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Statistical Analysis Plan

Version/Date	V1 / 13 SEP 2018
Title:	A single ascending dose trial investigating the safety, tolerability and pharmacokinetics of orally administered BDM-2 in healthy male subjects.
Project Number:	KNS11157.04 2017-004329-34 (EudraCT nr) QCL118184 (Site project nr)
Drug Name:	BDM-2
Indication:	the treatment of human immunodeficiency virus (HIV) infections
Drug Development Phase:	I
CRO:	Venn Life Sciences ED BV Lage Mosten 29 4822 NK Breda The Netherlands
Sponsor:	HIVIH 102, Avenue Gaston Roussel 93230 Romainville France
Principal Investigator:	Dr. Sharan Sidhu, MBChB BAO, MRCS, MFPM Quotient Sciences Trent House, Mere Way, Ruddington Fields Business Park, Ruddington, Nottinghamshire, NG11 6JS, United Kingdom

For Approval:

	Statistician	Clinical Consultant	Director Clinical Development	Sponsor representative
Company	Venn Life Sciences CRS	Venn Life Sciences ED BV	Venn Life Sciences ED BV	HIVIH
Name	Alice Tourneroche	Marieke van den Dobbelsteen *	Katsuhiro Mihara	Robert Miller
Signature				
Date	14 SEP 2018	17-Sep-2018	17-Sep-2018	14th Sep 2018

* Signed by K. Mihara in the absence of M. van den Dobbelsteen

Table of contents

1. LIST OF ABBREVIATIONS AND DEFINTIONS

1.1 Abbreviations

Abbreviation	Description of abbreviation
ADR	Adverse drug reaction
AE	Adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body mass index
CRO	Contract Research Organization
CTR	Clinical trial report
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
FIH	First-in-human
HIV(-AB 1+2)	Human immunodeficiency virus (antibodies 1+2)
ICF	Informed consent form
ICH	International Council for Harmonization
ISF	Investigator site file
MedDRA	Medical Dictionary for Regulatory Activities
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
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SOP	Standard Operating Procedure

TMF	Trial master file
ULN	Upper limit of the normal range

1.2 Definitions

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.

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).

Serious Adverse Drug 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.

2. STUDY INFORMATION

This Statistical Analysis Plan is based on the Clinical Trial Protocol, version 3.0 25-APR-2018 of trial[1].

2.1 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 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 washout period starts directly after intake of the drug. Therefore, the day of trial medication intake (Day 1) is defined as 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.

In table 1 the planned design of the trial is presented.

Table 1: Planned trial design

		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.

2.2 Trial population

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

A total up to 16 subjects have to complete the trial.

2.3 Treatment overview

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 2 in Section 2.3.

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 2nd to 7th 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 7th 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.

Table 2: 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).

2.4 Study 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.

2.5 Flowchart

Table 3: 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.

2.6 Determination of sample size

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.

2.7 Deviations from trial protocol

There are no deviations from the statistical part of the clinical protocol. Any future changes prior to database lock have to be described in an amendment of the SAP. Any changes or additions after database lock will be documented on a form: Addendum to SAP and described in the Clinical Study Report.

2.8 Blinding

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 analyzed 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.

2.9 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 4.

Table 4: 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.

2.10 Withdrawal and replacement of individual subjects

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.

2.10.1 Criteria for withdrawal

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 QTcinterval 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.

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

2.10.2 Replacement of individual subjects after withdrawal

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.

2.10.3 Follow-up of subjects withdrawn from treatment

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

For all subjects who are prematurely withdrawn from treatment, the reason will be documented carefully. For all subjects who were withdrawn after randomization, but before treatment with study medication, the reason why will be documented.

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

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.

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

3. ASSESSMENTS

3.1 Demographics

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, hematology and urinalysis
- Concomitant medication and AEs

3.2 Safety variables

Safety during study will be assessed by evaluation of the following variables as per protocol:

3.2.1 Adverse Events

Any adverse events (AEs) observed, mentioned upon general questioning or spontaneously reported will be documented accordingly.

3.2.2 Clinical Laboratory

- Haematology: 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.
- Biochemistry: 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).
- 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.

- Serology: Markers of viral hepatitis A, B and C (HAV IgM, HBsAg, anti-HCV-AB); HIV infection (anti-HIV-AB 1+2).
- Coagulation: Prothrombin time (PT) and activated partial thromboplastin time (aPTT).

