Title Page

Protocol Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with Two Open Label (Single Dose) Food Effect Panels

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Compound Name: MK-7762

Trial Phase: 1

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Short Title: A Phase 1 SAD/MAD Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect of MK-7762

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Principal Investigator Signature Page

I have read the Protocol, appendices, and accessory materials related to Gates MRI-TBD09-101 entitled "A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with Two Open Label (Single Dose) Food Effect Panels", and agree to the following:

- To conduct this study as described by the Protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with:
    - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - current International Council for Harmonization Guideline for Good Clinical Practice (GCP)
    - applicable laws and regulations
- To obtain Institutional Review Board (IRB)/Independent Ethics Committees (IEC) approval of the Protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain study records of each participant and all data required by the Protocol.

_____ _____

Principal Investigator Signature Date

Name:

Title:

Affiliation:

City and Country:

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List of Abbreviations

Abbreviation	Description
ADR	Adverse drug reaction
AE	Adverse event
Ae%	Percent of drug excreted in urine in a dosing interval
AESI	Adverse event of special interest
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-}inf}$	Area under the concentration-time curve extrapolated to infinity
$AUC_{0\text{-}24}$	Area under the concentration-time curve over first 24h
AUC_{last}	Area under the concentration-time curve calculated to last quantifiable observed sample
AUC metabolite /AUC MK-7762	Metabolite-to-parent ratio of AUCs
AUC_{ss}	Area under the concentration-time curve at steady-state
AUC_{tau}	Area under the concentration-time curve over the dosing interval
AUC_{tau} / $AUC_{0\text{-}24}$	Accumulation ratio
BMI	Body mass index
BPaL	Bedaquiline, pretomanid and linezolid
BPNS	Brief Peripheral Neuropathy Screen
CFU	Colony forming unit
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Oral clearance
CLr	Renal clearance
C_{max}	Maximum plasma drug concentration
$C_{max, ss}$	Maximum plasma drug concentration at steady state
$C_{min, ss}$	Minimum plasma drug concentration at steady state
COVID-19	Coronavirus disease-19
C-QTc	Concentration-QTc
CRF	Case report form
CRO	Contract research organization
CTU	Clinical trial unit
CUE	Cumulative urinary excretion
DAIDS	Division of Acquired Immunodeficiency Disease
DBP	Diastolic blood pressure
DR	Drug-resistant
DS	Drug-susceptible
ECG	Electrocardiogram
EDC	Electronic data capture
EM	Exposure multiple
EP	European Pharmacopoeia
ET	Early termination
FDA	Food & Drug Administration
FE	Food effect
FIH	First-in-human

Abbreviation	Description
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus antibody
Hep B	Hepatitis B virus
Hep C	Hepatitis B virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HR	Heart rate
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonization
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IRB	Institutional review board
IxRS	Interactive voice response system/Interactive web response system
JP	Japanese Pharmacopoeia
LDL	Low-density lipoprotein
LLN	Lower limit of normal
MAD	Multiple ascending dose
MAO	Monoamine oxidase
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
MIC_{90}	90% growth inhibition
MPS	Mitochondrial protein synthesis
Mtb	Mycobacterium tuberculosis
NA	Not applicable
NOAEL	No-observed-adverse-effect level
PBO	Placebo
PCR	Polymerase chain reaction
PE	Physical examination
PGx	Pharmacogenetics
PK	Pharmacokinetics
PKPD	Pharmacokinetics/Pharmacodynamics
PPD	Pharmacovigilance service provider
QD	Once daily
QTcF	QT interval corrected by Fridericia's
SAD	Single ascending dose
SAE	Serious adverse events
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SD	Single dose
SoA	Schedule of activities
SRT	Safety review team
$t_{1/2}$	Terminal elimination half-life
TB	Tuberculosis

Abbreviation	Description
TBD	To be determined
TEAEs	Treatment-emergent adverse events
T_{max}	Time to maximum plasma drug concentration
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
V_d/F	Oral volume of distribution
WBC	White blood cell
WHO	World Health Organization
XDR	Extensively-drug resistant

1 PROTOCOL SUMMARY

1.1 Synopsis

1.1.1 Title

Protocol Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with Two Open Label (Single Dose) Food Effect Panels

Short Title: A Phase 1 SAD/MAD Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, Pharmacokinetics, and Food Effect of MK-7762

1.1.2 Rationale

Despite the steady progress made over the past two decades responding to and controlling the global tuberculosis (TB) pandemic, there remains an urgent need for the development of new potent anti-TB agents and combination regimens with low toxicity that are effective against both drug-susceptible (DS) and drug-resistant (DR) strains of *Mycobacterium tuberculosis* (Mtb) — a 'pan-TB regimen'.

This trial will evaluate the safety, tolerability, and pharmacokinetics (PK) in healthy adults of MK-7762, a new member of the oxazolidinone class of antibacterial agents, with the goal of identifying appropriate doses of MK-7762 with acceptable safety and PK profiles for future evaluation in TB patients.

Oxazolidinones kill Mtb through interruption of mycobacterial protein synthesis via the inhibition of translation. Linezolid (Zyvox®), the first drug licensed from the class, is an important component of treatment regimens for multi-drug resistant (MDR) and extensively-drug resistant (XDR) TB. An important limitation of linezolid is its associated toxicities of myelosuppression, peripheral sensory neuropathy, optic neuropathy, and lactic acidosis. These toxicities are believed to be mediated through the inhibition of human mitochondrial protein synthesis (MPS). Linezolid is not suitable for use in the much larger population of DS-TB patients as a result.

In preclinical studies, MK-7762 had similar efficacy to linezolid when assessed by reduction in colony forming units (CFUs) of TB in the lungs of mice infected with Mtb. MK-7762 was less potent at MPS inhibition compared to linezolid with half maximal inhibitory concentration (IC_{50}) values of >50 to >100 μM versus 13 to 30 μM, respectively. Development of MK-7762 represents a unique opportunity to evaluate a new oxazolidinone agent that could contribute to a novel pan-TB regimen while mitigating the toxicities of linezolid.

In this trial, healthy adults will receive single or multiple oral doses of MK-7762 to enable assessment of its safety, tolerability, and PK. The effect of food on the rate and extent of absorption of two different single oral doses of MK-7762 will also be evaluated.

Table 1 Study Objectives, Endpoints, and Estimands

Estimand frameworks were developed as defined in ICH E9 R1 (2021).

Objectives	Endpoints/Estimands
Primary	
Safety	
• To characterize safety and tolerability of MK-7762 after administration of single doses or multiple doses in healthy adult participants **For Parts 1 and 2 (All Cohorts)**	The proportion of treated participants reporting treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and AEs of special interest (AESIs), assessed overall, by severity, by relationship to study drug, and by system organ class and preferred term according to the following windows: • Part 1, SAD Cohorts 1 - 5: Day 1 through Day 7 • Part 1, Food Effect (FE) Cohort 6: Day 1 through last day of washout period for first dosing period; Day 1 of second dosing period through Day 7 of second dosing period • Part 2, FE Cohort 7: Day 1 through last day of washout period for first dosing period; Day 1 of second dosing period through last day of washout period for second dosing period; Day 1 of third dosing period through Day 7 of third dosing period • Part 2, MAD Cohorts 8-10: Day 1 through Day 36
• To characterize laboratory results, electrocardiogram (ECG) parameters, and vital signs after administration of single doses or multiple doses of MK-7762 **For Parts 1 and 2 (All Cohorts)**	In treated participants, summaries (descriptive statistics and frequencies) of safety laboratory measures (by visit, worst grade, grade shift from baseline), vital signs (by visit, change from baseline), 12-lead ECG parameters (by visit, change from baseline) according to the same windows defined above for AEs. Safety laboratory measurements include clinical chemistry, hematology, coagulation, and urinalysis. Vital signs include temperature, heart rate, and blood pressure. ECG parameters include heart rate, RR interval, PR interval, QRS duration, QT interval, and QT interval corrected by Fridericia's formula [QTcF].
Secondary	
PK	
• To determine the PK of single doses of MK-7762 in plasma. **For Part 1 (SAD Cohorts 1-5)** • To evaluate the impact of food on the PK of single doses of MK-7762 in plasma **For Part 1 (FE Cohort 6)** **For Part 2 (FE Cohort 7)**	**Estimand framework:** • **Treatment:** 1) MK-7762 in escalating single doses or placebo (Part 1, SAD Cohorts 1-5) and 2); MK-7762 under fasted or fed conditions (Part 1, FE Cohort 6) and 3) MK-7762 under fasted or fed conditions (Part 2, FE Cohort 7) • **Population:** All participants who receive at least one dose of MK-7762 and have at least one non-zero PK result (PK Population) • **Participant-level endpoints:** o Maximum plasma drug concentration (C_{max}), o Time to maximum plasma drug concentration (T_{max}), area under the concentration-time curve (AUC) calculated to last quantifiable observed sample (AUC_{last}); extrapolated to infinity (AUC_{0-inf}); and over first 24h (AUC_{0-24}) o Terminal elimination half-life ($t_{½}$) o Oral clearance (CL/F) o Oral volume of distribution (V_d/F)

Objectives	Endpoints/Estimands
	• **Population-level summaries:** Descriptive statistics of endpoints noted above. • **Intercurrent events:** A treatment policy strategy will be used to summarize plasma PK results.
• To determine the PK of multiple doses of MK-7762 in plasma in fed and fasted states. **For Part 2 (MAD Cohorts 8-10)**	**Estimand framework:** • **Treatment:** MK-7762 in escalating multiple doses or placebo (Part 2, MAD Cohorts 8-10) • **Population:** All participants who receive at least one dose of MK-7762 and have at least one non-zero PK result (PK Population) • **Participant-level endpoints (all endpoints will be assessed in fed and fasted states):** **Day 1:** ○ C_{max} ○ T_{max} ○ $AUC_{(0-24)}$ **Day 28:** ○ C_{max} ○ T_{max} ○ AUC, AUC_{last}, AUC_{0-inf}, and AUC_{0-24} ○ $t_{½}$ ○ CL/F ○ V_d/F ○ Accumulation ratio (AUC_{tau} / AUC_{0-24}) ▪ Day 28 vs Day 1 • **Population-level summaries:** Descriptive statistics of endpoints noted above. • **Intercurrent events:** A treatment policy strategy will be used to summarize plasma PK results.
Exploratory	
• To determine the PK of single doses or multiple doses of MK-7762 in urine **For Part 1 (Cohort 4) and Part 2 (Cohort 9)**	In treated participants with at least one non-zero PK result, descriptive statistics of the following measures: • Urine PK concentrations • Percent of drug excreted in urine (in a dosing interval) (Ae%) • Renal clearance (CLr) • To estimate the metabolite-to-parent ratio (AUC metabolite/AUC MK-7762) and cumulative urinary excretion (CUE)
• To identify prominent circulating metabolites of MK-7762 in plasma following administration of single doses or multiple doses of MK-7762 **For Part 1 (Cohort 4) and Part 2 (Cohort 10)**	In treated participants with at least one non-zero PK result, qualitative characterization of potential metabolites
• To estimate the effect of MK-7762 on ECG parameters, including	In treated participants, descriptive statistics of the following endpoints, including placebo-corrected change from baseline measures, categorical

Objectives	Endpoints/Estimands
concentration-QTc (C-QTc) analysis, following single or multiple doses of MK-7762 **For Parts 1 and 2 (All Cohorts)**	outliers, and frequency of treatment-emergent T- and U-wave abnormalities: • Heart rate • RR interval • PR interval • QRS interval • QTcF interval This analysis may be undertaken based on observed PK and other project considerations. If so, the primary analysis will be based on concentration-QTc (C-QTc) modeling of the relationship between the plasma concentrations of MK-7762 and potential metabolites and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) >10 msec at clinically relevant plasma concentrations.
• To characterize the maximal hematological effect of single or multiple doses of MK-7762 or placebo in healthy participants **For Parts 1 and 2 (All Cohorts)**	In treated participants, the following binary classifications with respect to platelet count, absolute neutrophil count (ANC), white blood cell (WBC) count, reticulocyte count, red blood cell (RBC) count, and hemoglobin result: a. Post-baseline result that is <lower limit of normal (LLN) (yes/no) b. Post-baseline result that is <50% of LLN (yes/no) c. Post-baseline result that is ≥20% decrease relative to baseline (yes/no) d. Post-baseline result that is ≥50% decrease relative to baseline (yes/no) Summaries will include the following: • For each of (a) through (d), the proportion of participants who meet the criterion
• To characterize the effect of MK-7762 on neurologic assessments in healthy participants receiving multiple doses **For Part 2 (MAD Cohorts 8-10)**	In treated participants, descriptive summaries for each of the following measures: • For visual acuity score for each eye o Descriptive statistics for change in visual acuity score from baseline to lowest post-baseline score` o Proportion of participants with a post-baseline visual acuity score worse than 20/25 in either eye • For color vision assessment for each eye o Proportion of participants with a post-baseline color vision abnormality in either eye (overall and by severity grade) • For Brief Peripheral Neuropathy Screen (BPNS) score in each lower extremity o Proportion of participants with a reported new post-baseline peripheral neuropathy symptom on BPNS (overall and by severity grade) o Proportion of participants with a new post-baseline peripheral neuropathy objective physical finding on BPNS (overall and by severity grade) o Proportion of participants with new post-baseline peripheral neuropathy symptoms and objective physical finding on BPNS (overall and by severity grade)
• To evaluate the time to resolution of hematologic and neurologic AESIs	In treated participants who have ongoing hematologic or neurologic AESI at the time of treatment discontinuation:

Objectives	Endpoints/Estimands
following discontinuation of MK-7762 after multiple doses **For Part 2 (MAD Cohorts 8-10)**	• Kaplan-Meier analysis of time to resolution of category of AESI (hematologic or neurologic). Participants with unresolved AESI at the time of analysis will be censored on the date of last AE assessment. • Milestone rates at 5 days following treatment discontinuation
• To explore possible variability in MK-7762 metabolism due to genetic polymorphisms based on metabolite profile observed **For Parts 1 and 2 (All Cohorts)**	Will be defined in an Exploratory Statistical Analysis Plan (ESAP)

1.1.3 Study Design

This is a first-in-human (FIH) trial of MK-7762, administered orally to healthy adults. It is a randomized, double-blind, placebo-controlled, two-part trial evaluating participants in SAD cohorts who are administered single ascending oral doses in the fasted state and participants in MAD cohorts who are administered daily doses for 28 days in either the fed or fasted state. Treatment will be blinded for participants in Part 1, SAD Cohorts 1-5, and in Part 2, MAD Cohorts 8-10. Two open-label food effect cohorts will be enrolled (Part 1, FE Cohort 6, and Part 2, FE Cohort 7).

Healthy adult participants between 19 to 55 years of age (inclusive) of both sexes who are capable of and willing to provide informed consent will be eligible for the trial. See Section 5.1 and Section 5.2 for inclusion and exclusion criteria.

The trial will be conducted in two parts. Part 1 will consist of a single ascending dose (SAD) double-blind, placebo-controlled design evaluating up to 5 single doses of MK-7762 (N=40). An open-label food effect (FE) evaluation in 8 additional participants will be conducted utilizing an oral dose of MK-7762 demonstrated to be safe and well-tolerated in a previously completed SAD cohort.

Following completion of Part 1, an interim review of unblinded safety and PK data will be conducted. Any additional nonclinical data available will also be reviewed. Upon completion of this interim review, the Sponsor will select 3 dose levels of MK-7762 (low, medium, and high) to be administered daily for 28 days in a placebo-controlled, multiple ascending dose (MAD) design (N=48) in Part 2 of the trial (see Section 1.1.3.2). The results of the interim review are also intended for regulatory submission and comment prior to initiation of Part 2 of the trial.

Part 2 includes an open-label, three-period food effect cohort (FE Cohort 7) evaluating 9 participants who receive a single MK-7762 dose in the fasting state and after a standard meal breakfast and after a high-fat meal breakfast. Part 2 also consists of a multiple ascending dose (MAD) double-blind, placebo-controlled cohorts (MAD Cohorts 8-10, N=60), evaluating 3 dose levels of MK-7762 administered once-daily for 28 days.

1.1.3.1 Part 1 – SAD and Food Effect (SAD/FE)

Gates MRI-TBD09-101, Amendment 4 (Version 5.0)

Part 1 of this trial has been completed. See Section 2.3.2 for results from Part 1.

- The dose of MK-7762 for SAD Cohort 5 was 1200 mg.
- The dose of MK-7762 for FE Cohort 6 was 300 mg.
- The washout period between doses in FE Cohort 6 was 8 days.

In Part 1 of the trial (SAD/FE), up to five sequential cohorts will be enrolled to evaluate up to five escalating single doses of MK-7762; 8 participants in each cohort will be randomized (3:1) to receive MK-7762 or placebo. A sixth cohort will evaluate the effect of food on PK of single doses of MK-7762 utilizing an open-label, two-period design in 8 participants. The MK-7762 dose to be evaluated in the FE cohort will be a dose demonstrated to be safe and well-tolerated in a previously completed SAD cohort. All participants in Part 1 will be confined at the trial site from Day -1 until their end-of-trial visit (approximately 8 days for Cohorts 1-5 and 16 days for Cohort 6).

SAD Cohorts 1-4 will evaluate the safety and PK of single oral doses of MK-7762 of 50 mg, 150 mg, 300 mg, and 600 mg. The first two participants in Cohort 1 will be dosed as sentinel participants in a blinded manner, randomized 1:1 to MK-7762 or placebo. The Safety Review Team (SRT) will review safety data up to Day 4 following dosing for these two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 1 will receive single doses of study drug (randomized 5:1; MK-7762:placebo). Cohort 5 may evaluate a dose of MK-7762 that will be selected based on the safety and PK data from previous cohorts. The dose of MK-7762 chosen for evaluation in Cohort 5 will not result in predicted exposure higher than that allowable based on the nonclinical toxicology no observed adverse effect level (NOAEL).

For Cohort 6 (FE Cohort), eight participants will be dosed with MK-7762 in both fasted and fed states with a between-dose washout period of at least 5 half-lives of MK-7762 as determined by the PK results from previous SAD cohorts. The MK-7762 dose to be evaluated in the FE Cohort will be a dose demonstrated to be safe and well-tolerated in a previously completed SAD cohort. Two sentinel participants in Cohort 6 will be dosed in the fed state first. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing period. If recommended by the SRT and approved by the Sponsor, the two sentinel participants will be dosed with MK-7762 in the fasted state after the washout period previously determined, and the remaining 6 participants in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.

The doses of MK-7762 to be administered in the cohorts following Cohort 1 may be modified based on accumulating safety, tolerability, and PK data. The Protocol may be amended to enroll additional participants at any of the planned dose level(s) or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previously completed cohorts. The enrolment to Cohort 6 (FE) may start after PK and safety data from Cohort 2 become available.

Screening (Day -21 to -2)

Part 1 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 3 and Table 4 in Section 1.3.

Confinement Period

All Part 1 participants will be admitted to the Clinical Trial Unit (CTU) on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 3 and Table 4 in Section 1.3. Randomization to blinded treatment will occur prior to dosing on Day 1 for participants in Cohorts 1-5. Participants must have fasted for at least 8 hours prior to dosing.

In SAD Cohorts 1-5, participants will be admitted from Day -1 until Day 7 (±1 day; 8 days total) for the single dosing period. Participants in FE Cohort 6 will be admitted from Day -1 until Day 7 (±1 day) of the second dosing period. The exact duration of the confinement will be determined by the time required for an adequate washout period of at least five half-lives to be determined by PK results from the SAD cohorts.

Fasted Cohorts (SAD Cohorts 1-5)

Dose administration for SAD Cohorts 1-5 will occur after an 8-hour overnight fast on the morning of Day 1. Fasting will continue until 4 hours post-dose at which time a standardized meal will be provided. Clinical and safety laboratory assessments will be performed throughout the confinement period as per Table 3 for Cohorts 1-5.

Food Effect Cohort (FE Cohort 6)

Participants administered MK-7762 in the fasted state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants administered MK-7762 in the fed state will be provided the standard US Food & Drug Administration (FDA) high fat breakfast, which should be consumed within 30 minutes or less, with MK-7762 administration occurring approximately 30 minutes after the start of the meal. In both the fed and fasted settings, fasting will resume for 4 hours post-dose, at which time, a standardized meal will be provided.

1.1.3.2 Interim Review of Data from Part 1

Following completion of Part 1, a comprehensive interim review of cumulative clinical safety and PK data for Cohorts 1-6 will be conducted in an unblinded manner by the Sponsor to guide selection of appropriate doses to be evaluated in Part 2. Any additional relevant nonclinical data will also be reviewed as part of this process. The results of the interim review are intended for regulatory submission, comment and regulatory agreement to proceed prior to the Sponsor's agreement to initiate Part 2 of the trial. In the current amendment of the Protocol (Amendment 3, Version 4.0), the preliminary results from Part 1 are included in the current amendment of the Protocol, (Section 2.3.2) and Part 2 has been updated to reflect the results of the interim review.

1.1.3.3 Part 2 – Food Effect and MAD (FE/MAD)

In Part 2, an open-label, three-period food effect cohort (FE Cohort 7) will be enrolled to evaluate a single dose of MK-7762 600 mg in the fasted state, after ingestion of a standard meal breakfast, and after ingestion of a high-fat meal breakfast, in random fashion (Table 5). FE Cohort 7 will enroll a sufficient number of participants to ensure that 9 participants complete

each of the three dosing periods. All participants in FE Cohort 7 will be confined at the trial site from Day -1 until their end-of-trial visit on Day 8 of Period 3.

In MAD Cohorts 8-10, 3 dose levels of MK-7762 will be administered daily for 28 days in a placebo-controlled, multiple ascending dose (MAD) design (N=60) (see Section 1.1.3.1). MAD Cohort 8 will enroll in parallel with FE Cohort 7. The MAD doses in Part 2 were selected based on data from Part 1: MAD Cohort 8 will evaluate MK-7762 100 mg once daily (QD), MAD Cohort 9 will evaluate MK-7762 300 mg QD. The anticipated MK-7762 QD dose to be evaluated in MAD Cohort 10 is 500 mg. This may be modified through a protocol amendment after review of PK and safety data from FE Cohort 7 and MAD Cohorts 8 and 9. The dose in MAD Cohort 10 will not exceed 600 mg QD (See Section 2.6 for Justification for Dose).

Each of the three MAD cohorts will enroll approximately 20 participants randomized 4:4:1:1 to receive MK-7762 in fasted state, MK-7762 in fed state after a standard meal breakfast, placebo in fasted state, or placebo in fed state after a standard meal breakfast, respectively. All participants in Part 2 MAD Cohorts 8-10 will be confined at the trial site from Day -1 until their end-of-trial visit on Day 36.

Subsequently, a fourth MAD cohort may be considered to evaluate once daily doses of MK-7762 or placebo for up to 91 days, in the event of acceptable findings in the ongoing 4-month sub-chronic toxicology studies in rats and dogs.

In Part 2, effort will be made to enroll as many females as possible.

Screening (Day -21 to -2)

Potential participants in Part 2 will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 5 and Table 6 in Section 1.3.

Confinement Period

Participants in FE Cohort 7 will be admitted from Day -1 prior to first dosing period with confirmation of eligibility and baseline assessments performed as per Table 5 in Section 1.3. Randomization will occur prior to dosing on Day 1. They will remain in the CTU until Day 8 of the third dosing period.

All MAD Cohort 8-10 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 6 in Section 1.3. Randomization will occur prior to dosing on Day 1 for all cohorts. They will remain in the CTU until Day 36.

Food Effect Cohort 7

Participants will receive open-label MK-7762 600 mg utilizing a 3-period design. Participants will be randomized to one of the following 3 sequences:

- Fasted, standard meal, high-fat meal
- Standard meal, high-fat meal, fasted
- High-fat meal, fasted, standard meal

Between doses, there will be a washout period of at least 8 days, consistent with at least 5 half-lives. Participants administered MK-7762 in the fasted state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants administered MK-7762 in the standard meal fed state will be provided with a standard meal breakfast, which should be consumed within

30 minutes or less, with MK-7762 administration occurring approximately 30 minutes after the start of the meal. Participants administered MK-7762 in the high-fat meal fed state will be provided with a high-fat meal breakfast, which should be consumed within 30 minutes or less, with MK-7762 administration occurring approximately 30 minutes after the start of the meal. In both the fed and fasted settings, fasting will resume for at least 4 hours post-dose.

FE Cohort 7 clinical and safety laboratory assessments will be performed as per Table 5.

