of at least 7 days between consecutive BDM-2/placebo administrations in each individual subject and between the last trial medication intake and the follow-up visit. The day of trial medication intake (Day 1) is the first day of the washout period.

14 Blood samples for PK (BDM-2) will be taken predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 12, 16, 24, 36 and 48 hours postdose. Based on data from previous sessions it may be decided to adapt the PK blood sampling scheme, however, the total amount of blood collected from an individual subject in the trial will not exceed 550 mL in any 4-week period.

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2. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALLINI	Allosteric inhibitor of HIV integrase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the plasma concentration - time curve
AUC_{0-24h}	Area under the plasma concentration - time curve from time 0 to 24 hours postdose
BMI	Body mass index
CA	Competent Authority
CI	Confidence interval
CRO	Contract Research Organization
CTR	Clinical trial report
CTP	Clinical trial protocol
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DES	Dose escalation stopping
DNA	Deoxyribonucleic acid
EC	Ethics Committee
EC_{90}	90% maximal inhibitory concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EU	European Union
FIH	First-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAV	Hepatitis A virus
HBsAg	Hepatitis B virus surface antigen
HCV-AB	Hepatitis C virus antibody
HIV(-AB 1+2)	Human immunodeficiency virus (antibodies 1+2)
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IgM	Immunoglobulin M
ISF	Investigator site file
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
LS	Least square
MABEL	Minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency

n	Number
NOAEL	No observed adverse effect level
PA-EC_{90}	Protein-adjusted EC_{90}
PAD	Pharmacologically active dose
PBMC	Peripheral blood mononuclear cell
PIS	Participation Information Sheet
PK	Pharmacokinetic(s)
QA	Quality assurance
QP	Qualified Person
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDS	Sodium dodecyl sulfate
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TOPS	The Over Volunteering Prevention System
TMF	Trial master file

For abbreviations of clinical laboratory parameters, see Section 8.6.3. Abbreviations of PK parameters are given in Section 8.4.3.

3. INTRODUCTION

BDM-2 is a low molecular weight compound belonging to a new class of antiretrovirals, currently under development for the treatment of human immunodeficiency virus (HIV) infections. BDM-2 will be orally administered.

BDM-2 is a novel Allosteric Inhibitor of HIV Integrase (ALLINI) with a potent antiretroviral activity of 8.5 nM against NL4-3 HIV virus. ALLINIs are drugs blocking HIV replication with a new mechanism of action involving the disruption of virus maturation. BDM-2 retains full activity against viruses encoding resistance mutations to clinically approved drugs. The polymorphism of HIV integrase especially at positions 124-125 only weakly affects its potency. The protein-adjusted 90% maximal inhibitory concentration (PA-EC_{90}) of BDM-2 is 60 ng/mL against the least sensitive HIV polymorphs (NA, GA, GT at positions 124-125). PK modelling and efficacious dose prediction indicate a 10xPA-EC_{90} target attainment with 800 mg once daily dosing. However, due to enterohepatic cycling, models and related predictions based on animal data cannot be considered reliable: confirmation should be obtained in humans.

The safety and tolerability of BDM-2 was assessed through a series of non-clinical toxicity (including genotoxicity) and safety pharmacology studies. The genotoxicity studies (Ames test, an *in vitro* micronucleus test and *in vivo* micronucleus test, as part of the 2 weeks mouse study) revealed no mutagenic nor clastogenic effects. Also the safety pharmacology studies showed no relevant BDM-2-related effects, i.e., for all 3 studies the no observed adverse effect level (NOAEL) was set at the highest dose levels evaluated (i.e., 1000 mg/kg for the central nervous system mouse study and the respiratory mouse study and 300 mg/kg for the cardiovascular dog study).

In the repeat dose toxicity studies in mouse and dog the liver was identified as target organ, although no adverse findings were apparent.

In the 2-week mouse study this was evidenced by increased liver weights and reversible centrilobular hepatocyte hypertrophy and a lower incidence and/or severity of glycogen vacuolation. In the mouse there were no relevant increases in liver enzymes. The centrilobular hepatocyte hypertrophy as observed is commonly considered an adaptive response associated with the metabolism of xenobiotics or their metabolites.

In the 2-week dog study, also the liver weight was increased, and this finding was accompanied by increases in liver enzymes, in absence of microscopical findings. In the dog some vomiting and soft faeces were observed as well. Liver function will closely be monitored during the trial as a part of clinical laboratory assessments (see also Section 5.5.2 and Section 8.6.3.

Even though the liver enzymes were elevated, there was no damage at all in the studies as confirmed with histopathological data. In addition, the findings on liver enzymes were fully reversible after het 2-week recovery period. Therefore, in both studies the findings were considered non-adverse due to the magnitude of the findings and in general the reversibility of findings as observed after the 2-week recovery period. As a result, for both studies the NOAEL was set at the highest dose administered (i.e., 500 mg/kg/dose twice daily, 1000 mg/kg/day for the mouse and 150 mg/kg/dose twice daily, 300 mg/kg/day for the dog).

The studies as performed till now (2-weeks toxicity) are designed to support the single and multiple ascending dose studies in the clinic. So, whether these effects will end turn out to be adverse (after long term treatment), will be evaluated in long term toxicity studies. Based on the information above, the dose of 150 mg/kg/dose twice daily (300 mg/kg/day) was selected as the NOAEL (dog) for this trial.

Based on the data package presented in the Investigator's Brochure (IB) of BDM-2[1], it is concluded that BDM-2 has a low toxicity profile (i.e., no adverse findings in any of the safety studies as performed, up to the highest dose levels tested, see also Section 5.5.2). In the current first-in-human (FIH) trial only single doses will be administered and it is not expected that any of the findings as described will be relevant/adverse for humans after single dose.

This compound profile supports further clinical development of BDM-2.

3.1 Rationale for the Trial

BDM-2 has not been tested in humans and, therefore, the safety, tolerability, pharmacokinetics (PK) as well any food effect need to be established. This is a Phase 1, FIH, single ascending dose (SAD) trial to examine the safety, tolerability, and PK of increasing oral single doses of BDM-2 in healthy male subjects. In addition, the food effect on the PK of BDM-2 will be evaluated at a single dose level in healthy male subjects.

4. TRIAL OBJECTIVES

The objectives of the trial are:

Primary

- To investigate the safety and tolerability of BDM-2 following single-dose oral administration in healthy male subjects.

Secondary

- To investigate the PK of BDM-2 in plasma following single-dose oral administration in healthy male subjects;
- To investigate the effect of food on the PK of BDM-2 following single-dose oral administration in healthy male subjects.

Exploratory

- To collect blood samples from healthy male subjects who received BDM-2 to bank deoxyribonucleic acid (DNA) for future association studies of genotype with the PK and safety characteristics obtained in this trial.

5. CLINICAL TRIAL PLAN

5.1 Definition of Terms

Start and End of the Trial

Start of the trial is defined as the day of the signature of the informed consent form (ICF) of the first subject.

End of the trial is defined as the point at which the sponsor determines that any remaining optional groups are not required to meet the objectives of the trial i.e., signed dose decision document. If all optional groups are utilized, completion of the last follow-up visit or unscheduled follow-up visit will be considered the end of the trial. Any changes to this definition will be notified as a substantial amendment.

Enrolment, Inclusion and Randomization

A subject is defined as enrolled when a signed and dated ICF is available.

A subject is defined as included when he is judged eligible by the investigator; date of inclusion is to be documented in the electronic case report form (eCRF).

A subject is defined as randomized when a subject number has been allocated to a subject. Randomization will take place just prior to administration of trial medication in the first session and a subject number will be given to each subject.

Trial Periods

Pretreatment period lasts from a maximum of 28 days prior to the first intended trial medication administration (Day 1 of the first session) of a subject, comprises the assessments during screening visit, and the time until inclusion and ends just prior to the first intended intake of trial medication.

In-treatment period starts with the first intended intake of trial medication and lasts until the follow-up visit.

5.2 Trial Design

This is a FIH, double-blind, placebo-controlled, randomized trial in healthy adult male subjects, to evaluate the safety, tolerability and PK of single ascending oral doses of BDM-2. The effect of food on the PK of a single dose of BDM-2 will also be evaluated.

In Sessions I to VI, 6 single, orally administered ascending doses of BDM-2 or placebo will be investigated, alternately dosed in 2 cohorts of 8 healthy male subjects each (Cohorts A and B). For each dose, 6 subjects will receive active treatment and 2 subjects will receive placebo. Subjects will be randomized in such a way that for each dose different subjects receive placebo. In Sessions I to VI, doses are planned to be administered under fasted conditions.

Dose escalation to the next dose level will be done after a blinded interim evaluation meeting of the safety (at least up to 48 hours) and PK (at least up to 24 hours) results of the previous dose(s) by the investigator, the sponsor, and Venn Life Sciences (Venn). Based on these results, decisions will be made on the next dose and the blood sampling scheme. The total amount of blood collected from an individual subject in the trial will not exceed 550 mL in any 4-week period. An

intermediate dose may be administered, or de-escalation may be performed. It will also be decided whether trial medication intake in the next session will take place under fasted or fed conditions.

For dose escalation to proceed, data must be available from a minimum of 6 subjects who have completed the planned safety assessments up to 48 hours after trial medication intake and the planned PK assessments up to 24 hours after trial medication intake to ensure at least 4 subjects had received active treatment. If there are incomplete datasets for PK data, the principal investigator can decide to proceed with dose escalation/de-escalation based on the safety data.

To investigate the food effect, it is anticipated that in Session VII trial medication will be administered in the fed state, however administration with food may take place in earlier sessions, depending on emerging data from the interim data evaluations. If Session VII goes ahead as planned, one of the doses administered in a previous fasted session will be administered following the intake of a standardized breakfast to the same subjects (Cohort A or B), i.e., subjects who received BDM-2 will receive BDM-2 again and subjects who received placebo will receive placebo again in Session VII, respectively.

In total, BDM-2 is planned to be administered as a single dose in up to 7 occasions. For the first 2 sessions (Session I for Cohort A and Session II for Cohort B), a sentinel approach will be followed. The choice of the sentinel approach in these 2 sessions is to reduce the risks associated with exposing all subjects in a session simultaneously for the first trial medication intake in each cohort and not because of any known preclinical safety concerns. The staggered design will be spread over 2 days: the first sub-group (2 subjects) will receive trial medication (1 on active treatment, 1 on placebo) at least 24 hours prior to the second sub-group (6 subjects; 5 on active treatment, 1 on placebo). After interim evaluation meetings of the first 2 sessions it will be decided whether a sentinel approach will be followed in the next session(s).

The washout period between consecutive BDM-2/placebo administrations in each individual subject will be at least 7 days. The day of trial medication intake (Day 1) is the first day of the washout period.

In all sessions, BDM-2 and placebo will be administered as an oral suspension.

Full PK profiles of BDM-2 will be determined up to 48 hours after trial medication intake, unless data from previous sessions suggest using a different sampling schedule.

A mandatory blood sample to bank DNA for future association studies of genotype with the PK and safety characteristics obtained in this trial will be taken once for all subjects.

Safety and tolerability will be assessed throughout the trial from signing of the ICF until the subject's last trial-related activity.

The total trial duration is expected to be approximately 18 weeks for the cohort participating in Session VII and approximately 14 weeks for the other cohort, including screening and follow-up.

Below the planned design of the trial is presented.

		Week											
Cohort	**≤28 days before Day 1 of first session**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
A (n=8)	screening	D1 fasted SI	Wash out + interim evaluation			D3 fasted SIII	Wash out + interim evaluation			D5 fasted SV	Wash out (or FU) + interim evaluation		
B (n=8)	screening			D2 fasted SII	Wash out + interim evaluation			D4 fasted SIV	Wash out + interim evaluation			D6 fasted SVI	Wash out (or FU) + interim evaluation

	Week	
Cohort	**11 or 13**	**12 or 14**
A or B (n=8)	Dx* fed SVII	FU

D = Dose; fasted = intake under fasted conditions; fed = intake under fed conditions; S = Session; * to be determined; FU = follow-up visit; Washout = the washout period between consecutive BDM-2/placebo administrations in each individual subject (and between the last trial medication intake and the follow-up visit) will be at least 7 days; Interim evaluation: a blinded interim evaluation of the safety (at least up to 48 hours) and PK data (at least up to 24 hours) of the previous dose(s) will be performed via a meeting. Based on the results, decisions will be made on sentinel approach (only after evaluation of the first 2 sessions), dose, PK blood sampling scheme and food status in the next session.

5.3 Justification

5.3.1 Justification of Design

A double-blind design with 2 alternating cohorts of subjects receiving consecutive higher single doses of trial medication is commonly applied to explore the safety and tolerability, and the PK profile of investigational compounds in healthy subjects (Sessions I to VI). When the previous dose level has proven to be safe and well tolerated, the next dose level will be initiated.

An alternating design gives the possibility to investigate intra- and intersubject variation and the possibility to have an escalation to the next dose with a sufficient long washout period for individual subjects.

The principle of a sequential design will be applied to investigate food effect on the PK of BDM-2 and to assess the intrasubject variability.