3.2.3 12-Lead ECG

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 tmax 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**Error! Reference source not found.**) and Fridericia (QTcF**Error! Reference source not found.**) formulae. ECGs will be assessed by the investigator and any abnormalities will be recorded in the eCRF

3.2.4 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.

3.2.5 Respiratory Rate

Respiratory rate measurements will be done at time points as indicated in the flow chart.

3.2.6 Physical Examination

A complete physical examination (general appearance, head/neck/thyroid, ears/nose/throat, cardiovascular system, respiratory system, lymph nodes, abdomen, dermatological, musculoskeletal, neurological/CNS, ocular/ophthalmology, other) 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 **Error! Reference source not found.**).

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

4. ANALYSIS POPULATIONS

The final selection of subjects for the analysis populations will be discussed in the Data Review Meeting (DRM). Reasons for exclusion of subjects from analysis sets will be documented in the DRM minutes.

4.1 Analysis set

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 evaluable 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 are 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.

5. STATISTICAL METHODS AND GENERAL STATISTICAL CONSIDERATIONS

All data included in the database will be listed. All listings will be sorted by subject number, dose group, day and time point if applicable. Placebo subjects will be pooled. Listings of AEs and concomitant medication will be listed by dose and subject number in chronologic order.

Descriptive statistics for continuous variables will be mean (Mean), standard deviation (SD), median (Median), minimum (Min) and maximum (Max). The number of decimal places for the mean and the median and standard deviation will be the number of decimals in the source data plus 1. For categorical variables the absolute (N) and relative frequency (%) will be tabulated. Number of available values and number of missing values will be also presented.

All tables will be presented by dose group (and pooled placebo group) except for 14.1 Demographic Data which will be represented by Cohort only.

All programming of tables and listings will be performed using statistical software package SAS® version 9.4[2].

5.1 Baseline assessments

Baseline is defined as the last non-missing measurement before dosing. If all pre-dose measurements are missing then baseline will be considered as missing, and no changes from baseline and no percentage reduction from baseline will be computed.

5.2 Data handling

5.2.1 Values below detection limit

Handling of plasma concentrations below the quantification limit for PK analysis is described in the PK analysis plan.

5.2.2 Outliers

All available data points will be included in analysis unless a clear reason is available to exclude data. This will be defined in the Blinded Data Review Meeting.

5.2.3 Missing data

Missing data will not be imputed.

6. DATA ANALYSIS AND REPORTING

Venn Life Sciences will produce data listings, descriptive tables and figures related to the demographics; safety and PK analysis. All data that appear in the study database will be presented; these include data collected on the Case Report Form (CRF), laboratory data, MedDRA coded medical history and AEs and WHO Drug Dictionary coded concomitant medication and medication history.

AEs and medical histories: Medical Dictionary for Regulatory Activities (MedDRA) v21.0 (or most recent version) using the following:

- Lower Level Term (code)
- Preferred Term (code)
- System Organ Class (code)

Medications: World Health Organisation Drug Dictionary Enhanced (WHO DDE) Drug Reference List (2017 version or more recent version) using the following Anatomical Therapeutic Chemical (ATC) Classification codes:

- Drug name
- Preferred name (code)
- Therapeutic Subgroup (ATC 2nd level code)
- Chemical Subgroup (ATC 4th level code)

Coding will be performed by data management of Quotient Sciences, Edinburgh, UK.

All planned tables, listings and figures planned for safety analyses for this study, including examples, will be described in more detail in APPENDIX A: PLANNED TABLES LISTINGS AND FIGURES. The PK analyses plan will describe all tables and figures planned for the PK analyses.

If during the analysis, it appears that additional analyses would provide more insight in the data; these will be performed after confirmation of the sponsor and documented according to Section **Error! Reference source not found.**.

6.1 Study population

6.1.1 Disposition

A summary overview (number and percentage) will be given of subjects randomized, subjects with at least 1 dose of drug taken will be provided, subjects discontinued/completed the study as well as well as the reasons for all post-randomization discontinuations, grouped by dose group. Dose group will be split in active and passive placebo.