MAD Cohorts 8-10

Participants in the MAD cohorts will be randomized 4:4:1:1 to receive MK-7762 in fasted state, MK-7762 in fed state after a standard meal breakfast, placebo in fasted state, or placebo in fed state after a standard meal breakfast, respectively. Dosing in the fasted state or after standard breakfast meal will follow same procedures as FE Cohort 7 described above.

Clinical and safety laboratory assessments will be performed as per Table 6 for MAD Cohorts 8-10.

1.1.4 Study Drug Administration

Capsules containing MK-7762 will be supplied as 10 mg (size 3), 100 mg (size 0), and 300 mg capsules (size 00) with matching placebo capsules for oral administration. The doses evaluated in Part 1 and planned for Part 2 are listed in Table 2 below. See Section 2.6 for rationale for doses selected. All doses of MK-7762 and placebo will be administered with 240 mL (8 ounces) of water.

Table 2 Study Drug Administration

Part	Cohort	Period	Drug	Dose	Dose Strength	Dose Frequency
1 (SAD and FE)	1	NA	MK-7762	50 mg	10 mg	Single Dose
			Placebo	NA	NA	Single Dose
	2	NA	MK-7762	150 mg	10 mg and 100 mg	Single Dose
			Placebo	NA	NA	Single Dose
	3	NA	MK-7762	300 mg	100 mg and/or 300 mg	Single Dose
			Placebo	NA	NA	Single Dose
	4	NA	MK-7762	600 mg	100 mg and/or 300 mg	Single Dose
			Placebo	NA	NA	Single Dose
	5	NA	MK-7762	TBD[1]	10 mg, 100 mg and/or 300 mg	Single Dose
			Placebo	NA	NA	Single Dose
	6 (FE)	1	MK-7762	TBD[1]	10 mg, 100 mg and/or 300 mg	Single Dose, fed[2] or fasted
		2	MK-7762	TBD[1]	10 mg, 100 mg and/or 300 mg	Single Dose, fed[2] or fasted
2 (FE and MAD)	7 (FE)	1	MK-7762	600 mg	100 mg and/or 300 mg	Single Dose, fed or fasted[2]
		2	MK-7762	600 mg	100 mg and/or 300 mg	Single Dose, fed or fasted[1]
		3	MK-7762	600 mg	100 mg and/or 300 mg	Single Dose, fed or fasted[2]
	8	NA	MK-7762	100 mg	10 mg and/or 100 mg	Once daily, 28 days fed[3] or fasted
			Placebo	NA	NA	Once daily, 28 days fed[3] or fasted

Part	Cohort	Period	Drug	Dose	Dose Strength	Dose Frequency
	9	NA	MK-7762	300 mg	10 mg, 100 mg and/or 300 mg	Once daily, 28 days fed[3] or fasted
			Placebo	NA	NA	Once daily, 28 days fed[3] or fasted
	10	NA	MK-7762	500 mg	10 mg, 100 mg and/or 300 mg	Once daily, 28 days fed[3] or fasted
			Placebo	NA	NA	Once daily, 28 days fed[3] or fasted

Abbreviations: NA = not applicable; TBD = to be determined
[1] Cohort 5: 1200 mg; Cohort 6: 300 mg (see Section 2.3.2)
[2] The fed state in FE Cohort 7 will be a standard breakfast meal or a high-fat breakfast meal
[3] The fed state in MAD Cohorts 8-10 will be a standard breakfast meal

1.1.4.1 Safety Review and Dose Escalation Decisions

A Safety Review Team (SRT) will be established as the team responsible for safety review and dose escalation recommendations during Part 1 and Part 2 of the trial. Details on the membership of the SRT will be contained in a charter that will describe the SRT review of blinded safety and PK data and the deliberation processes (including the format of data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment and, if PK data are available, only aggregated mean PK data will be provided.

The Principal Investigator will be responsible for the identification of any event(s) which meet one or more of the pausing rules and the notification of the SRT, as outlined in Section 4.5.1. If a pausing rule is met, the SRT will ask the Independent Data Monitoring Committee (IDMC) to conduct a review of unblinded safety data. The IDMC will make a recommendation to the Sponsor regarding the further conduct of the trial.

1.1.4.2 IDMC

The IDMC will operate according to a charter approved by the Sponsor and all IDMC members. The IDMC structure, participants, and other details will be provided in the charter. The charter will be approved prior to Screening of the first trial participant in either Part 1 or Part 2.

The role of the IDMC will be to review unblinded safety data if a pausing rule is met and make recommendations to the Sponsor as outlined in the IDMC charter.

The recommendations of the IDMC when evoked, along with the Sponsor's decision, will be communicated to the Investigator, to the responsible Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and to the United States (US) FDA.

See Section 4.5.2. for further details on the trial IDMC.

1.1.5 Rules for Discontinuation of Study Drug for Individual Participants in Part 2, MAD Cohorts 8-10

Treatment will be discontinued for participants in Part 2, MAD Cohorts 8-10, that experience one or more of the following safety laboratory abnormalities at any time from Day 1 through the end of their dosing period:

- Hemoglobin <11.5 g/dL for males and <10.0 g/dL for females or >2 g/dL decrease from Day -1 for both males and females
- Total WBC count <2,000 cells/mm^3

- ANC <1,200 cells/mm^3
- Platelet count <100,000 cells/mm^3 or >50% decrease from Day -1
- Alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal

Part 2, MAD Cohort 8-10, participants with a safety laboratory result meeting one of these criteria should have the relevant test repeated to confirm the finding before discontinuation of treatment.

Treatment will be discontinued for participants in Part 2, MAD Cohorts 8-10, that experience any of the following clinical AEs at any time from Day 1 through the end of their dosing period:

- Grade 2 or higher peripheral neuropathy
- Optic neuritis of any grade confirmed by an ophthalmologist

The Principal Investigator will be responsible for the identification of safety laboratory abnormalities and/or clinical AEs which meet the rules of discontinuation of study drug for individual participants, as outlined above. In such instance, the Principal Investigator will ensure discontinuation of study drug and thereafter inform the SRT.

Study treatment discontinuation in one or more participants in MAD Cohorts 8-10 does not require a pause in trial enrollment or in dosing for all currently enrolled participants. Individual participant study treatment discontinuations will be considered by the SRT during MAD dose escalation review meetings.

1.1.6 Number of Participants and Duration of Participation

Because this trial is aimed at characterizing the safety, tolerability, and PK of MK-7762, it is designed to be descriptive and is not based on formal hypothesis testing. Therefore, this trial is not powered to detect any pre-specified differences in potential safety or PK data between treatment groups. A total of approximately 117 participants will be randomized (48 in Part 1 and 69 in Part 2), and a total of approximately 95 participants will be exposed to MK-7762 (38 in Part 1 and 57 in Part 2).

All participants will undergo a Screening period lasting up to 20 days (Day -21to -2) followed by a confinement period in the CTU of varying length according to their assigned cohort. In Part 1, the maximum duration of participation, including the Screening period, will be up to approximately 30 days for participants in Part 1, SAD Cohorts 1-5 and approximately 38 days for participants in FE Cohort 6 (to be confirmed once washout period of at least 5 half-lives is determined). The duration of participation for participants in Part 2, FE Cohort 7, will be up to approximately 44 days, which includes a washout period of at least 8 days between the open-label doses of MK-7762. In Part 2, MAD Cohorts 8-10, the maximum duration of participation, including the Screening period, will be up to approximately 54 days for participants.

The duration of participants' participation may be adjusted (increased or decreased) based on emerging PK data collected during the study.

Trial Site(s): The trial will be conducted at one site in the United States.

Blinding: The trial has a double-blind design in which participants in SAD Cohorts 1-5 and MAD Cohorts 8-10 and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at the trial site who will prepare the oral doses of MK-7762 and placebo appropriately masked for site personnel who are authorized to administer

treatment. All doses of MK-7762 administered to all participants in Part 1 FE Cohort 6 and in Part 2 FE Cohort 7 will be open-label.

1.1.7 Criteria for Evaluation

Safety Variables: AEs; vital signs (blood pressure, heart rate (HR), temperature); weight and body mass index (BMI); 12-lead ECG parameters (heart rate, RR, PR, QRS, QT, and corrected QT [QTcF] intervals); continuous Holter monitoring with pre-dose and post-dose ECG extractions, as applicable; clinical laboratory assessments, including hematology, biochemistry, coagulation, and urinalysis; and physical examination findings, including visual acuity, color vision, and peripheral neuropathy screenings and assessments.

PK Variables:

Plasma: C_{max}, T_{max}, AUC, AUC_{last}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}24}$, $t_{½}$; CL/F; and V_d/F. For MAD cohorts, AUC over the dosing interval (AUC_{Tau}); C_{max} at steady state ($C_{max\ ss}$), predose levels (C_{trough}); and AUC_{Tau} / $AUC_{0\text{-}24}$ for Day 28 vs. Day 1. Time to reach steady state will be estimated visually.

Urine: urine PK concentrations of MK-7762, Ae%, CLr, metabolite-to-parent ratio (AUC metabolite/AUC MK-7762), and CUE.

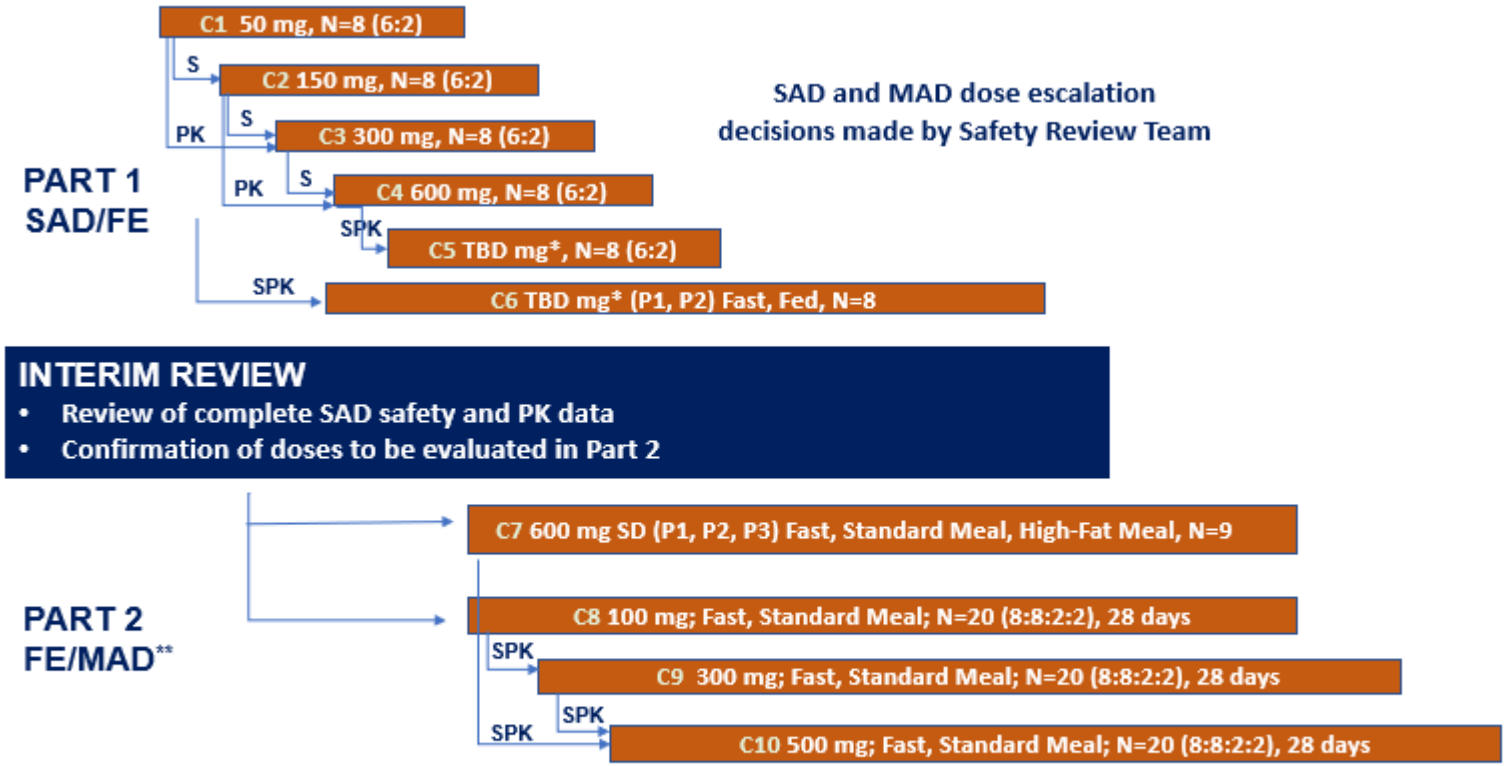
See the SoA in Section 1.3 and Section 8 for details of assessments to be conducted and their schedules.

Analysis: See Section 9.

Additional study design details are included in Section 4.

1.2 Schema

Figure 1 Study Schema



C = Cohort; P = Period; S = Safety data; PK = Pharmacokinetic data; SPK = Safety and PK data; TBD = To be determined; SD = Single dose
*C5 dose = 1200 mg; C6 dose = 300 mg (Section 2.3.2)
**In C8-10, participants randomized 8:8:2:2 to receive MK-7762 in fasted state, MK-7762 after standard breakfast meal, placebo in fasted state, or placebo after standard breakfast meal

1.3 Schedule of Activities (SoA)

Table 3 Schedule of Activities for Part 1, SAD Cohorts 1-5

Procedure	Screening	Trial Days					End-of-Trial Visit	Early Termination [a]
Day	(Day -21 to -2)	Day -1	Day 1	Day 2	Day 3	Day 4	Day 7	
Trial Timepoint (hours)			0-12	24	48	72		
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographic information	X							
Medical history	X							
Medication history	X							
Prior and concomitant medication review	X	X	X	X	X	X	X	X
Safety ECG [b]	X	X	X	X			X	X
Continuous ECG recordings [c]			X	X				
Vital signs [d]	X	X	X	X	X	X	X	X
Physical examination	X	X			X		X	X
Neurologic assessments [e]	X							
Ophthalmologic assessments [f]	X							
Height	X							
Body weight	X	X						
Screening laboratory assessments [g]	X							
Screening SARS-CoV-2 PCR		X						
FSH testing (confirmation of post-menopausal state only) [h]	X							
Urine cotinine screen	X	X						
Urine drug screen	X	X						
Check-in/Clinic Admission		X						
Urine alcohol screen	X	X						
Randomization			X					
Drug administration			X					
Safety laboratory assessments [i]		X		X		X	X	X
Blood sample collection for PK analysis [j]			X	X	X	X	X	X
Urine collection for PK analysis [k]		X	X	X	X	X		
Sample collection for PGx Screening [l]		X						
Discharge from clinic							X	X
Adverse events [m]	X	X	X	X	X	X	X	X

For abbreviations, see List of Abbreviations

a: In the event of a participant's early withdrawal, efforts will be made to perform end-of-trial procedures at the time of participant withdrawal.

b: 12-lead safety ECG for on-site evaluation will be recorded at Screening, on Day -1, on Days 1, 2, and at the end of the trial (Day 7). The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the first ECG. All ECGs will be recorded in triplicate at least 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Day 2 and Day 7 should be taken at approximately the same time as the study drug was administered. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator.

c: A continuous ECG recording will be performed for 25 hours, starting one hour pre-dose on Day 1, in all dose groups in which participants receive MK-7762 or placebo in the fasted state. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: at 3 time points within one hour prior to dosing (e.g., -45, -30 and -15 minutes) and at one time point each at approximately 1, 2, 3, 4, 5, 6-, 8-, 12-, and 24-hours post-dose. Participants will be supinely resting for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by safety ECGs then vital signs, except ECG extractions may occur before blood sample collection.

d: Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and pre-dose on Day 1 within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times:

- Day 1: 30 minutes (±10 minutes) post-dose and then at each PK sample timepoint (±30 minutes).
- Day 2: 24 and 36 hours (±30 minutes) post-dose.
- Day 3: 48 hours (±30 minutes) post-dose.
- Day 4: 72 hours (±30 minutes) post-dose
- End-of-trial (Day 7) visit: ±30 minutes of time of Day 1 dose administration

e: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool.

f: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates.

g: Screening labs include Hep B, C, & HIV

h: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.

ii: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. Blood and urine for post-dose safety laboratory assessments should be collected within a ±2-hour time window from the same time of day as study drug administration on Day 1.

j: Blood samples for PK analysis will be collected at the following times:

- Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2).
- Day 3: 48 hours (±10 minutes) post-dose
- Day 4: 72 hours (±10 minutes) post-dose
- Day 7: Within ±1-hour time window of time of study drug administration on Day 1

Additional blood will be collected at the same time points for participants in Cohort 4 for storage for potential future qualitative and/or quantitative analysis of any significant metabolites identified.

k: Urine will be collected for PK analysis at the following times from Cohort 4 only:

- Pre-dose (spot check) collected as first morning void
- Day 1: 0-4, 4-8, 8-12, 12-24 hours
- Day 2: 24-36 and 36-48 hours
- Day 3: 48-72 hours

l: Samples will be collected and stored for potential pharmacogenetic (PGx) analysis (see Section 8.4.10)

m: Adverse events will be collected from the time of signed informed consent

Gates MRI-TBD09-101, Amendment 4 (Version 5.0)
Part 1 of this trial has been completed. See Section 2.3.2 for results from Part 1. • The washout period between doses in FE Cohort 6 was 8 days.

Table 4 Schedule of Activities for Part 1, FE Cohort 6

Procedure	Screening (Day -21 to -2)	First Period (P1)					Second Period (P2)[a]					End-of-Trial Visit	Early Termination [b]
Day/Period		Day -1	Day 1	Day 2	Day 3	Day 4	Day -1 Period 2	Day 1 Period 2	Day 2 Period 2	Day 3 Period 2	Day 4 Period 2	Day 7 Period 2	
Trial Timepoint (hours)			0-12	24	48	72		0-12	24	48	72		
Informed consent	X												
Inclusion/exclusion criteria	X												
Demographic information	X												
Medical history	X												
Medication history	X												
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety ECG [c]	X	X	X	X			X	X	X			X	X
Vital signs [d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X			X		X			X		X	X
Neurologic assessments [e]	X												
Ophthalmologic assessments [f]	X												
Height	X												
Body weight	X	X											
Screening laboratory assessments [g]	X												
Screening SARS-CoV-2 PCR		X											
FSH testing (confirmation of post-menopausal state only) [h]	X												
Urine cotinine screen	X	X											
Urine drug screen	X	X											
Check-in/Clinic Admission		X											
Urine alcohol screen	X	X											
Randomization			X										

Procedure	Screening (Day -21 to -2)	First Period (P1)					Second Period (P2)[a]					End-of-Trial Visit	Early Termination [b]
Day/Period		**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day -1 Period 2**	**Day 1 Period 2**	**Day 2 Period 2**	**Day 3 Period 2**	**Day 4 Period 2**	**Day 7 Period 2**	
Trial Timepoint (hours)			**0-12**	**24**	**48**	**72**		**0-12**	**24**	**48**	**72**		
Drug administration [i]			X					X					
Safety lab assessments [j]		X		X		X	X		X		X	X	X
Blood sample collection for PK analysis [k]			X	X	X	X	X	X	X	X	X	X	X
Sample collection for PGx Screening [l]		X											
Discharge from clinic [m]												X	X
Adverse events [n]	X	X	X	X	X	X	X	X	X	X	X	X	X

For abbreviations, see List of Abbreviations

a: Day 1 of Period 2 will not occur until at least five half-lives of MK-7762 have elapsed as determined by PK results from Cohorts 1-5.

b: In the event of a participant's early withdrawal, efforts will be made to perform end-of-trial procedures at the time of participant withdrawal.

c: 12-lead safety ECG for on-site evaluation will be recorded at Screening, on Days -1, 1, 2, 8, 9, and 10, and at the end of the trial (Day 15). The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with at least 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 Period 1 and Day 1 Period 2 should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Day 2, Day 7, Day 9, and Day 14 of Periods 1and 2 should be taken at approximately the same time as the study drug was administered. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator. When safety ECGs coincide with vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs.

d: Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and pre-dose on Day 1 and Day 9 within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times:

- Day 1 of Periods 1 and 2: 30 minutes (±10 minutes) post-dose and then at each PK sample timepoint (±30 minutes).
- Day 2 of Periods 1 and 2: 24 and 36 hours (±30 minutes) post-dose.
- Day 3 of Periods 1 and 2: 48 hours (±30 minutes) post-dose.
- Day 4 of Periods 1 and 2: 72 hours (±30 minutes) post-dose
- Day 8 of Period 1 (Day -1 Period 2): ± 30 minutes of time of Day 1 Period 1 dose administration
- Day 7 of Period 2 end of trial: ±30 minutes of time of Day 1 Period 2 dose administration

e: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool.

f: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates.

g: Screening labs include Hep B, C, & HIV

h: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.

i: Participants will receive a single dose in 2 treatment periods: one after a high fat, high calorie breakfast (fed) and the second treatment period under fasted conditions (or the opposite order). The fed and fasted treatment periods will be separated by a washout period of at least five half-lives. See Section 4.1

j: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. Blood and urine for post-dose safety laboratory assessments should be collected within a ±2-hour time window from the same time of day as study drug administration on Day 1Period 1 or Day 1 Period 2, accordingly.

k: Blood samples for PK analysis **in Period 1** will be collected in each period at the following times:

- Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2).
- Day 3: 48 hours (±10 minutes) post-dose
- Day 4: 72 hours (±10 minutes) post-dose
- Day 7: within ±1-hour time window of time of study drug administration on Day 1

NOTE: No PK sample is collected on Day 8 Period 1

Blood samples for PK analysis in **Period 2** will be collected at the following times:

- Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2 Period 2).
- Day 3: 48 hours (±10 minutes) post-dose
- Day 4: 72 hours (±10 minutes) post-dose
- Day 7: within ±1-hour time window of time of study drug administration on Day 1 Period 2

l: Blood samples will be collected and stored for potential PGx analysis (see Section 8.4.10)

m: Participants will stay in the CTU through Day 7 of Period 2 and will be discharged following the end of trial evaluations.

n: Adverse events will be collected from the time of signed informed consent

Table 5 Schedule of Activities for Part 2, FE Cohort 7

Procedure	Screening (Day -21 to -2) before Period 1	Periods 1, 2, and 3						End-of-Trial Visit	Early Termination [b]
Day		**Day -1**	**Day 1[a]**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Period 3 Day 8**	
Trial Timepoint (hours)			**0-12**	**24-36**	**48**	**72**	**168**		
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographic information	X								
Medical history	X								
Medication history	X								
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X
Safety ECG [c]	X	X	X	X	X		X	X	X
Continuous ECG recording [d]			X	X	X				
Vital signs [e]	X	X	X	X	X	X	X	X	X
Physical examination	X	X			X		X	X	X
Neurologic assessments [f]	X								
Ophthalmologic assessments [g]	X								
Height	X								
Body weight	X	X[h]							
Screening laboratory assessments [i]	X								
Screening SARS-CoV-2 PCR		X[h]							
FSH testing (confirmation of post-menopausal state only) [j]	X								
Urine cotinine screen	X	X [h]							
Urine drug screen	X	X [h]							
Check-in/Clinic Admission		X [h]							
Urine alcohol screen	X	X [h]							
Randomization			X						
Drug administration [k]			X						
Safety lab assessments [l]		X		X		X	X	X	X
Blood sample collection for PK analysis [m]			X	X	X	X	X	X	X
Sample collection for PGx Screening [n]		X [h]							
Discharge from clinic [o]								X	X
Adverse events [p]	X	X	X	X	X	X	X	X	X

For abbreviations, see List of Abbreviations

a: Day 1 of Period 2 and 3 will not occur until at least 8 days have elapsed since Day 1 of Period 1 and 2, respectively.

b: In the event of a participant's early withdrawal, efforts will be made to perform end-of-trial procedures at the time of participant withdrawal.

c: 12-lead safety ECG for on-site evaluation will be recorded at Screening, on Days -1, 1, 2, 3 and 8 for each Period and at the end of the trial (Day 8 of Period 3). The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with approximately 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 Period 1, on Day 1 Period 2 and Day 1 Period 3 should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Day 2, Day 3, and Day 8 should be taken at approximately the same time of day as the study drug was previously administered. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator. When safety ECGs coincide with vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs.

d: In each of the dosing periods a continuous ECG recording will be performed for 50 hours, starting two-hours pre-dose on Day 1. 12-lead ECGs will be extracted from the continuous ECG recording at the following time points, paired with PK sampling: at 3 time points within two hours prior to dosing (e.g., -75, -60 and -45 minutes) and at one time point each at approximately 1, 2, 4, 6, 8, 12, 24, 36, and 48-hours post-dose. Participants will rest in a supine position for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by safety ECGs then vital signs, except ECG extractions may occur before blood sample collection.