A washout period of at least 3 days between consecutive administrations of BDM-2/placebo to the same subject within a cohort is considered sufficient to avoid carry-over effects from previous sessions. This is based on animal toxicokinetic data (the half-live of BDM-2 is approximately 1.1 to 4.1 hours in mice, 2.3 to 3.2 hours in rats, and 15.2 hours in dogs after oral single dose administrations). The relatively short half-lives mean that a minimum 7-day washout period is more than adequate for the purposes of redosing the subjects in this Phase 1 SAD trial.

The use of a placebo group is justified on the grounds that the data obtained from placebo subjects will serve as control data for the safety evaluation. Double-blind methodology will enable the avoidance of bias in the interpretation of results.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups (active treatment or placebo), to increase the likelihood that known and unknown subject characteristics (e.g., demographic and baseline characteristics) are equally balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

5.3.2 Justification of Population

Healthy male subjects aged between 18 and 55 years (inclusive) will be included in this trial, which will allow for careful evaluation of safety and PK parameters without interference of concomitant disease or medication. Preclinical results showed differences between male and female animals. Given the exploratory nature of this trial, and the lack of reproductive toxicity data and the possibility of some gender effects seen in animals, only male subjects are included in this trial to reduce variation of the results. Female participants will be included in later phases of development.

5.3.3 Justification of Dose

The doses of BDM-2 anticipated to be investigated in this trial range from 50 mg to 3600 mg as single doses with the tentative dose escalation scheme: 50, 150, 450, 900, 1800, and 3600 mg BDM-2. Definite selection of the doses will be performed after evaluation of the safety (at least up to 48 hours) and the PK results (at least up to 24 hours) of the previous dose(s).

The safe starting dose of BDM-2 for administration to humans is calculated based on scaling by body surface area (conversion to human equivalent dose) and a pharmacokinetically-guided approach using an estimate of the human maximum observed plasma concentration (C_{max}) and human area under the plasma concentration - time curve (AUC), based on allometry, expressed per mg dose for a human with a body weight of 60 kg.

Overall, the integrated safe starting dose varies between 65 and 1000 mg per day. This means that, when the lowest value as obtained with these calculations is taken for the first clinical dose, a safe starting dose is <65 mg per day. Accordingly, a starting dose of 50 mg per day is selected (see IB[1]).

Given the fact that for BDM-2 the target is an exogenous one (i.e., HIV virus) that is not present in the current population of treatment (i.e., healthy subjects), no target-induced biological effects are anticipated and the minimal anticipated biological effect level (MABEL) approach for determination of the safe starting dose is not considered relevant.

Antiretroviral potency was assessed using a multiple cycle infection assay on MT4 cells as well as HIV-1 clinical isolates infecting peripheral blood mononuclear cell (PBMC). The maximum EC_{50} of BDM-2 against 4 clinical isolates infecting PBMC (9.4 nM) was subsequently used to calculate the PA-EC_{90}, resulting in a value of 60 ng/mL (150 nM) against the least sensitive HIV polymorphs (NA, GA, GT at positions 124-125). As this value has taken into account a serum/plasma effect, no correlation for plasma protein binding was considered necessary for efficacy

predictions. PK modelling and efficacious dose prediction indicated a 10xPA-EC_{90} target attainment (anticipated C_{trough}) with 800 mg once daily dosing (see IB[1]), which is considered to be the pharmacologically active dose (PAD).

Currently, an effective dose range has not been foreseen yet in the protocol as it is not known. The primary objective of this FIH trial is to investigate the safety and tolerability of the new compound BDM-2. For determination of the maximum dose i.e., exposure limits, the human exposure should not exceed the exposures based on the dog NOAEL (see below) and we anticipate dosing maximally 3600 mg under the assumption that the human exposure will not exceed the dog NOAEL limits at a lower dose. For estimation of the maximum dose, we normally take a 3 to 5-fold increase of the anticipated efficacious dose. This would result in a maximum dose for BDM-2 in this trial between 2400 and 4000 mg BDM-2. For the dose escalation steps, we have taken 2-fold increases in the last 3 steps from PK perspective, because with smaller increments you might not see that much of an effect due to the variability of the results. Based on these assumptions above, we chose a tentative maximum dose of 3600 mg (still to be confirmed based on safety data of the previous sessions) for this trial. This is a 4.5-fold increase compared to the PAD of 800 mg, also to allow the collection of safety data to support further multiple dosing.

Data retrieved from the dogs and mice has been used to calculate the anticipated human exposure (see IB[1]). The anticipated human exposure including the safety margins based on the exposures at NOAEL in mice as well as dog has also been calculated based on the modelling and simulation results. These predictions were comparable to the obtained prediction of human exposure based on the dog kinetic data. Therefore, these data are considered most representatives for the human exposure expectations. In addition, as the effects that have been observed in the non-clinical repeat dose toxicity studies are considered related to AUC from time 0 to 24 hours postdose (AUC_{0-24h}) and not as much to C_{max}, AUC exposure data comparisons are leading in this respect. The predicted human mean exposure at the starting dose and at the planned maximal dose is shown in Table 1 (full anticipated dose range can be found in IB[1]).

Table 1: Human Exposure

Anticipated clinical doses (mg)	Expected human exposure (AUC) based on modelling and simulation data) (µg.h/mL)	Safety factor dog data (mean AUC_{0-24h} at NOAEL [i.e., 255 µg.h/mL) / Expected human exposure])
50	1.6	159.4
3600	112.2	2.3

Given the fact that the data above is obtained from 2-week dose toxicity exposure data, it is expected that exposure after single dose administration will stay below NOAEL and will not cause any issues in humans, for more detail also refer to Section 6.7. Dose escalation decisions will follow the predefined escalation criteria as described in Section 6.8.

5.4 Food and Beverages

Intake of food and beverages will be standardized over the entire course of in-house confinement. Food (including candy and chewing gum) and beverages not supplied by the trial site will be forbidden during confinement to the trial site.

On Day 1 of each session, subjects must have fasted overnight for at least 10 hours before trial medication intake (intake under fasted conditions) or before start of breakfast (intake under fed conditions). Intake of water is allowed until 1 hour before intake of trial medication. Thereafter, water intake is only allowed for intake of trial medication (and breakfast, if applicable). From 1 hour after trial medication intake, intake of water is allowed ad libitum. No food is allowed until 4 hours after trial medication intake. Subjects will receive a standard lunch approximately 4 hours after trial medication intake. The start of this lunch will be after the 4-hour PK sampling. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of trial medication intake.

In the morning of Day 1 of Session VII (trial medication intake under fed conditions) subjects will receive a standardized breakfast consisting of 1 bowl of Kellogg's Cornflakes/Kellogg's Rice Krispies/Kellogg's Special K (25 g), 240 mL skimmed milk, 1 sachet sugar, 2 slices bread / bread roll and 1 pat of flora per slice, 1 mug (200 mL) of decaffeinated tea or coffee plus 40 mL of skimmed milk and 1 sachet of sugar (energy content: 552 kcal; protein content: 14 g; carbohydrate content: 89 g; fat content: 22 g).

The standardized breakfast should be ingested completely within 25 minutes. A single dose of the trial medication will be administered 30 minutes after intake of the meal has been started.

5.5 Risks Related to the Participation in the Clinical Trial

5.5.1 Procedure Related Risks

Vein puncturing for the purpose of blood sampling may be accompanied by some mild pain. There is a small risk of bleeding, bruising or infection at the site of injection. In addition, the subject might feel dizzy during the blood sampling procedures.

Electrocardiogram stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

The total volume of blood to be drawn from each subject during the entire trial (see Table 2) will not exceed 550 mL in any 4-week period. No safety related risk is expected from this protracted blood withdrawal schedule.

Table 2: Blood Volumes

Visit		Bio-chemistry incl Serology (5 mL)	Haema-tology (2 mL)	Coagu-lation (4.5 mL)	PK* (2.5 mL)	Pharmaco-genomics (10 mL)	Total Blood Volume (mL)
Screening		5	2	4.5	-	-	11.5
Per session	Day -1	5	2	4.5	-	-	
	Day 1	-	-	-	42.5	10	
	Day 2	5	2	4.5	5	-	
	Day 3	-	-	-	2.5	-	
Total of 1 session		23			50	-	73
Follow-up		5	2	4.5	-	-	11.5
Total for group with 4 sessions		115			200	10	**325**
Total for group with 3 sessions		92			150	10	**252**

*Includes 0.5 mL per sample discard from the cannula

5.5.2 Risks Related to the Investigational Product(s)

Even though the risk of BDM-2 as a single administration to humans is considered low, several parameters will be monitored with special interest based on the preclinical findings as summarized below. Full details can be found in the IB[1].

- Liver enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and alkaline phosphatase (ALP).

  At 500 mg/kg/dose twice daily (1000 mg/kg/day) for 7 days, BDM-2 induced a potential treatment-related effect in liver enzymes (AST, ALT and creatine phosphokinase [CPK], up to 3.2-fold increase, 6.3-fold increase and 3.2-fold increase, respectively, when compared to the highest values of control group) in a few male mice, which were considered as non-adverse[4].
  In the 2-week mouse study there were no relevant increases in liver enzymes[12].
  At 200 mg/kg/dose twice daily (400 mg/kg/day) during 13 days, BDM-2 induced changes in liver enzymes (marked increases in ALT, AST and ALP) in dogs without any microscopic findings in the liver[3].
  Increases in ALT (approximately 10 to 13-fold in males and 5 to 9-fold in females), ALP (approximately 74% to 4-fold in males), and AST (approximately 3-fold in 2 males and 2-fold in 1 female) were noted in animals administered 150 mg/kg/dose twice daily for 14 days (300 mg/kg/day). Complete recovery was noted at the end of the recovery phase[11].

- Cholesterol and triglycerides

  At 500 mg/kg/dose twice daily (1000 mg/kg/day) for 7 days a treatment-related increase was observed in mean total cholesterol (+108% when compared to the mean control values) in all female mice, which was considered as non-adverse. In addition, a trend to a decrease in mean triglycerides was observed in the males (-51%) and in the females (-28%), when compared to mean control group[4].
  On Day 15 of the 2-week dosing phase, increased cholesterol concentrations (83%) were noted in female mice administered 500 mg/kg/dose twice daily (1000 mg/kg/day), compared to controls. Complete recovery was noted at the end of the recovery phase[12].
  An increase in cholesterol was noted in animals administered 150 mg/kg/dose twice daily for 14 days (300 mg/kg/day; 33 to 43% for males and 34 to 49% for females). At the end of the recovery phase, the values were still higher (73% for males and 48% for females), compared to controls. Increases in triglyceride were noted in all males and two females administered 150 mg/kg/dose twice daily for 14 days (300 mg/kg/day; 77 to 91% for males and approximately 3-fold in females), compared to controls. Complete recovery was noted for females, but the values for males were still 74% higher than controls at the end of the recovery phase[11].

- Sodium:

  Slightly decreased sodium concentration (between 1 and 3%) was noted in male dogs administered 150 mg/kg/dose twice daily (300 mg/kg/day) during the 14-days dosing phase. Complete recovery was noted at the end of the recovery phase[11].

- Body temperature:

  Oral administration of BDM-2 at single dose levels of 300 or 1000 mg/kg caused a dose-dependent and transient decrease in body temperature in male mice, which was not considered adverse due to the absence of any behavioural observations. At 300 mg/kg, body temperature was decreased at 0.5, 1 and 2 hours postdose by 4.5, 3.4 and 1.3%, respectively, when compared to the vehicle-treated group. At 1000 mg/kg, body temperature was decreased at 0.5, 1, 2 and 3 hours postdose by 5.7, 5.7, 5.0 and 2.9%, respectively[9].
  Single oral administration of BDM-2 at dose levels of 10, 40 and 150 mg/kg had no effect on body temperature in the male dogs[9].

- Respiratory rate:

  Oral administration of BDM-2 at single dose levels of 100, 300 and 1000 mg/kg caused a slight decrease in respiratory rate by 16%, 26% and 30%, respectively, compared to an increase by 4% in the vehicle-treated group. The effect was dose dependent in the first 30 minutes period postdose in male mice. The decrease seen was statistically significant at 300 and 1000 mg/kg. Minute volume and tidal volume were unaffected. As the changes seen were transient and not as great as the overall decreases seen over the time of the experiment, these changes were not considered adverse[10].

With the information available at the time of this protocol preparation, the safety risk in healthy subjects is considered to be low. At the highest predicted human exposure (based on AUC calculated using modelling and simulation data; after 3600 mg anticipated clinical dose) there is still a 2.3-fold safety margin as compared to the mean exposure at NOAEL in dogs.

6. TRIAL POPULATION

Non-institutionalized healthy adult male subjects will be enrolled in the trial.

6.1 Planned Number and Source

A total of 16 subjects have to complete the trial. Subjects will be selected by the trial site in accordance with the inclusion and exclusion criteria (see Sections 6.2 and 6.3). Screening for eligible subjects will be performed within 28 days prior to Day 1 of the first session of a subject.

Quotient Sciences must have a full medical history from each subject's General Practitioner (GP) within the last 12 months, prior to enrolment in the trial.

