Clinical Study Protocol

A Two-Part Controlled Clinical Study to Evaluate Safety, Tolerability, Response, Pharmacokinetics and Pharmacodynamics of Single and Multiple Oral Doses of GM-1020 in Patients with Major Depressive Disorder

Investigational Medicinal Product: GM-1020

Sponsor Reference: GLG-100X
MAC Number: MAC 169
EudraCT Number: 2023-000724-11

Protocol Version: Final 9.0
Protocol Date: 04 February 2025
Clinical Development Phase: IIa

Sponsor: Gilgamesh Pharmaceuticals
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[redacted]

SPONSOR SIGNATURE PAGE

For and on behalf of the Study Sponsor:

Signature: Date:

[redacted]

COORDINATING INVESTIGATOR SIGNATURE PAGE

The undersigned confirm that the following Protocol has been agreed and accepted and that the Coordinating Investigator agrees to conduct the study in compliance with the approved Protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (SOPs) and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical study without the prior written consent of the Sponsor.

I also confirm that I will, when required by the Sponsor, make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be provided; and that any discrepancies and serious breaches of GCP from the study as planned in this Protocol will be explained.

Coordinating Investigator:

Signature: Date:

[redacted]

INVESTIGATOR SIGNATURE PAGE

The undersigned confirm that the following Protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the study in compliance with the approved Protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs and other regulatory requirements as amended.

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Principal Investigator:

Signature: Date:

[redacted]

SUMMARY OF CHANGES: CLINICAL STUDY PROTOCOL AMENDMENT 8 (VERSION 9.0)

This version of the Protocol will supersede the previous version (Version 8.0, dated 06 January 2025).

The rationale for this amendment is to include an interim analysis of complete Part A data and available Part B data following the completion of Part A. It has also been clarified that the study plans to randomise up to 49 patients.

The changes to the Protocol are detailed below:

Section	Description of Change
Synopsis (Page 16) – Study Design	**Previous text:** The study plans to randomise 49 patients with a diagnosis of MDD. **Amended text:** The study plans to randomise up to 49 patients with a diagnosis of MDD.
Synopsis (Page 16) – Study Design	**Previous text:** In Part A, 42 patients are planned to be randomised into two cohorts (minimum 21 patients per cohort). **Amended text:** In Part A, up to 4~~2~~9 patients are planned to be randomised into two cohorts (minimum 21 patients per cohort).
Section 3 (Page 36) – Study Design	**Previous text:** The study plans to randomise 49 patients with a diagnosis of MDD. **Amended text:** The study plans to randomise up to 49 patients with a diagnosis of MDD.
Section 3 (Page 36) – Study Design	**Previous text:** In Part A, 49 patients are planned to be randomised into two cohorts (minimum 21 patients per cohort). **Amended text:** In Part A, up to 49 patients are planned to be randomised into two cohorts (minimum 21 patients per cohort).
Section 5.7 (Page 43) – Blinding	**Previous text:** Only the Pharmacy staff involved in handling the study drug (and staff involved in performing a pre-database lock unblinding delivery, if required) will be unblinded during the study and will have access to the randomisation list. **Amended text:** Only the Pharmacy staff involved in handling the study drug ~~(~~and staff involved in performing ~~a pre-database lock unblinding delivery, if required)~~ the interim analysis will be unblinded during the study and will have access to the randomisation list.
Section 11.6.5 (Page 69) – Interim Analysis	**Previous text:** **11.6.5. Ongoing Review of Data** Quality-controlled safety, tolerability, plasma PK, PD (CADSS, 5D-ASC, DEQ and PharmacoEEG) and efficacy endpoints will be analysed using the methods described above for all patients following completion of Part A; this will not impact patients' progression to Part B of the study. The safety and tolerability data to be analysed will include, at a minimum, AEs, physical examinations, 12-lead ECGs, vital signs, C-SSRS, MOAA/S and clinical laboratory evaluation results, using the appropriate methods described previously.

Section	Description of Change
	Amended text: **11.6.5. ~~Ongoing Review of Data~~Interim Analysis** ~~Quality controlled~~ Following the completion of Part A for all patients, an interim analysis of select safety, tolerability, plasma PK, PD ~~(CADSS, 5D-ASC, DEQ and PharmacoEEG)~~ and efficacy ~~endpoints~~ tables, figures and listings (TFLs) will be ~~analysed~~ performed for all patients using complete Part A data and available Part B data, using the statistical methods described above. ~~for all patients following completion of Part A; t~~This interim analysis will not impact patients' progression to Part B of the study. ~~The safety and tolerability data to be analysed will include, at a minimum, AEs, physical examinations, 12 lead ECGs, vital signs, C-SSRS, MOAA/S and clinical laboratory evaluation results, using the appropriate methods described previously.~~ Further information (including the specification of TFLs to be included in the interim analysis) will be described in the SAP.