e: Blood pressure, heart rate, and temperature will be measured with participant in supine position after resting for ≥3 minutes at Screening, Day -1 check-in, and pre-dose on Day 1 of each period within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times:

- Day 1 of Periods 1, 2, and 3: 30 minutes (±10 minutes) post-dose and then at each PK sample timepoint (±30 minutes).
- Day 2 of Periods 1, 2, and 3: 24 and 36 hours (±30 minutes) post-dose.
- Day 3 of Periods 1, 2, and 3: 48 hours (±30 minutes) post-dose.
- Day 4 of Periods 1, 2, and 3: 72 hours (±30 minutes) post-dose
- Day 8 of Periods 1, 2 and 3: ±30 minutes of time of Day 1 dose administration of Period 1, Period 2 or Period 3, respectively

f: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool.

g: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates

h: Performed at Period 1 only.

i: Screening labs include Hep B, C, & HIV

j: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.

k: Participants will receive a single dose in 3 periods: one after a high fat, high calorie breakfast, one after a standard breakfast, and under fasted conditions separated by a washout period of at least 8 days. See Section 4.2.

l: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. Blood and urine for post-dose safety laboratory assessments should be collected within a ±2-hour time window from the same time of day as study drug administration on Day 1 of each dosing period.

m. Blood samples for PK analysis will be collected in each of the three periods at the following times:

- Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 4, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2).
- Day 3: 48 hours (±10 minutes) post-dose
- Day 4: 72 hours (±1 hour) post-dose
- Day 5: 96 hours (±1 hour) post-dose
- Day 6: 120 hours (±1 hour) post-dose
- Day 7: 144 hours (±1 hour) post-dose
- Day 8: 168 hours (±1 hour) post-dose

n: Blood samples will be collected and stored for potential PGx analysis (see Section 8.4.10)

o: Participants will stay in the CTU through Day 7 of Period 3 and will be discharged following end of trial evaluations.

p: Adverse events will be collected from the time of signed informed consent

Table 6 Schedule of Activities for Part 2, MAD Cohorts 8-10

	Screening (Day -21 to -2)	Day -1	Day 1	Day 2	Day 3	Day 4 to Day 27	Additional Activities on Day 7, Day 14, & Day 21	Day 28	Day 29	Day 30	Day 31	Day 33	Day 36	Early Termination
Informed Consent	X													
Inclusion/exclusion criteria	X													
Demographic information	X													
Medical history	X													
Prior and concomitant medication review	X	X	X	X	X	X		X	X		X	X	X	X
Vital signs [a]	X	X	X	X	X		X	X	X		X	X	X	X
Height	X													
Weight	X	X					X	X			X	X	X	X
Physical Examination	X	X			X		X	X			X	X	X	X
Neurologic assessments [b]	X	X					X		X		X	X	X	X
Ophthalmologic assessments [c]	X	X					X		X		X	X	X	X
Screening laboratory assessments [d]	X													
Screening SARS-CoV-2 PCR		X												
FSH testing (confirmation of post-menopausal state only) [e]	X													
Urine cotinine test	X	X												
Urine drug screen	X	X												
Urine alcohol screen	X	X												
Safety ECG [f]	X	X	X	X	X		X	X	X	X	X		X	X
Continuous ECG recording [g]			X	X				X	X	X				
Admission to CTU		X												
Randomization			X											
Discharge from the unit [h]													X	X
Study Treatment Administration [i]			X	X	X	X		X						
Safety laboratory assessments [j]		X		X		X	X		X		X	X	X	X
Blood sample collection for PK Analysis [k]			X	X	X	X	X	X	X	X	X	X	X	X
Urine sample collection for PK Analysis [l]								X	X					
Sample collection for PGx Screening [m]		X												
Adverse Event Monitoring [n]	X	X	X	X	X	X	X	X	X		X	X	X	X

For abbreviations, see List of Abbreviations

a: Blood pressure, heart rate, and temperature will be measured with participant in supine position after resting for ≥3 minutes at Screening, Day -1 check-in, and Day 1 pre-dose within 60 minutes prior to dosing. Blood pressure and heart rate only will be measured at the following times:

- Day 1: 30 minutes (±10 minutes) post-dose and then at each PK sample timepoint (±30 minutes).
- Day 2-3: predose and 12 hours (±60 minutes) post-dose.
- Day 7, 14, 21, and 28: predose (±60 minutes) (blood pressure, heart rate, and temperature should be measured)
- Day 28: 12 hours (±30 minutes) post-dose

- Day 29: 24 hours after Day 28 dose (±3 hours)
- Day 31: 72 hours after Day 28 dose (±3 hours)
- Day 33: 120 hours after Day 28 dose (±3 hours)
- Day 36: 168 hours after Day 28 dose (±3 hours) (end-of-trial visit) (blood pressure, heart rate, and temperature should be measured)

b: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool. The assessments should be conducted within ±3 hours of that day's dose when scheduled on a study day after Day 1.

c: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates. The assessments should be conducted within ±3 hours of that day's dose when scheduled on a study day after Day 1.

d: Screening labs include Hep B, C, & HIV

e: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.

f: 12-lead safety ECG for on-site evaluation will be recorded at Screening, Day -1, Days 1-3, 7, 14, 21, 28, 29, 30, 31 and 36. The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with approximately 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 and Day 28 should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Days 2, 3, 7, 14, and 21 should be taken within 60 minutes prior to dosing on that day. ECGs on Day 29, Day 30, Day 31 and Day 36 should be taken at approximately the same time as the study drug was administered on Day 28. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator or designee

g: Continuous ECG recordings will be performed for 26 hours beginning on Day 1, and 50 hours beginning on Day 28, starting two pre-dose on Day 1 and Day 28. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: At 3 time points within two hours prior to dosing (eg, -75, -60 and -45 minutes) and at one time point each at approximately 1, 2, 4, 6-, 8-, 12-, and 24-hours post-dose on Day 1 and Day 28), and at approximately 36- and 48-hours post-dose on (Day 28 only. Participants will rest in a supine position for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by safety ECGs then vital signs, except ECG extractions may occur before blood sample collection.

h: Participants will be admitted to the CTU from Day -1 until Day 36.

i: For Cohort 8-10 a daily dose of MK-7762 or placebo will be administered for 28 days at the same time (+/- 1 hour) of the day either fasted or within 30 min of a standard breakfast meal.

j: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. From Day 4 to 27, safety laboratory assessments will be performed on Days 4, 7, 10, 14, 17, 21, and 24. Blood and urine for safety laboratory assessments should be collected within a ±2-hour window from that day's dosing.

k: Blood samples for PK analysis will be collected at the following times:

- Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 4, 6, 8, and 12 hours (±5 minutes) postdose
- Days 2-27: pre-dose within 60 minutes of that day's dose
- Days 7,14 and 21: 8 hours ± 2 hours post dose
- Day 28: Within 60 minutes of that day's dose, and at 1, 2, 4, 6, 8, and 12 hours (±5 minutes) postdose
- Day 29: 24 hours (±30 minutes) after the Day 28 dose
- Day 30: 48 hours (±3 hours) after the Day 28 dose
- Days 31-36 (±1 day) within ±3-hour time window of time of last study drug administration on Day 28

Additional blood will be collected at the same time points for participants in MAD Cohort 10 for storage for potential future qualitative and/or quantitative analysis of any significant metabolites identified.

l: Urine will be collected for PK analysis at the following times only from MAD Cohort 10

- Day 28: Pre-dose (spot check collected as first morning void) and 0-4, 4-8, 8-12, 12-24-, and 24-48-hours post dose.

m: Blood samples will be collected and stored for potential PGx analysis (see Section 8.4.10)

n: Adverse events will be collected from the time of signed informed consent and continuously while in CRU.

2 INTRODUCTION

2.1 Tuberculosis and Burden of Disease

Tuberculosis (TB) is a bacterial disease caused by Mtb. TB most commonly occurs in the lungs (pulmonary TB) but can occur anywhere throughout the body (extrapulmonary TB). One-fourth of the world's population is estimated to be latently infected with Mtb and at risk of developing active TB. Ten million people develop active TB each year and, despite recent declines in incidence and mortality, TB remains a leading cause of death from an infectious disease in the world with 1.5 million people dying from TB in 2020 (World Health Organization (WHO) 2021 Report). The COVID-19 pandemic has had significant negative impacts on TB control efforts worldwide with increases in TB burden and mortality expected for years to come (McQuaid et al, 2021).

2.2 TB Treatment

The current standard of care for treating individuals of all ages with DS TB consists of an intensive phase of 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE) followed by a continuation phase of 4 months of isoniazid and rifampin; this treatment regimen was first introduced as the standard of care more than 40 years ago (WHO Treatment Guidelines for National TB Programs, 2020). Though highly efficacious, several key issues are associated with administering this regimen effectively on a global scale. The duration and complexity results in missed doses and incomplete courses, which leads to suboptimal treatment response (failure and relapse) and emergence of resistance, including MDR Mtb strains resistant to at least isoniazid and rifampin with on-going spread of the infection. While treatment options for MDR TB have improved in the last decade with regards to shorter duration and improved efficacy, toxicities remain significant, and access to these improved regimens, such as the recently WHO-endorsed 6-month regimens of bedaquiline (B), pretomanid (Pa), and linezolid (L; BpaL) and BpaL plus moxifloxacin (M; BpaLM), are currently limited Mirzayev et al, 2021).

2.3 MK-7762

MK-7762 is a member of the oxazolidinone class. Oxazolidinones are active against Mtb, and linezolid (Zyvox®), the first drug licensed from the class, is an important component of treatment regimens for MDR- and XDR-TB. Linezolid has demonstrated the ability to durably cure upwards of 71% of patients with chronic XDR-TB even when it was likely the only anti-TB agent with significant activity administered (Lee et al, 2015; Tang et al, 2015). More recently, linezolid, administered in combination with bedaquiline and pretomanid for at least 6 months, resulted in 90% durable cure of a difficult-to-treat MDR- and XDR-TB population (Conradie et al, 2020); these results provided support for the approval of pretomanid for use in combination with bedaquiline and linezolid (BpaL) by the FDA and the European Medicines Agency (EMA) for treatment of treatment-intolerant or non-responsive MDR-TB and XDR-TB. MK-7762, like other oxazolidinones, interrupts protein synthesis via the inhibition of translation by binding with the 23S subunit of the 50S ribosome resulting in the inability to form the tRNA initiation complex. No drugs currently used for DS-TB treatment target mycobacterial protein synthesis, resulting in low rates of pre-existing resistance and cross-resistance. Given this low existing resistance and their potency, oxazolidinones represent an important class for inclusion in potential new regimens.

An important limitation of linezolid is its associated toxicities of hematologic toxicity (anemia, leukopenia, thrombocytopenia), peripheral sensory neuropathy, optic neuropathy, and lactic acidosis. These toxicities are thought to be mediated through the inhibition of human MPS. In short-term healthy volunteer studies (21 to 28 days) of linezolid and other oxazolidinones (tedizolid and delpazolid) (Lodise et al, 2016; Choi et al, 2018), hematologic changes were observed in some participants within 14-28 days as evidenced by decreases in platelet counts, hemoglobin, and other indices. Such hematologic changes may reflect early signs of myelosuppression and are in line with early hematologic changes observed in linezolid-treated patients within the first 25 days of treatment (Gerson et al, 2002). The 28-day dosing period of MK-7762 in the multiple ascending dose part of this trial is designed to evaluate for potential hematologic toxicities of MK-7762 based on this known class effect.

Linezolid and other oxazolidinones also reversibly inhibit monoamine oxidase (MAO)-A and -B, which can precipitate serotonin toxicity. MAO-A and MAO-B aid in serotonin clearance in the central nervous system. The risk of serotonin toxicity from oxazolidinones is significantly increased when they are co-administered with other drugs that inhibit serotonin metabolism or if tyramine-containing foods or beverages are consumed.

2.3.1 Nonclinical Development of MK-7762

In vitro studies with MK-7762 were found to have similar anti-mycobacterial potency to linezolid with minimum inhibitory concentration required for 90% growth inhibition (MIC_{90}) of 0.78 uM and 1.6 uM, respectively. MK-7762 exhibited comparable reduction in CFUs of TB with linezolid and sutezolid in a chronic mouse TB infection model. MK-7762 showed similar additive CFU reduction to linezolid, but less than sutezolid, when added to a 2-drug backbone of bedaquiline and pretomanid in BALB/c mice.

Importantly, MK-7762 was found to be less potent at MPS inhibition compared to linezolid with IC_{50} values of >50 to >100 μM versus 13 to 30 μM, respectively.

MK-7762 was characterized in 28-day pivotal Good Laboratory Practices (GLP) studies in rats and dogs following once daily oral administration at 50, 250, and 1000 mg/kg/day in rats and 5, 25, and 75 mg/kg/day in dogs. The primary effect of MK7762 in rats was significant lowering of food consumption and body weights in females that triggered a sequalae of secondary effects, including findings in adrenal glands, bone marrow, lymphoid organs, and female reproductive organs at doses ≥250 mg/kg/day. The primary effect of MK7762 in dogs in a 14-day exploratory or 28-day pivotal study was decreased body weight gain and/or body weight loss at doses ≥75 mg/kg/day. Bone and bone marrow (decreased cellularity) were identified as target organs in 1 male at 200 mg/kg/day in the 14-day study; however, these findings did not progress in longer duration studies, and no target organs were identified at doses up to 75 mg/kg/day in the 28-day study. Based on these findings, the NOAEL in dogs was 75 mg/kg/day. The rat was identified as the most sensitive species, and because of sex differences in toxicity, the NOAEL was considered to be 50 mg/kg/day in female rats. Additional studies to assess the mutagenic potential of MK-7762 in mammalian cells concluded that the compound did not induce mutation at the *hprt* locus of Chinese hamster ovary (CHO) cells when tested up to the maximum concentration required by regulatory guidelines. The overall conclusion from the submitted genotoxicity package, and the additional studies, was that MK-7762 was not genotoxic.

Notable inhibition of MAO-B (IC_{50}: 6.8 μM) by MK-7762 occurred at concentrations that could be achievable in human plasma at the proposed initial clinical doses. Inhibition of MAO-B could

impact disposition of dietary tyramine, and interaction with serotonergic drugs is possible. Concomitant medications that may also increase serotonin levels, such as MAO inhibitors and selective serotonin reuptake inhibitor antidepressants, will not be permitted in this FIH trial (see Appendix 2).

PK studies in animals suggest an elimination half-life appropriate for once-daily dosing (12 hours) and a predicted human daily dose range of 150-300 mg to maintain trough plasma levels above the minimum inhibitory concentration (MIC). In vitro dissolution and animal data suggest there is little potential for food to impact the PK of MK-7762. Nevertheless, early characterization of a potential food effect will support the future development of MK-7762.

Full details of the nonclinical toxicology, pharmacology, and PK studies of MK-7762 can be found in the Investigator's brochure.

2.3.2 Clinical Development of MK-7762 - Results from Part 1

TBD09-101 Part 1 was completed on 18 July 2023. A comprehensive interim review of the unblinded clinical safety and PK data for Cohorts 1 through 6 is summarized herein.

The highest dose tested in Part 1 was 1200 mg following SRT review of cumulative safety and mean PK results from earlier cohorts. The maximal exposure produced by a single 1200 mg dose was predicted to be below the NOAEL levels established in the 28-day GLP toxicology study (AUC_{ss} 1040 µM·h and $C_{max,ss}$ of 66 µM; see Table 7).

The dose selected to be administered to the FE Cohort (Part 1, Cohort 6) was 300 mg based on the Sponsor's review of the available MK-7762 safety and PK data collected from earlier cohorts. The washout period was established as at least 8 days, consistent with 5 half-lives of MK-7762 determined by the SAD cohorts' PK results.

2.3.2.1 Part 1 Safety Results

Overall, in Part 1, 48 participants were enrolled with 10 receiving placebo and 38 receiving MK-7762. In SAD Cohorts 1-5,40 participants were enrolled with 10 receiving placebo and 30 receiving MK-7762 (6 participants in each cohort received 50 mg, 150 mg, 300 mg, 600 mg, or 1200 mg). In FE Cohort 6, 8 participants received a single dose of 300 mg MK-7762 in a randomized crossover design evaluating both fasted and fed states. Across all cohorts, all participants received the assigned treatment and completed the trial.

In Part 1, MK-7762 was generally well-tolerated with an acceptable safety profile. TEAEs in the Safety Population were observed in 4 participants (11%) who received MK-7762 at any dose and 2 participants (20%) in the placebo group. Of the 4 participants who received MK-7762 and reported any TEAE, 3 had a maximal severity of Grade 1 (mild) and 1 had a maximal severity of Grade 2 (moderate). Of the 4 participants who received MK-7762 and experienced a TEAE, 2 participants (5%) experienced TEAEs considered to be related to study drug. Among the 10 participants who received placebo, 2 (20%) reported any TEAE (1 was Grade 1 and 1 was Grade 2). No TEAEs led to trial discontinuation. There were no Grade 3 (severe) or 4 (potentially life-threatening) TEAEs. There were no SAEs, AESIs or deaths in Part 1 of the trial. There was no TEAE reported by more than 1 participant receiving MK-7762. Two participants in FE Cohort 6 had a Grade 3 elevated low-density lipoprotein (LDL) cholesterol laboratory abnormality (neither reported as an AE). There were no Grade 4 laboratory abnormalities and no clinically significant trends in the laboratory results (including hematologic parameters), vital signs, or ECGs.

2.3.2.2 Part 1 PK Results

Table 7 summarizes the observed mean PK results from Part 1 of the trial. Review of the time versus concentration profiles for all Part 1 participants suggests that plasma levels notably increased for all participants within several hours after dosing. Dose proportional increases in exposure were observed up through 300 mg after which plateauing of C_{max} occurred and non-linear increases in AUC_{last} were seen. The observed half-life was 20-27 hours across all cohorts, notably longer than the 12-hour half-life projected from animal studies (see Section 2.3.1). Ingestion of a high-fat, high-calorie meal prior to MK-7762 administration resulted in a 56% and 12% increase in mean C_{max} and $AUC_{0\text{-}inf,}$ respectively, compared to administration in the fasted state.

Table 7 MK-7762 Mean PK Parameters in µM Following a Single Dose Administration of MK-7762 – Cohorts 1 to 6 (Part 1)

	Cohort							
	1 – SAD	2 – SAD	3 – SAD	4 – SAD	5 – SAD	6 – FE[c]		
	50 mg MK-7762	150 mg MK-7762	300 mg MK-7762	600 mg MK-7762	1200 mg MK-7762	300 mg MK-7762 (fasted)	300 mg MK-7762 (fed)	Geometric Mean Ratio (fed:fasted)
PK Parameter (Unit)	N = 6	N = 6	N = 6	N = 6	N = 6	N = 8	N = 8	N = 8
$AUC_{0\text{-}24}$ (h*µM)	25.80 (19.6)	71.40 (21.5)	136.0 (25.4)	143.0 (29.6)	128.0 (18.1)	119.0 (19.9)	164.0 (17.3)	1.378
$AUC_{0\text{-}72}$ (h* µM)	44.10 (30.0)	166.0 (13.8)	284.0 (28.4)	399.0 (27.2)	441.0 (20.2)	293.0 (23.2)	339.0 (21.2)	1.157
AUC_{last} (h* µM)	43.90 (30.8)	184.0 (21.2)	309.0 (34.0)	473.0 (30.5)	676.0 (41.0)	341.0 (33.5)	394.0 (26.8)	1.155
$AUC_{0\text{-}inf}$ (h* µM)	50.50 (29.8)	215.0 (11.8) [a]	326.0 (32.3)	490.0 (30.0)	486.0 (11.3) [b]	362.0 (30.2)	406.0 (27.0)	1.121
C_{max} (µM)	1.440 (15.5)	3.590 (22.1)	7.310 (30.0)	7.240 (27.2)	7.770 (19.1)	6.190 (20.0)	9.680 (17.0)	1.564
C_{24} (µM)	0.812 (30.8)	3.140 (13.1)	5.470 (32.0)	7.060 (24.6)	6.650 (18.3)	5.580 (18.9)	6.590 (21.6)	1.181
t_{max} (hours)	4.50 (3.00 – 8.00)	10.00 (5.00 – 24.00)	10.02 (6.00 – 24.00)	24.00 (8.00 – 36.00)	30.01 (8.01 – 72.1)	18.00 (6.00 – 24.00)	7.00 (5.00 – 24.00)	-11[d]
$t_{1/2}$ (hours)	20.3 (15.6)	27.4 (9.4)[a]	21.2 (19.7)	21.7 (13.9)	22.2 (14.3)[b]	25.3 (20.0)	24.8 (22.9)	NA

AUC=Area under the curve; C_{max}=Maximum concentration, NA=Not applicable
Note: All values were presented as geometric mean (geometric coefficient of variation (CV)(%) except for t_{max} which is presented as median (min-max)
[a] N = 5 due to AUC Extrapolation >20% (i.e., terminal phase unreliable)
[b] N = 3 due to AUC Extrapolation >20% (i.e., terminal phase unreliable)
[c]Food effect following a high fat meal.
[d]Absolute change in the T_{max} of fed vs fasted

2.4 Trial Rationale

Despite the steady progress made over the past two decades in responding to and controlling the global TB pandemic, there remains an urgent need for the development of new potent anti-TB agents and combination regimens with low toxicity that are effective against both DS and DR strains of Mtb ('pan-TB' regimens) and can shorten duration of TB treatment. MK-7762 has the potential to be a safer oxazolidinone than linezolid based on nonclinical studies showing anti-TB

activity comparable to linezolid, lower in vitro MPS inhibition, which is believed to be the off-target mechanism for oxazolidinone class toxicities, and established NOAELs in pivotal repeat-dose studies with sufficient multiples. The more limited use of linezolid essentially for DR-TB to date and current lack of other Mtb protein synthesis inhibitors further support development of MK-7762 as a potential key component in a novel TB treatment regimen.

The goal of the clinical development program for MK-7762 is to develop a safe, effective, and affordable anti-TB agent that can meaningfully contribute to a pan-TB regimen capable of treating DS and DR pulmonary TB in 3 months or less. The clinical development approach is to first evaluate MK-7762 across a wide range of doses in healthy participants in single and multiple doses to assess its safety and PK. MK-7762 will be specifically evaluated in cohorts administered MK-7762 for 1 month and at the projected clinically efficacious dose to characterize the compound's longer term safety profile with specific attention to the known hematologic and neurologic toxicities associated with the oxazolidinone class.

2.5 Human Efficacious Concentration Prediction

The minimum acceptable PK threshold for MK-7762 is considered to be one that matches the efficacious concentrations of linezolid, another oxazolidinone with the same mechanism of action. The potency of MK-7762 against Mtb H37Rv was determined as 0.93 µM and the MIC_{90} (i.e., the concentration required for complete growth inhibition of 90% (MIC_{90}) was determined for a panel of 50 clinical Mtb isolate strains) as 0.78 µM. Given that protein binding in human plasma is approximately 30%, the estimated linezolid-equivalent efficacy target in total plasma is 1.1 µM. Therefore, the following efficacy exposure thresholds based on MIC_{90} were identified:

- minimal (trough) concentrations ($C_{min,ss}$) above efficacy level: $C_{24h} \geq 1.1$ µM (for a once daily (QD) regimen).
- daily exposure at least 80 times higher than the MIC (for linezolid at 600 mg twice daily, the area under the concentration curve to MIC [AUC/MIC] ratio is ≥80) (Dietze et al, 2008)

To further understand the predicted efficacy of MK-7762, a recognized mouse-to-human translational platform was used (Ernest et al, 2023). This platform, previously verified with clinical early bactericidal activity (EBA) data from other anti-TB drugs, utilizes preclinical in vivo mice pharmacokinetic-pharmacodynamic (PKPD) data in combination with a model-centric translational pharmacology method to predict the clinical bactericidal activity of MK-7762.

This translational platform was developed using an exhaustive preclinical and clinical data repository on PK, PD, and initial bacterial growth for a collection of ten anti-TB drugs, including linezolid (Ernest et al, 2023). These drugs, which were instrumental in the creation and validation of the platform, include a bacteriostatic antibiotic (ethambutol), five bactericidal antibiotics (isoniazid, delamanid, pretomanid, linezolid, and moxifloxacin), as well as four sterilizing antibiotics (rifampin, rifapentine, pyrazinamide, and bedaquiline). The translational model has been shown to accurately predict clinical efficacy as measured by the observed daily decreases of CFU in the first 2 days of treatment and between day 2 and day 14 in the clinical EBA trials previously conducted for these ten drugs.