Before subjects are admitted to the trial site, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not participated in a trial at another site within at least 3 months of the day of trial medication intake in the first session.

6.2 Inclusion Criteria

Subjects must meet all the following requirements prior to inclusion in the trial:

1. Healthy male aged between 18 and 55 years at screening, inclusive.
2. Body Mass Index (BMI) 18.0-32.0 kg/m^2 at screening, inclusive.
3. Good physical and mental health as established by medical history, physical examination, respiratory rate, electrocardiogram (ECG) and vital signs (including tympanic body temperature) recording, and results of biochemistry, coagulation, haematology and urinalysis tests during screening as judged by the investigator.
4. Non-smoker/non-user of nicotine containing products for at least 3 months prior to screening, to be confirmed by a urine cotinine dipstick test at screening and on Day -1 of the first session.

5. Availability and willingness to complete the trial and follow the instructions of the investigator or trial-site personnel.
6. Willing and able to adhere to the prohibitions and restrictions specified in the protocol (see Section 6.4).
7. Easy venous accessibility.
8. Must have signed an ICF prior to screening, indicating that he understands the purpose of, and procedures required for the trial, and is willing to participate in the trial.
9. Must agree to provide a blood sample for DNA research.
10. Subject who is heterosexually active with a woman of childbearing potential must agree to use 2 effective methods of birth control (i.e., male condom with either female intrauterine device, diaphragm, cervical cap or hormone-based contraceptive), during the trial and for at least 90 days after receiving the last dose of trial medication.

    If the female sexual partner is postmenopausal for at least 2 years, or is surgically sterile (has had a total hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise is incapable of becoming pregnant, the birth control methods mentioned are not applicable, however, subjects should use a condom during the trial and for at least 90 days after receiving the last dose of trial medication to prevent unintended exposure via the ejaculate.

    Subjects who had vasectomy and have a female partner of childbearing potential must use a male condom during the trial and for at least 90 days after receiving the last dose of trial medication.

    Note: A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.

    Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial medication (during the trial and for at least 90 days after receiving the last dose of trial medication). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.

    Note: Subjects will be instructed that if their partner becomes pregnant during the trial this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the trial but confirmed after completion of the trial. In the event that a subject's partner is subsequently found to be pregnant after the subject is included in the trial, then consent will be sought from the partner and, if granted, any pregnancy will be followed, and the status of mother and/or child will be reported to the sponsor after delivery.
11. Must agree not to donate sperm during the trial and for at least 90 days after receiving the last dose of trial medication.

6.3 Exclusion Criteria

Subjects meeting one or more of the following criteria cannot be included:

1. History of or current clinically significant medical illness including (but not limited to) gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, endocrinologic, genitourinary, renal, hepatic, respiratory, inflammatory, neoplastic, or infectious disease, or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the trial results.
2. Clinically significant abnormalities of haematology or biochemistry (out of range values should be considered as to their significance and the subject should not be included if the value is considered to be detrimental). This includes, but is not limited to, liver function tests.
3. Subjects with Gilbert's syndrome.
4. Clinically significant presence or history of allergy or intolerance (including lactose), or presence or history of clinically significant allergy requiring treatment, as judged by the investigator (hay fever is allowed unless it is active).
5. Positive serology for hepatitis A virus (HAV) immunoglobulin M (IgM), hepatitis B virus surface antigen (HBsAg), anti-hepatitis C virus antibodies (anti-HCV-AB), or anti-HIV antibodies 1+2 (anti-HIV-AB 1+2) at screening.
6. History of alcohol or drug abuse within the last 2 years before screening or positive test result(s) for alcohol and/or drugs of abuse at screening or on Day -1 of first session.
7. Regular alcohol consumption >21 units per week (1 unit = ½ pint beer, 25 mL of 40% spirit or a 125-mL glass of wine).
8. Surgery of gastro-intestinal tract that might interfere with absorption (subjects who have had cholecystectomy may be included). Subject has currently significant and active diarrhoea, nausea, or constipation that in the investigator's opinion could influence drug absorption or bioavailability.
9. Intake of any disallowed therapies (see Section 7.10) before the first dose of trial medication (on Day 1 of the first session).
10. Donation of blood or blood products or substantial loss of blood (more than 500 mL) within 3 months before first dose of trial medication (on Day 1 of the first session) or the intention to donate blood or blood products during the trial.
11. Major surgery, fracture, or prolonged immobilization (more than 2 weeks) within 3 months preceding screening, or surgery has been planned during the time the subject is expected to participate in the trial.
12. Plans to father a child while enrolled in the trial or within 90 days after receiving the last dose of trial medication.
13. History of hypersensitivity or idiosyncrasy to any of the components of the investigational drug.
14. Participation in a clinical trial within 3 months before first dose of trial medication (on Day 1 of the first session).

15. Participation in a trial of an investigational product or an experimental medical device within 3 months or within a period less than 5 times the drug's half-live, whichever is longer, prior to the first dose (on Day 1 of the first session) or during this trial.
16. Trial site employee or immediate family members of a trial site or sponsor employee.
17. Have previously been enrolled in this trial.

NOTE: Investigators should ensure that all trial enrolment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of trial medication is administered, such that he no longer meets all eligibility criteria, then the subject should be excluded from participation in the trial.

6.4 Prohibitions and Restrictions

Potential subjects must be willing to adhere to the following prohibitions and restrictions during the trial to be eligible for participation:

1. Intake of the following products is not allowed from 72 hours prior to trial medication intake until after the last PK sampling of each session:
    - xanthine-containing products (e.g., caffeine, tea, cola, chocolate). In addition, the intake of xanthine-derivates containing beverages should be limited to 3 cups per day during the remainder of the trial
    - alcohol containing beverages, to be confirmed by a negative test result for alcohol on Day -1 of each session
    - grapefruit, grapefruit juice and Seville oranges
    - beverages containing quinine (e.g., tonic, bitter lemon, bitter alcoholic beverages containing quinine)
2. Smoking and nicotine use is not allowed from 3 months prior to screening until after the last PK sampling in the last session, to be confirmed by a urine cotinine dipstick test on Day -1 of each session.
3. Use of drugs such as amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabis, methadone, methamphetamine/ecstasy, morphine/opiates, phencyclidine, and tricyclic antidepressants is not allowed from screening until completion of the trial, to be confirmed by a negative test result(s) for drugs of abuse on Day -1 of each session.
4. Strenuous physical exercise (including competitive sports) must be avoided from 72 hours prior to admission to the trial site until after the last PK sampling of each session.
5. Consumption of poppy-seeds is not allowed within 72 hours before each urine drug test to avoid false results of this test.
6. If a subject has had a recent febrile illness (>38°C) within 72 hours of the scheduled trial medication intake, the trial medication intake should be postponed until the body temperature has been normal for at least 72 hours.

7. Donation of blood is not allowed in the previous 3 months of first trial medication intake and during participation in the trial, and subject will be advised not to donate blood for at least 2 months after completion of the trial and not to participate in an investigational drug/medical device trial for at least 1 month after completion of the trial.
8. Subjects must not use any concomitant medication including over the counter products, vitamins, and herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's wort), except for sporadic use of paracetamol, from at least 14 days prior to Day -1 of the first session until the end of the trial. Enzyme affecting drugs (e.g., cytochrome P450 [CYP] or transport inhibitor or inducer) must have been discontinued at least 30 days or 5 terminal half-lives of the drug, whichever is longer, or the known duration of the inhibitor or inducer effect, prior to Day -1 of the first session (see Section 7.10).
9. Subjects should avoid exposure to sunlight or sunbathing, as well as the use of tanning devices (e.g., sunbed, solarium) and topical tanning products from 24 hours prior to trial medication intake until 72 hours postdose (which is equivalent to approximately 5 times the half-live of BDM-2 in dogs) in each session. Exposure of skin and eyes to the sun should be avoided by using appropriate clothing (hat, gloves,...) and/or sun cream from 24 hours prior to trial medication intake until 72 hours postdose in each session. These precautions should be taken in all weather conditions; regardless if the sun is out or not.

6.5 Discontinuation of Subjects from Treatment or Assessment

Subjects may discontinue from the trial at any time and for any reason. The reason for discontinuation should be documented in the eCRF.

Subjects who discontinue the trial will be advised, for their own safety, to undergo the assessments as defined for the follow-up visit.

6.6 Removal of Subjects from Treatment or Assessment

6.6.1 Withdrawal Criteria for Included Subjects

Subjects **must** be withdrawn from the trial if:

1. The subject withdraws his consent;
2. The subject is lost to follow-up.

Subjects **must** be withdrawn from the study drug if:

1. The investigator considers it is in the best interest of the subject (this should be discussed first with the sponsor) to be withdrawn from the study drug;
2. The subject experiences diseases or adverse events (AEs) requiring treatment which, in the opinion of the investigator, would probably prevent achievement of the trial objectives (this should be discussed first with the sponsor);
3. The subject experiences a serious adverse event (SAE), related to the investigational product administration, or a severe AE, related to the investigational product administration, including, but not limited to:

- QT interval corrected for heart rate (QTc) of >500 ms or increase in QTc interval of >60 ms from baseline (confirmed following a repeat ECG)
- ALT or AST concentration ≥3x the upper limit of the normal range (ULN);

4. The randomization code is broken by the investigator or trial-site personnel.

For the purpose of withdrawal criteria, baseline will be considered as the last measurement before intake of trial medication in the first session (Session I for Cohort A and Session II for Cohort B).

For a subject who withdraws because of an AE related to the trial medication, every effort will be made to ensure the subject completes follow-up procedures. Any subject withdrawn or discontinuing the trial or study drug prematurely because of an AE related to the trial medication or due to termination of the trial will be considered to have completed the trial and will not be replaced.

Subjects withdrawing for other reasons may be replaced at the discretion of the investigator and sponsor.

The date and the reason for discontinuation must be noted in the eCRF (if applicable).

All subjects prematurely discontinuing the trial or the study drug are strongly advised to be seen, if consent is not withdrawn, for a follow-up visit (see flow chart in Section 1.2) and the corresponding forms of the eCRF will be completed.

6.6.2 Subject Numbers

Subject numbers will be allocated on the morning of trial medication intake in the first session (Session I for Cohort A and Session II for Cohort B) according to the code 001 to 016 using the lowest number available. Replacement subjects will be allocated subject numbers 101 to 116, where the last 2 digits are the same as those of the original subject (e.g., if Subject 005 withdraws, the replacement will have Subject Number 105 and will be assigned the same cohort and treatment sequence as Subject 005).

6.6.3 Replacements

Subjects withdrawn/withdrawing due to an AE related to the trial medication or termination of the trial will not be replaced.

Subjects withdrawn/withdrawing for other reasons may be replaced at the discretion of the investigator and sponsor.

Per cohort, maximally 2 subjects may be replaced.

A subject who is replacing a dropout will be assigned the same cohort and treatment sequence as the affiliating dropout. The replacement subject will replace the dropout from the time point onwards when the subject dropped out.

6.6.4 Termination of the Trial

The sponsor reserves the right to terminate the trial at any time for any reason. In case of an early termination of the trial or temporary halt by the sponsor, the Ethics Committee (EC) and Competent Authority (CA) should be notified within 15

calendar days, including a detailed written explanation of the reasons for the termination/halt.

When the trial ends, Venn will submit an end of trial declaration to the CA by using the “Declaration of the end of trial form”. The “Declaration of the end of trial” will also be sent to the principal investigator for submission to the EC. The declaration will be submitted within 90 days of the end of the trial.

In case of early termination, Venn provides all essential documents maintained in the trial master file (TMF) as defined in the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

Reasons for termination of a trial by the sponsor may include, but are not limited to:

- Successful completion of the trial at the trial site.
- Failure of the investigator to comply with the protocol, International Council for Harmonization – Good Clinical Practice (ICH-GCP) guidelines or local requirements.
- Serious safety concerns.
- Inadequate recruitment of subjects by the investigator(s).
- Discontinuation of further trial medication development.
- If the total number of dropouts is so high or the number of included subjects is so low that proper completion of the trial will not realistically be expected.
- A serious adverse reaction (i.e., an SAE considered related to investigational product administration) in 1 subject;
- Severe non-serious adverse reactions (i.e., severe non-serious AEs considered related to investigational product administration) in 2 subjects in the same cohort, independent of within or not within the same system organ class.

The trial may be terminated if across both cohorts, a subject experiences a drug related SAE or 2 or more subjects experience severe, non-serious drug related AEs during BDM-2 therapy (after unblinding). Alternatively, de-escalation may be performed in the next session in order to study an intermediate dose.

The trial may be terminated based on dose escalation stopping (DES) criteria as described in Section 6.8.

6.7 Interim Analysis

The subjects, the investigator, and the sponsor will be blinded to treatment assignment during the trial. Upon finalization of a session, the sponsor may request the treatment codes, if deemed required.

At the end of each session (Sessions I to VI), a meeting will be organized with the investigator, the sponsor and Venn Life Sciences (Venn), at which a blinded review of safety, tolerability (AEs, vital signs, respiratory rate, ECGs, physical examination, and clinical laboratory assessments) and PK information will be performed, to establish if any of the DES criteria described in Section 6.8 have been met, or if dose de-escalation may occur.