6.1.2 Protocol deviations

Protocol deviations as defined in the data management plan of 09 May 2018 observed during the clinical phase or by subsequent monitoring will be recorded on a protocol deviation form within the workbook and entered into the subject's eCRF and will be presented in a listing, if applicable. The protocol deviations will also be described in the clinical study report.

6.1.3 Demographic data and initial characteristics

A summary table will present the descriptive statistics of demographics and initial subject characteristics (age, race/ethnicity, drinking (alcohol and caffeine) and smoking habits, height, body weight, BMI, physical examination, drug, alcohol and urine cotinine screen, medical and surgical history at screening).

Medical history at screening, MedDRA v21.0 (or most recent version) coded by Quotient Sciences, will be listed by subject number and by system in chronologic order. A summary table will show numbers and percentages of subjects who have any medical history by System Organ Class (SOC) and preferred term.

All results performed at screening will be listed and summarized.

6.1.4 Prior and Concomitant medication

All medication used prior to the study and concomitant medication taken between dosing and Follow Up visit will be listed. The number and percentage of subjects taking concomitant medication will be summarized by WHO drug name and dose group.

6.2 Efficacy analysis

Not applicable.

6.3 Exposure and compliance

Administration times, amount of study drug and meal times will be listed. Exposure to the study drug will be calculated as the cumulative amount during study. Exposure and duration of exposure will be tabulated. In case subjects participate in two dose steps, this will be taken into account in the cumulative exposure.

6.4 Safety analysis

6.4.1 Adverse events

Safety and tolerability will be assessed by incidence of AEs, including clinically significant abnormal laboratory values which need to be reported as an AE. All AEs will be MedDRA coded (by Quotient Sciences with version v21.0 (or most recent version) of MedDRA) and listed by subject number and AE number.

Deaths, other serious AEs and AEs leading to early discontinuation will be listed separately (if applicable).

The number and percentage of subjects with AEs per SOC and preferred term will be tabulated by dose group and pooled placebo group, and by severity and relationship to study drug.

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.

6.4.2 Clinical laboratory variables

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.

6.4.3 Other clinical laboratory variables

At screening, blood was additionally analyzed for presence of Hepatitis A, B and C serology and anti-HIV 1/2.

Urine was screened for drugs of abuse (barbiturates, amphetamines/ methamphetamines, opiates, methadone, benzodiazepines, cannabinoids, cocaine metabolites) at screening and at baseline. An alcohol breath test was performed at screening, at baseline, and at screening and at Day -1 of each dosing period.

6.4.4 ECG measurements

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.

Additional for QTcF and QTcB values per dose and per time point:

- Frequency tables for QTcF and QTcB values:
    - >450 mSec
    - >480 mSec
    - >500 mSec

- Frequency tables of change from baseline for QTcF and QTcB values:
    - <30 mSec increase from baseline
    - 30 – 60 mSec increase from baseline
    - >60 mSec increase from baseline

6.4.5 Vital signs

Baseline values and change from baseline (predose) in SBP, DBP, pulse rate, tympanic body temperature and respiratory 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. 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 for all vital signs and changes from baseline will be presented.

6.4.6 Clinical Assessments

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

7. AMENDMENT PROCEDURES

Deviations from planned analysis prior to database lock have to be described in an amendment of the SAP. Additional analysis and generated tables and plots generated after database lock will be documented on a form: Addendum to SAP.

SAP, amendments and addenda will be effective at the time all signatures have been collected. Amendments and addenda will be attached to the original of the analysis plan.

8. REPORTING

No formal statistical report will be written. Results will be described in the sections 10-12 of the Clinical Study Report. Tables and Figures will be depicted in Section 14 of the Clinical Study Report, individual Listings will be presented in Appendix 16.2 to the Clinical Study Report

9. QUALITY

9.1 Quality assurance and review

The statistician will be responsible for the performance of all planned and additional statistical analysis. Analysis and generation of tables, listings and figures might also be assigned to qualified employees.

The SAS codes and output will be reviewed by experienced SAS programmers, while the results of statistical endpoints will be reviewed by an independent statistician.

All applicable data will be stored and retrievable according to standardized procedures.

All data generated during statistical process will be saved electronically.