For MK-7762, mouse PK and PKPD models were established to identify an exposure-response relationship and used to make predictive translations of bactericidal activity of MK-7762 administered as monotherapy and in combination with bedaquiline and pretomanid in a Phase 2a

EBA study. The estimated effective trough MK-7762 concentrations predicted to achieve 50% (EC_{50}), 80% (EC_{80}), and 90% (EC_{90}) of maximum response when administered alone (monotherapy) were 11.15 µM, 23.32 µM, and 35.87 µM (data on file). The estimated effective trough MK-7762 concentrations predicted to achieve 50% (EC_{50}), 80% (EC_{80}), and 90% (EC_{90}) of maximum response when administered in combination with bedaquiline and pretomanid were 4.08 µM, 16.36 µM, and 36.77 µM, respectively (data on file).

The human efficacious concentrations predicted from the in vitro MIC_{90} were used to select the range of doses to be evaluated in Part 1 (SAD/FE). Both the in vitro MIC_{90} and the in vivo translational PKPD model were used to select the doses to be evaluated in Part 2 (MAD/FE) along with the Part 1 safety and PK data (see Section 2.3.2).

2.6 Justification for Doses

2.6.1 Part 1 (SAD/FE)

The preliminary selection of the dose range to be tested in Part 1 is based on NOAEL values from the 28-day GLP toxicology studies and in vitro and in vivo efficacy.

The NOAEL/NOEL doses, human equivalent dose (HED), exposures, and projected safety multiples in rats and dogs from pivotal toxicology studies are shown in Table 8 below. The rat was identified as the most sensitive species in the pivotal 28-day study. Due to sex differences in toxicity, the NOAEL in rats was 50 mg/kg/day in females. The NOAEL in rats supports a Maximum Recommended Starting Dose (MRSD) of 48.6 mg (FDA, 2005) with an applied safety factor of 10, which approximates the proposed clinical starting dose of 50 mg in this Investigational New Drug (IND)-opening Phase 1 study in healthy adult volunteers. This NOAEL also provides approximate exposure multiples of 47 based on predicted human AUC at a 50 mg dose.

Table 8 Projected Safety Multiples for Pivotal MK-7762 Studies

Species and Study	NOAEL/NOEL					EMs at SAD Doses [a]		
	Dose (mg/kg)	Dose [b] (mg/m^2)	AUC [c] (µM•h)	C_{max} [c] (µM)	HED [b] (mg)	Parameter	50 mg [b] (30.8 mg/m^2)	600 mg [b] (370 mg/m^2)
Rat, females, NOAEL 28-day toxicity	50	300	1040	66.6	486	Dose	9.7	0.81
						AUC	47	3.9
						C_{max}	47	3.7
Dog, NOAEL 28-day	75	1500	1210	71.8	2432	Dose	49	4.0
						AUC	55	4.6
						C_{max}	51	4.0
Rat, NOEL CNS, SD	250	1500	NA	47.4[d]	2432	Dose	49	4.1
						C_{max}	34	2.7
Rat, NOEL respiratory, SD	1000	6000	NA	67.2[d]	9730	Dose	195	16
						C_{max}	48	3.8
Dog, NOEL CV, SD	40	800	NA	43.9[e]	1297	Dose	26	2.2
						C_{max}	31	2.5

Species and Study	NOAEL/NOEL					EMs at SAD Doses [a]		
	Dose (mg/kg)	Dose [b] (mg/m^2)	AUC [c] (µM•h)	C_{max} [c] (µM)	HED [b] (mg)	Parameter	50 mg [b] ($30.8 mg/m^2$)	600 mg [b] ($370 mg/m^2$)

AUC=Area under the curve; C_{max}=Maximum concentration; CNS=Central nervous system; CV=Cardiovascular; EM=Exposure multiples; GLP=Good Laboratory Practice; HED=Human equivalent dose; NA=Not applicable; NOAEL=No observed adverse effect level; SAD=Single ascending dose; SD=Single dose

[a] Based on proposed human starting and ending doses of 50 and 600 mg respectively, and projected systemic exposure of 1.4 µM (C_{max}) and 22 µM•h (AUC) at 50 mg and 17.7 µM (C_{max}) and 265 µM•h (AUC) at 600 mg.

[b] Conversion of doses based on body surface area using the following conversion factors: rat ~6; dog ~20; human ~37. The conversion factor for humans is based on 60 kg body weight.

[c] Unless indicated, data represent mean steady-state AUC and C_{max} values from female rats and sex-averaged from monkeys.

[d] Data represents mean C_{max} in males on Day 1 in the 28-day rat GLP study.

[e] Data represents mean C_{max} in females on Day 1 in 14-day dog study (no sex differences in dogs in 28-day study).

The highest dose to be tested in Part 1 is not pre-defined and will be determined following SRT review of evolving safety data (number, severity, and frequency of AEs) and available PK data from earlier cohorts. The maximal exposure target will be below the NOAEL levels (AUC_{ss} 1040 µM·h and $C_{max,ss}$ of 66 µM).

Selection of the dose administered to the FE Cohort (Part 1, Cohort 6) will be made by the Sponsor and will be determined by available MK-7762 PK data collected from earlier cohorts.

The wide dose range to be tested in healthy adults will cover the anticipated target exposures in TB patients. The safety and PK data from Part 1 will enable proceeding to Part 2 following the planned interim review (see Section 1.1.3.2) where multiple doses of MK-7762 will be administered.

2.6.2 Part 2

2.6.2.1 Food Effect Cohort 7

The goal of FE Cohort 7 is to describe the variability in exposure caused by the two different meal types to further investigate the increase in mean exposure observed after administration of 300 mg of MK-7762 in FE Cohort 6 with a high-fat, high-calorie meal (see Table 8). A dose of 600 mg was selected for evaluation in FE Cohort 7 based on the overall safety analysis in Part 1, in which single doses were administered up to 1200 mg in the fasted state and 300 mg in the fed state (high-fat meal) and where a non-linear increase in exposure was observed above 300 mg in Part 1. MAD participants will be randomized to receive MK-7762 or placebo in the fasted or fed state after a standard breakfast, and the safety and PK results of FE Cohort 7 will inform selection of the MK-7762 dose to be evaluated in MAD Cohort 10.

2.6.2.2 MAD Cohorts 8-10

The goal of the MAD portion of Part 2 is to characterize the safety of multiple dose levels of MK-7762 administered once daily for 28 days that generate steady-state exposures at and/or above the efficacy targets (see Section 2.5). Three dose levels are planned to be tested in the 28-day MAD cohorts in Part 2: MAD Cohort 8 will evaluate MK-7762 100 mg once daily (QD); MAD Cohort 9 will evaluate MK-7762 300 mg QD; and the anticipated MK-7762 QD dose to be evaluated in MAD Cohort 10 is 500 mg, which may be modified through a protocol amendment after review of PK and safety data from FE Cohort 7 and MAD Cohorts 8 and 9. The dose in MAD Cohort 10 will not exceed 600 mg QD. These doses are selected based on the range of

doses evaluated in Part 1 and the safety profile associated with the observed exposures. In addition, these doses are projected to result in efficacious concentrations in patients.

In Part 1, healthy participants received single doses of MK-7762 50 mg – 1200 mg administered in the fasted state and 300 mg in the fed state after a high fat meal. The detailed PK results are included in Section 2.3.2.2. Across the dose range and observed exposures, MK-7762 was generally well-tolerated and had an acceptable safety profile (Section 2.3.2.1). The greatest observed $C_{max,ss}$ observed in Part 1 was 9.7 µM with 300 mg (fed) in FE Cohort 6 and the greatest observed AUC_{ss} was 676 µM*hr with 1200 mg (fasted) in SAD Cohort 5.

A population PK model was developed to describe the concentration time profiles from Part 1 of the trial (SAD+FE). This model was used in a simulation mode to predict steady state exposures following various multiple dose scenarios (Population PK Report). The predicted mean (95% CI) steady state exposures at the planned doses for MAD Cohorts 8-10 are shown in Table 9.

Table 9 Predicted Multi-Dose Steady State Exposures

PK Parameter	Fasted			Fed (high fat meal)		
	100 mg QD	300 mg QD	500 mg QD	100 mg QD	300 mg QD	500 mg QD
$C_{max,ss}$ (µM)	5.97 (4.16, 8.80)	17.2 (11.3, 30.2)	21.9 (13.8, 43.0)	7.26 (5.06, 10.7)	21.0 (13.7, 36.7)	26.7 (16.7, 52.3)
$C_{min,ss}$ (µM)	4.21 (2.84, 6.47)	9.98 (6.46, 16.6)	14.9 (8.68, 28.3)	5.13 (3.45, 7.87)	12.2 (7.86, 20.1)	18.1 (10.6, 34.4)
AUC_{ss} (µM*hr)	121 (84.9, 176)	316 (213, 494)	444 (283, 790)	147 (103, 215)	385 (259, 601)	540 (345, 962)

Source: Population PK Report

The low dose in the first MAD cohort, 100 mg QD, is predicted to have a mean $C_{max,ss}$ of 5.97 µM in the fasted state and 7.26 µM in the fed state, which is below the highest exposure observed in Part 1 (9.7 µM). The predicted mean $C_{max,ss}$ for all planned doses in Part 2 are less than the MPS inhibition threshold (50 µM) and below the NOEL/NOAEL observed in the safety pharmacology and 28-day pivotal GLP studies. The predicted mean AUCss for all 3 planned doses are less than the highest exposure observed in Part 1 (676 h*µM) and are also below the NOAEL observed in 28-day pivotal GLP studies (1040 h*µM).

The proposed duration for MAD Cohorts 8-10 is 28 days of daily dosing. In short term studies (21 to28 days) of linezolid and other oxazolidinones (tedizolid and delpazolid), hematologic changes were observed in some participants within 14-28 days (Gerson et al, 2002; Lodise et al, 2016; Choi et al, 2018). While steady-state plasma levels of MK-7762 are expected to be reached in 7 days based on the population PK model predictions, the 28-day dosing period of MK-7762 in the multiple ascending dose part of this trial is designed to evaluate the potential hematologic effects of MK-7762 based on this known class effect.

Lastly, with regard to safety, all participants in Part 2 will be admitted to the CTU for close monitoring during dosing and until 1 week post dosing (Section 1.1.3.3). Enrollment of the MAD cohorts will be sequential and safety and PK data from each cohort will be reviewed prior to enrollment of participants to receive higher doses (Section 4.4).

Additionally, the planned doses provide a range of concentrations across which MK-7762 may be efficacious as predicted by various methodologies (Section 2.5). All 3 doses of MK-7762 are projected to produce mean minimal (trough) concentrations at steady-state ($C_{min,ss}$) which are

more than 2-fold greater than the efficacy exposure threshold of 1.1 μM based on MIC_{90} and also result in a daily exposure more than 80 times the MIC_{90} (area under the concentration curve at steady-state AUC_{ss}/MIC_{90} ratios). The projected $C_{min,ss}$ for MK-7762 100 mg (4.21 μM and 5.13 μM in the fasted and fed states, respectively) and for MK-7762 300 mg (9.98 μM and 12.2 μM in the fasted and fed states, respectively) are in the range of the predicted EC_{50} (4.08 uM) using the in vivo translational PKPD model for MK-7762 when administered with bedaquiline and pretomanid. Similarly, the projected $C_{min,ss}$ for MK-7762 500 mg (14.9 μM and 18.1 μM in the fasted and fed states, respectively) is in the range of the EC_{80} (16.36 μM).

In summary, the doses selected for the Part 2 MAD cohorts are expected to be safe and well tolerated by participants and below the NOAEL observed in the 28-day pivotal GLP studies. The low dose is predicted to result in exposures below the highest exposure observed in Part 1, and, during dose escalations, participants will be confined to clinic and closely monitored for safety during the dose escalations. Additionally, the planned doses will provide a range of exposures across which MK-7762 may be efficacious as predicted by various methodologies, which will help to inform dose selection in future studies of bactericidal effects and efficacy of MK-7762.

2.7 Benefit/Risk Assessment

The clinical risks when MK-7762 is administered to humans have not yet been established and no direct benefits are anticipated for the healthy adults enrolled in this Phase 1 FIH trial.

Anticipated potential risks to humans from administration of MK-7762 stem from the known oxazolidinone class toxicities which include hematologic toxicity (anemia, leukopenia, and thrombocytopenia), neuropathies (peripheral and optic neuropathy), lactic acidosis, and serotonin syndrome.

Reversible hematologic toxicities, particularly thrombocytopenia, have been observed in healthy participants administered linezolid, tedizolid (another marketed oxazolidinone), and delpazolid (an investigational oxazolidinone) for 21 days. A similar pattern is observed in TB patients administered linezolid (Lodise et al, 2016; Choi et al, 2018).

Neuropathies take longer to appear than hematologic toxicities in TB patients receiving linezolid; the majority of patients in the Nix-TB trial that interrupted linezolid due to peripheral neuropathy (with linezolid administered at 1200 mg once daily) did so after 3 months of treatment (Conradie et al, 2020).

Serotonin syndrome attributed to linezolid is rare and almost always occurs when another serotonergic medication or food is taken concomitantly (ZYVOX® Product Label, 2013).

In vitro data indicate that MK-7762 has markedly reduced potency for inhibition of MPS than linezolid, which is believed to be the underlying mechanism for toxicities attributed to oxazolidinones. Inhibition of MAO-B by MK-7762 occurs at concentrations that could be achievable in human plasma in the initial clinical trials, which could impact disposition of dietary tyramine, and interaction with serotonergic drugs is possible.

MK-7762 showed reduced activity against linezolid-resistant clinical isolates with mutations in the same domain of the 23S ribosomal ribonucleic acid (rRNA) gene in in vitro experiments confirming they share a common binding site. Knowledge of the global epidemiology of the emergence of Mtb resistance to linezolid is limited, but the use of linezolid in the treatment of MDR- and XDR-TB has significantly increased in recent years due to more evidence of its contribution to durable TB cure and WHO guidelines recommending its use for DR-TB (WHO,

2020). It will be important to expand population-based surveillance of resistance to linezolid and other oxazolidinones among DS- and DR-TB populations to assess the impact of any emerging resistance on the potential utility of oxazolidinones like MK-7762 to contribute to a pan-TB regimen.

3 OBJECTIVES AND ENDPOINTS

Table 1 in Section 1.1 outlines study objectives, endpoints, and estimands.

4 TRIAL DESIGN

This is a first-in-human trial of MK-7762, administered to healthy adults. It is a randomized, double-blind, placebo-controlled, two-part trial. Healthy adult participants between 19 to 55 years of age (inclusive) of both sexes who are capable of and willing to provide informed consent will be eligible for the trial. See Section 5.1 and Section 5.2 for inclusion and exclusion criteria.

The trial will be conducted in two parts: Part 1 - 5 SAD cohorts (double-blind, placebo-controlled) (N=40) and a FE cohort (open-label) enrolling 8 participants and Part 2 - 3 MAD cohorts (double-blind, placebo-controlled) (N=60) and a FE cohort (open-label) enrolling 9 participants. Because this trial is aimed at characterizing the safety, tolerability, and PK of MK-7762, it is designed to be descriptive and is not based on formal hypothesis testing. Therefore, this trial is not powered to detect any pre-specified differences in potential safety or PK data between treatment groups. A total of approximately 117 participants will be randomized (48 in Part 1 and 69 in Part 2), and a total of approximately 95 participants will be exposed to MK-7762 (38 from Part 1 and 57 from Part 2).

The trial has a double-blind design in which all participants in SAD Cohorts 1-5 and MAD Cohorts 8-10 and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at the trial site who will prepare oral doses of MK-7762 and placebo appropriately masked for site personnel who are authorized to administer treatment. All doses of MK-7762 administered to all participants in FE Cohort 6 and FE Cohort 7 will be open-label.

4.1 Part 1 – SAD and Food Effect (SAD/FE)

Gates MRI-TBD09-101, Amendment 4 (Version 5.0)
Part 1 of this trial has been completed. See Section 2.3.2 for results from Part 1. • The dose of MK-7762 for SAD Cohort 5 was 1200 mg. • The dose of MK-7762 for FE Cohort 6 was 300 mg. • The washout period between doses in FE Cohort 6 was 8 days.

In Part 1 of the trial (SAD/FE), five sequential cohorts will be enrolled to evaluate 5 escalating single doses of MK-7762; eight participants in each cohort will be randomized (3:1) to receive MK-7762 or placebo. A sixth cohort will evaluate the effect of food on PK of single doses of MK-7762 utilizing an open-label, single-dose cross-over design in 8 participants. The MK-7762 dose to be evaluated in the FE Cohort will be a dose demonstrated to be safe and well-tolerated in previously completed SAD cohorts. All participants in Part 1 will be confined at the trial site from Day -1 until their end-of-trial visit (approximately 8 days for Cohorts 1-5 and 16 days for Cohort 6).

Cohorts 1 - 4 are planned to evaluate the safety and PK of single oral doses of MK-7762 of 50 mg, 150 mg, 300 mg, and 600 mg. Cohort 5 may evaluate a dose of MK-7762 that will be selected based on the safety and PK data from previous cohorts. The dose of MK-7762 chosen for evaluation in Cohort 5 will not result in greater predicted exposure than that allowable based on the nonclinical toxicology NOAEL.

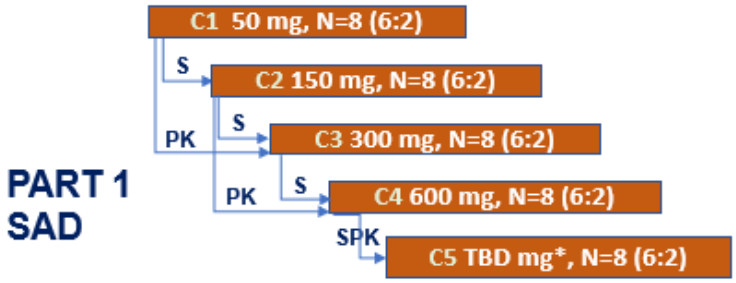
For Cohort 6 (the FE Cohort), eight participants will be dosed with MK-7762 in both fasted and fed states with a between-dose washout period of at least 5 half-lives of MK-7762 determined by

the SAD cohorts PK results. The MK-7762 dose to be evaluated in the FE Cohort will be a dose demonstrated to be safe and well-tolerated in a previously completed SAD cohort. Two sentinel participants in Cohort 6 will be dosed in the fed state first followed by the second dose in the fasted state after washout. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing period. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 6 will receive MK 7762 in fed and fasted states in a crossover manner employing the washout period previously determined. The FE Cohort may start following review of 4 days of safety data from Cohort 4, and 48-hour PK data from Cohort 3. The FE Cohort (Periods 6 and 7) may start before Cohort 5 if PK data from Cohorts 1-4 are sufficient for selecting the dose to be evaluated in the FE Cohort.

The doses of MK-7762 to be administered in any of the cohorts following Cohort 1 may be modified based on accumulating safety, tolerability, and PK data. The Protocol may be amended to enroll additional participants at any of the planned dose level(s) or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previously completed cohorts.

If more than 1 participant from Cohort 6 is withdrawn from the trial after receiving the first dose but before receiving the second dose of study drug, additional participants will be enrolled to replace the withdrawn participants. No replacements are required if only one participant is withdrawn from Cohort 6 before receiving the second dose of study drug.

Figure 2 Schema of Part 1, SAD Cohorts 1-5



C = Cohort; S = Safety data; PK = Pharmacokinetic data; SPK = Safety and PK data; TBD = To be determined
*C5 dose = 1200 mg (Section 2.3.2)

Table 10 Single Ascending Dose (Part 1) – Planned Dose Cohorts 1-5

Cohort	n	Dose Levels				
1	6	50 mg				
	2	PBO				
2[a]	6		150 mg			
	2		PBO			
3[b]	6			300 mg		
	2			PBO		
4[c]	6				600 mg	
	2				PBO	
5[d]	6					TBD[e]
	2					PBO

PBO = placebo
All suggested doses may be adjusted based on evaluation of safety, tolerability, or PK data observed in previous participants.
[a] Cohort 2 dosing will occur after review of safety data through at least Day 4 post dose administration for all participants in Cohort 1 (no PK data will be reviewed).
[b] Cohort 3 dosing will occur after review of safety data through at least Day 4 post dose administration for all participants in Cohort 2. Aggregated 48-hour PK data (mean) from Cohort 1 will be available for review.
[c] Cohort 4 dosing will occur after review of safety data through at least Day 4 post dose administration for all participants in Cohort 3. Aggregated 48-hour PK data (mean) from Cohort 2 will be available for review.
[d] Cohort 5 dosing will occur after review of safety data through at least Day 4 post dose administration for all participants in Cohort 4. Aggregated 48-hour PK data (mean) from Cohort 4 will be available for review.
[e] TBD = 1200 mg (see Section 2.3.2)

Figure 3 Schema of Part 1, FE Cohort 6

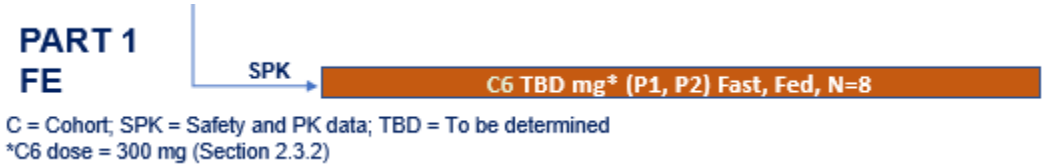


Table 11 Food Effect (Part 1) – Planned Dose Cohort 6

Cohort	Sequence	n	Period	
			1[a]	2[a]
6 (FE)	1	3	TBD mg fasted[b]	TBD mg fed[b]
	2	5	TBD mg fed[b]	TBD mg fasted[b]

TBD = to be determined
Cohort 6 MK-7762 dose to be administered will be selected based on evaluation of safety, tolerability, or PK data observed in previous participants.
[a] The second dose of MK-7762 will be administered no earlier than 5 half-lives of MK-7762 after PK data from prior dose levels are reviewed to determine half-life. Two sentinel participants will be dosed in the fed state first followed by the second dose in the fasted state after washout. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing period. If recommended by the SRT and approved by the Sponsor, the remaining six participants will receive doses of MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.
[b] TBD = 300 mg (see Section 2.3.2)

4.1.1 Screening (Day -21 to -2)

See Section 1.1.3.1 for details of the screening and confinement periods for all Part 1 participants (SAD Cohorts 1-5 and FE Cohort 6).

4.2 Part 2 –Food Effect and MAD (FE/MAD)

Screening and enrollment of participants in Part 2 of the trial will not commence until after the planned interim review of data from Part 1 and any available additional nonclinical data, and Sponsor agreement to continue the trial after regulatory review and approval (see Section 1.1.3.2).

Part 2 of the trial will consist of a FE cohort and three sequential MAD cohorts to evaluate escalating once daily doses of MK-7762 or placebo for 28 days. FE Cohort 7 will be an open-label, three-period evaluation of 600 mg of MK-7762 in at least 9 participants who should

complete each of the three dosing periods, separated by a washout period of at least 8 days (See Figure 4 and Table 12). If a participant from Cohort 7 withdraws from the trial after receiving no more than a single dose of MK-7762, the participant will be replaced. Participants who withdraw from the trial after receiving at least 2 doses of MK-7762 will not be replaced. Within each MAD cohort, half of the participants will be dosed in the fasted state and half of the participants will be dosed after a standard breakfast meal. Each of the three MAD cohorts will have approximately 20 participants randomized 4:4:1:1 to receive MK-7762 in fasted state, MK-7762 after standard breakfast meal, placebo in fasted state, or placebo after standard breakfast meal. See Figure 5 and Table 10. If more than two participants from a MAD cohort are withdrawn from the trial before the Day 29 visit assessments are completed, additional participants will be enrolled with blinded treatment assignment matching that of the withdrawn participants. No replacement participants are required if two or fewer participants are withdrawn from a cohort before their Day 29 visit.

An additional MAD cohort may be considered for subsequent enrolment after protocol amendment to evaluate once daily doses of MK-7762 or placebo for up to 91 days based on findings from the 28-day MAD cohorts and the ongoing 4-month sub-chronic toxicology studies in rats and dogs.

In Part 2, effort will be made to enroll as many females as possible.