The safety data (at least up to 48 hours) and the PK results (at least up to 24 hours) of the previous dose(s) will be evaluated by the investigator, the sponsor, and Venn before proceeding to the next dose level. Dose progression will only occur if the previous dose is shown to be safe and tolerable, the dose selected is not expected to exceed the mean exposure levels as described below.

For dose escalation to proceed, data must be available from a minimum of 6 subjects who have completed the planned safety assessments up to 48 hours after trial medication intake and the planned PK assessments up to 24 hours after trial medication intake to ensure at least 4 subjects had received active treatment. If there are incomplete datasets for PK data, the principal investigator can decide to proceed with dose escalation/de-escalation based on the safety data.

As described in Section 5.3.3, the dog kinetic data are considered most representative for the human exposure expectations. Mean exposure levels including the variability will be taken into account during the interim evaluation meetings. The maximum exposure observed in individual subjects in this trial will not exceed 255 µg.h/mL, the mean $AUC_{0\text{-}24h}$ observed in non-clinical repeated toxicity studies in dogs at the NOAEL.

Given the low toxicity profile of BDM-2 (i.e., no adverse findings in any of the safety studies as performed, up to the highest dose levels tested) in both mice and dogs, and the fact that only single dose levels will be administered in the current clinical trial, it is not expected that any of the non-adverse findings in the repeated toxicity studies will be relevant/adverse for humans after single dose.

Based on these results, decisions will be made on the dose, the food status, and the blood sampling scheme in the next session. Furthermore, after interim evaluation meetings of the first 2 sessions it will be decided whether a sentinel approach will be followed in the next session(s). An intermediate dose may be administered, or de-escalation may be performed, based on the emerging data.

6.8 Definition of Dose Escalation Stopping Criteria

Each dose progression shall be performed if, and only if, in the judgment of the investigator, the medical expert of the sponsor and Venn, the results of the safety, tolerability and exposure analyses of the preceding dose regimen are satisfactory.

Following are defined as DES criteria (using the Common Terminology Criteria for Adverse Events [CTCAE] grading table, latest version, for safety and tolerability parameters):

1. If at least 1 subject in a session has an AE that is serious and considered to be related to the investigational product administration or the severity prevents further escalation, as judged by the investigator and sponsor.
2. If 2 or more subjects in a session show a QT interval corrected for heart rate according to Fridericia (QTcF) >500 ms or a change versus baseline >60 ms, (confirmed following a repeat ECG).
3. If 2 or more severe or clinically significant non-serious AEs, CTCAE grade 3 or higher, that are considered to be related to investigational product administration, which are similar in nature, occur in a session.

4. If 2 or more subjects in a session show significant abnormalities in either biochemistry, coagulation or haematological parameters which are confirmed by a repeat sample obtained within 24 hours (after the investigator became aware of the abnormalities) and indicate a health risk. Such abnormalities are for example an increase in ALT or AST >3x ULN, which does not normalize after several days.
5. If 1 or more subjects in a session have confirmed ALT or AST >3x ULN combined with total bilirubin >2x ULN, for which no alternative aetiology is identified.
6. If 1 or more subjects in a session have confirmed ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) or other symptoms which, according to the clinical judgement of the investigator, could be considered as symptoms of acute hepatitis and for which no alternative aetiology is identified.
7. If the sponsor or the investigator considers dose escalation not safe for a reason not described above.
8. If 1 or more subjects in a session have an $AUC_{0\text{-}24h}$ higher than 255 µg.h/mL.

If any of the DES criteria is met, dosing will be stopped, and the trial will be put on hold. If, following an internal safety review, the sponsor deems it appropriate to restart the trial, a substantial amendment will be submitted for approval prior to implementation of the substantial amendment.

7. TREATMENTS/TRIAL MEDICATION

7.1 Treatments Administered

This trial is planned with 7 different doses with or without food, alternately administered in 2 cohorts of 8 subjects each (Cohorts A and B).

In 7 sessions, subjects in Cohort A and Cohort B will receive treatment as described in Table 4 in Section 7.6.

In the first session (Session I), a single dose of 50 mg BDM-2 or placebo will be administered under fasted conditions. Tentative doses for Sessions II to VI are 150, 450, 900, 1800, and 3600 mg BDM-2 or placebo. In Session VII, one of the doses administered in the former sessions under fasted conditions will be administered under fed conditions.

The BDM-2 doses for the 2^{nd} to 7^{th} sessions and whether administration will take place under fasted or fed conditions, will be determined based on the safety (at least up to 48 hours) and the PK results (at least up to 24 hours) of the dose(s) administered in the former session(s).

The subjects in Cohorts A and B will be randomized. In each session, 6 subjects will receive active BDM-2 and 2 subjects will receive placebo in a double-blind way, in such way that for each dose different subjects will receive placebo, except for the 7^{th} session (or earlier sessions under fed conditions), where the same treatment

allocation as in the session of the selected dose (administered under fasted conditions) will be used.

For further details on randomization, see Section 7.4.

7.2 Identity of Investigational Products

The investigational product, BDM-2, will be manufactured in compliance with Good Manufacturing Practice (GMP) and provided under the responsibility of the sponsor.

The investigational product for the different treatments is formulated as follows:

1. Test Product name:	BDM-2 in Bottle (50 mg – 3600 mg)
Active ingredient:	BDM-2
Strength:	50 mg to 3600 mg
Dosage form:	oral suspension

2. Reference Product name:	Placebo for BDM-2 in Bottle (50 mg – 3600 mg)
Active ingredient:	Not applicable
Strength:	Not applicable
Dosage form:	oral suspension (visually matching the active trial medication)

BDM-2 in bottle or matching placebo will be reconstituted with a 100 mL vehicle (0.2% SDS and water) to achieve a suspension for oral administration. Although referred to as a suspension, at low dose levels the trial medication may present a solution-like appearance.

The investigator acknowledges that the drug supplies are investigational and as such must be handled strictly in accordance with the protocol and the container label. Supplies must be retained in a limited access area and under the appropriate conditions as specified per label on delivery. Supplies should be dispensed under the supervision of the investigator or a member of the trial team. Local regulations should be adhered to.

7.3 Packaging and Labelling

The trial medication per subject will be prepared, labelled and released in a single labelled bottle per subject per trial medication intake occasion.

The trial medication will be labelled according to the regulations set in Annex 13 to the Current Edition of the GMP Guidelines[5].

Furthermore, the trial medication will be labelled according to the local regulatory requirements.

Packaging of all the investigational products will allow blinded administration.

7.4 Method of Assigning Subjects to Cohorts/Randomization

After screening, the first cohort of 8 eligible subjects will be assigned to Cohort A and the second cohort of 8 eligible subjects will be assigned to Cohort B.

The subjects of both cohorts will be randomized to one of 4 sequences (n=2 per sequence) as shown in Table 3.

Table 3: Randomization Scheme

	Week 1	**Week 5**	**Week 9**
Cohort A (n=8)	D1	P	D5
	D1	D3	P
	P	D3	D5
	D1	D3	D5
	Week 3	**Week 7**	**Week 11**
Cohort B (n=8)	D2	P	D6
	D2	D4	P
	P	D4	D6
	D2	D4	D6

D=Dose and P=Placebo.

In each session (Sessions I to VI), 6 subjects will receive active BDM-2 and 2 subjects will receive placebo in a double-blind way. Over the 1st, 3th and 5th session (Cohort A) and over the 2nd, 4th and 6th session (Cohort B), different subjects will receive placebo.

In the 7th session (Session VII, intake under fed conditions) the same treatment allocation as in the session of the selected dose (intake under fasted conditions) will be used.

For the first 2 sessions, a sentinel approach will be followed. The choice of the sentinel approach in these 2 sessions is to reduce the risks associated with exposing all subjects in a session simultaneously for the first trial medication intake in each cohort and not because of any known preclinical safety concerns. The staggered design will be spread over 2 days: the first sub-group (2 subjects) will receive trial medication (1 on active treatment, 1 on placebo) at least 24 hours prior to the second sub-group (6 subjects; 5 on active treatment, 1 on placebo). After interim evaluation meetings of the first 2 sessions it will be decided whether a sentinel approach will be followed in the next session(s).

A randomization list will be prepared by Quotient Sciences.

The unblinded Qualified Person (QP) or designee at the trial site will receive a copy of the final randomization list for preparation of the trial medication and preparation of the treatment allocation list.

The bioanalysis scientist, responsible for the interim bioanalysis, will receive the randomization list. However, at no point and under no circumstances the responsible bioanalytical scientist or other personnel will communicate the treatment of the subjects to the trial-site personnel and to Venn/sponsor personnel.

7.5 Blinding and Unblinding

This is a double-blind trial. Treatment assignment will not be known to the subjects, the sponsor or the staff who are involved in the clinical evaluation of the subjects and the analysis of data. The randomization list and disclosure envelopes will be generated by an unblinded statistician at Quotient Sciences according to Quotient Sciences Standard Operating Procedures (SOPs). The unblinded statistician will not be involved in any decisions relating to populations for analysis prior to unblinding. Prior to database lock and unblinding, all original randomization materials, including the original final signed and dated randomization list, will be held by the Quality Assurance (QA) department at Quotient Sciences. The Data Sciences department will not have access to the randomization list before database lock and unblinding.

Three sets of disclosure envelopes (i.e., sealed envelopes containing individual subject randomization details) will be provided. One set will be held in the clinical area and another set retained in the investigator site file (ISF). The third set will be kept by Drug Safety Solutions Ltd. (DSSL), responsible for expedited safety reporting. These sets of disclosure envelopes may be used in the event of an emergency by the investigator. Any request for information on the randomization list after initial issue must be made using a randomization disclosure form, except in the case of emergency unblinding, which must be recorded on the emergency unblinding form.

Access to trial medication assignment will be immediately available if the investigator deems it necessary to break the trial blind in the interest of a subject's medical safety, in case of a medical emergency, or if warranted during scheduled safety reviews. The medical expert of the sponsor and the trial manager at Venn must be contacted immediately following disclosure of trial medication assignment.

The date, time, and reason for the code breaking must be recorded on the corresponding eCRF. In addition, the reason must be documented in the Adverse Event Section of the eCRF.

If the code is broken by the investigator, the subject must be withdrawn from the trial and must be appropriately followed. If the code is broken by the sponsor for safety reporting purposes, the subject may remain in the trial.

All code envelopes, whether opened or sealed, will be collected, receipt documented and destructed by the monitor at the end of the trial and this will be documented in the TMF.

Placebo PK samples will not be analysed by the bioanalysis laboratory unless unexpected results should occur. To allow selection of samples, the bioanalysis laboratory will receive randomization lists per session. Unblinding of the treatment code will be performed at the bioanalytical laboratory only.

Interim PK parameter estimations will be performed using bioanalytical data applied with subject aliases in order to maintain the trial blind. There may be instances where interim PK data have the potential to be treatment revealing e.g., missed blood sampling occasions. In these cases, every effort will be made by the pharmacokineticist to maintain the trial blind by appropriate presentation of data to

the trial team. Data demonstrating extremes of exposure will always be presented, regardless of the potential to reveal the trial blind.

The trial blind will be broken after the trial database has been locked and the safety population has been defined. Any subsequent request for issue of the randomization list prior to unblinding must be made using a randomization disclosure form.

7.6 Administration of Investigational Product

The anticipated treatments are described in Table 4. Exact trial medication dose, PK blood sampling scheme and food status in each session, and sentinel approach (only after evaluation of the first 2 sessions) will depend on the findings of the previous session(s).

Table 4: Treatment (Sessions I to VII)

Session	Cohort	Period	Anticipated Treatment[a] (number of subjects)	Anticipated Trial Medication Administration
I	A	1	A single oral dose of 50 mg BDM-2 (n=6) or placebo (n=2) on Day 1; Fasted conditions	100 mL oral suspension containing 50 mg BDM-2 or matching placebo
II	B	1	A single oral dose of 150 mg BDM-2 (n=6) or placebo (n=2) on Day 1; Fasted conditions	100 mL oral suspension containing 150 mg BDM-2 or matching placebo
III	A	2	A single oral dose of 450 mg BDM-2 (n=6) or placebo (n=2) on Day 1; Fasted conditions	100 mL oral suspension containing 450 mg BDM-2 or matching placebo
IV	B	2	A single oral dose of 900 mg BDM-2 (n=6) or placebo (n=2) on Day 1; Fasted conditions	100 mL oral suspension containing 900 mg BDM-2 or matching placebo
V	A	3	A single oral dose of 1800 mg BDM-2 (n=6) or placebo (n=2) on Day 1; Fasted conditions	100 mL oral suspension containing 1800 mg BDM-2 or matching placebo
VI	B	3	A single oral dose of 3600 mg BDM-2 (n=6) or placebo (n=2) on Day 1; Fasted conditions	100 mL oral suspension containing 3600 mg BDM-2 or matching placebo
VII	A or B	4	A single oral dose of x mg BDM-2 (n=6) or placebo (n=2) on Day 1; Fed conditions	100 mL oral suspension containing x mg BDM-2 or matching placebo

[a] The BDM-2 doses for the 2nd to 7th session, the PK blood sampling scheme, sentinel approach (only after evaluation of the first 2 sessions) and the food status will be determined, based on the safety (at least up to 48 hours) and the PK results (at least up to 24 hours) of the dose(s) evaluated in the former session(s).