9.2 Contents of the statistical study file

The statistical study file will include at least:

- Statistical analysis plan and, if applicable, amendments and/or addenda;
- Programming folder (including database, analysis dataset programs and analysis programs for Tables, Listings and figures)
- Tables, Listings and Figures (TLFs) (Corresponding to section 14 & section 16.2 of the Clinical Study Report);

9.3 Storage

The statistical study file will be merged with the Trial Master File at the end of the study. The complete Trial Maser File will be transferred to the Sponsor after the finalization of the CSR.

REFERENCES

1. Clinical Study Protocol, Version 3, dated 25 Apr 2018 of trial BDM-2-C001: A single ascending dose trial investigating the safety, tolerability and pharmacokinetics of orally administered BDM-2 in healthy male subjects.

2. SAS version 9.4
   SAS Institute Inc.,
   Cary, NC, USA.

10. PLANNED TABLES, LISTINGS AND FIGURES

This section gives a more detailed description of the safety analysis and representation all planned tables, listings and figures (TLF's) in the study.

10.1 Contents of tables

TABLES AND FIGURES (Section 14 of the Clinical Study Report)

14.1 DEMOGRAPHIC DATA

Table 14.1.01	Subject disposition by cohort
Table 14.1.02	Study duration and premature discontinuation from study by cohort
Table 14.1.03	Demographic data by cohort
Table 14.1.04	Medical and surgical history at screening
Table 14.1.05	Medication history at screening
Table 14.1.06	Physical examination at screening, during the study and follow up by cohort
Table 14.1.07	Height, body weight and BMI at screening and during the study by cohort
Table 14.1.08	Drug, alcohol and cotinine screen at screening and baseline by cohort
Table 14.1.09	Virology measurements at screening by cohort

14.2 PHARMACOKINETIC DATA

Pharmacokinetic tables will be described in the PK analysis plan.

14.3 SAFETY DATA

14.3.1 TABLES OF ADVERSE EVENTS

Table 14.3.01.01	Treatment emergent adverse events – Overview by dose
Table 14.3.01.02	Treatment emergent adverse events – Incidence by SOC and preferred term by dose
Table 14.3.01.03	Treatment emergent adverse events by relatedness by dose
Table 14.3.01.04	Treatment emergent adverse events by severity by dose
Table 14.3.01.05	At least possible related adverse events by dose

14.3.2 LISTINGS OF DEATHS, OTHER SERIOUS AND SIGNIFICANT ADVERSE EVENTS

Table 14.3.02.01	Listing of deaths

Table 14.3.02.02 Listing of non-lethal serious adverse events

14.3.3 NARRATIVES OF DEATHS, OTHER SERIOUS AND SIGNIFICANT ADVERSE EVENTS

Table 14.3.03.01 Narratives of deaths, other serious and significant adverse events

14.3.4 LABORATORY VALUES

Table 14.3.04.01 Hematology measurements by dose by timepoint – Absolute values

Table 14.3.04.02 Hematology measurements by dose by timepoint – Change from baseline

Table 14.3.04.03 Hematology measurements by dose by timepoint – Abnormalities

Table 14.3.04.04 Biochemistry measurements by dose by timepoint – Absolute values

Table 14.3.04.05 Biochemistry measurements by dose by timepoint – Change from baseline

Table 14.3.04.06 Biochemistry measurements by dose by timepoint – Abnormalities

Table 14.3.04.07 Urinalysis measurements by dose by timepoint

Table 14.3.04.08 Coagulation measurements by dose by timepoint – Absolute values

Table 14.3.04.09 Coagulation measurements by dose by timepoint – Change from baseline

Table 14.3.04.10 Coagulation measurements by dose by timepoint – Abnormalities

14.3.5 ECG MEASUREMENTS

Table 14.3.05.01 QTcB by dose by timepoint – Absolute values

Table 14.3.05.02 QTcB by dose by timepoint – Change from baseline

Table 14.3.05.03 QTcF by dose by timepoint – Absolute values

Table 14.3.05.04 QTcF by dose by timepoint – Change from baseline

Table 14.3.05.05 QT by dose by timepoint – Absolute values

Table 14.3.05.06 QT by dose by timepoint – Change from baseline

Table 14.3.05.07 ECG Mean Ventricular Rate by dose by timepoint – Absolute values

Table 14.3.05.08 ECG Mean Ventricular Rate by dose by timepoint – Change from baseline