Strikethrough text indicates deletions. Underlined text indicates additions.

KEY STUDY CONTACTS

Sponsor	Gilgamesh Pharmaceuticals 113 University Place Suite 1019 New York NY 10003 USA
Coordinating Investigator	[redacted]
Contract Research Organisation	MAC Clinical Research Kaman Court 1 Faraday Way Blackpool Lancashire FY2 0JH United Kingdom

SYNOPSIS

Study Title: A Two-Part Controlled Clinical Study to Evaluate Safety, Tolerability, Response, Pharmacokinetics and Pharmacodynamics of Single and Multiple Oral Doses of GM-1020 in Patients with Major Depressive Disorder

Investigational Medicinal Product: GM-1020

Clinical Phase: IIa

Objectives:

Part A

The primary objective of Part A of the study is to characterise the safety and tolerability of single oral doses of GM-1020 in patients with major depressive disorder (MDD).

The secondary objectives of Part A of the study are:

- To characterise the efficacy of a single oral dose of GM-1020 in MDD patients.
- To assess the plasma pharmacokinetics (PK) of single oral doses of GM-1020 [redacted] in MDD patients.
- To characterise the pharmacodynamics (PD) of single oral doses of GM-1020 in MDD patients.

Part B

The primary objective of Part B of the study is to characterise the safety and tolerability of multiple oral doses of GM-1020 in MDD patients.

The secondary objectives of Part B of the study are:

- To assess the plasma PK of multiple oral doses of GM-1020 [redacted] in MDD patients.
- To characterise the PD of multiple oral doses of GM-1020 in MDD patients.

The exploratory objective of Part B of the study is to characterise the efficacy of two dose levels of multiple oral doses of GM-1020 in MDD patients over a 2 week period.

Endpoints:

Part A

The primary endpoints of Part A of the study are the clinical safety data from adverse event (AE) reporting, 12-lead electrocardiogram (ECG), vital signs (supine blood pressure, heart rate, respiration rate, tympanic temperature), clinical laboratory evaluations (biochemistry, haematology and urinalysis), emergence of suicidal thoughts and ideations (Columbia-Suicide Severity Rating Scale [C-SSRS]) and sedation (Modified Observer's Assessment of Alertness/Sedation [MOAA/S] scale).

The secondary endpoints of Part A of the study are:

- The following efficacy assessments:
  - Structured Interview Guide for the Montgomery-Åsberg Depression Rating Scale (MADRS-SIGMA)
  - Clinical Global Impressions Scale – Improvement (CGI-I)
  - Clinical Global Impressions Scale – Severity (CGI-S)

- Plasma PK concentrations and parameters, including: area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC_{last}), AUC from zero to infinity (AUC_{inf}), the extrapolated area from AUC_{last} to AUC_{inf} as a % of the total AUC ($AUC_{inf(\%extrap)}$), maximum plasma concentration (C_{max}), metabolite to parent ratio of the AUC corrected by the molecular weight ratio of parent to metabolite (MPR), time to C_{max} (t_{max}), half-life ($t_{1/2}$) and lag-time (time delay between drug administration and first observed concentration above the lower limit of quantification [LLOQ] in plasma [t_{lag}]).

- The following PD assessments:
    - Neurophysiological/neuropsychological test battery:
        - PharmacoEEG (resting-state EEG [rsEEG], auditory steady-state response [ASSR])
        - Somno-Art (wearable device to evaluate sleep architecture)
    - Questionnaires:
        - Clinician-Administered Dissociative States Scale (CADSS)
        - 5-Dimensional Altered States of Consciousness Rating Scale (5D-ASC)
            - 11-Dimensional Altered States of Consciousness (11D-ASC) scoring also will be obtained from the answers to the 5D-ASC
        - Drug Effects Questionnaire (DEQ)
    - Patient Health Questionnaire-9 (PHQ-9)
    - Sheehan Disability Scale (SDS)
    - Continuous Passive Behavioural Assessment
    - Reward Functioning

Part B

The primary endpoints of Part B of the study are the clinical safety data from AE reporting, 12 lead ECG, vital signs (supine blood pressure, heart rate, respiration rate, tympanic temperature), clinical laboratory evaluations (biochemistry, haematology and urinalysis), emergence of suicidal thoughts and ideations (C-SSRS) and sedation (MOAA/S).