Trial medication will be administered as described in the flow chart in Section 1.2.

For each session, subjects will enter the trial site on Day -1 in the morning (approximately 24 hours prior to trial medication intake). Single oral doses of BDM-2 or placebo will be administered on Day 1 in the morning. Subjects will stay at the trial site until 48 hours after trial medication intake (morning of Day 3). Seven days after trial medication intake in the last session (a window of ±2 days is allowed) a follow-up assessment will be performed.

For each individual subject in Cohorts A and B, there will be a time interval of at least 7 days between 2 subsequent dose administrations of BDM-2/placebo.

NOTE: Based on the safety (at least up to 48 hours) and the PK results (at least up to 24 hours) of the dose(s) evaluated in the former session(s), it will be decided whether trial medication intake in the next session will take place under fasted or fed conditions.

Cohort A: Sessions I, III, and V and Cohort B: Sessions II, IV, and VI: single dose administration under fasted conditions

Intake of BDM-2 or placebo (100 mL of oral suspension in each session) will take place in the morning of Day 1. The trial medication will be taken after at least 10 hours of fasting (see Section 5.4). To ensure there is no detectable taste difference between the BDM-2 and placebo, taste will be masked by administration of Bitrex®. Immediately prior to administration of the BDM-2 or placebo, subjects will be asked to gargle with a 20 mL solution of Bitrex® (5 x 10-5% w/v) and then spit out. Afterwards the subject will be asked to swallow the trial medication in the form of an oral suspension of 100 mL. After administration of the oral suspension, the dosing vessel will be rinsed with water and subjects will consume the rinse solution immediately after dosing. Subjects will consume further water, to make a total volume of 240 mL (including the suspension [100 mL] and the volume water used to rinse the dosing vessel [100 mL; 2 x 50 mL rinses]).

On Days 2 and 3 of each session, the 24-hour and 48-hour PK sampling, respectively, will be performed after at least 10 hours of fasting. The start of breakfast on Days 2 and 3 will be after the PK sampling.

Before the mornings on which a safety blood sample is collected, subjects shall fast overnight for at least 10 hours.

On Day 1, time of trial medication intake and start time of lunch should be recorded in the eCRF. On Days 2 and 3, start time of breakfast should be recorded in the eCRF.

Cohort A or Cohort B: Session VII: single dose administration under fed conditions

Intake of BDM-2 or placebo (100 mL of oral suspension) will take place in the morning of Day 1. The trial medication will be taken 30 minutes after intake of a standardized breakfast has been started (see Section 5.4). On Day 1 subjects must have fasted overnight for at least 10 hours before the start of the standardized breakfast. To ensure there is no detectable taste difference between the BDM-2 and placebo, taste will be masked by administration of Bitrex®. Immediately prior to administration of the BDM-2 or placebo, subjects will be asked to gargle with a 20 mL solution of Bitrex® (5 x 10-5% w/v) and then spit out. Afterwards the subject will be asked to swallow the trial medication in the form of an oral suspension of 100 mL. After administration of the oral suspension, the dosing vessel will be rinsed with water and subjects will consume the rinse solution immediately after dosing. Subjects will consume further water, to make a total volume of 240 mL (including the suspension [100 mL] and the volume water used to rinse the dosing vessel [100 mL; 2 x 50 mL rinses]).

On Days 2 and 3, the 24-hour and 48-hour PK sampling, respectively, will be performed after at least 10 hours of fasting. The start of breakfast on Days 2 and 3 will be after the PK sampling.

Before the mornings on which a safety blood sample is collected, subjects shall fast overnight for at least 10 hours.

On Day 1, time of trial medication intake, start and stop times of standardized breakfast and start time of lunch should be recorded in the eCRF. On Days 2 and 3, start time of breakfast should be recorded in the eCRF.

7.7 Drug Accountability

The investigator or his/her designees must maintain an adequate record of the receipt and distribution of all trial supplies using a drug delivery form, a drug accountability form and a drug destruction form. These forms must be available for inspection at any time.

Supplies must be dispensed under the supervision of the investigator. Local regulations should be adhered to.

All used material must be appropriately discarded at the trial site after approval by the monitor and destroyed at Quotient Sciences after approval by the sponsor.

This must be documented on a drug destruction form. A written explanation regarding the disposition of missing products or their containers is required.

7.8 Storage

All trial medication must be handled strictly in accordance with the protocol and the container labels. Storage and dispensing instructions and expiration dates are supplied with the investigational materials on delivery. Access to trial medication should be restricted to designated trial personnel.

The trial medication must be stored in a locked area in accordance with the storage conditions.

All supplies of BDM-2 must be stored in the original containers delivered under the responsibility of the sponsor and under the conditions indicated on the labels.

The manufacturing of the trial medication will be performed at Quotient Sciences. After manufacturing, the trial medication will be transported internally from the manufacturing laboratory to the clinically dispensary of Quotient Sciences. Temperature monitoring of the internal transport is not required.

Temperature logging at the trial site should be performed. Should a deviation in storage conditions occur, the trial site must not further dispense the affected trial medication and must provide the monitor immediately with the following information:

- Date and duration of the deviation;
- Minimum temperature below the range and/or maximum temperature above the range that the product was exposed to.

Deviations in storage conditions will be evaluated by the Qualified Person (QP).

The monitor will periodically check the supplies of trial medication held by the investigator to ensure accountability (see also Section 7.7) and appropriate storage conditions of all trial treatments used.

7.9 Treatment Compliance

All trial medication administrations at the trial site are witnessed by the investigator or by trial-site personnel. The trial-site personnel will check hands and the oral cavity of each subject after administration.

If a subject's trial medication intake is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol.

7.10 Prior and Concomitant Therapy

During the entire trial, subjects must not use any medication other than the trial medication. All medication, including over the counter products, vitamins, and herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's wort), except for sporadic use of paracetamol, must have been discontinued at least 14 days prior to Day -1 of the first session. Enzyme affecting drugs (e.g., CYP or transport inhibitor or inducer) must have been discontinued at least 30 days or 5 terminal half-lives of the drug, whichever is longer, or the known duration of the inhibitor or inducer effect, prior to Day -1 of the first session.[7]

Paracetamol may be used up to 1 day before the administration of trial medication in the first session. The investigator may permit the use of paracetamol thereafter until the end of the trial at no more than 4x500 mg per day (intakes separated by 6 hours) and no more than 3 grams per week. In case paracetamol is used, the indication, the dose and dose regimen must be recorded on the corresponding eCRF.

Checks for concomitant medication(s) will be performed at each visit to the trial site. All concomitant medication(s) is to be documented in the eCRF. The investigator will decide together with the medical expert and the clinical consultant of Venn whether the subject must be excluded.

For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented in the AE Section of the eCRF.

8. ASSESSMENTS

8.1 Timing of Assessments

The timing of the assessments is presented in the flow chart (see Section 1.2).

If multiple assessments are scheduled for the same time point, procedures should preferably be performed in the following order: ECG, vital signs, respiratory rate, (PK) blood sampling.

Blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the eCRF.

For all subjects, a mandatory blood sample to bank DNA will be collected for future association studies of genotype with the PK and safety characteristics obtained in this trial (pharmacogenetics). In the event of DNA extraction failure, a replacement pharmacogenetic blood sample may be requested from the subject.

8.2 Demographics and Other Subject Characteristics

Subjects will be screened prior to inclusion to ensure that they are clinically healthy.

If the start of the trial is delayed for any reason so that the interval between screening and the first dose of trial medication (on Day 1 of the first session) exceeds 28 days, all or part of the screening procedures may be repeated at the discretion of the investigator.

Subjects previously screened generically may participate in this trial provided they meet the subject selection criteria. Procedures required by this protocol will only be done if they were not performed during generic screening. All screening data must be obtained within 28 days prior to Day 1 of the first session, as stipulated above.

The following assessments will be performed after signing the ICF within 28 days before Day 1 of the first session of a subject:

- Check of in- and exclusion criteria
- Complete physical examination including height and body weight measurement
- Medical history/medical review
- Urine drug test and alcohol breath test
- Urine cotinine dipstick test
- Serology including HIV-1 and 2, hepatitis A, B and C
- 12-lead ECGs (supine after at least 5 minutes rest in supine position)
- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate); all measures taken supine after at least 5 minutes rest in supine position; and tympanic body temperature
- Respiratory rate
- Blood and urine samples for biochemistry, coagulation, haematology and urinalysis
- Concomitant medication and AEs

8.3 Follow-up Visit

The follow-up visit is performed to verify that the subject has not experienced an AE. A follow-up visit should be performed in all cases where a subject was exposed to any trial medication.

The follow-up visit will be performed 7±2 days after the trial medication intake in the last session, or 7±2 days after dropout/withdrawal. In case of dropout due to an AE, the follow-up visit will take place at the moment of dropout or as soon as possible within 7 days after discontinuation.

The following assessments will be performed during the follow-up visit:

- Complete physical examination including body weight measurement
- 12-lead ECGs (supine after at least 5 minutes rest in supine position)
- Vital signs (SBP, DBP, and pulse rate); all measures taken supine after at least 5 minutes rest in supine position; and tympanic body temperature
- Respiratory rate
- Blood and urine samples for biochemistry, coagulation, haematology and urinalysis
- Concomitant medication and AEs

For follow-up of any AE which remains unresolved at the time point of last subject's visit, see Section 8.6.1.4.

Subject non-compliance will result in withdrawal from the trial.

8.4 Pharmacokinetics

8.4.1 Sample Collection and Handling

All samples for PK will be taken at time points as indicated in the flow chart in Section 1.2 and will be processed, handled and identified according to the laboratory manual for this trial. The sampling scheme for PK in a session may be adapted based on the results of the former session(s), however the total amount of blood collected from an individual subject will not exceed 550 mL in any 4-week period.

Exact dates and times of blood sampling will be recorded on the PK blood sampling source documents and in the eCRF.

The acceptable deviations from the nominal postdose blood sampling times are as follows:

- The predose blood sample will be taken ≤2 hours before trial medication intake.
- 0 to 1 hour postdose samples will be taken within ±2 min of the nominal postdose sampling time.
- >1 to 12 hours postdose samples will be taken within ±10 minutes of the nominal postdose sampling time.
- >12 hours postdose samples will be taken within ±30 minutes of the nominal postdose sampling time if subjects are resident at the trial site.
- >12 hours postdose samples will be taken within ±2 hours of the nominal postdose sampling time if subjects are attending a return visit.

Samples may be used by the sponsor for further exploratory work on PK, metabolites, plasma protein binding, biochemistry and proteins.

8.4.2 Bioanalytical Methods

All bioanalytical analyses in plasma will be performed by the bioanalytical laboratory in a Good Laboratory Practice (GLP) compliant setting.

The determination of BDM-2 in plasma samples will be performed using a validated liquid chromatography coupled to tandem mass spectrometry detection (LC-MS/MS) chromatographic method. The methodologies and their characteristics will be described in respective SOPs or other appropriate documents. The results of the analyses will be reported in an Analytical Report.

Pharmacokinetic samples from subjects assigned to placebo treatment will not be analysed unless unexpected results should occur. All PK samples from subjects on active treatment will be analysed for BDM-2 concentrations. To allow selection of samples, the bioanalytical laboratory will receive randomization lists per cohort. Unblinding of the treatment code will be performed at the bioanalytical laboratory only and will be subjected to a procedure that will ensure that codes will not be revealed to anyone involved in the execution of the trial.

Interim (blinded) plasma concentration data will be made available for dose escalation discussions.

8.4.3 Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual sampling times (see flow chart Section 1.2), the following PK parameters will be derived for BDM-2:

Cohorts A and B; Sessions I to VI): Single Dose Administration in Fasted Conditions

- On Day 1 of each session: C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $AUC_{0\text{-}24h}$, λ_{α} (if applicable), λ_z, $t_{1/2\alpha}$ (if applicable), $t_{1/2term}$, CL/F, V_d/F

Cohort A or B; Session VII: Single Dose Administration in Fed Conditions

- On Day 1: C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $AUC_{0\text{-}24h}$, λ_{α} (if applicable), λ_z, $t_{1/2\alpha}$ (if applicable), $t_{1/2term}$, CL/F, V_d/F, Ratio $C_{max,test/ref}$*, Ratio $AUC_{last,test/ref}$* and Ratio $AUC_{\infty,test/ref}$*

* test = BDM-2 in fed conditions, and ref = BDM-2 in fasted conditions (same dose)

Additional parameters may be included in the analysis when deemed necessary.