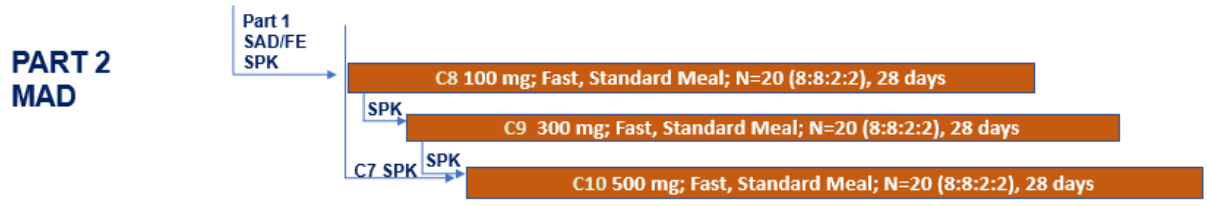
Figure 4 Schema of Part 2, FE Cohort 7

C = Cohort; P = Period; SPK = Safety and PK data; SD = Single dose

Table 12 Food Effect (Part 2) – Cohort 7

Cohort	Sequence	Period 1	Period 2	Period 3
7 (FE)	1	600 mg fasted	600 mg fed-standard meal	600 mg fed-high-fat meal
	2	600 mg fed-standard meal	600 mg fed-high-fat meal	600 mg fasted
	3	600 mg fed-high-fat meal	600 mg fasted	600 mg fed-standard meal

Figure 5 Schema of Part 2, MAD Cohorts 8-10



C = Cohort; SPK = Safety and PK data
*In C8-10, participants randomized 8:8:2:2 to receive MK-7762 in fasted state, MK-7762 after standard breakfast meal, placebo in fasted state, or placebo after standard breakfast meal

Table 13 Multiple Ascending Dose (Part 2) –Cohorts 8-10

Cohort	n	Dose Levels		
8	8	100 mg (fast)		
	8	100 mg (standard meal)		
	2	PBO (fast)		
	2	PBO (standard meal)		
9[a]	8		300 mg (fast)	
	8		300 mg (standard meal)	
	2		PBO (fast)	
	2		PBO (standard meal)	
10[b]	8			500 mg (fast)
	8			500 mg (standard meal)
	2			PBO (fast)
	2			PBO (standard meal)

PBO = placebo
All suggested doses may be adjusted based on evaluation of safety, tolerability, or PK data observed in previous participants.
[a] Cohort 9 dosing will occur after review of all safety data collected through Day 28 and PK data through Day 14 in Cohort 8 are available for review.
[b] Cohort 10 dosing will occur after review of all safety data collected through Day 28 and PK data through Day 14 in Cohort 9 are available for review.

4.2.1 Screening and Confinement Periods

See Section 1.1.3.3 for details of the screening, confinement, and post-discharge follow-up periods for all Part 2 participants (Cohort 7 FE and MAD Cohorts 8-10).

4.3 Trial Drug Administration

See Section 1.1.4 and Table 2 for details regarding study drug administration.

See the Schedule of Activities in Section 1.3 and Section 8 for details of assessments to be conducted and the schedules.

4.4 Criteria for Evaluation

4.4.1 Safety Variables

Safety variables will include adverse events; vital signs (blood pressure, heart rate, temperature); weight and BMI; 12-lead ECG parameters (RR, HR, PR, QRS, QT, and corrected QT [QTcF] intervals); continuous Holter monitoring with pre-dose and post-dose ECG extractions, as applicable; clinical laboratory assessments, including hematology, biochemistry, coagulation, and urinalysis; and physical examination findings, including assessments of visual acuity and color vision, and peripheral neuropathy screenings.

4.4.2 PK Variables

Plasma: C_{max}; T_{max}; AUC, AUC_{last}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}24}$; $t_{½}$; CL/F; and V_d/F.

Urine: Ae%, CLr, AUC metabolite/AUC MK-7762, and CUE.

See Section 9 for additional details regarding analysis.

4.5 Dose Escalation Decisions and Safety Review Team

A Safety Review Team (SRT) will be established as the team responsible for safety review and dose escalation recommendations during Part 1 and Part 2 of the trial. Details of the SRT will be contained in a charter that will describe the SRT review of blinded safety data and the deliberation processes (including the format of data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment (for SAD Cohorts 1-5 and MAD Cohorts 8-10), and when PK data are available, only aggregated mean PK data will be provided.

During Part 1 of the study, the SRT will convene after all participants in a specific cohort have completed 4 days of follow-up post-dosing and all safety data collected through Day 4 are available for review. Safety review will be conducted after completion of each of Cohorts 1, 2, 3, 4, and 5 (see Section 1.1.3). The SRT will have access to available aggregated mean PK data during its meetings to consider escalation to Cohorts 3, 4, and 5. The SRT may recommend dose escalation to a subsequent planned cohort if no pausing rule is present.

The first two participants in Cohort 1 will be dosed as sentinel participants in a blinded manner, randomized 1:1 to MK-7762 or placebo. The SRT will review safety data up to Day 4 following dosing for these two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 1 will receive single doses of study drug (randomized 5:1; MK-7762:placebo). If dose escalation is recommended following completion of Cohort 1 (50 mg), the single dose to be evaluated in Cohort 2 is planned as 150 mg. If dose escalation is recommended following completion of Cohort 2, the dose to be evaluated in Cohort 3 is planned as 300 mg. If dose escalation to Cohort 4 is recommended following completion of Cohort 3, the dose to be evaluated in Cohort 4 is planned as 600 mg. The dose to be evaluated in Cohort 5 will be decided by analysis of the safety and PK data available from the previously completed Cohorts 1 through 4.

In Cohort 6, two sentinel participants in Cohort 6 will be dosed in the fed state first followed by the second dose in the fasted state after washout. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing period. If recommended by the SRT and approved by the Sponsor, the two sentinel participants will be dosed with MK-7762 in the fed state after the washout period previously determined and the remaining 6 participants in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.

As described in Section 1.1.3.2, an interim review of data from Part 1 will be conducted in an unblinded manner by the Sponsor. Any additional relevant nonclinical data will also be reviewed as part of this process. The results of the interim review are intended for regulatory submission and comment and agreement prior to Part 2 of the trial.

After regulatory authority agreement and Sponsor approval to proceed, Part 2 will initiate.

The SRT will convene after all participants in MAD Cohorts 8 have completed 28 days of dosing and all safety data collected through Day 28 and PK data through Day 14 are available for review. If no pausing rule is present, the SRT may recommend dose escalation to MAD Cohort 9. Data from FE Cohort 7 is not required for the SRT's dose escalation recommendation from MAD Cohort 8 to MAD Cohort 9. The SRT will convene after all participants in MAD Cohort 9 have completed 28 days of dosing and all safety data collected through Day 28 and PK data through Day 14 are available for review. If no pausing rule is present, the SRT may

recommend dose escalation to MAD Cohort 10. The anticipated MK-7762 dose in MAD Cohort 10 may be modified through a protocol amendment after review of PK and safety data from FE Cohort 7 and MAD Cohorts 8 and 9.

4.5.1 Trial Pausing Rules

The SRT must assess the data as showing no significant safety concerns before recommending proceeding with MK-7762 administration to participants in SAD and/or MAD cohorts to receive higher doses of MK-7762. Events necessitating a pause in enrollment and/or participant dosing in the study Part 1 (SAD and FE) or Part 2 (MAD and FE), and, in turn, requiring an ad hoc IDMC review, include:

- At least one participant experiences a Grade ≥3 AE assessed as related to study drug by the Investigator or Sponsor. The qualifying AE should occur within 4 days of receipt of a dose of study drug (see Appendix 1 for the AE grading table to be used for the trial). The Investigator should assess clinical significance of safety laboratory abnormalities before reporting as an AE.
- At least one participant experiences a SAE assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug.
- At least two participants experience Grade ≥2 AEs of a similar nature assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug.
- Any occurrence of anaphylaxis or Grade 4 hypersensitivity reaction.
- Any other findings that, at the discretion of the Investigator, SRT, or Sponsor, indicate dose escalation should be paused.
- Note: A qualifying AE for meeting a trial pausing rule can be either a clinical AE or a safety laboratory abnormality.

The Principal Investigator will monitor individual participant safety and be responsible for the identification of any event(s) which meet one or more of the pausing rules listed above and notifying the SRT. If a pausing rule is confirmed, the SRT will ask the IDMC to conduct a review of unblinded safety data. The IDMC will make a recommendation to the Sponsor regarding the further conduct of the trial.

4.5.2 IDMC

The IDMC will operate according to a charter approved by the Sponsor and all IDMC members. The IDMC structure, participants, and other details will be provided in the charter. The charter will be approved prior to Screening of the first trial participant enrolled in Part 1 or Part 2.

The role of the IDMC will be to review unblinded safety data if a pausing rule is met and make recommendations to the Sponsor as outlined in the IDMC charter.

The recommendations of the IDMC when evoked, along with the Sponsor's decision, will be communicated to the Investigator, to the responsible IRBs/IECs, and to the US FDA.

4.5.3 Rules for Discontinuation of Treatment of Individual Participants in Part 2 MAD Cohorts

See Section 1.1.5 for rules for discontinuing study treatment for individual participants.

4.6 End of Trial Definition, Participant Completion of Trial, and Follow up of Adverse Events

The end of the trial is defined as the date of the last visit of the last participant, last scheduled procedure shown in the SoA for the last participant, or early withdrawal visit if last participant is withdrawn early from the trial.

Any participant withdrawn from the trial before their last scheduled trial visit for reasons not related to a safety event will be asked to return for an early termination visit within 2 weeks. Assessments to be conducted at the early termination visit are specified in Section 1.3.

An individual participant is considered to have completed the trial if he/she completes the final scheduled visit for their assigned cohort. If a participant has an AE that has not resolved or is not otherwise explained at the final trial visit, the AE will be documented as either “Not Resolved/Not Recovered” or “Resolving/Recovering”. Follow up of safety events associated with withdrawal of study drug is described in Section 7.2.

5 TRIAL POPULATION

Approximately 117 healthy adult participants between 19 to55 years of age (inclusive) of both sexes who are capable of and willing to provide informed consent will be eligible for the trial. Inclusion and exclusion criteria are outlined below in Section 5.1 and Section 5.2, respectively. Prospective approval of deviations to recruitment and eligibility criteria, also known as protocol waivers or exemptions, will not be permitted.

Various methods of recruitment may be used to identify trial participants, such as site databases, advertising, referrals, word-of-mouth, or other appropriate means.

5.1. Inclusion Criteria

To be included in this trial, an individual must satisfy all the following criteria:

1. Is ≥19 to ≤55 years of age.
2. Is healthy as determined by the Investigator via medical history and clinical examination before enrollment in the trial.
3. Can understand and comply with the trial and site procedures, understand the risks involved in the trial, and provide written informed consent before the first trial-specific procedure.
4. Can complete all Screening period evaluations and stay in the clinical research facility for the duration of the inpatient periods of the trial.
5. Has BMI between 18 and 32 kg/m^2, inclusive, and body weight not less than 50 kg at Screening.
6. Has resting vital signs at Screening within the following ranges:
   Systolic blood pressure (SBP) ≥100 mmHg
   Diastolic blood pressure (DBP) ≥50 mmHg
   Heart rate ≤100 beats per minute (bpm)
   Note: If vital signs are out of range, the Investigator may obtain two additional readings within the Screening period.
7. Has a 12-lead ECG consistent with normal cardiac conduction and function at Screening, including: HR between 45 and 100 bpm (inclusive); QTcF ≤450 ms for males and ≤470 ms for females; QRS interval <120 ms; PR interval <220 ms; and morphology consistent with healthy cardiac conduction.
8. Is a nonsmoker within the previous 6 months before Screening, and does not use tobacco-containing, or nicotine-containing products, including, but not limited to, cigarettes, pipes, cigars, chewing tobacco, e-cigarettes, nicotine patch, or nicotine gum.
9. Has clinical chemistry (fasted for at least 8 hours), coagulation, and complete urinalysis results at Screening within the reference ranges for the testing laboratory unless the out-of-range results are deemed not clinically significant by the Investigator.
10. For Part 2 only: Has clinical hematology results for total white blood cell count, absolute neutrophil count, absolute lymphocyte count, hemoglobin, red blood cell count, and platelet count at Screening within the reference ranges for the testing laboratory.
11. Has negative results for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab) within 3 months prior to Day -1 or at Screening.
12. Has negative test results for HIV antibody within 3 months prior to Day -1 or at Screening.
13. Has a negative urine drug screen result at Screening and on Day -1. The presence of alcohol or marijuana in the urine is not exclusionary unless the Investigator determines that the

participant's marijuana use qualifies as substance abuse (see Section 5.2, Exclusion Criteria 6).

14. If individual's assigned sex at birth is female, they must be of non-childbearing potential based on either of the following:
    a. Is post-menopausal defined as amenorrhea for at least 12 months in absence of any exogenous hormonal treatments and follicle stimulating hormone (FSH) levels in the laboratory-defined postmenopausal range, or,
    b. Reports being surgically sterilized (ie, tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy), and provides written documentation [(ie, medical record(s)] to document such procedure(s) to the Principal Investigator.
15. If individual is assigned male sex at birth, is not sterilized, and is sexually active with a female partner of childbearing potential, agrees to use condoms from Day -1 through 90 days after the last dose of study drug. They must also agree to not donate sperm during the trial and for 3 months (90 days) after receiving the last dose of study drug.

5.2. Exclusion Criteria

If an individual meets any of the following criteria, they are ineligible for this trial:

1. Has current or past history of a clinically significant cardiovascular, cerebrovascular, respiratory, gastrointestinal, hematologic, renal, hepatic, immunologic, metabolic, urologic, neurologic, dermatologic, psychiatric, or other major disease, as determined by the Investigator.
2. Has history of or Screening findings of abnormalities of vision, including corrected visual acuity worse than 20/25 in either eye based on Screening assessment using Snellen chart and Rosenbaum pocket chart, or color vision impairment based on Screening assessment using Ishihara plates. Candidates with ametropia corrected to 20/25 or better do not have to be excluded.
3. Has history of or Screening findings of peripheral neuropathy, such as numbness or abnormal reflexes.
4. Has history of or current clinically relevant cardiovascular disorder, such as heart failure, coronary artery disease, uncontrolled hypertension, arrhythmia, tachyarrhythmia, prolonged QT syndrome, or presence of symptom(s) strongly suggestive of such a problem, such as exertional chest pressure/pain or unexplained syncope.
5. Had an active malignancy within 5 years from Screening, except basal cell or squamous cell skin cancers. Any history of breast cancer or melanoma will be exclusionary.
6. Has history of any drug abuse within 1 year prior to Screening or has used any hard drugs (such as cocaine, phencyclidine [PCP], natural and synthetic opiates, and amphetamine derivatives) within 1 year prior to Screening. Individuals that have taken an opioid or amphetamine medication within the previous year prior to Screening that was prescribed by a healthcare provider will not be excluded unless they are currently taking the medication at the time of Screening.
7. Has history of regular alcohol consumption exceeding 14 drinks/week (1 drink = 5 ounces [150 mL)] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months of Screening or alcohol abuse within 1 year prior to Screening

8. Had any surgical or medical condition or history that, in the opinion of the Investigator, may potentially alter the absorption, metabolism, or excretion of study treatment, such as, but not limited to, gastric bypass or banding surgery or gastric or duodenal ulcers
9. Is taking any of the following prohibited medications or vaccinations:
    a. Any prescription or over-the-counter medication, vitamin or dietary supplement, or herbal product within 14 days prior to Day -1.
    b. Received any vaccination within 14 days prior to Day -1, including COVID-19 vaccination.
10. Has a contraindication to study drugs or its excipients and/or history of a clinically significant allergic or anaphylactic reaction to a medication.
11. Has participated in other trials involving administration of an investigational drug or device within 30 days or5 half-lives, whichever is longer, before Screening for the current trial and during participation in the current trial.
12. Has a positive polymerase chain reaction (PCR) or antigen test result for COVID-19/SARS-CoV-2 at check-in to the Clinical Trials Unit.
13. Has a condition that the Investigator believes would interfere with the participant's ability to provide written informed consent, comply with trial instructions, or which might confound the interpretation of the trial results or put the participant at undue risk.
14. Has donated blood within 2 months before entering the trial or planning to donate blood during the trial or within 12 weeks after the final visit.

5.3. Lifestyle Considerations

Participants with assigned male sex at birth who are not sterilized and are sexually active with a female partner of childbearing potential must agree to use condoms from Day -1 through 90 days after the last dose of study drug.

At Screening, participants should confirm their intention to abstain from alcohol, recreational drugs, and tobacco-containing and nicotine-containing products throughout their participation in the trial.

5.4. Screening

Screening assessments can be done at any time during the Screening window (Day -21 to Day -2; see Section 1.3), except for written informed consent, which must be completed prior to any Screening procedure.

5.4.1. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to a study intervention/entered in the trial. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (ie, why eligibility criteria were not met), and any SAE.

5.4.2. Re-Screening

Re-Screening is only permitted under one or more of the following conditions:

- If a participant presents with an acute illness on the day of planned study intervention (eg, acute respiratory illness or urinary tract infection), and meets all other eligibility criteria they can be rescreened after resolution of their illness either within the original Screening window for that cohort or the window period for a subsequent cohort (see Section 1.3).
- If there are technical or operational difficulties with collection, processing, or running of Screening laboratory tests (eg, laboratory reports hemolyzed blood) or conducting a Screening procedure (eg, ECG machine error) or an abnormal urinalysis due to menstruation or urinary tract infection, and the participant can be rescreened within the original Screening window for that cohort or the window period for a subsequent cohort (see Section 1.3).
- If a participant does not enroll in a cohort due to an administrative reason, such as the cohort enrollment is already complete, they can be rescreened for a subsequent cohort.
- If a participant is undergoing Screening and the trial reaches a pausing rule, the participant may be re-screened, if and when the IDMC recommends, and the Sponsor determines, that the trial may continue.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a participant according to the trial protocol.

Two study interventions will be used in this trial: participants will either receive MK-7762 or placebo by the oral route based on randomization or treatment assignment as described in the section on trial design (Section 4).

6.1. Study Drug Administration

In Part 1 (SAD), up to 5 sequential cohorts will be exposed to escalating single oral doses of MK-7762 or placebo in a randomized fashion. The first 2 participants in FE Cohort 6 termed sentinel participants, will receive open-label MK-7762 in a fed state and a second dose of MK-7762 in a fasting state after a washout period of at least 5 half-lives of MK-7762, as determined by PK data available from previously completed cohorts. After SRT review of safety and PK data from the two sentinel participants, the remaining 6 participants in Cohort 6 will be dosed fed and fasted in random manner with the washout period between doses as previously determined.

After completion of Part 1 of the study, an interim review of safety and PK data as well as any additional nonclinical data available will be conducted and submitted for regulatory review and agreement prior to the Sponsor's decision to initiate Part 2 of the study (see Section 1.1.3.2).

In Part 2, initiation of Cohort 7 (FE cohort) will occur following enrollment of MAD Cohort 8. Trial design details are included in Section 1 and Section 4. See Table 2 for details regarding study drug administration.

6.2. Composition of Trial Interventions

The MK-7762 drug product is presented in three strengths/configurations:

- MK-7762, 10 mg Capsule (size 3), 34's
- MK-7762, 100 mg Capsule (size 0), 24's
- MK-7762, 300 mg Capsule (size 00), 24's

MK-7762 capsules are composed of white hard hydroxypropyl methylcellulose (HPMC) capsules filled with formulated drug substance powder and common compendial excipients suitable for oral use. The quantitative composition, function, and quality of each ingredient in the study interventions is provided in Table 11 and Table 12.

Similarly, MK-7762 placebo capsules are presented in three different sizes (size 3, size 0 and size 00) in order to match the active drug product for blinding purpose. Identical, but fewer, compendial excipients are used in placebo drug product with a comparable fill weight.

Table 14 Composition of the MK-7762 Capsules

MK-7762 Capsules	10 mg	100 mg	300 mg		
Ingredient	**mg/capsule**	**mg/capsule**	**mg/capsule**	**Function**	**Grade**
Fill Composition					
MK-7762	10.0	100.0	300.0	API	In house
Microcrystalline cellulose	28.6	56.4	44.50	Binder	USP/NF/EP/JP
Lactose monohydrate	114.2	225.6	178.0	Filler	USP/NF/EP/JP
Croscarmellose sodium	4.8	12.0	16.505	Disintegrant	USP/NF/EP/JP
Colloidal silicon dioxide	0.8	2.0	5.500	Glidant	USP/NF/EP/JP
Magnesium stearate[2]	1.6	4.0	5.500	Lubricant	USP/NF/EP/JP
Total fill composition	160.0	400.0	550.0	NA	NA
Capsule Shell Composition					
HPMC capsule shell, white opaque body/white opaque cap TiO_2: 2% Hypromellose: QSP 100%	46.0 (size 3)	93.0 (size 0)	115.0 (size 00)[1]	Encapsulation	USP/NF

API=Active pharmaceutical ingredient; EP=European Pharmacopoeia; HMPC=Hydroxypropyl methylcellulose; JP=Japanese Pharmacopoeia; NA=Not applicable, NF=National Formulary; QSP=Sufficient quantity; TiO_2=Titanium dioxide; USP=United States Pharmacopeia.[1] In addition to hypromellose and TiO_2, carrageenan, potassium chloride, plus carnauba wax and corn starch is applied to surface of capsules as lubricant

Table 15 Composition of the MK-7762 Placebo Capsules

Ingredient	mg/capsule	mg/capsule	mg/capsule	Function	Grade
Fill Composition					
Microcrystalline cellulose	74.25	198.0	222.8	Binder	USP/NF/EP/JP
Lactose monohydrate	74.25	198.0	222.8	Filler	USP/NF/EP/JP
Magnesium stearate	1.50	4.00	4.5	Lubricant	USP/NF/EP/JP
Total fill composition	150.0	400.0	550.0	NA	NA
Capsule Shell Composition					
HPMC capsule shell, white opaque body/white opaque cap TiO_2: 2% Hypromellose: QSP 100%	47.0 (size 3)	74.1 (size 0)	114.2 (size 00)[1]	Encapsulation	USP/NF

API=Active pharmaceutical ingredient; EP=European Pharmacopoeia; HMPC=Hydroxypropyl methylcellulose; JP=Japanese Pharmacopoeia; NA=Not applicable, NF=National Formulary; QSP=Sufficient quantity; TiO_2=Titanium dioxide; USP=United States Pharmacopeia; %w/w=Percent weight by weight.
[1] In addition to hypromellose and TiO_2, carrageenan, potassium chloride, plus carnauba wax and corn starch is applied to surface of capsules as lubricant

6.3. Preparation/Handling/Storage/Accountability

Further guidance and information about preparation, handling, storage, and accountability are provided in the Pharmacy Manual.

6.3.1. Preparation and Handling

MK-7762 has been developed and produced as a solid oral dosage form and is presented in three strengths of MK-7762 capsules (10 mg,100 mg and 300 mg). No special preparation and handling are required prior to administration.

6.3.2. Storage

MK-7762 capsules are packaged into induction sealed 75 cc high-density polyethylene bottle and closed with 45 mm polypropylene cap. Finished investigational product is recommended to be stored at refrigerated conditions (2℃– 8℃/35.6℉-46.4℉) and not frozen. Excursions outside the storage conditions (2℃– 8℃/35.6℉-46.4℉) which may be experienced in pharmacy and warehouse, and during shipping, are allowed. Spikes outside the permissible range for longer duration need to be assessed in the light of 3-months stability data at 40℃/75%RH and 30℃/65%RH.

Storage conditions can be changed as more data become available.

6.3.3. Accountability

Trial interventions are to be supplied and administered by the Investigator or appropriately qualified site personnel named on the delegation of authority log. Under no circumstances will the Investigator allow the study drug to be used other than as directed by this protocol. Although appropriate personnel may be designated to administer study drug and maintain drug accountability records, the Investigator is ultimately responsible for all study drug accountability.

The trial pharmacist or qualified designee is responsible for confirming appropriate that temperature conditions have been maintained during transit and during site storage for all study drug received and that any discrepancies are reported and resolved before use of the study drug. The trial pharmacist is also responsible for making an inventory of the study drug upon receipt, ensuring adequate accountability of all used and unused study drug, and record maintenance (ie, receipt, reconciliation, and final disposition records). All used and unused study drug must be retained until final reconciliation or as indicated by the Sponsor.

The Investigator or designee must maintain accurate records of the receipt and disposition of all study drug. Documentation of study drug disposition should identify the participant receiving the study drug, the amount and date of dispensation, and any unused study drug(s). This documentation is required in addition to drug accountability information recorded on the Case Report Forms (CRFs). A written explanation must be provided for any discrepancies.

Authorization for any unused study drug and supplies to be destroyed is the responsibility of the Sponsor. Unused supplies will be destroyed as per the facility's institutional policy or per local regulations. Any disposal of study drug conducted at the clinical site must be documented in the trial file.