The secondary endpoints of Part B of the study are:

- Plasma PK concentrations and parameters, including: AUC_{last}, AUC_{inf}, $AUC_{inf(\%extrap)}$, C_{max}, MPR, t_{max}, $t_{1/2}$ and t_{lag}.

- The following PD assessments:
    - Neurophysiological/neuropsychological test battery:
        - PharmacoEEG (rsEEG, ASSR)
        - Somno-Art
    - Questionnaires:
        - CADSS
        - 5D-ASC
            - 11D-ASC (obtained from 5D-ASC answers)
        - DEQ
    - Face Emotion Recognition Task (FERT)
    - Reward Functioning
    - Continuous Passive Behavioural Assessment

The exploratory endpoints of Part B of the study are the following efficacy endpoints:

- MADRS-SIGMA
- CGI-I
- CGI-S
- PHQ-9
- SDS
- EuroQol 5 Dimension 5 Level (EQ-5D-5L) Quality of Life Scale

Study Design:

Part A of this study is a randomised, double-blind, placebo-controlled, 2-period, crossover study to assess a single oral dose level (140 mg) of GM-1020 in male and female patients with a diagnosis of MDD. Part B of the study is a randomised, double-blind extension phase to evaluate twice-weekly administration of two oral dose levels of GM-1020 for 2 weeks in male and female patients with a diagnosis of MDD.

The study plans to randomise up to 49 patients with a diagnosis of MDD. For the purposes of this Protocol, a randomised patient is defined as one who has been randomised in the study and received the first dose of study drug on Day 1. In the event of patient withdrawal or drop-out from the study (for non-safety reasons only), the Sponsor reserves the right to replace any randomised patient that receives the study treatment in either crossover period of Part A. Patients will take part in both Part A and Part B. In Part A, up to 49 patients are planned to be randomised into two cohorts (minimum 21 patients per cohort). Both cohorts will take part in two treatment periods, in which they will receive either a single dose of GM-1020 (140 mg) or a single dose of placebo in each treatment period. Overall, all patients will receive a single dose of 140 mg GM-1020 and a single dose of placebo in Part A of the study.

Patients will be required to attend the Clinical Research Unit (CRU) for a Screening visit up to 42 days prior to first dosing to ensure they meet the inclusion/exclusion criteria and are in good general health. A SAFER interview will also be conducted during the Screening period by an independent interviewer via telephone. Patients will attend a virtual visit 1 day prior to first dosing (Day -1) for the collection of baseline PD and efficacy assessments. Patients will attend the CRU in the morning of Day 1 for Treatment Period 1, in which they will receive a single oral dose of either 140 mg GM-1020 or placebo following collection of predose safety, PK and PD assessments. Randomisation (for both Part A and Part B) will take place prior to first dosing on Day 1. Patients will be randomised to one of four treatment sequences to assign both Part A treatment sequence (i.e., 140 mg GM-1020 → Placebo, or Placebo → 140 mg GM-1020) and Part B dose level (i.e., 140 mg GM-1020 or 210 mg GM-1020). Patients will remain in the CRU until completion of the postdose safety, PK and PD assessments (minimum of 8 hours postdose) and will be discharged from the CRU on Day 1 at the discretion of the Investigator.

A virtual post-treatment visit will be conducted on Day 2. During a 14-day (±1 day) washout period, patients will return to the CRU on Day 4 for an outpatient visit and will attend a virtual visit on Day 8 and Day 11. During this period, patients will be passively monitored with smartphone technology capable of inferring the trajectory toward relapse of depressive symptoms remotely.

Patients will attend a virtual visit 1 day prior to the second dosing (Day 14) for the collection of baseline PD and efficacy assessments. Following a washout period of 14 days (±1 day), patients will attend the CRU on Day 15 for Treatment Period 2 to receive a single oral dose of the alternative treatment (either 140 mg GM-1020 or placebo, whichever was not previously administered) following collection of predose safety, PK and PD assessments. As in Treatment Period 1, patients will remain in the CRU until completion of the postdose safety, PK and PD assessments (minimum of 8 hours postdose) and will be discharged from the CRU on Day 15 at the discretion of the Investigator. The assessments conducted in Treatment Period 1 and Treatment Period 2 will be the same.

A virtual post-treatment visit will be conducted on Day 16. During a second 14-day (±1 day) washout period, patients will return to the CRU on Day 18 for an outpatient visit and will attend a virtual visit on Day 22, Day 25 and Day 28. During this period, patients will be passively monitored with smartphone technology capable of inferring the trajectory toward relapse of depressive symptoms remotely.