For the plasma PK parameters, definitions and methods of calculation are:

- C_{max} maximum observed plasma concentration;
- t_{max} time to reach the maximum observed plasma concentration;
- $AUC_{0\text{-}24h}$ AUC from time 0 to 24 hours postdose, calculated by linear-linear trapezoidal summation;
- AUC_{last} AUC from time 0 to the time of the last measurable (non-below quantification limit [BQL]) concentration, calculated by linear-linear trapezoidal summation;

- AUC_{∞} AUC from time 0 to infinity, calculated as $AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last observed measurable (non-BQL) concentration; extrapolations of more than 20.00% of the total AUC are reported as approximations;
- CL/F total apparent oral clearance, calculated as dose/AUC_{∞} after single dose, or as dose/AUC_{τ} at steady-state;
- V_d/F apparent volume of distribution, calculated as dose/ (λ_z *AUC_{∞});
- λ_{α} apparent initial elimination rate constant, estimated by linear regression using the first elimination phase of the ln-linear plasma concentration-time curve;
- λ_z apparent terminal elimination rate constant, estimated by linear regression using the terminal phase of the ln-linear plasma concentration-time curve;
- $t_{1/2\alpha}$ apparent initial elimination half-life, calculated as 0.693/λ_{α};
- $t_{1/2term}$ apparent terminal elimination half-life, calculated as 0.693/λ_z;
- Ratio $C_{max,test/ref}$ ratio of individual C_{max} values between test and reference;
- Ratio $AUC_{last,test/ref}$ ratio of individual AUC_{last} values between test and reference;
- Ratio $AUC_{\infty,test/ref}$ ratio of individual AUC_{∞} values between test and reference.

The following requirements should be met for an acceptable calculation of AUC_{∞}, $t_{1/2term}$, λ_z, $t_{1/2\alpha}$ and λ_{α}:

A) at least 3 data points are used in the calculation (preferably not including t_{max}), otherwise AUC_{∞}, $t_{1/2term}$, λ_z, $t_{1/2\alpha}$ and λ_{α} are not assessable;

B) coefficient of determination (r^2_{adj}) is at least 0.90.

If requirement (B) is not met, AUC_{∞}, $t_{1/2term}$, λ_z, $t_{1/2\alpha}$ and λ_{α} AUC_{∞}, $t_{1/2term}$ and λ_z will be reported as approximations.

Dose-normalization will be done by dividing the relevant PK parameter by the dose (D).

Actual sampling times will be checked for major aberrations. Deviation of scheduled time points is allowed, however in case a major aberration occurs for an actual sampling time of >20.00% deviation from the scheduled time, or a sample is not taken on the scheduled day, this plasma concentration will be excluded from descriptive statistics in the plasma concentration table.

8.5 Pharmacogenetics

A mandatory blood sample to bank DNA for future association studies of genotype with the PK and safety characteristics obtained in this trial will be taken once for all subjects, preferably predose on Day 1 of the first session of a subject. Samples will be stored at the bioanalytical laboratory for future analysis. Collection of blood for future DNA research is part of the trial, important for understanding the results of the trial and will allow for genetic research to help understand BDM-2.

Genetic analysis will be conducted if it is hypothesized that this may help resolve issues with the clinical data. DNA samples will only be used for genetic research related to BDM-2 or HIV infections.

Pharmacogenetic sampling is mandatory for all subjects.

8.6 Safety

8.6.1 Adverse Events

8.6.1.1 Definition of Adverse Events

ADVERSE EVENT (AE)

Any untoward medical occurrence in a patient or clinical investigation subject treated with a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6; 1.2).

ADVERSE DRUG REACTION (ADR)

An ADR is an AE that is related to the trial medication according to the investigator.

A non-drug related AE is defined as not related.

UNEXPECTED ADVERSE DRUG REACTION

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (i.e., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

SERIOUS ADVERSE EVENT (SAE)

Any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect (ICH E6; 1.50)

Or

- Is another medically important event or reaction.

Note

- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

  Examples of such events are intensive treatment in an emergency unit or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalization.
- Hospitalizations that were planned prior to the signing of informed consent, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- The term “life threatening“ in the definition refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.6.1.2 Checks for AEs

Adverse events will be recorded from the time of providing written informed consent until discharge from the trial at the follow-up visit.

Adverse events will be checked during in-house assessments and at every visit and reported from signing the ICF onwards until the last trial-related visit. Pre-existing complaints or symptoms that increase in intensity or frequency after the subject has signed the ICF must be recorded in the eCRF as AEs. Checks for AEs will be performed in a non-leading manner according to the flow chart (see Section 1.2). Furthermore, the subjects will be asked to report any AEs spontaneously, whether or not they occur during confinement. Occurrence of AEs will be reported in the AE Section of the eCRF. Severity and drug relationship of AEs towards BDM-2 will be recorded.

A physician will be available throughout the entire trial and all subjects will be observed for signs of clinical toxicity during the entire trial.

8.6.1.3 Documentation of AEs

Reporting of any AE (including clinically relevant laboratory values) will be done individually for each trial subject. Any AE reported by a subject or observed by the trial-site personnel will be documented in the eCRF at first by the trial-site personnel using the English language and additionally assessed by the investigators using the English language. For each AE, the time of onset and stop time, any action taken (e.g., medical action taken to overrule the AE) and intensity will be recorded in the eCRF. Evaluation of outcome, seriousness, period, treatment and the relationship with the trial medication (causality) will be classified only for AEs.

All AEs of subjects being part of the analysis sets defined in Section 9.2.2 will be listed and described in the report. The relationship of each AE will be assessed. Investigators will be responsible for any ratings of AEs including causality. Expectedness of related AEs will be classified by the sponsor. All AEs emerging from this FIH trial will be rated as unexpected.

Classification of intensity of AEs

In the course of the trial, the investigator will determine whether any AE has occurred and will grade their intensity using the CTCAE grading table, except if the AE is not defined in the CTCAE grading table. In that case, the intensity of the AE will be graded as follows:

Mild The AE impairs the normal functional level of the subject only slightly, if at all.

Moderate The AE impairs the normal functional level of the subject to a certain extent.

Severe The AE represents a clear-cut, marked impairment of the subject's normal functional level.

The maximum intensity of an AE is to be considered for classification.

Classification of causality of AEs to the trial medication

Every AE experienced during the clinical trial must be evaluated for its relationship to the investigational product administered by the investigator. Causal relationships of SAEs will also be assessed by the sponsor. Causality rating by the investigator will be performed by introspection. Causality can be assessed as either:

NOT RELATED

An AE, which is not related to the use of the investigational product.

RELATED

An AE, which is considered at least a reasonable possibly related to the use of the investigational product (see Addendum **Error! Reference source not found.** for guidance on causality assessment).

Specification of the outcome of AEs

The outcome of an AE is to be classified as follows:

Resolved

Resolving

Ongoing

Resolved with sequelae

Death

Unknown

8.6.1.4 Follow-up of Subjects after Adverse Events

The trial-site personnel have to monitor the trial subject's safety from the occurrence of an AE until satisfactory recovery.

Any AE which remains unresolved at the time point of subject’s last visit requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found; in case of drug-related and clinical relevant AEs every effort has to be made to follow-up trial subjects in order to determine the final outcome.

It is the investigator's responsibility to assure that subjects experiencing adverse reactions will receive definitive treatment for any adverse reaction, if required. Details of follow-up care are to be provided (i.e., if treatment or hospitalization is required). The responsibility to provide adequate follow-up for AEs includes periodically repeating laboratory tests yielding clinically abnormal results at the end of trial evaluation. This follow-up for AEs is to be reported in the eCRFs.

All subjects will come for a follow-up visit, scheduled 7 days (a window of ±2 days is allowed) after the last administration of BDM-2 or placebo. All drug-related AEs still ongoing at the follow-up visit will be followed until satisfactory resolution (i.e., value back to baseline value) or stabilization (to be agreed upon in collaboration with the sponsor).

Special attention will be paid to those subjects who discontinue the trial for an AE, or who experience a severe AE, or an SAE. In case of dropout due to an AE, subjects will be strongly advised, if consent not withdrawn, for a follow-up visit at the moment of dropout or as soon as possible within 7 days after discontinuation.

New AEs reported during the follow-up period of the trial will be followed until the AE has been resolved or a reasonable explanation for its persistence is found; in case of drug-related and clinical relevant AEs, every effort has to be made to follow-up trial subjects in order to determine the final outcome.

8.6.1.5 Measurements in Case of Serious Adverse Events

SAEs occurring within the clinical trial (between signing of ICF and follow-up visit) will be reported. SAEs are to be documented in detail on an SAE form in addition to the regular AE documentation in the eCRF. Any SAEs with a relationship to the trial medication occurring after the end of the trial must be reported according to the described procedures.

The start date of the SAE documented on the SAE form should be the date the AE first fulfilled any serious criterion. If a change in severity is noted for the existing AE, it must be recorded as a new AE. If a worsened AE meets the criteria for an SAE, the start date of the SAE must be the same as the start date of the worsened AE.

Any SAE should be reported immediately by telephone after the investigator becoming aware of the event to the sponsor and to the pharmacovigilance vendor (DSSL), followed by an SAE form transmitted in PDF format by e-mail (not to exceed 24 hours). Any event that is life-threatening or fatal should be reported. These preliminary reports will be followed as soon as possible by detailed descriptions that will include a completed SAE form, copies of hospital case reports, autopsy reports, and other documents, when requested and applicable, and sent as PDF per email to:

<u>For the Sponsor</u>

Name **Dr. Robert Miller**

Phone/fax **+44 203 291 3032**

Mobile **+44 7826 555254**

E-mail **robert.miller@artemidapharma.com**

For the pharmacovigilance vendor DSSL:

Safety Mailbox: cases@drugsafetysolutions.co.uk

Standard SAE form templates can be found in the ISF. Minimal information should include:

- An identifiable subject,
- A unique trial code;
- An identifiable reporting source,
- All related AEs,
- The suspect investigational product.

Follow-up of SAEs

If / when supplementary information is available, a follow-up SAE form must be completed by the site and sent as PDF within 24 hours to robert.miller@artemidapharma.com.

Once sent, the SAE form and accompanying documentation should be placed in the SAE Section of the ISF. If supplementary information on an SAE must be sent, the SAE form must be used marked as “follow-up report”.

DSSL will assume responsibility for appropriate reporting of SAEs to the CAs. According to local regulations, DSSL will also report all SAEs that are unlisted and associated with the use of the drug (suspected unexpected serious adverse reaction [SUSAR]) to the Investigators and EC. For reported deaths, the Investigator should supply the sponsor and the EC with any additional requested information (i.e., autopsy reports and terminal medical reports).

After termination of the clinical trial (last subject last visit in the trial), any unexpected safety issue that changes the risk benefit analysis and is likely to have an impact on the subjects who have participated in it, should be reported as soon as possible to the CA(s) concerned together with proposed actions.

8.6.2 Emergency Measures

In case of emergency, standard emergency procedures will be employed. The investigator is to be consulted and informed immediately.

The investigator will provide all the necessary emergency equipment and specially trained trial-site personnel to handle emergency events during this trial.

The trial site is responsible for ensuring 24 hours emergency availability.

All cases of emergency have to be immediately reported to the medical expert and to the trial manager of Venn and will be noted in the eCRF.

8.6.3 Clinical Laboratory

Blood samples for biochemistry, coagulation, haematology, and serology and urine samples for urinalysis will be taken at time points as indicated in the flow chart (see Section 1.2). All laboratory samples will be handled according to the laboratory manual.

The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:

- The predose blood sample will be taken ≤2 hours before trial medication intake.
- Postdose blood samples will be taken ±1 hour from the nominal blood sampling time except when the time point coincides with the PK blood sampling time. In this situation, the time window for the PK sample applies.

The acceptable deviations from the nominal urine sampling time points for urinalysis are:

- The predose urine sample will be taken ≤3 hours before trial medication intake or the first void of the day.
- Postdose urine samples will be taken ±2 hours from the nominal urine sampling time.

Before the mornings on which a safety blood sample is collected, subjects shall fast overnight for at least 10 hours.

The laboratory reports must be filed with the source documents. The laboratory report must be interpreted, signed, and dated by the investigator. Any clinically relevant abnormalities occurring during the trial, from signing the ICF onwards, must be recorded in the AE Section of the eCRF.

Standard methods for clinical laboratory parameters will be used. Documentation of the methods and reference ranges will be part of the TMF and the clinical trial report (CTR). Furthermore, the quality certificates being valid during the time of the trial will be included into the documentation.

8.6.3.1 Haematology

The following assessments will be performed:

Erythrocyte sedimentation rate (ESR), haemoglobin (Hb), haematocrit (Ht), red blood cell (RBC) count, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count, WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

8.6.3.2 Coagulation

Determination of the following coagulation parameters will be performed:

Prothrombin time (PT) and activated partial thromboplastin time (aPTT).

8.6.3.3 Biochemistry

The following assessments will be performed:

Total protein, AST, ALT, ALP, gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, urea, creatinine, sodium, potassium, chloride, bicarbonate, calcium (corrected for albumin), phosphate,

lipase, human serum albumin, (fasting) glucose, globulin, lipids (fasting): cholesterol, triglycerides, low density lipoproteins (LDL), high density lipoproteins (HDL).

8.6.3.4 Serology

The following additional assessments will be performed:

- Markers of viral hepatitis A, B and C (HAV IgM, HBsAg, anti-HCV-AB);
- HIV infection (anti-HIV-AB 1+2).