6.4. Measures to Minimize Bias: Randomization and Masking

6.4.1 Randomization

Randomization will be based on a randomly generated sequence of participant identification (identifier) numbers (randomization schedule), possibly using a validated Interactive Voice/Web Response System (IXRS). In Part 1, participants in Cohorts 1 through 5 will be randomized 3:1 to MK-7762 or placebo. All participants in FE Cohort 6 will receive open-label MK-7762

300 mg. The 2 sentinel participants in Cohort 6 will receive open-label MK-7762 in the fed state in the first dosing period with open-label dosing of MK-7762 in the fasted state in the second dosing period. After the 2 sentinel participants are dosed in the fed state, the remaining 6 participants will be randomized 1:1 to fed vs fasting in their first dosing period with crossover in their second dosing period following washout.

In Part 2, effort will be made to enroll as many females as possible in FE Cohort 7 and in MAD Cohorts 8-10. Randomization to treatment group within a cohort will be stratified by sex. Cohort 8 will be enrolled first, and following its enrollment completion, at least 9 participants will be enrolled in FE Cohort 7. After FE Cohort 7 enrollment is complete, MAD Cohorts 9 and 10 will be enrolled sequentially with dose escalation recommendations made by the SRT (see Section 4.5). All participants in FE Cohort 7 will receive open-label MK-7762 600 mg and be randomized 1:1:1 to the three possible sequences of standard meal, high-fat meal, and fasted state in a crossover design with washout between dosing periods; no sentinel participants will be included in Cohort 7. Participants in MAD Cohorts 8-10 (approximately 20 participants per cohort) will be randomized 4:4:1:1 to MK-7762 in fasted state, MK-7762 in fed state after standard breakfast meal, placebo in fasted state, or placebo in fed state after standard breakfast meal. Randomization and treatment of each participant in a MAD cohort will take place on Day 1.

6.4.2 Masking (Blinding)

The trial has a double-blind design for Part 1 SAD Cohorts 1-5 and Part 2 MAD Cohorts 8-10 in which participants and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at the trial site who will prepare oral doses of MK-7762 and placebo appropriately masked for site personnel who are authorized to administer treatment. There will be an unblinded review of safety and PK data following completion of Part 1 prior to initiation of Part 2. A trial unblinding plan will be prepared before the trial begins. In Part 1 FE Cohort 6 and Part 2 FE Cohort 7 the MK-7762 doses administered will be open-label.

Only the following personnel will have access to the treatment allocation while the trial remains masked:

- Unblinded Sponsor staff (specific staff to be unblinded will be detailed in the trial unblinding plan)
- Site pharmacist and pharmacy staff, as noted above
- Statistician preparing the randomization list
- Statistician preparing the IDMC reports, as applicable
- Pharmacometrician preparing the PK data for the IDMC, as applicable
- IDMC members, as applicable
- Unblinded site monitors

Additional roles that may have access to unblinding information include the following: supplies manager, IXRS designer, and the PK modeling and simulation vendor.

All unblinded persons must take care to not reveal individual group assignments to any other member of the trial team.

Any trial staff that become inadvertently unblinded must not participate in the evaluation of AEs. The Investigator will be blinded during the entire trial.

The Safety Review Team will review blinded aggregated safety data by cohort only for SAD Cohorts 1-5 and MAD Cohorts 8-10 and may be allowed to access aggregated mean PK data by treatment group within and across cohorts to inform dose escalation decisions (see Section 4.4). Unblinded Sponsor staff attending SRT meetings will not disclose unblinded clinical results, if known. An unblinding plan will be prepared to provide more details related to the maintenance of the trial blind and unblinding procedures.

6.4.3 Masking (Blinding) Break

The IXRS will be programmed with blind-breaking instructions. In addition, instructions on emergency unblinding in case of system outage will be provided. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is unblinded at any time during the trial, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

6.5. Trial Intervention Compliance

All study drugs will be administered at the clinical site and participant compliance will be recorded on their CRF.

6.6. Concomitant and Prohibited Medications

Participants receiving any prescription or over-the-counter medication, vitamin or dietary supplement, herbal product, or vaccine (including COVID-19 vaccination) within 14 days prior to Day -1, are not eligible to participate in the trial (see Section 5.2).

Investigators may treat AEs with concomitant medications, as needed, from Day -1 onward. Medications associated with serotonin syndrome (listed in Appendix 2) and oxazolidinone antibiotics (e.g., linezolid and tedizolid) are prohibited. Any prescription or over-the-counter medication, vitamin or dietary supplement, herbal product, or vaccine that a participant receives from enrollment through their end-of-trial visit must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding a concomitant or prior therapy.

6.7. Dose Modification

No dose modification of study drugs is allowed beyond the dose escalations explained in Section 4.

6.8. Intervention after the End of the Study

There is no intervention planned after the end of the trial.

7 DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION

7.1. Discontinuation of Study Drug

A participant withdrawn from the study drug (ie, any participant who does not receive the study intervention) will be withdrawn from the study

7.1.1. Pausing Rules

Pausing rules (reasons for pausing the study) are in effect during the active enrollment and dosing period. . The Principal Investigator will be responsible for the identification of any event(s) which meet one or more of the pausing rules and notification of the SRT, as outlined in Section 4.5.1.

If any of the pausing criteria are met, enrollment/participant accrual as well as dosing of enrolled participants will be suspended pending IDMC's review of all available safety data, and the U.S FDA will be notified in an expedited manner. In contrast to trial pausing rules, discontinuation of treatment for individual MAD participants (per rules outlined in Section 1.1.5) do not require cessation of participant enrollment or of dosing of all enrolled participants in MAD cohorts.

Refer to Section 4.5 for the role of SRT and Section 4.5.2 for the role of the IDMC. If the Investigator and/or the SRT observes that a pausing rule has been met, the Investigator will inform the Sponsor and/or the SRT as soon as possible and within 24 hours of the observation. The SRT and/or Sponsor will notify the Investigator and the IDMC members of the pause in enrollment and participant dosing as soon as possible and within 24 hours of receiving notification of the pausing rule being met.

When a pausing rule is met, the IDMC members will convene an urgent ad hoc review meeting, review all relevant unblinded safety data, and make a recommendation to the Sponsor. The FDA will be advised of the IDMC actions and recommendations.

The IDMC may recommend continuation of the study pause or resumption of enrollment and dosing with or without changes to the Protocol. The final decision to pause or resume study activities will always be the responsibility of the Sponsor. All IDMC recommendations will be stored according to the IDMC Charter.

All Sponsor decisions will be documented in a memorandum to the study file. The Sponsor or delegate is responsible for prompt communication to the study site of decisions related to pausing or resuming the study activities, including notification to the Investigator, relevant IRBs/IECs and regulatory authorities.

The clinical site will be allowed to resume activities only upon receipt of written notification from the Sponsor.

7.2. Participant Discontinuation or Withdrawal from the Study

A participant may request withdrawal from the study at any time. A participant may also be withdrawn from the study at any time for the following reasons:

- at the request of the primary care provider if being in the study is no longer in the best interest of the participant

- participant is judged by the Investigator to be at significant risk of failing to comply with the provisions of the Protocol as to cause harm to self or seriously interfere with the validity of the study results
- at the discretion of the IRB/IEC or government agencies as part of their duties, Investigator, or Sponsor.

If possible, a discontinuation visit should be scheduled for any participant who wishes to discontinue or withdraw from the study. At this visit, topics around participant safety as well as the use of already collected biospecimens will be discussed, and the procedures and specimen collection indicated in the SoAs will be performed if possible and as needed.

The time and reason for withdrawal should be noted in the space provided for this purpose in the CRF. Possible reasons responsible for withdrawal include:

- no receipt of study intervention
- SAE
- non-serious AE (including AESI and/or safety laboratory abnormality)
- protocol violation (specify)
- consent withdrawal not due to an AE*
- move from study area
- other (specify)

*If a participant withdraws consent, the reason, if specified, will be documented in the CRF.

Participants who are withdrawn from study drug because of the occurrence of a safety event should be clearly distinguished from participants who are withdrawn for other reasons. Participants who are withdrawn because of a safety event, including a SAE, an AESI, a non-serious AE, or a safety laboratory abnormality, will be followed until the planned end-of-study visit for that participant, and the required safety assessments will be performed at each visit. Ongoing SAEs at the time of the end-of-study visit will be followed until resolution or stabilization.

All data collected until the date of withdrawal/last contact of the participant will be used for the analysis, unless the participant requests destruction of any samples taken and not tested. The Investigator must document this in the site study records and the CRF. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such withdrawal of consent.

If the participant leaves the study, the participant's medical information will still be used or shared to the extent allowed by law. Any leftover samples will be destroyed after testing is completed unless the participant withdraws consent to sample use, in which case the samples will be destroyed at that time. Any test results from the samples collected before withdrawal can still be included in the analyses.

7.3. Lost to Follow-Up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit

schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant through telephone calls and mail. These contact attempts should be documented in the participant's medical record and the CRF.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up from the study.

8. TRIAL ASSESSMENTS AND PROCEDURES

Trial assessments and procedures are described in this section and summarized in the SoAs in Section 1.3. Protocol waivers or exemptions are not allowed. No trial assessments or procedures may be conducted before the participant provides written informed consent.

8.1. Screening Assessments for Eligibility

Prior to any trial procedure, all eligible participants will be assigned a unique participant identifier. This participant identifier will be used throughout the trial for participant identification.

Screening procedures will be conducted during the 21-day Screening period. Screening assessments can be done at any time during this period. Eligibility for randomization will be based on the inclusion and exclusion criteria described in Section 5.1 and Section 5.2.

Eligibility criteria will be checked during the Screening period and prior to study drug administration to ensure that each randomized participant meets all the inclusion criteria and none of the exclusion criteria. The Investigator will also maintain a Screening log to record details of all participants screened to confirm eligibility or record reasons for Screening failure, as applicable.

To evaluate eligibility criteria, the following assessments and procedures will be conducted:

- Demography and medical and treatment history
- Prior and concomitant medication review
- 12-lead ECG
- Vital signs (supine blood pressure, supine heart rate, and temperature), weight, and height
- Physical examination (PE)
- Assessment of visual acuity and color vision
- Peripheral sensory neuropathy screening
- Laboratory safety tests (hematology, chemistry, coagulation, and urinalysis)
- Hepatitis B and C testing
- HIV testing
- FSH testing (only for participants with female sex assigned at birth who are not surgically sterilized)
- PCR for SARS-CoV-2
- Urine cotinine screen
- Urine drug screen
- Urine alcohol screen

Details on the assessments and procedures unique to the Screening period are provided in this section. Details on the assessments and procedures common to the Screening and Treatment Phase and/or Post-Study Visit are provided in the sections to follow.

8.2. Demography and Medical and Treatment History

Information on demographic characteristics (eg, age, date of birth, sex/gender, ethnicity, and race) will be obtained and a medical and treatment history will be conducted during the Screening period to assess eligibility. Identifying and location information will be kept at the

trial site and will not be entered into the trial database. All conditions that exist prior to Screening will be recorded in the medical history section of the CRF. Any clinically relevant new condition or fluctuation of an existing condition observed during the Screening period or treatment period will be recorded as an AE (see Section 10.2.7).

8.3. Prior and Concomitant Medication Review

Prior and concomitant prescription or over-the-counter medications, vitamin or dietary supplements, herbal products, or vaccines (including COVID-19 vaccination) will be assessed starting 30 days before Screening and throughout the trial. Participants receiving any of the above within the 14-day period prior to Day -1 are not eligible for the trial (see Section 5.2). Any prescription or over-the-counter medication, vitamin or dietary supplement, herbal product, or vaccine that a participant receives from Screening through their end-of-trial visit must be recorded along with:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose, route, and frequency.

All medications and therapies for treatment of an AE or which caused an AE until the end of the trial will be recorded on an eCRF.

The Medical Monitor should be contacted if there are any questions regarding a concomitant or prior therapy.

8.4. Assessments

Immediate safety concerns should be discussed with the Sponsor and/or Contract Research Organization (CRO) immediately upon occurrence or awareness by the Investigator.

8.4.1. Vital Signs and Body Mass Index (BMI)

Any out-of-range vital sign observed in the trial may be repeated twice with at least 5 minutes intervening.

At Screening, SBP, DBP, HR, and body temperature (BT) will be taken after the participant has rested in the supine position for ≥3 minutes. Body weight and height will be recorded at the Screening visit. Weight will be recorded on Day -1 to serve as the baseline value for all cohorts. BMI will be determined based on the height and weight for eligibility assessment. BMI will be calculated as:

- Weight in kg / (height in meters)^2

At **subsequent scheduled visits**, HR, SBP, and DBP will be measured after the participant has rested in the supine position for ≥3 minutes per the SoA.

When ECG (safety or continuous extraction), vital signs, PK sample collection, and/or safety sample (blood or urine) samples are to be obtained at the same time point, PK and safety blood sample collection should be done first followed by ECGs then vital signs.

In the MAD cohorts in Part 2, weight will be assessed weekly and then on Day 31, 33, and 36.

8.4.2. Physical Examination

A complete PE will be conducted during the Screening period to assess eligibility, then at intervals as shown on SoA. The complete PE should include ear/nose/throat, dermatological, cardiovascular, respiratory, gastrointestinal, central nervous system, lymph nodes, and musculoskeletal assessments. An Investigator can examine other body systems if indicated, at their discretion. Care should be taken to examine and assess any abnormalities that have been indicated as potentially present by medical history.

A focused PE should be done to evaluate any new symptoms and to follow-up findings on previous PE. A focused PE will include assessments of body systems involved in the complaint (ie, symptom-directed). If a participant withdraws early from the trial, a focused PE should be conducted.

8.4.3. Visual Assessment

A visual assessment will be conducted at Screening to assess eligibility for all trial participants and repeated during the treatment period for Part 2 MAD participants per the SoA to assess for possible signs of optic neuropathy toxicity from repeat dosing. During Screening, the Investigator or their delegate will conduct assessments of visual acuity and color vision. At subsequent visits in Part 2 MAD Cohorts 8-10, trial staff will conduct tests of visual acuity and color vision. Visual acuity will be assessed on each eye separately by means of a Snellen chart and Rosenbaum pocket chart. Color vision will be assessed on each eye separately using the Ishihara color plates. Investigators should refer participants with significant findings to an ophthalmologist for an evaluation to assist in the assessment of potential treatment-emergent AEs.

8.4.4. Peripheral Sensory Neuropathy Screening

Peripheral sensory neuropathy screening will be conducted using the BPNS test at Screening to assess eligibility and repeated during the treatment period for Part 2 MAD Cohort 8-10 participants per the SoA to assess for signs of peripheral neuropathy toxicity from repeat dosing. The non-invasive BPNS test combines questions regarding neuropathic symptoms in the feet and lower legs with objective testing of ankle reflexes and vibration sensation in the big toes.

8.4.5. Electrocardiogram and Holter Monitoring

At the **Screening visit**, triplicate standard 12-lead ECGs will be performed for eligibility determination. The triplicate ECGs should be separated by approximately 1 minute. Any clinically significant findings will be recorded. The average QTcF value will be used to assess against the eligibility criterion.

At all **subsequent trial visits** where an ECG is scheduled, ECGs will be performed as triplicate readings with approximately 1 minute between ECGs.

ECGs should be performed after the participant has rested in the supine position ≥5 minutes before the first ECG at a time point. When ECG (safety or continuous extraction), vital signs, PK sample collection, and/or safety samples (blood or urine) are to be obtained at the same time point, PK and safety blood sample collection should be done first followed by ECGs then vital signs. An Investigator should provide an interpretation of each ECG.

Continuous 12-lead ECGs (Holters) will be recorded on Day 1 in Part 1 Cohorts 1-5, on Day 1 in Part 2 Cohort 7, and on Day 1 and Day 28 in Part 2 Cohorts 8-10. ECGs to be used in the ECG exposure-response analysis will be selected by pre-determined time points as defined in the separate analysis plan (see Section 9.4.2).

8.4.6. Clinical Laboratory Assessments

Clinical laboratory assessments will be performed at Screening to assess eligibility and throughout the trial as outlined in Section 1.3. If premature discontinuation occurs, clinical laboratory assessments will be conducted as defined in the SoA at the Early Termination assessment.

Clinical laboratory assessments include:

1. **Hematology:** complete blood count (red blood cells, hemoglobin, platelets, and WBC); red blood cell parameters (eg, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red cell distribution width); white blood cell differential (absolute counts), including neutrophils, lymphocytes, monocytes, eosinophils and basophils; and reticulocyte count
2. **Serum chemistry**: alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total and direct bilirubin, creatinine, blood urea nitrogen (BUN) or urea, creatine kinase, sodium, potassium, bicarbonate or CO2, chloride, glucose, and lipid profile (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides)
3. **Serum coagulation:** PT, PTT, and INR
4. **FSH**: Screening only for participants assigned female at birth who have not been surgically sterilized and report being post-menopausal (see Section 5.2).
5. **Urinalysis:** Dipstick for pH, specific gravity, glucose, protein, blood, leukocyte esterase, nitrites, ketones, bilirubin, and urobilinogen. Microscopic examination for red blood cells, white blood cells, casts, and bacteria will be performed if urine dipstick is positive for protein, blood, leukocyte esterase, or nitrites.
6. **HIV:** a combination HIV antigen/antibody test will be performed at Screening
7. **HBsAg and HCV Ab** testing will be performed at Screening
8. **SARS-CoV-2 PCR:** performed at check-in to CTU on Day -1 for eligibility determination and can be repeated during the trial to comply with the trial site's COVID-19 standard procedures.

Laboratory results will be reviewed by the Investigator or their delegate Investigator with each abnormal test evaluated as clinically significant or not clinically significant. Clinically significant abnormal laboratory values that represent an unexpected change from baseline should be assessed as AEs.

In the event that one or more abnormal laboratory values is are obtained prior to randomization that is judged to be clinically significant by the Investigator, the participant will be excluded from study enrollment. However, for Part 2 of the trial, the following hematology parameters with screening results outside the respective normal range will require exclusion from enrollment (Section 5.1): total white blood cell count, absolute neutrophil count, absolute lymphocyte count, hemoglobin, red blood cell count, and platelet count.

Abnormal results and findings that deem the participant ineligible will be discussed with the participant and the participant will be referred for follow-up care with their healthcare provider, if necessary.

If laboratory values from non-protocol specified clinical safety laboratory assessments require a change in participant management or are considered clinically significant by the Investigator (eg, AE or SAE), then the results must be recorded in the CRF.

Additional tests may be performed at any time during the trial as determined necessary by the Investigator or required by local regulations.

Please refer to the Laboratory Manual and the SoA (see Section 1.3) for further guidance and instructions on all protocol-required clinical laboratory assessments.

8.4.7. Drug Screening

Urine drug, alcohol, and cotinine testing will be done at Screening for eligibility assessment. Urine drug testing will include testing for cannabinoids, cocaine, opiates, opioids, benzodiazepines, amphetamines, methamphetamines, phencyclidine, and barbiturates. Urine testing for drugs, cotinine, and alcohol will be repeated on Day -1 upon admission to the CTU to re-confirm eligibility.

8.4.8. Adverse Events and Serious Adverse Events

AEs will be detected through medical histories, AE reviews, physical examinations, and safety laboratory tests. See Section 10.2 for the definitions of an AE, SAE, and AESI to be used in this trial. Investigators must proactively follow up previously identified AEs at subsequent visits. AEs must be followed until the end of the trial if not resolved; SAEs and non-serious AESIs must continue to be followed until resolved or stabilized even if follow-up extends beyond the end of a participant's scheduled trial participation. See Section 10.2 for details of AE, SAE, and AESI assessment, reporting, grading, causality assessment, follow-up, and outcome classification.

8.4.9. Pharmacokinetic Assessment

PK sampling will be performed per the SoAs in Section 1.3. Table 16 through Table 18 provide summaries of pharmacokinetic sampling timepoints for Part 1 and Part 2 participants. Additional blood will be collected from participants in Part 1, SAD Cohort 4 and Part 2, MAD Cohort 10 at the same PK sampling timepoints for storage for possible future qualitative and/or quantitative analysis of any significant metabolites identified. Urine collection for PK will only be conducted for Part 1, SAD Cohort 4 and Part 2, MAD Cohort 9.

Details on sample collection and processing procedures are provided in the Laboratory Manual.

8.4.10. Pharmacogenomics (PGx) Assessment

During the informed consent process, participants will be asked to provide consent for collecting a sample for pharmacogenetic analysis to look for genetic determinants of variability in drug metabolism of MK-7762 between participants. Participants who do not consent to collect a sample for pharmacogenetic analysis will remain eligible to participate in the trial. A pharmacogenomics sample will be collected on Day -1 from all participants providing consent for (potential) genetic analysis. PGx assessment will include an evaluation for potential associations of genetic polymorphisms with PK, and possibly, safety results. The samples will be

stored, and the final list of blood samples and genes that may be investigated will be selected before analysis to allow new scientific information to inform it. PGx samples of participants not selected for the PGx analysis will be destroyed. PK (and safety) data summarized by genotypes will be presented based on data availability.

Table 16 Plasma PK Sampling Timepoints for Part 1, Cohorts 1-5

Timepoint (day)	Day 1 – Cohorts 1 – 6 Day 8[a] – Cohort 6									Day 2 – Cohorts 1 – 6 Day 9 [a] – Cohort 6		Day 3 – Cohorts 1 – 6 Day 10 [a] – Cohort 6	Day 4 – Cohorts 1 – 6 Day 11 [a] – Cohort 6	Day 7 – Cohorts 1 – 6 Day 14 [a] – Cohort 6	ET
Timepoint (hours)	0	1	2	3	4	5	6	8	12	24	36	48	72	144	NA
PK sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
a: Start of second dosing period for Cohort 6 (FE Cohort) to be determined by PK results from previous SAD cohorts to ensure washout period of at least 5 half-lives between ET = Early Termination															

Table 17 Plasma PK Sampling Timepoints for Part 2, FE Cohort 7

Timepoint (day)	Periods 1, 2 [a], and 3 [a]															ET
	Day 1							Day 2		Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	
Timepoint (hours)	0	1	2	4	6	8	12	24	36	48	72	96	120	144	168	NA
PK sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	a: Start of second and third dosing period for Part 2 Cohort 7 (FE Cohort) is after a washout period of at least 8 days to ensure washout period of at least 5 half-lives between doses. ET = Early Termination															

Table 18 Plasma PK Sampling Timepoints for Part 2, MAD Cohorts 8-10

Timepoint (Day)	D1							D2	D3	D4	D5	D6	D7		D8-13	D14		D15-20	D21		D22-27
Timepoint (Hour)	0	1	2	4	6	8	12	0	0	0	0	0	0	8	0	0	8	0	0	8	0
PK sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Timepoint (Day)	D28							D29	D30-36												
Timepoint (Hour)	0	1	2	4	6	8	12	--	--												
PK sample	X	X	X	X	X	X	X	X[a]	X[b]												
Timepoint 0 is within 60 minutes before dosing (120 minutes for Day 1) D = Day; C = Cohort; ET = Early Termination a: To be collected 24 hours after last dose (i.e., last dose administered on Day 28 for Cohorts 8-10) b: Days 30-36 PK sample for Cohorts 8-10 should be collected within ±3-hour time window of time of last study drug administration on Day 28																					

8.4.11. Early Termination Assessments

Participants withdrawing early from the trial for any reason should undergo an early termination visit with assessments performed per the SoA. The Investigator may perform additional assessments based on their clinical judgement and the reason for a participant's early withdrawal.

9. STATISTICAL CONSIDERATIONS

This section contains a brief summary of the statistical analyses to support the primary and secondary objectives of this trial. A full description of the statistical analyses will be presented in a SAP.

When summary statistics are planned to be reported by treatment and dosing condition, this refers to summarizing as follows.

- For Part 1, SAD Cohort 1-5, participants will be counted once according to the dose level (or placebo) received. Pre-dose observations on Day 1 or Day -1 are used as the baseline.
- For Part 1, FE Cohort 6, participants will be counted in each period according to the dosing condition (fed or fasted) in that period. Pre-dose observations on Day 1 or Day -1 will be used as the baseline for both dosing periods.
- For Part 2, FE Cohort 7, participants will be counted in each period according to the dosing condition (fasted or fed) in that period. Pre-dose observations on Day 1 or Day -1 will be used as the baseline for each of the three dosing periods.
- For Part 2, MAD Cohorts 8-10, participants will be counted once according to the dose level (or placebo) received. Observations on Day -1 or Day 1 before the first administration of study drug will be used as the baseline.