Following the second washout period, patients will attend a Part A Follow-up visit on Day 29 (-1/+7 days). During this visit, patients will receive their first administration of one of two dose levels of GM-1020 (140 mg or 210 mg), which will be administered twice-weekly for a period of 2 weeks. This will be Part B of the study. The second dose level (210 mg), not administered in Part A of the study, has been chosen based on the safety, tolerability, PK and PD of GM-1020 in the Phase I single ascending dose (SAD) trial. Patients will be administered their first Part B dose during this visit (Day 29 [-1/+7 days]) and will remain in the CRU until completion of the postdose safety, PK and PD assessments (minimum of 8 hours postdose) before being discharged from the CRU, at the discretion of the Investigator.

Patients will return to the CRU for outpatient visits on Day 32 (±2 days), Day 36 (±2 days) and Day 39 (±2 days), during which they will be administered a dose of GM-1020, and will attend post-treatment visits on Day 30 (±2 days; virtual), Day 33 (±2 days; virtual), Day 37 (±2 days; virtual), Day 40 (±2 days; in-clinic) and Day 42 (±2 days; virtual). Part B dosing days (Day 29, Day 32, Day 36 and Day 39) have windows to aid scheduling of patients. The minimum interval required between doses is 48 hours, and the post-treatment visits (Day 30, Day 33, Day 37 and Day 40) must always occur the day after the respective dosing.

The Part B Follow-up visit on Day 67 (±2 days) will conclude the patients' participation in the study. The maximum duration of participation for each patient is expected to be approximately 16 weeks.

Treatment Duration:

Part A: 2 days (Day 1 and Day 15).
Part B: Twice-weekly for 2 weeks (Day 29, Day 32, Day 36 and Day 39).

Study Participants:

Generally healthy male and female participants with a diagnosis of recurrent MDD, aged between 18 to 65 years (inclusive), with a body mass index of 18.0 to 35.0 kg/m^2 (inclusive). Additionally, patients must meet the following criteria:

- Patient meets the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for recurrent MDD without psychotic features based on the Mini-International Neuropsychiatric Interview (MINI) at Screening.
- Patient currently has moderate to severe MDD as confirmed with a MADRS-SIGMA total score >22 and CGI-S score >3 at Screening and Day -1.
- Patient is either not currently taking antidepressants (and hasn't for at least 6 weeks prior to Screening) or is being treated with an antidepressant drug according to national guidelines during the current MDD episode.
    - If the patient is currently being treated with antidepressants, these have been prescribed at a stable dose and the dose has remained unchanged for at least 6 weeks prior to Screening.
- Changes in current drug treatment or psychological treatment for depression are not foreseen for the duration of the study.

Dose and Route of Administration:

In Part A of the study, patients will be administered a single oral dose of either 140 mg GM-1020 or placebo on Day 1. Following a washout period of 14 days (±1 day), patients will be administered a single oral dose of the alternative treatment (either 140 mg GM-1020 or placebo, whichever was not previously administered) on Day 15.

In Part B of the study, patients will be administered one of two dose levels of GM-1020 (140 mg or 210 mg) twice-weekly for a period of 2 weeks.

Criteria for Evaluation:

Safety will be assessed through AE reporting, vital signs, clinical laboratory evaluations data, physical examinations, 12-lead ECG, the C-SSRS and the MOAA/S. Blood samples will be collected for assessment of PK.

Pharmacodynamics will be assessed through the following assessments:

- Neurophysiological/neuropsychological test battery:
    - PharmacoEEG (rsEEG, ASSR)
    - Somno-Art
- Questionnaires:
    - CADSS
    - 5D-ASC
        - 11D-ASC (obtained from 5D-ASC answers)
    - DEQ
- PHQ-9 (Part A only)
- SDS (Part A only)
- FERT (Part B only)
- Reward Functioning
- Continuous Passive Behavioural Assessment

Efficacy will be assessed through the following assessments:

- MADRS-SIGMA
- CGI-I
- CGI-S
- PHQ-9 (Part B only)
- SDS (Part B only)
- EQ-5D-5L (Part B only)

Statistical Analysis:

All safety, tolerability, PK, PD and efficacy variables will be summarised using descriptive statistics. Descriptive statistics for categorical variables will include frequency and percentage. Descriptive statistics for continuous variables will include number of patients (n), mean, standard deviation, median, minimum and maximum. Summaries of change from baseline variables will include only patients who have both a baseline value and corresponding value at the timepoint of interest. Separate summaries will be presented for each part of the study.