8.6.3.5 Urinalysis

Urinalysis will be performed using a dipstick method, which provides information regarding leukocytes, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose in the urine. If deemed necessary based on a clinically significant positive test, microscopic examination of sediment will be done.

At the screening visit and on Day -1 of each session a urine cotinine dipstick test and a urine drug test will be performed. The urine drug test involves analysis for amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabis, methadone, methamphetamine/ecstasy, morphine/opiates, phencyclidine, and tricyclic antidepressants.

8.6.3.6 Other Laboratory Assessments

An alcohol breath test will be performed at screening and on Day -1 of each session, according to the flow chart (see Section 1.2).

8.6.4 Clinical Assessments

Any clinically relevant abnormalities occurring during the trial must be recorded in the AE Section of the eCRF.

8.6.4.1 Vital Signs

Systolic blood pressure, diastolic blood pressure and pulse rate (all measures taken supine after at least 5 minutes rest in supine position) and tympanic body temperature will be recorded at time points as indicated in the flow chart (see Section 1.2).

The acceptable deviations from the nominal vital signs measurement time points are:

- The predose vital signs measurements will be taken ≤2 hours before trial medication intake.
- Postdose vital signs measurements will be taken ±15 minutes from the nominal postdose time points.
- Discharge vital signs measurements will be taken ±1 hour from the nominal time point.
- For return visits vital signs measurements will be taken ±2 hours from the nominal return visit time point.

Blood pressure and pulse rate measurements will be assessed with a completely automated device consisting of an inflatable cuff and an oscillatory detection system. All values will be registered on a built-in recorder so that measurements are observer independent.

8.6.4.2 Electrocardiogram

ECGs will be recorded at time points as indicated in the flow chart (see Section 1.2). ECGs will be performed supine after at least 5 minutes rest in supine position.

The acceptable deviations from the nominal ECG measurement time points are:

- The predose ECG measurements will be taken ≤2 hours before trial medication intake.
- Postdose ECG measurements will be taken ±15 minutes from the nominal postdose time point.
- Discharge ECG measurements will be taken ±1 hour from the nominal time point.
- For return visits ECG measurements will be taken ±2 hours from the nominal return visit time point.

Predose on Day 1 of each session, triplicate 12-lead ECGs are required: 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 5 minutes. Evaluation of the triplicate 12-lead ECGs will be based on the mean value of the triplicate parameters.

At all other time points, single 12-lead ECGs will be recorded.

Time points of ECG recordings may change depending on the observed t_{max} of BDM-2.

For determination of QTc interval from single ECG recordings, the ECG needs to be of good quality and 3 measurable beats (preferably consecutive beats) are to be taken to determine the QT intervals. In case the read out from the automated ECG gives abnormal ECGs with regard to PR, or QTc, these should be measured manually.

Twelve-lead ECGs will be recorded so that the different ECG intervals (heart rate, PR interval, QRS interval, RR interval and QT interval) will be measured. The QT interval will be calculated, corrected for heart rate according to Bazett ($QTcB^2$) and Fridericia ($QTcF^6$) formulae. ECGs will be assessed by the investigator and any abnormalities will be recorded in the eCRF.

8.6.4.3 Respiratory Rate

Respiratory rate measurements will be done at time points as indicated in the flow chart (see Section 1.2).

8.6.4.4 Physical Examination

A complete physical examination including height (only at screening) and body weight measurement will be performed at screening, on Day -1 of each session, and at the follow-up visit. In addition, a symptom directed physical examination

(general appearance, cardiovascular system, respiratory system, and abdomen, including symptom-driven physical examination) will be done in each session predose on Day 1 and at 24 and 48 hours postdose, as indicated in the flow chart (Section 1.2).

To obtain the actual body weight, subjects must be weighed lightly clothed. The height should be measured barefoot.

8.7 Appropriateness of Measurements

All methods used for safety assessments are standard methods for which reliability, accuracy and relevance have been documented for the purposes of the present trial (e.g., blood pressure, tympanic body temperature, urine dipstick, alcohol breath test).

9. SAMPLE SIZE AND STATISTICAL METHODS

9.1 Sample Size Calculation

By experience, the number of subjects to be enrolled in this trial is considered sufficient to achieve the objectives of the trial. Therefore, given the stage of development and the nature of these exploratory investigations, no formal sample size calculations have been performed.

Subjects who do not complete all sessions and assessments may be replaced.

9.2 Statistical Methods

9.2.1 Disposition of Subjects

The number of subjects randomized and treated, and completed the clinical trial will be tabulated by treatment. Treatments will be separated in active treatment and placebo. This will also be presented in a disposition graph.

9.2.1.1 Screening Failures

Screening failures are subjects who are enrolled but not randomized.

9.2.1.2 Dropouts

A dropout is a subject who prematurely discontinues participation after being randomized, before having completed all planned trial sessions and assessments.

9.2.2 Analysis Sets

All subjects treated group: all randomized subjects who received at least 1 dose of trial medication.

All subjects treated-PK evaluable group: all subjects treated for whom at least 1 plasma concentration is available.

In essence, all subjects for whom bioanalytical data are available will be included in the PK analysis. In general, bioanalytical data will not be excluded from PK analysis, and this will only be done in case of clear reasons based on eCRF data or

other reported information. In case bioanalytical data is excluded the reason is reported in the CTR.

Comprehensive justification for the classification of a protocol violation as “major” will be given in the CTR.

Only data of subjects who are part of at least one of the defined analysis sets will be included in the database i.e., their data will be listed; consequently, screening failures will not be included in the database.

9.2.3 Initial Subject Characteristics

Statistical demographic analysis will be done by Venn.

All demographic (age, height, body weight, BMI, ethnic origin) and other initial subject characteristics (smoking history, physical examination, medical and surgical history, concomitant diseases and concomitant medication) will be tabulated and analysed descriptively.

9.2.4 Pharmacokinetics

9.2.4.1 Pharmacokinetic Analyses

Pharmacokinetic analyses of BDM-2 will be done by Venn in accordance with Venn’s SOPs.

Pharmacokinetic and statistical analysis will be done using Phoenix™ WinNonlin® (Tripos L.P.). Noncompartmental analysis model 200 (extravascular input, plasma data) will be applied for the PK analysis. Furthermore, Microsoft Excel® (Microsoft, Redmond, Washington, US), and SAS (SAS Institute Inc., Cary, NC, US) will be used.

Descriptive statistics will be calculated for the plasma concentrations of BDM-2 at each applicable time point, and for the derived plasma PK parameters. Statistics include sample size (n), mean, standard deviation (SD), coefficient of variation (CV), geometric mean, median, minimum, and maximum.

For each subject, plasma concentration-time data of BDM-2 will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. Pharmacokinetic parameters will be subjected to an exploratory graphical analysis including various transformations in order to get a general overview.

Actual and/or dose-normalized PK parameters will be graphically displayed for BDM-2 as function of the dose.

To assess the effect of food, the PK parameters of BDM-2 for the treatment in fed conditions (Session VII in Cohort A or B), and for the same dose level in fasted conditions (one of the Sessions I to VI in Cohort A or B) will be graphically displayed and descriptive statistics will be prepared. The PK parameters of interest for this will be C_{max}, AUC_{last} and AUC_{∞}.

Statistical analysis will be performed for BDM-2 using treatment in fed conditions (Session VII in Cohort A or B) as test and the same dose in fasted conditions (one of the Sessions I to VI in Cohort A or B) as reference. The primary PK parameters

will be C_{max}, AUC_{last} and AUC_{∞} on the logarithmic scale. AUC_{∞} will be rejected as primary parameter for a treatment if more than half of the subjects do not have a reliable value for that treatment. All observations for test and reference, paired and unpaired, will be included in the statistical analysis. The least square (LS) means of the primary parameters for each session will be estimated with a linear mixed effects model, controlling for treatment (fed or fasted) as fixed effect, and subject as a random effect. A 90% confidence interval (CI) will be constructed around the difference between the LS means of test and reference. Both the difference between the LS means and the 90% CIs will be retransformed to the original scale.

9.2.5 Safety Analyses

Statistical analysis for safety and tolerability will be done by Venn. Baseline will be considered as the last assessment before intake of trial medication in the first session (Session I for Cohort A and Session II for Cohort B).

Details of statistical analysis for safety and tolerability will be described in a Statistical Analysis Plan (SAP). The SAP should be finalized, in principle, at least 1 week before database lock and should describe the analytical and statistical methods for the safety measurements in detail.

9.2.5.1 Adverse Events

All events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA, latest version).

Type and incidence of all AEs will be tabulated. Severity and drug relatedness of all reported AEs will be tabulated.

Separate tabulations will be provided for those subjects who have discontinued the trial for an AE, or who experienced a severe or a serious AE.

The incidence of AEs under active treatment will be compared with the incidence of AEs under placebo.

9.2.5.2 Clinical Laboratory

Clinical laboratory data will be listed by treatment and subject. For the clinical laboratory data, descriptive statistics (actual values and changes from baseline or change over time) will be generated for all tests performed. Graphical presentation of changes in laboratory tests will be made as applicable. Laboratory abnormalities will be determined according to the normal ranges of the clinical laboratory. Laboratory abnormalities will be tabulated by treatment and subject.

9.2.5.3 12-Lead ECG

All quantitative and qualitative ECG data will be listed by treatment and subject.

Summary statistics will be calculated for all ECG parameters collected and changes from baseline (predose) will be presented.

9.2.5.4 Vital Signs

Baseline values and change from baseline (predose) in SBP, DBP and pulse rate will be summarized by treatment. All vital signs data will be listed by treatment and subject. All values outside the normal reference range will be flagged.

Summary statistics will be calculated for all vital signs and changes from baseline will be presented.

9.2.5.5 Respiratory Rate

Respiratory rate data will be summarized by treatment and subject. All values outside the normal reference range will be flagged.

Summary statistics will be calculated and changes from baseline will be presented.

9.2.5.6 Clinical Assessments

Physical examination results will be tabulated per visit and treatment. Abnormalities will be listed.

10. TRIAL MATERIALS

10.1 Trial Documents

The following documents must be available before release of trial medication to the trial site:

- A signed and dated protocol and amendment(s), if any.
- A copy of the signed and dated written EC approval specifying the documents being approved: the protocol, amendments, Subject Participation Information Sheet and Informed Consent Form (PIS-ICF), any other written information provided to the subject and subject recruitment materials. This approval must clearly identify the trial by protocol title and trial number.
- Competent Authority approval or notification, if required.
- Documentation on which the assessment of the investigator's qualifications was based (e.g., curriculum vitae).

The following documents must be provided to the monitor prior to enrolment of the first subject:

- The names of the current members or composition of the EC or their credentials. In case the investigator is a member of the EC, documentation must be obtained to state that this person did not participate in the voting for the trial.
- Signed and dated trial agreement, if applicable.
- Signed and dated financial agreement.
- Current laboratory normal ranges for all tests required by the protocol that will be performed.
- Laboratory documentation demonstrating competence and test reliability (e.g., accreditation/license), if applicable.

If the trial site has to be closed prematurely, Venn will provide all essential documents maintained in the TMF as defined in the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

10.2 Source Data

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known and are accessible for verification by the monitor. If electronic records are maintained, the method of verification must be discussed between the trial-site personnel and the monitor.

Source documents should include sequential notes containing at least but are not limited to the following information for each subject:

- Subject identification (name, date of birth, gender).
- Documentation that subject meets eligibility criteria, i.e., history, physical examination (to support inclusion and exclusion criteria).
- Participation in trial (including trial number and subject number).
- Trial discussed and date of informed consent.
- Dates of all visits.
- Laboratory reports.
- ECGs.
- Documentation that protocol specific procedures were performed.
- Start and end date (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well).
- Record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity).
- Concomitant medication (including start and end date, and dose. If relevant, dose changes should be motivated).
- Date of trial completion and reason for early discontinuation, if applicable.

It is recommended that the author of an entry in the source documents is identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.

10.3 Electronic Case Report Forms (eCRFs)

Good Clinical Practice requires that trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. A trial monitor and an unblinded trial monitor, independent of Quotient Sciences, will be appointed to verify that the trial is conducted in accordance with current GCP, regulatory requirements, the protocol and that the data are authentic, accurate and complete.

The investigator agrees to receive visits from a trial monitor and provide assistance to verify protocol implementation, source workbook completion and transcription of data into the eCRF, document storage and AE reporting.

Quotient Sciences will extend the professional privilege of access to the subjects' clinical source documents to the trial monitor, EC, regulatory bodies or other authorized personnel (e.g., auditor) for the purposes of source data verification.

Following completion of the trial both trial related documents and subject data may be sent to the sponsor at a location outside of the United Kingdom where data protection laws differ. In the interests of confidentiality, subjects will not be identified on any such documents or data, and specific subject consent for such a disposition will be obtained.

Source data will be transcribed into a validated eCRF database (InForm v5.0 or a more recent version) which has an audit trail to log all subsequent changes to the data. All queries will be resolved within InForm with the assistance of clinical staff and reference to the source workbook.

10.4 Archiving

The investigator shall maintain the trial documents as specified in “Essential Documents for the Conduct of a Clinical Trial” (ICH E6, Section 8) and as required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained a written approval of the sponsor.