9.1. Populations for Analysis

Analysis populations are defined below:

Safety Population: All participants who received the study intervention. Participants will be analyzed according to the intervention they received.

Per protocol (PP) Population: All participants who received study intervention and did not significantly deviate from study procedures. Participants will be analyzed according to the intervention they received.

PK Population: All participants who received MK-7762 and have at least one non-zero PK result available.

The QT/QTc Population: All participants in the Safety Population with measurements at baseline as well as on-treatment with at least 1 post-dose timepoint with a valid ΔQTcF value. This population will be used for the by-timepoint and categorical analyses of cardiodynamic ECG parameters.

The PK/QTc Population: All participants who are in both the QT/QTc and PK Populations with at least 1 pair of postdose PK and ΔQTcF data from the same timepoint as well as participants in the QT/QTc Population who received placebo. This population will be used for the concentration-QTc analysis.

9.2. Statistical Hypotheses

This trial is an exploratory trial to characterize the safety, tolerability, and PK of a single dose (in the SAD design) or multiple doses (in the MAD design) of MK-7762. The trial is designed to be descriptive and is not based on formal hypothesis testing.

9.3. Statistical Methods

This section includes a brief outline of the planned analyses. A detailed SAP will provide comprehensive details of the planned analyses to support the primary and secondary objectives. The SAP will define analysis populations, statistical methods, and general conventions, including handling of missing data. Pooling of MK-7762 safety data will also be described in the SAP. Exploratory analyses will be described either in the SAP or in a separate exploratory SAP.

9.3.1. Primary Analyses of Safety

For Part 1, the primary analysis will cover the time period from pre-dose on Day 1 to Day 7 for SAD Cohorts 1-5, and Day 7 of each dosing period (fed or fasted) for FE Cohort 6 (Food Effect Cohort).

For Part 2, FE Cohort 7, the primary analysis will cover the time period from pre-dose on Day 1 to Day 8 for each dosing period (fed or fasted). For Part 2, MAD Cohorts 8-10, the primary analysis will cover the time period from pre-dose on Day 1 to Day 36. Safety summaries will be inclusive of all participants in the safety population, unless stated otherwise. .

9.3.1.1. Treatment-emergent AEs, SAEs and AESI

All AEs, inclusive of SAEs and AESI will be recorded from Screening through Day 7 for Part 1, SAD Cohorts 1-5, through Day 7 of the second dosing period for Part 1, FE Cohort 6, through Day 8 of the third dosing period for Part 2, FE Cohort 7, and through Day 36 for Part 2, MAD Cohorts 8-10. Treatment-emergent AEs (TEAEs) are defined as AEs with onset after receipt of one or more doses of study drug through the end of study period for that participant (see Section 10.2.2).

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and TEAEs, SAEs, and AESIs will be summarized by System Organ Class (SOC), Preferred Term (PT) and treatment and dosing condition as well as by all MK-7762 dose levels combined (including the FE Cohorts). TEAEs leading to withdrawal from the study will also be summarized.

The following will be summarized by dose level and across all placebo cohorts:

- TEAEs regardless of causality, by grade of severity
- SAEs regardless of causality, by grade of severity
- TEAEs leading to discontinuation of study drug, by grade of severity

In addition, all summaries will also be produced for TEAEs related to study drug. TEAE summaries will include overall incidence by system organ class and preferred term and by the maximum severity grade that the participant experienced.

9.3.1.2. Laboratory Abnormalities

All laboratory values collected at visits will be included in the summaries and listings.

Descriptive summaries (n, mean, standard deviation, median, minimum, and maximum) of observed values and change from baseline (last result available on or before receiving the study intervention) at each scheduled post baseline visit will be presented for each continuous variable test parameter.

Summaries by Division of Acquired Immunodeficiency Disease (DAIDS) toxicity grade (and/or the laboratory normal range) (Appendix 1) and graded shifts in laboratory values from baseline to each post baseline visit will be also presented. All safety laboratory summaries will be presented by treatment and dosing condition, as appropriate, and across all MK-7762 dose levels combined.

9.3.1.3. Adverse Events of Special Interest

The following events will be considered as AESIs for this trial:

- Hepatotoxicity, as defined by presence of all of the following:
  - Elevated ALT or AST >3× upper limit of normal (ULN),
  - Elevated total bilirubin >2× ULN, and
  - No evidence of cholestasis (normal or minimally elevated ALP)
- Grade ≥2 peripheral neuropathy
- Grade ≥3 anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia
- Optic neuritis of any grade confirmed by an ophthalmologist

AESI summaries will be similar to those described above for TEAEs.

9.3.1.4. ECG Analyses

ECG data will be collected based on 12-lead recording in triplicate and based on continuous Holter monitoring, as per the SoAs in Section 1.3. The primary analysis of ECG will be based on the 12-lead recording. Data from the continuous Holter monitoring will be analyzed if deemed necessary based on PK, safety, or other development considerations and will be considered exploratory (see Section 9.4.2).

Twelve-lead ECGs in triplicate will be collected at each time point and the mean value of each parameter will be used for analysis. No formal inferential statistics will be applied to the ECG data. For the primary endpoint analysis, descriptive analyses of the following ECG parameters will be created for each post-dose ECG timepoint: heart rate, RR interval, PR interval, QRS duration, QT interval, and QTcF by treatment and dosing condition. Changes in these ECG parameters from the pre-dose ECGs will also be presented for each post-dose ECG timepoint. Summaries of abnormal findings of ECG parameters categorized by severity grading will be compiled along with descriptive summaries of continuous ECG records.

ECGs will be read by the Principal Investigator or delegate with central reading when indicated or requested.

9.3.1.5. Other Safety Measures

For vital signs (temperature, blood pressure, and heart rate), summary statistics will be tabulated by treatment and dosing condition, as appropriate, and across all MK-7762 dose levels. Frequencies of abnormal vital signs post-dosing will be listed by severity grade. Any other relevant information will be presented in participant data listings. Further details will be provided in SAP.

9.4. Secondary and Exploratory Analyses

9.4.1. Pharmacokinetics

No formal inferential statistics will be applied to the pharmacokinetic data. MK-7762 plasma concentrations will be listed and summarized descriptively by analyte, cohort, dose, fasted/fed condition, and nominal PK sampling time. Individual subject and median profiles of the plasma concentration-time data will be plotted by dose using actual and nominal times respectively for MK-7762. Median profiles will be presented on both linear-linear and log-linear scales.

The plasma PK parameters $AUC_{0-\infty}$, $AUC_{0-last,}$ $C_{max,}$ T_{max}, $t_{1/2}$, CL/F and Vz/F for MK-7762 will be summarized descriptively by cohort, fasted/fed condition, and dose. Each of the PK parameters will be summarized using descriptive statistics (eg, arithmetic mean, standard deviation, arithmetic percent coefficient of variation (CV), median, minimum, maximum, geometric mean, and geometric percent (CV), and the number of participants, as appropriate.

Dose normalized (to a 1 mg) $AUC_{0-\infty}$, $AUC_{0-last,}$ and $C_{max,}$ of MK-7762 will be plotted against dose (using a logarithmic scale) and will include individual subject values and the geometric means for each dose. These plots will be used to help understand the relationship between the plasma PK parameters and dose.

In addition to calculating the PK parameters using Non-Compartment Analysis (NCA) methods, MK-7762 PK plasma data obtained in this study may be used to develop a population PK model to aid in the prediction of dose levels in multiple dose scenarios and to assess potential impact of covariates on the between subject variability.

9.4.2. ECG Exposure-Response Analysis

If deemed necessary based on PK, safety, or other development considerations, the relationship between QTcF based on continuous Holter monitoring and MK-7762 plasma concentrations may be explored graphically and through the development of a pharmacodynamic model to characterize these relationships. In this case, the details of the analyses will be described in a separate ECG analysis plan and will be considered exploratory.

9.5. Interim Analyses

No formal interim analyses are planned for the study, but blinded safety data will be monitored by the trial SRT at the conclusion of each dosing level to inform dose escalation decisions within the SAD and MAD components (see Section 1.1.4.1). An unblinded review of safety and PK data will be conducted after completion of Part 1 to be submitted for regulatory review and agreement to proceed to Part 2 (see Section 1.1.3.2).

9.6. Sample Size and Power

Because this trial is aimed at characterizing the safety, tolerability, and PK of MK-7762, it is designed to be descriptive and is not based on formal hypothesis testing. Therefore, this trial is not powered to detect any pre-specified differences in potential safety or PK data between treatment groups.

Assuming all cohorts receive MK-7762 treatment as planned, 95 participants will be exposed to MK-7762 (30 from SAD cohorts, 8 from FE Cohort 6, 9 from FE Cohort 7, and 48 from MAD cohorts).

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Trial Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This trial will be conducted in accordance with the Protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The Protocol, protocol amendments, informed consent form (ICF), and other relevant documents (eg, diary cards) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.

10.1.2. Trial Oversight

The Sponsor, the SRT, the IDMC, the IRB/IEC, the institution through which the research is performed, all members of the Principal Investigator's clinical team, and the national regulatory authority share responsibility for ensuring the safety of participants in this trial.

The Principal Investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently, in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of ICH and GCP guidelines, US FDA Regulations, the IRB/IEC, and all other applicable country and local regulations.
- Closely monitoring trial participants and taking whatever measures necessary to ensure their safety. The Principal Investigator may delay an individual's study drug administration or pause study drug administration altogether if the Investigator is concerned that the study drug might place a participant or participants at significant risk. Where specified, the responsibilities of the Principal Investigator may be delegated to a medically qualified team member (designee). The Investigator determines severity and causality with respect to the study drug for each AE.
- The Principal Investigator will be responsible for the identification of safety laboratory abnormalities and/or clinical AEs which meet the rules of discontinuation of study drug for individual participants. In such instance, the Principal Investigator will ensure discontinuation of study drug and thereafter inform the SRT.

- The Principal Investigator will monitor individual participant safety and be responsible for the identification of any event(s) which meet one or more of the pausing rules and notifying the SRT.

The Sponsor has an institutional responsibility to ensure participant safety and is ultimately accountable for safety oversight. Local Medical Monitors and the SRT play an important role in this regard and support the Sponsor.

The local Medical Monitor is the Sponsor's representative and is a physician or surgeon in their country of residence. The local Medical Monitor:

- reviews the safety of the product for protocols in a specific region and, in conjunction with the Sponsor, determines expectedness of AEs.
- Is responsible for safety oversight in-country and plays an important role in the reporting of SAEs, ADRs and pregnancies, as described in the Protocol.
- in consultation with the Sponsor, may assess the severity and causality for AEs and may upgrade the degree of severity and causality determined by the Principal Investigator or designee

The Safety Review Team (SRT):

- The operational details of the SRT, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to the time that the first participant is enrolled in either Part 1 or Part 2.
- The SRT will review the blinded safety and tolerability data accumulated from SAD and MAD cohorts (see Section 1.1.4.1. and Section 4.5). The SRT may request additional meetings as deemed appropriate.
- If the SRT observes that a pausing rule is met, the Sponsor will be informed as soon as possible and within 24 hours of becoming aware of the event. The IDMC will then review all relevant unblinded safety data and recommend the next course of action(s) to the Sponsor (see Section 4.5).
- If a pausing event does not occur, the SRT may recommend that enrollment and/or dose escalation can continue. The SRT recommendation will be communicated to the Sponsor Chief Medical Officer for endorsement to proceed.

The IDMC

- The operational details of the IDMC, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to the time that the first participant is enrolled either Part 1 or Part 2.
- The role of the IDMC will be to review unblinded safety data if a pausing rule is met and make recommendations to the Sponsor as outlined in the IDMC charter.

The recommendations of the IDMC when evoked, along with the Sponsor's decision, will be communicated to the Investigator, to the responsible IRBs/IECs, and to the US FDA. The IRB or IEC has institutional responsibility for the safety of research participants. The IRB or EC has the authority to terminate, suspend or require changes to the clinical trial.

The national regulatory authority, US FDA, has the authority to terminate, suspend or require changes to the clinical trial.

10.1.3. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.4. Informed Consent Process

Written informed consent will be obtained prior to conducting any trial-related procedures.

Participants must be informed that their participation is voluntary. The Principal Investigator or designee will explain the trial to the participant and answer all questions regarding the trial. The Principal Investigator or designee will conduct the consent discussions in a group environment initially followed by an individual discussion with each participant. Adequate time will be allowed for all questions to be addressed.

10.1.5. Informed Consent Forms

10.1.5.1. Informed Consent for Trial Participation

Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations (CFR) 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The informed consent will be obtained by the use of a written or electronic consent form approved by the IRB or IEC.

Sample testing will be in line with the consent of the participant.

A copy of the signed consent forms shall be given to the participant prior to conducting any trial related- procedures.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form (ICF).

If there is a change to the ICF during the conduct of the trial, actively enrolled participants will be re-consented to the most current version of the ICF.

Any withdrawal of consent for sample testing will be documented in the CRF.

Assay analysis will be conducted in laboratory(ies) working on behalf of Gates MRI and located, but not limited to the US.

Samples will be kept for a maximum of 3 years from the end of the trial.

10.1.6. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant record or dataset that is transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.

The participant must be informed that his/her trial-related data will be used by the Sponsor in accordance with local data protection law. The level of data disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7. Dissemination of Clinical Trial Data

Study information and resultant trial data from this protocol will be posted on publicly available clinical trials registers (www.clinicaltrials.gov) before enrolment of participants begins.

The final trial report will include all available safety data, clinical assessments, and concomitant medications through the final study visit. The database will be locked prior to unmasking and preparation of the final study report. All of the above data must have been entered, reviewed, and all queries related to the data addressed. Modifications or additions to the analyses will be included in the relevant SAP. Any decisions to deviate from the planned analyses described in the Protocol and in the SAP will be described in detail in the final study report.

The final clinical study report will be reviewed and approved by the Sponsor signatory and the Principal Investigator.

10.1.8. Data Quality Assurance

All participant data relating to the trial will be recorded in CRFs, unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator or designee is responsible for verifying that data entries are accurate and correct by-electronically signing the CRF.

The Investigator must maintain accurate documentation that supports the information entered in the CRF.

The trial will be monitored regularly by the Sponsor or its designee throughout the study period. The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for 15 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9. Source Documents

Source documentation consists of existing medical records and/or trial records developed and maintained by the Investigator. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

Data recorded on source documents will be transcribed in the CRFs by the Investigator's Site.

Data entered in the CRF that are transcribed from any paper source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial.

For the purpose of monitoring and auditing the trial, source documentation will consist of existing medical records and/or trial records developed and maintained by the Investigator.

10.1.10. Publication Policy

The results of this trial may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of Adverse Event

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) • NOTE: In this trial, any AE reported by a participant after signing of the informed consent form is to be recorded as an AE
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.

• A new condition or recurrence of an intermittent condition (eg, headache) not present at baseline, even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of Treatment-Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is any AE that occurs after receipt of one or more doses of study drug through the end of study for that participant. All definitions of AEs as shown in Section 10.2.1 will apply to TEAEs.

10.2.3. Definition of ADR

“Adverse drug reaction” or “adverse reaction” means a response to a medicinal product in humans which is noxious and unintended, which occurs at any dose, and which can also result from overdose, misuse or abuse of a medicine. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

10.2.4. Definition of SAE

If an event is not an AE per definition above, then it cannot be a SAE even if serious conditions are met.

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Is a medically significant / important event or reaction: Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.2.5. Definition of Serious Adverse Drug Reaction (Serious ADR)

When an AE is judged to be serious and related to an investigational product, it is referred to as Serious ADR and is subject to expedited reporting based on the parameters of this study (see Section 10.2.9).

10.2.6. Definition of AESI

AESIs are adverse events that the Sponsor wants to monitor carefully and which are subject to expedited reporting to the Sponsor (within 24 hours of identification; see Section 10.2.9).

In this trial, the following AEs will be collected and reported as AESIs:

- Hepatotoxicity, as defined by the presence of all of the following:
  - Elevated ALT or AST >3× ULN,
  - Elevated total bilirubin >2× ULN, and
  - No evidence of cholestasis (normal or minimally elevated ALP)
- Grade ≥2 peripheral neuropathy
- Grade ≥3 anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia
- Optic neuritis of any grade confirmed by an ophthalmologist

10.2.7. Recording and Follow-up of AEs (including SAEs and AESIs)

Recording
• Care will be taken not to introduce bias when detecting AE and SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences that are not detected by laboratory tests. • When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the CRF. • AE will be reported on the AE CRF using a recognized medical term or diagnosis that accurately reflects the event. • AE evaluations will be reviewed by the Investigator or a medically qualified delegate. AE CRF pages are to be completed by members of the trial team designated in writing by the Investigator. The onset and resolution dates of an AE and action taken in response to the AE will be documented.

- After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAE and non-serious AESI will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the medical monitor, the IDMC, or the Sponsor. In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- SAE will be assessed for severity and causal relationship to the study investigational medicinal product.

Follow-up and Resolution

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the trial or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology, if available.
- New or updated information will be recorded in the CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- The onset and resolution dates of the event and medical care taken in response to the event will be documented.
- AEs will be considered resolved when the condition returns to normal or returns to the participant's baseline status as established during Screening, or when the condition has stabilized with the expectation that it will remain chronic.
- If the event has not resolved by the final trial visit, it will be documented as either "Not Resolved/Not Recovered" or "Resolving/Recovering" on the eCRF, however, follow-up of a SAE must continue until resolved or the condition has stabilized. Information recorded on the CRF must be substantiated in the source documents.
- The resolution date to be recorded on the CRF is the last date on which the participant experienced the AE.

10.2.7.1. Assessment of AE Intensity (Severity)

Assessment of Intensity (Severity)

The Investigator will make an assessment of intensity for each AE reported during the study and assign it to 1 of 5 categories:
Grade 1 Mild symptoms, causing no or minimal interference with usual social and functional activities with intervention not indicated
Grade 2 Moderate symptoms, causing greater than minimal interference with usual social and functional activities with intervention indicated
Grade 3 Severe symptoms, causing inability to perform usual social and functional activities with intervention or hospitalization indicated
Grade 4 Potentially life-threatening symptoms, causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
Grade 5: Fatal

It is recommended that definitions of severity provided in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 of July 2017 (reported in Appendix 1) be followed. The DAIDS Table provides definitions of intensity grades 1 to 4 for numerous major clinical conditions and laboratory parameters, organized by body system.
It should be noted that the Investigator is not obliged to use the definitions of severity reported in Appendix 1 and medical judgement should prevail.
An event is defined as 'serious' when it meets at least 1 of the predefined criteria as described in the definition of an SAE (see Section 10.2.4), not when it may be rated as severe.

10.2.7.2. Assessment of AE Causality (Relatedness)

Assessment of Causality (Relatedness)
All AEs will be evaluated by the Principal Investigator or by a medically qualified designee (ie, Investigator, study physician) to assess the relationship between study intervention and each occurrence of each AE. The causality assessment will be determined using a two-level scale as follows: **Not related:** There is no reasonable possibility that the event may have been caused by the study intervention. There are other more likely causes for the TEAE. **Related:** There is a reasonable possibility that the study intervention contributed to the AE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. For each AE, the Investigator **must** document in the source documents that they have reviewed the AE and provided an assessment of causality. There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always makes an assessment of causality before the initial transmission of the SAE data. The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Sponsor or designee will have the opportunity to confirm the seriousness and case causality based on the clinical judgement of the medical monitor and Sponsor designee. If a SAE is considered unrelated by the Investigator but the Sponsor believes that there is a reasonable possibility that the event is related, the Sponsor will upgrade the case to a 'related' status. The Sponsor or designee will never downgrade a case from serious to non-serious or related to not related.

10.2.7.3. Assessment of AE Expectedness

AE Expectedness
Expected adverse events are adverse events consistent with the applicable product information provided by the Sponsor (ie, Investigator's brochure for MK-7662)

10.2.7.4. Assessment of AE Outcome

AE Outcome
The outcome of each AE must be reported to the Sponsor. The outcome of all AEs will be classified as one of the following: • Resolved • Resolved with Sequelae • Not Resolved/Not Recovered • Resolving/Recovering • Fatal

10.2.8. Treatment of Overdose

The study intervention will be administered by trained staff. Therefore, overdose is considered unlikely. In case of overdose, appropriate medical treatment will be instituted, guided by a full physical exam and any laboratory investigations. The participant will remain at the CTU until any symptoms of the overdose have disappeared or, in the Investigator's opinion, it is safe to discharge the participant.

10.2.9. Reporting of SAEs, AESIs and Other Immediately Reportable Events

10.2.9.1. Reporting to Sponsor and/or Pharmacovigilance Service Provider (PPD)

There are two required methods for reporting an SAE and/or AESI by the Investigator to the Sponsor and PPD.

1) PPD Notification: The first step of reporting an SAE or AESI by the Investigator to PPD will be using paper CRFs. This report must be sent to PPD within 24 hours of discovery or notification at the clinical site.
2) Sponsor Notification: The second step of reporting an SAE or AESI by the Investigator to the Sponsor will be the electronic data capture (EDC) system. The Investigator will complete the electronic SAE/AESI, CRF, as appropriate with all the current information.

All initial and follow-up SAEs or AESIs (regardless of assessment of causal relationship to the study intervention) will require following the two methods of reporting detailed above. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested. For hospitalizations, all attempts to obtain the hospital record should be documented in the source documents.

Any SAE or AESI that is attributable to study treatment by the Investigator will be reported even after the trial is completed if the Sponsor, Medical Monitor, or Investigator becomes aware of the SAE or the AESI.

Contacts for SAE and AESI reporting and for all safety personnel are contained in the Team Contact List which will be stored on-site in the Site Regulatory Binder and maintained by the Sponsor.

The Investigator is responsible for ensuring an adequate transmission of the facsimile or email and will store the distribution confirmation in the trial file.

At a minimum, the following information should be included in an initial report:

- Protocol number
- Name and contact number of the Investigator
- Site and participant identification number
- Date(s) participant received study intervention
- Event term [with a brief summary of the event(s) and causality assessment]

Pregnancy reports (initial and follow up) must be sent to PPD within 24 hours of discovery or notification at the clinical site by scanning and emailing the forms or faxing the completed paper forms. In rare circumstances and in the absence of facsimile equipment or email capability, notification by telephone is acceptable with a copy of the SAE/AESI or Pregnancy form(s) sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE/AESI, and/or Pregnancy paper forms within the designated reporting time frames.

10.2.9.2. Other Events Requiring Immediate Reporting

Other Events Requiring Immediate Reporting

The following events also require immediate reporting to PPD within 24 hours of learning of the event:

- Pregnancy (see Section 10.2.9.1)

10.3. Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Female of Childbearing Potential (FOCBP)

A female is considered fertile following menarche. If fertility is uncertain (e.g., amenorrhea in adolescents) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered. If in doubt, the participant should be considered fertile.

Females of non-childbearing potential are defined as:

- Females who are premenarchal or of post-menopausal status. Post-menopausal status is defined as 12 months with no menses without alternative medical cause.
- Females who have had surgical sterilization (medically documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy)
- For females with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), written documentation [ie, medical record(s)] to document such condition(s) should be provided to the Principal Investigator.

This trial will only enroll adult females of non-childbearing potential. Post-menopausal females will have confirmation of menopausal status with FSH testing during Screening (see SoA in Section 1.3).

Contraception Guidance:

Since only females of non-childbearing potential will be enrolled in this trial, there is no contraception requirement for female participants. Male participants who are not sterilized and are sexually active with a female partner of childbearing potential must agree to use condoms from Day -1 through 90 days after the last dose of study drug. They must also agree to not donate sperm during the trial and for 3 months (90 days) after receiving the last dose of study drug.

Collection and Reporting Pregnancy Information

In the event of a pregnancy by a female participant, the processes outlined below must be followed:

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the Pregnancy Form and submitted to PPD by email or facsimile within 24 hours of learning of a participant's pregnancy.
- Investigators must make an effort to collect outcomes of pregnancies discovered during the trial and communicate any known outcome to PPD. The health status of the mother and child, the date of delivery, and the child's sex, birth weight and multiparity should be recorded and be reported to the medical monitor after delivery. If delivery occurs before the last scheduled study visit, the participant should continue to be followed to determine the outcome of the pregnancy and for SAEs through the final trial visit unless withdrawal of

consent has occurred. If delivery occurs after the final trial visit, the Investigator should attempt to maintain contact with the participant to obtain information after delivery.

- The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be processed as such.
- Any post-study pregnancy-related SAE considered related to the study intervention by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.