Table 14.3.05.09 PR Interval by dose by timepoint – Absolute values

Table 14.3.05.10 PR Interval by dose by timepoint – Change from baseline

Table 14.3.05.11 QRS duration by dose by timepoint – Absolute values

Table 14.3.05.12 QRS duration by dose by timepoint – Change from baseline

Table 14.3.05.13 RR Interval by dose by timepoint – Absolute values

Table 14.3.05.14 RR Interval by dose by timepoint – Change from baseline

14.3.6 VITAL SIGNS

Table 14.3.06.01 Systolic blood pressure by dose by timepoint – Absolute values

Table 14.3.06.02 Systolic blood pressure by dose by timepoint – Change from baseline

Table 14.3.06.03 Diastolic blood pressure by dose by timepoint – Absolute values

Table 14.3.06.04 Diastolic blood pressure by dose by timepoint – Change from baseline

Table 14.3.06.05 Pulse rate by dose by timepoint – Absolute values

Table 14.3.06.06 Pulse rate by dose by timepoint – Change from baseline

Table 14.3.06.07 Respiratory rate by dose by timepoint – Absolute values

Table 14.3.06.08 Respiratory rate by dose by timepoint – Change from baseline

Table 14.3.06.09 Tympanic body temperature by dose by timepoint – Absolute values

Table 14.3.06.10 Tympanic body temperature by dose by timepoint – Change from baseline

14.3.7 OTHER SAFETY PARAMETERS

Table 14.3.07.01 Concomitant medication used during study by dose

10.2 Contents of listings

16.2.1 DISCONTINUED SUBJECTS

Listing 16.2.01.01 Discontinued patients

16.2.2 PROTOCOL DEVIATIONS

Listing 16.2.02.01 Protocol deviations

16.2.3 SUBJECTS EXCLUDED FROM THE EFFICACY ANALYSIS

NA

16.2.4 DEMOGRAPHIC DATA

Listing 16.2.04.01 Demographic characteristics and informed consent

Listing 16.2.04.02 Medical and surgical history

Listing 16.2.04.03 Physical examination

Listing 16.2.04.04 Height, body weight and BMI

Listing 16.2.04.05 Drug, alcohol and cotinine screen

Listing 16.2.04.06 Inclusion and exclusion criteria

Listing 16.2.04.07 Eligibility check

Listing 16.2.04.08 Randomisation

16.2.5 COMPLIANCE AND/OR DRUG CONCENTRATION DATA

Listing 16.2.05.01 Visit dates

Listing 16.2.05.02 Drug allocation by dose

Listing 16.2.05.03 Meal times

Listing 16.2.05.04 PK blood sampling times

Listing 16.2.05.05 Pharmacogenetics sampling times

16.2.6 INDIVIDUAL EFFICACY RESPONSE DATA

NA

16.2.7 ADVERSE EVENTS LISTINGS

Listing 16.2.07.01 Adverse events – Details

Listing 16.2.07.02 Adverse events – Severity, relatedness and actions taken

Listing 16.2.07.03 Adverse events – Coding

16.2.8 LISTINGS OF INDIVIDUAL LABORATORY MEASUREMENTS BY SUBJECT

Listing 16.2.08.01 Laboratory reference ranges

Listing 16.2.08.02 Haematology measurements – results

Listing 16.2.08.03 Haematology measurements – evaluation

Listing 16.2.08.04 Biochemistry measurements – results

Listing 16.2.08.05 Biochemistry measurements – evaluation

Listing 16.2.08.06 Serology measurements – results

Listing 16.2.08.07 Serology measurements – evaluation

Listing 16.2.08.08 Urinalysis measurements – results

Listing 16.2.08.09 Urinalysis measurements – evaluation

Listing 16.2.08.10 Microscopic measurements – results

Listing 16.2.08.11 Microscopic measurements – evaluation

Listing 16.2.08.12 Coagulation measurements – results

Listing 16.2.08.13 Coagulation measurements – evaluation

16.2.9 ECG MEASURENTS

Listing 16.2.09.01 ECG measurements

16.2.10 VITAL SIGNS

Listing 16.2.10.01 Vital signs, including respiratory rate and tympanic body temperature

16.2.11 OTHER SAFETY PARAMETERS

Listing 16.2.11.01 Concomitant medication prior and during study

16.2.12 OTHER SUBJECT DATA

Listing 16.2.12.01 End of study information