If it becomes necessary for the sponsor or the appropriate CA to review any documentation relating to this trial, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the ICF.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the trial.

11. DATA QUALITY CONTROL / ASSURANCE

The trial will be monitored by the dedicated persons as specified in the Trial Contact List and according to their current Standard Operating Procedure for the monitoring of clinical trials.

Shortly before the trial starts, the monitor will meet with the investigator and all trial-site personnel involved, to review the procedures regarding trial conduct and recording the data in the eCRF. During the trial, the investigator shall permit the monitor to verify the progress of the trial at the trial site as frequently as necessary. Key data transcribed into the eCRF, such as the subject's sex, date of birth, assessment dates, test results etc., will be reviewed against source documents. Personal information will be treated as strictly confidential and will not be made publicly available. Any inconsistency between source data and data recorded in the eCRF will be corrected.

An independent QA department, CAs and/or ECs may review this trial. This implies that auditors/inspectors will have the right to inspect the trial site at any time during and/or after completion of the trial and will have access to source documents, including the subject's file. By participating in this trial, investigators agree to this requirement.

For any data transfer, measures will be undertaken to protect subject data handed over against disclosure to unauthorized third parties and subject confidentiality will be maintained at all times.

12. ETHICS, REGULATORY CONSIDERATIONS AND FINANCES

12.1 Ethics Committee (EC) and Regulatory Approval

This trial can only be undertaken after favourable opinion of the clinical trial protocol (CTP), PIS-ICF, any other written information given to subjects, and subject recruitment materials has been obtained from the EC and approval of the CTP and Investigational Medicinal Product Dossier (IMPD) and any supporting documents by the CA. The favourable opinion document issued by the EC must be dated and clearly identify the trial and the documents being approved, including the subject compensation programs. In addition, written and dated approval by the CA has to be received for the documents required by the European Union (EU) GCP directive including CTP as well as any subsequent substantial amendments.

The EC is responsible for continuous review of the trial. At least once a year, the investigator will provide the EC with a progress report to allow review of the trial. Additional progress reports should be provided if required by the EC.

These requests and (re)approvals, if applicable, should be documented in writing. At the end of the trial, the investigator will notify the EC about the trial completion.

12.2 Amendments

Any change to the clinical trial must be written and filed as an amendment to this protocol. All parties who sign the protocol will sign the amendments.

If the protocol amendment is considered “substantial”, it must be submitted to the EC and CA for review. It would be considered substantial if the amendment is likely to have significant impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the dose, quality or safety of any investigational product used in the trial.

Approval / favourable opinion of the EC and CA shall be obtained before such change is implemented.

Only in case the sponsor and/or investigator must take urgent safety measures to protect trial subjects from immediate hazard, deviations from the protocol can be made before a formal substantial protocol amendment is submitted and/or before

approval / favourable opinion is received from EC (and/or CAs). In such cases, the EC (and/or CAs) shall be notified of the new events, the measures taken and the plan for further action. This will be done as soon as possible by telephone, followed by a written report. When the trial was halted (i.e., recruitment stop, interruption of treatment), the EC (and/or CAs) must be notified in writing within the timelines as outlined in the local regulations. The protocol amendment must be submitted as soon as possible for approval / favourable opinion. If the trial was halted, approval from EC (and/or CAs) must be obtained before recommencement of the trial.

Administrative changes of the protocol ("non-substantial", i.e., not considered to have impact on the safety or physical or mental integrity of the subjects, the scientific value of the trial, the conduct or management of the trial, or the dose, quality or safety of any investigational product used in the trial), will be collected ongoing as items for a non-substantial protocol amendment with a justification why it is considered "non-substantial", from which date this item is effective and signed by the sponsor, investigator and Venn. These items for a non-substantial amendment will be kept on file (both at the investigators' and Venn) and made available on request at the trial site(s) and/or the sponsor's premises, as appropriate.

Changes or clarifications for e.g., specific subjects or assessments which do not have implications for the protocol will be filed as notes to file at the Contract Research Organization (CRO).

12.3 Protocol Deviations

The trial must be conducted in accordance with the CTP. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances should be reported to Medicines and Healthcare Products Regulatory Agency (MHRA) as a serious breach of GCP and the CTP.

Protocol waivers are not acceptable.

Deviations from the protocol will be recorded in the source workbook as noted by the clinical staff. If necessary, the sponsor will be informed of the deviation.

Any protocol deviations assessed as major will be discussed with the sponsor in order to determine if the withdrawal criteria have been met.

12.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, ICH-GCP Guidelines, EU-GCP directives and the applicable local/national regulatory requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

12.5 Subject Participation Information Sheet and Informed Consent (PIS-ICF)

Prior to entry in the trial, the investigator or a person designated by the investigator must explain to potential subjects the trial and the implications of participation.

The EC should have given its favourable opinion on the blank PIS-ICF. The subject will receive a PIS together with the ICF. The document should always be provided in the subject's native language. The subject will be given sufficient time to read the PIS-ICF and to ask additional questions. After this explanation and before entry in the trial, consent should be appropriately recorded by means of the subject's personally dated signature. The ICF must also be signed and dated by the investigator or the member of the trial team who conducted the informed consent discussion with the subject. After having obtained the consent, a copy of the signed and dated ICF must be given to the subject.

Any information relevant to the subject's willingness to participate in the trial will be provided to the subject in a timely manner by means of an updated PIS-ICF. This amended ICF will be signed by the subject and the investigator or the member of the trial team who conducted the informed consent discussion with the subject, to document the willingness of the subject to continue with the trial.

This signed and dated amended version will be filed together with the initial signed and dated ICF.

12.6 Safety Reporting to Ethics Committees and Competent Authorities

12.6.1 Events Requiring Expedited Reporting

SUSARs are subject to expedited reporting to the MHRA, European Medicines Agency (EMA) and EC.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an investigational product or that would be sufficient to consider changes in the investigational product administration or in the overall conduct of the trial, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- SAEs that occur after the subject has completed the clinical trial where the sponsor considers them to be a SUSAR
- new events related to the conduct of the trial or the development of investigational products and likely to affect the safety of the subjects, such as:
  - an SAE which could be associated with the trial procedures and which could modify the conduct of the trial
  - a major safety finding from a newly completed animal study (such as carcinogenicity)
  - any anticipated end or temporary halt of a trial for safety reasons and conducted with the same investigational products in another country by the same sponsor

12.6.2 Urgent Safety Measures

If Quotient Sciences or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of subjects participating in a clinical study
- A serious risk or potentially serious risk to human health
- An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the trial or that pose a risk to trial subjects.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

Quotient Sciences will take responsibility for informing appropriate CAs, and the EC.

12.6.3 Reporting

Reporting Serious Adverse Events

The investigator is required to notify the trial sponsor and pharmacovigilance provider within 24 hours of becoming aware of the occurrence of an SAE or serious adverse reaction. A copy of the written report of the event should promptly be sent to the trial sponsor for information purposes, in accordance with ICH guidelines for GCP.

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

Expedited Reporting of Events

It is the responsibility of the sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

Fatal or life-threatening SUSARs

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. This responsibility may be delegated to the pharmacovigilance provider.

The investigator is required to notify the EC of any SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

Any additional relevant information should be sent within 8 days of the report.

Other SUSARs

It is the responsibility of the sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. This responsibility may be delegated to the pharmacovigilance provider.

The investigator is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

Any additional relevant information should be sent within 8 days of the report.

Reporting of Urgent Safety Issues

Quotient Sciences is required to inform the appropriate CAs and the EC within 3 calendar days of the urgent safety issue.

12.7 Serious Breaches

It is the responsibility of the sponsor to notify the licensing authority of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the trial or the scientific value of the trial.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

12.8 Finances and Insurance

12.8.1 Indemnification

The sponsor undertakes to indemnify and hold harmless the investigator and the trial-site personnel from any claim, demand or cost arising from the activities to be carried out in compliance with the protocol.

12.8.2 Insurance

Every subject is insured against damage to health which might occur during the conduct of the trial and the material damages which might occur in connection thereto.

The subject insurance is taken out by the sponsor. A copy of the insurance certificate has to be available at the trial site.

13. INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

An up-to-date version of the contact details of sponsor, laboratories and other third parties will be available in the ISF and TMF.

14. REPORTING AND PUBLICATION

14.1 Reporting

The results of the trial will be reported in a CTR according to ICH standard and Venn template or a summary of the CTR. The final CTR or a summary of the CTR will be provided to all investigators having contributed subjects to the trial, to the applicable CAs and EC if required by the applicable regulatory requirements.

14.2 Publication

The investigator has no right to publish the results of this trial, without prior written consent of the sponsor. Sponsor and investigator will make their best efforts to reach an agreement on the issue of conditions of the publication of the trial results. In case of repeated disagreement, the sponsor shall be the sole party to decide under what conditions and release period the results of this trial should be published.

The sponsor undertakes that, prior to publication of any information, article, paper, report or other material concerning any trial results, a copy of such publication will be submitted to the investigator who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendments are reasonable, the sponsor shall be obliged to incorporate prior to such publication.

15. REFERENCES

1. BDM-2 Investigator's Brochure, Edition 1.0, December 2017.
2. Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920; 7: 353–370.
3. Bichet N. BDM-2: Oral Dose Range Finding Toxicity Study in dogs (3 day or 7-day escalating Dose Phase followed by a 8-day or 13-day fixed Dose Phase). Covance Laboratory SAS, Porcheville, France. Study number 8306-151. December 2015
4. Bichet N. BDM-2: Oral Dose Range Finding Toxicity Study in mice (3-day escalating Dose Phase followed by a 7-day fixed Dose Phase). Covance Laboratory SAS, Porcheville, France. Study number 8306-152. December 2015.
5. EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Volume 4, Annex 13, Investigational Medicinal Products: July 31, 2010.
6. Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. Acta Med Scand 1920; 53: 469–486.
7. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007); http://medicine.iupui.edu/clinpharm/ddis/main-table/).
8. Noy D. BDM-2: Effects on Cardiovascular System in the Conscious Dog using Radiotelemetry Following Oral Administration. Covance Laboratories Ltd, Harrogate, UK. Study number 8306243. November 2017.
9. Noy D. BDM-2: Effects on General Activity, Behaviour and Body Temperature in the Mouse Following Oral Administration. Covance Laboratories Ltd, Harrogate, UK. Study number 8306241. January 2018.
10. Noy D. BDM-2: Measurement of Respiratory Parameters in the Freely Moving Conscious Mouse Using Whole Body Plethysmography. Covance Laboratories Ltd, Harrogate, UK. Study number 8306242. October 2017.
11. Thiollier T. BDM-2: 14 Day Oral (Gavage) Twice Daily Administration Toxicity Study in the Dog Followed by a 2 Week Recovery Period. Covance Laboratories Ltd, Harrogate, UK. Study number 8306251. December 2017.
12. Thiollier T. BDM-2: 14 Day Oral (Gavage) Twice Daily Administration Toxicity Study in the Mouse Followed by a 2 Week Recovery Period. Covance Laboratories Ltd, Harrogate, UK. Study number 8306250. December 2017.

16. ADDENDA

16.1 Addendum 1: FURTHER GUIDANCE ON THE ASSESSMENT OF CAUSALITY

The following factors should be considered when deciding if there is a “reasonable possibility” that an adverse event (AE) may have been caused by the investigational product.

- **Time course of events and exposure to investigational product**. Has the subject actually received the investigational product? Did the AE occur in a reasonable temporal relationship to the administration of investigational product?
- **Consistency with known drug profile**. Was the AE consistent with the previous knowledge of the investigational product (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- **Dechallenge experience**. Did the AE resolve or improve on stopping or reducing the dose of the investigational product?
- **No alternative cause**. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- **Rechallenge experience**. Did the AE reoccur if the investigational product was reintroduced after having been stopped?

A “reasonable possibility” could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a “reasonable possibility” of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Ambiguous cases should be considered as being a “reasonable possibility” of a causal relationship unless further evidence becomes available to refute this.

17. SIGNATURE PAGES

SIGNATURE PAGE

Sponsor:

This clinical trial protocol has been reviewed and approved by the representative of the sponsor in order to ensure compliance with ICH-GCP guidelines.

Name: Dr. R. M. Miller
Medical Expert of HIVIH

Affiliation: Artemida Pharma Ltd., Hertfordshire, United Kingdom

1st MAY 2018

Signature and Date:

SIGNATURE PAGE

Contract Research Organization (CRO):

This clinical trial will be performed in compliance with ICH-GCP guidelines, including the archiving of essential documents.

Name: K. Mihara
Director Clinical Development

Affiliation: Venn Life Sciences, Breda, the Netherlands

Signature and Date:

30-APR-2018

SIGNATURE PAGE

Principal Investigator:

I have read all pages of this clinical trial protocol for which HIVIH is the Sponsor. I agree to conduct the trial as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the trial in accordance with ICH-GCP guidelines. I will also ensure that investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH-GCP guidelines to enable them to work in accordance with the provisions of these documents.

Name: Dr. S. Sidhu

Affiliation: Quotient Sciences, Nottinghamshire, United Kingdom

Signature and Date: Sharan 01 MAY 2018