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APPENDIX 1. DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, VERSION 2.1 OF JULY 2017

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

Table of Contents

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

DAIDS AE Grading Table Corrected Version 2.1-July 2017
Page 1

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations
The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term
When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

Instructions for Use

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ 7 days of age	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ 7 days of age	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

DAIDS AE Grading Table Corrected Version 2.1-July 2017
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Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18]**, High** (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171* to < *290.7*	≥ 17 ≥ *290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2* to < *324.9*	≥ 19 ≥ *324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5* to < *376.2*	≥ 22 ≥ *376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8* to < *410.4*	≥ 24 ≥ *410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 ≥ *239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 ≥ *171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 ≥ *136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

APPENDIX 2. MEDICATIONS ASSOCIATED WITH SEROTONIN SYNDROME

Examples of agents that can precipitate serotonin syndrome

Mechanism	Agent involved
Increases serotonin formation	Tryptophan, oxitriptan*
Increases release of serotonin	Amphetamines (including dextroamphetamine, methamphetamine)
	MDMA (ecstasy)
	Amphetamine derivatives (including fenfluramine, dexfenfluramine, phentermine)
	Cocaine
	Mirtazapine
Impairs serotonin reuptake from the synaptic cleft into the presynaptic neuron	Cocaine
	MDMA (ecstasy)
	Meperidine
	Tramadol
	Pentazocine
	Dextromethorphan
	Selective serotonin reuptake inhibitors (SSRIs; citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline)
	Serotonin-norepinephrine reuptake inhibitors (SNRIs; desvenlafaxine, duloxetine, levomilnacipran, milnacipran, and venlafaxine)
	Sibutramine
	Bupropion¶
	Serotonin modulators (nefazodone, trazodone, vilazodone, and vortioxetine)
	Cyclic antidepressants (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine)
	St. John's wort (*Hypericum perforatum*)
	5-HT3 receptor antagonists (dolasetron, granisetron, ondansetron, palonosetron)
	Cyclobenzaprine
	Methylphenidate, dexmethylphenidate
Inhibits serotonin metabolism by inhibition of MAO	MAO inhibitors, nonselective (isocarboxazid, linezolid, phenelzine, Syrian rue [*Peganum harmala*, harmine], and tranylcypromine)
	MAO-A inhibitors$^{\Delta}$ (methylene blue, moclobemide)
	MAO-B inhibitors$^{\Delta}$ (rasagiline, safinamide, and selegiline)
Direct serotonin receptor agonist	Buspirone
	Triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan)
	Ergot derivatives (including dihydroergotamine, ergotamine, methylergonovine)
	Fentanyl
	Lysergic acid diethylamide (LSD)
	Lasmiditan
	Lorcaserin$^{\diamond}$
	Metaxalone
Increases sensitivity of postsynaptic serotonin receptor	Lithium

Serotonin syndrome is a potentially life-threatening condition associated with increased serotonergic activity in the CNS. Serotonin syndrome can occur with therapeutic medication use, overdose, or as the result of additive or synergistic effects due to drug interaction(s). For additional information on clinical use and precautions related to serotonergic effects, refer to UpToDate topic reviews including the serotonin syndrome topic and Lexicomp drug monographs and drug interactions tool included within UpToDate.

MAO: monoamine oxidase; CNS: central nervous system; OTC: over-the-counter.

* Within the United States, tryptophan (L-tryptophan) and oxitriptan are available as OTC supplements. In other areas, these agents may be available OTC or by prescription.

¶ Bupropion inhibits neuronal uptake of dopamine and norepinephrine without known effects on serotonin; however, there have been case reports of serotonin syndrome when co-administered with other serotonergic drugs (eg, SSRIs); in some cases this may have been due to bupropion's inhibition of SSRI metabolism by CYP2D6.

Δ MAO selectivity is lost at higher doses and with drug interactions that increase serum drug concentrations. Inhibition of MAO-A is more likely to result in increased levels of serotonin within the CNS (ie, increased risk of serotonin syndrome) relative to MAO-B inhibition.

◇ Withdrawn from United States market.

Data from:

1. Boyer EW, Shannon M. The serotonin syndrome. NEJM 2005; 352:1112.
2. Finberg JPM, Rabey JM. Inhibitors of MAO-A and MAO-B in psychiatry and neurology. Front Pharmacol 2016; 7:340.

APPENDIX 3. DOCUMENT HISTORY

DOCUMENT HISTORY	
Document	Date
Original Protocol (Version 1.0):	27 Sep 2022
Amendment 1 (Version 2.0):	19 Dec 2022
Protocol Clarification Letter #1	10 Feb 2023
Protocol Clarification Letter #2	02 Mar 2023
Amendment 2 (Version 3.0)	04 Apr 2023
Amendment 3 (Version 4.0)	08 Sep 2023
Amendment 4 (Version 5.0)	30 Oct 2023

Changes in Version 2.0:

Content-related changes are summarized in the table below. In addition, updates and revisions related to grammar, punctuation, reference format and links, and consistency were also incorporated into this protocol amendment version. The amendment has been classified as an "Other Amendment" according to the Sponsor's relevant standard operating procedure.

Section Number	Text in Version 1	Text in Version 2 (Amendment 1)
Title Page	N/A	Added Amendment number and date
Multiple locations	Healthy adults will receive single and multiple doses of MK-7762…	Healthy adults will receive single or multiple doses of MK-7762…
Table 1 – first primary safety endpoint	• Part 1, Cohorts 1 and 2, first dosing period: Day 1 through day before the second dose • Part 1, Cohorts 1 and 2, second dosing period: Day 1 of second dosing period (date of second dose) through Day 7 of the second dosing period • Part 1, Cohort 3: Day 1 through Day 7 • Part 1, Cohort 4 (Food Effect):	• Part 1, Cohorts 1 through 5: Day 1 through Day 7 • Part 1, Cohort 6 (Food Effect):
Table 1 – first secondary PK objective	N/A	• "To evaluate the impact of food on the PK of MK-7762 in plasma" added as an objective
	Treatment: MK-7762 in escalating single doses or placebo (Part 1, Cohorts 1-3), with randomized crossover to high dose MK-7762 or placebo (Part 1, Cohorts 1 and 2); MK-7762 under fasted or fed conditions (Part 1, Cohort 4)	• Treatment: 1) MK-7762 in escalating single doses or placebo (Part 1, Cohorts 1-5) and 2); MK-7762 under fasted or fed conditions (Part 1, Cohort 6)
Table 1 – exploratory objective on ECGs	QTc interval	• QTcF interval
	The trial will be conducted in two parts. Part 1 will consist of a single ascending dose (SAD) design and food effect (FE) evaluation (N=34), and Part 2 will consist of a multiple ascending dose (MAD) design (N=48).	• The trial will be conducted in two parts. Part 1 will consist of a single ascending dose (SAD) double-blind, placebo-controlled design evaluating up to 5 single doses of MK-7762 (N=40). An open-label food effect (FE) evaluation in 8 additional participants will be conducted utilizing an oral dose of MK-7762 demonstrated to be safe and well-tolerated in a previously completed SAD cohort. • Following completion of Part 1, an interim review of unblinded safety and PK data will be conducted. Any additional nonclinical data available will also be reviewed. Upon completion of this interim review, the Sponsor will select 3 dose levels of MK-7762 (low, medium, and high) to be administered daily for 28 days in a placebo-controlled, multiple ascending dose (MAD) design (N=48) in Part 2 of the trial (see Section 1.1.3.2). The results of the interim review are also intended for regulatory submission and comment prior to initiation of Part 2 of the trial.

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1.1.3.1 – Part 1 – SAD and Food Effect (SAD/FE)	In Part 1 of the trial (SAD/FE), three sequential cohorts will be enrolled to evaluate five escalating single doses of MK-7762; participants in each cohort will be randomized to receive MK-7762 or placebo. A fourth cohort will evaluate the effect of food on PK of single doses of MK-7762. All participants in Part 1 will be confined at the trial site from Day -1 until their end of-trial visit (approximately 8-22 days depending on the cohort). Cohorts 1 and 2 in Part 1 will have a crossover design. In the first dosing period of each cohort, nine participants will be randomized 2:1 to MK-7762 or placebo. For the second dosing period, Cohort 1 and 2 participants will cross over to receive a placebo or a higher single dose of MK 7762, respectively, following a washout period of approximately two weeks. That is, the six participants who receive MK-7762 in their first dosing period will be randomized 1:1 to receive a higher dose of MK-7762 or placebo in the second dosing period, while the three participants who receive placebo in their first dosing period will all receive the higher dose MK 7762 in the second dosing period. This ensures that a total of 12 participants in Cohorts 1 and 2 will receive both MK-7762 and placebo in a randomized crossover fashion. For Cohort 3, eight participants will be randomized 3:1 to MK-7762 or placebo. For Cohort 4 (the FE Cohort), all 8 participants will be dosed with MK-7762 and randomized 1:1 to receive their first dose fasting (N=4) or after consuming a high fat meal (N=4) and then vice versa for their second dose. The doses of Cohorts 1-3 may be modified based on accumulating safety, tolerability, and PK data. Additional cohorts may be enrolled after protocol amendment to repeat a dose level or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previous cohorts.	• In Part 1 of the trial (SAD/FE), up to five sequential cohorts will be enrolled to evaluate up to five escalating single doses of MK-7762; 8 participants in each cohort will be randomized (3:1) to receive MK-7762 or placebo. A sixth cohort will evaluate the effect of food on PK of single doses of MK-7762 utilizing an open-label, two-period design in 8 participants. The MK 7762 dose to be evaluated in the FE cohort will be a dose demonstrated to be safe and well tolerated in a previously completed SAD cohort. All participants in Part 1 will be confined at the trial site from Day -1 until their end of-trial visit (approximately 8 days for Cohorts 1-5 and 16 days for Cohort 6). • Cohorts 1 through 4 will evaluate the safety and PK of single oral doses of MK-7762 of 50 mg, 150 mg, 300 mg, and 600 mg. Cohort 5 may evaluate a dose of MK-7762 that will be selected based on the safety and PK data from previous cohorts. The dose of MK-7762 chosen for evaluation in Cohort 5 will not result in predicted exposure higher than that allowable based on the nonclinical toxicology no observed adverse effect level (NOAEL). • For Cohort 6 (the FE Cohort), eight participants will be dosed with MK-7762 in both fasted and fed states with a between-dose washout period of at least 5 half-lives of MK-7762 as determined by the PK results from previous SAD cohorts. The MK-7762 dose to be evaluated in the FE Cohort will be a dose demonstrated to be safe and well-tolerated in a previously completed SAD cohort. Two sentinel participants in Cohort 6 will be dosed in the fed state first followed by the second dose in the fasted state after washout. The SRT will review safety data up to Day 4 and PK data up to Day 2 following completion of the dosing periods for the two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined. • The doses of MK-7762 to be administered in the cohorts following Cohort 1 may be modified based on accumulating safety, tolerability, and PK data. The Protocol may be amended to enroll additional participants at any of the planned dose level(s) or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previously

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		completed cohorts. The enrolment to Cohort 6 (FE) may start after PK and safety data from Cohort 2 become available.
1.1.3.1 (Confinement Period)	Randomization will occur prior to dosing on Day 1 for all cohorts. Participants must have fasted for at least 8 hours prior to dosing. Cohort 1 and 2 participants will be admitted from Day -1 until Day 21 (±1 day; 22 days total) for their two dosing periods. In Cohort 3, participants will be admitted from Day -1 until Day 7 (±1 day; 8 days total) for their single dosing period. Participants in Cohort 4 (FE Cohort) will be admitted from Day -1 until Day 14 (±1 day; 15 days total) for their two dosing periods.	• Randomization to blinded treatment will occur prior to dosing on Day 1 for participants in Cohorts 1 through 5. Participants must have fasted for at least 8 hours prior to dosing. • In Cohorts 1-5, participants will be admitted from Day -1 until Day 7 (±1 day; 8 days total) for the single dosing period. Participants in Cohort 6 (FE Cohort) will be admitted from Day -1 until Day 7 (±1 day) of the second dosing period. The exact duration of the confinement will be determined by the time required for an adequate washout period of at least five half-lives to be determined by PK results from the SAD cohorts.
1.1.3.1 (Food Effect Cohort)	Participants will be randomized 1:1 to receive their first dose of MK-7762 fasting or fed on Day 1. Participants randomized to administration in fasting state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants randomized to administration in fed state will be provided the standard US Food & Drug Administration (FDA) high fat breakfast, which should be consumed within 30 minutes or less, with study drug administration occurring approximately 30 minutes after the start of the meal. Fasting will resume for 4 hours post-dose, at which time, a standardized meal will be provided.	• Participants will receive open-label MK-7762. The first two participants in this cohort will be termed sentinel participants and will receive MK-7762 in a fed state and then, following a washout period of at least five half-lives, a second dose of MK-7762 will be administered in the fasted state. The SRT will review safety data up to Day 4 and PK data up to Day 2 following completion of the dosing periods for the two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining six participants in Cohort 6 will receive doses of MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined. • Participants administered MK-7762 in the fasted state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants administered MK-7762 in the fed state will be provided the standard US Food & Drug Administration (FDA) high fat breakfast, which should be consumed within 30 minutes or less, with MK-7762 administration occurring approximately 30 minutes after the start of the meal. In both the fed and fasted settings, fasting will resume for 4 hours post-dose, at which time, a standardized meal will be provided.
1.1.3.2 (Interim Review of Data from Part 1)	N/A (new section)	• Following completion of Part 1, a comprehensive interim review of cumulative clinical and PK data will be conducted in an unblinded manner by the Sponsor to guide selection of appropriate doses to be evaluated in Part 2. Any additional relevant nonclinical data will also be reviewed as part of this process. The results of the

<table>
<tr><th>Section Number</th><th>Text in Version 1</th><th>Text in Version 2 (Amendment 1)</th></tr>
<tr><td></td><td></td><td>interim review are intended for regulatory submission and comment prior to initiation of Part 2 of the trial.</td></tr>
<tr><td>1.1.3.3 (Part 2 – MAD, Confinement Period)</td><td>In Part 2, MK-7762 may be dosed shortly after a meal (fed condition) or under fasting conditions. PK data collected in the FE Cohort will be considered in deciding how study drug will be administered. Additional information regarding how FE Cohort data will be used to decide if study drug will be dosed with food or under fasted condition in Part 2 will be discussed in the SAP.

Participants in Cohorts 1-3 will be admitted on Day -1 until Day 33 (±2 days; 34 days total).

Clinical and safety laboratory assessments will be performed throughout the confinement period as per Table 6 for Cohorts 1-3.</td><td>• In Part 2, MK-7762 will be dosed either shortly after a meal (fed condition) or under fasting conditions depending on the PK results of the FE evaluation in Part 1.
•
• Part 2 participants in Cohorts 1-3 will remain in the CTU until Day 33 (±2 days; 34 days total).
• Clinical and safety laboratory assessments will be performed throughout the confinement period as per Table 5 for MAD Cohorts 1-3.</td></tr>
<tr><td>1.1.4 (Study Drug Administration)</td><td>MK-7762 will be supplied as 10 mg (size 3), 100 mg (size 0), and 300 mg capsules (size 00) with matching placebo for oral administration. The planned doses for each cohort in Part 1 are listed in the table below. The doses of SAD Cohorts 2-3 may be modified based on accumulating safety, tolerability, and PK data. Additional cohorts may be enrolled after protocol amendment to repeat a dose level or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previous cohorts. The dose for Cohort 4 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previous SAD cohorts. The doses for MAD Cohorts 1-3 will be selected after review of PK and safety data from Part 1.</td><td>• Capsules containing MK-7762 will be supplied as 10 mg (size 3), 100 mg (size 0), and 300 mg capsules (size 00) with matching placebo capsules for oral administration. The planned doses for each cohort in Part 1 are listed in Table 2 below. All doses of MK-7762 and placebo will be administered with 240 mL (8 ounces) of water. The doses of MK-7762 for Part 1 Cohorts 2 through 4 may be modified based on accumulating safety, tolerability, and PK data. The dose for Cohort 5 will be determined after review of cumulative safety and PK data from the previously completed cohorts. Additional cohorts may be enrolled after protocol amendment to enroll additional participants at any of the planned dose level(s) or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previously completed cohorts. The dose for Cohort 6 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previously completed SAD cohorts. The MK-7762 doses for daily administration in MAD Cohorts 1-3 will be selected after the interim review described above (see Section 1.1.3.2).</td></tr>
<tr><td>Table 2 – Study Drug Administration</td><td><table>
<tr><th>Part</th><th>Cohort</th><th>Period</th><th>Drug</th><th>Dose</th><th>Dose Strength</th><th>Dose Frequency</th></tr>
<tr><td>1 (SAD)</td><td>1</td><td>1</td><td>MK-7762</td><td>50mg</td><td>10 mg</td><td>Single Dose</td></tr>
<tr><td></td><td></td><td></td><td>Placebo</td><td>NA</td><td>NA</td><td>Single Dose</td></tr>
<tr><td></td><td>2</td><td>2</td><td>MK-7762</td><td>150mg</td><td colspan="2">10 mg and 100 mg</td></tr>
<tr><td></td><td colspan="2">Single Dose</td><td></td><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td><td>Placebo</td><td>NA</td><td>NA</td><td>Single Dose</td></tr>
</table></td><td>• Part Cohort Period Drug Dose Dose Strength Dose Frequency
• 1 (SAD) 1 NA MK-7762 50 mg 10mg Single Dose
• Placebo NA NA Single Dose
• 2 NA MK-7762 150 mg 10 mg and 100 mg Single Dose</td></tr>
</table>

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	1 3 MK-7762 300mg 100 mg and/or 300 mg Single Dose Placebo NA NA Single Dose 2 4 MK-7762 600mg 100 mg and/or 300 mg Single Dose Placebo NA NA Single Dose 3 5 MK-7762 TBD 10 mg, 100 mg and/or 300 mg Single Dose Placebo NA NA Single Dose 4 (FE) 6 MK-7762 TBD 10 mg, 100 mg and/or 300 mg Single Dose, fed or fasted 7 MK-7762 TBD 10 mg, 100 mg and/or 300 mg Single Dose, fed or fasted 2 (MAD) 1 8 MK-7762 TBD 10 mg, 100 mg and/or 300 mg Once daily, 28 days Placebo NA NA Once daily, 28 days 2 9 MK-7762 TBD 10 mg, 100 mg and/or 300 mg Once daily, 28 days Placebo NA NA Once daily, 28 days 3 10 MK-7762 TBD 10 mg, 100 mg and/or 300 mg Once daily, 28 days Placebo NA NA Once daily, 28 days SAD: single ascending dose; MAD: multiple ascending dose; FE: food effect; TBD: to be determined; NA: not applicable	• Placebo NA NA Single Dose • 3 NA MK-7762 300 mg 100 mg and/or 300 mg Single Dose • Placebo NA NA Single Dose • 4 NA MK-7762 600 mg 100 mg and/or 300 mg Single Dose • Placebo NA NA Single Dose • 5 NA MK-7762 TBD 10mg, 100 mg and/or 300 mg Single Dose • Placebo NA NA Single Dose • 6 (FE) 1 MK-7762 TBD 10mg, 100 mg and/or 300 mg Single Dose, fed or fasted • 2 MK-7762 TBD 10 mg, 100 mg and/or 300 mg Single Dose, fed or fasted • 2 (MAD) 1 NA MK-7762 TBD 10 mg, 100 mg and/or 300 mg Once daily, 28 days • Placebo NA NA Once daily, 28 days • 2 NA MK-7762 TBD 10 mg, 100 mg and/or 300 mg Once daily, 28 days • Placebo NA NA Once daily, 28 days • 3 NA MK-7762 TBD 10 mg, 100 mg and/or 300 mg Once daily, 28 days • Placebo NA NA Once daily, 28 days
1.1.4.1 Safety Review and Dose Escalation Decisions	• A Safety Review Team (SRT) will be established as the team responsible for safety review and the dose escalation recommendations for the trial. Details on the membership of the SRT will be featured in a charter that will be developed for the SRT's review of blinded data and deliberation processes (including the format of data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment. • In Part 1 (see Figure 1 and Table 2), Period 2 may start following review of safety data through Day 4 from Period 1 (without PK data review being required). Periods 3 and 4 may start following review of 4 days of safety data from Periods 2 and	• A Safety Review Team (SRT) will be established as the team responsible for safety review and dose escalation recommendations during Part 1 and Part 2 of the trial. Details on the membership of the SRT will be contained in a charter that will describe the SRT review of blinded safety and PK data and the deliberation processes (including the format of data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment and, if PK data are made available, only aggregated mean PK data will be provided. • During Part 1 of the study, the SRT will convene after all participants in a specific cohort have completed 4 days of follow-

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	3 respectively, and 48-hour PK data from Periods 1 and 2, respectively. Period 5 may start following review of 4 days of safety data and 48-hour PK data from the previous period. The FE Cohort may start following review of 4 days of safety data from Period 4, and 48-hour PK data from Period 3. The FE Cohort (Periods 6 and 7) may start before Cohort 3 (Period 5) if PK data from Cohorts 1 and 2 are sufficient for selecting the dose to be evaluated in the FE Cohort. In Part 2, the MAD component, Cohort 1 may start following review of 4 days of safety data and 48-hour PK data from Part 1 Period 3. Cohorts 2 and 3 in the MAD component, may start following a review of a minimum of 14 days of safety data and 7 days of PK data from MAD Cohorts 1 and 2, respectively.	up post-dosing and all safety data collected through Day 4 are available for review. Safety review will be conducted after completion of each of Cohorts 1, 2, 3, and 4 (see Figure 1). The SRT will have access to available aggregated mean PK data during its meetings to consider progression to Cohorts 3, 4, and 5. The SRT may recommend dose escalation to a subsequent planned cohort if no pausing rule is present. If dose escalation is recommended following completion of Cohort 1 (50 mg), the single dose to be evaluated in Cohort 2 is planned as 150 mg. If dose escalation is recommended following completion of Cohort 2, the dose to be evaluated in Cohort 3 is planned as 300 mg. If dose escalation to Cohort 4 is recommended following completion of Cohort 3, the dose to be evaluated in Cohort 4 is planned as 600 mg. The dose to be evaluated in Cohort 5 will be decided by analysis of the safety and PK data available from the previous cohorts. • As described in Section 1.1.3.2, an interim review will be conducted following completion of Part 1 and prior to any activities of Part 2. With regulatory agreement and Sponsor approval to proceed to the Part 2, MAD Cohort 1 may be initiated with MK-7762 (low dose) to be administered once daily for 28 days (either with or without food depending on results of the FE evaluation results of Part 1 Cohort 6). • The SRT will convene after all participants in MAD Cohort 1 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 2 (medium dose of MK-7762 administered once daily for 28 days) if no pausing rule is present. • The SRT will convene after all participants in MAD Cohort 2 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 3 (high dose of MK-7762 administered once daily for 28 days) if no pausing rule is present.
1.1.4.2 Pausing Rules	The SRT must assess the data as showing no significant safety concerns before recommending proceeding with MK-7762 administration for the next highest dose group. Events	• The SRT must assess the data as showing no significant safety concerns before recommending proceeding with MK-7762 administration to participants in SAD and/or MAD cohorts

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	necessitating a pause in enrollment and participant dosing, and, in turn, requiring an ad hoc SRT review, include: • At least one participant experiences a Grade 3 AE assessed as related to study drug by the Investigator or Sponsor. The qualifying AE should occur within 4 days of the last dose of study drug received (see Appendix 1 for the AE grading table to be used for the trial). The Investigator should assess clinical significance of safety laboratory abnormalities before reporting as an AE. • At least one participant experiences a SAE assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of the last dose of study drug received. • At least two participants experience Grade 2 AEs of a similar nature assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of the last dose of study drug received. • Any occurrence of anaphylaxis or Grade 4 hypersensitivity reaction. • Any other findings that, at the discretion of the Investigator, SRT, or Sponsor, indicate dose escalation should be paused.	scheduled to receive higher doses of MK-7762. Events necessitating a pause in enrollment and/or participant dosing in both parts of the trial, and, in turn, requiring an ad hoc SRT review, include: • At least one participant experiences a Grade ≥ 3 AE assessed as related to study drug by the Investigator or Sponsor. The qualifying AE should occur within 4 days of receipt of a dose of study drug (see Appendix 1 for the AE grading table to be used for the trial). The Investigator should assess clinical significance of safety laboratory abnormalities before reporting as an AE. • At least one participant experiences a SAE assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug. • At least two participants within any of the cohorts (SAD or MAD) experience Grade ≥ 2 AEs of a similar nature assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug. • Any occurrence of anaphylaxis or Grade 4 hypersensitivity reaction. • Any other findings that, at the discretion of the Investigator, SRT, or Sponsor, indicate dose escalation should be paused.
1.1.6 – Number of Participants and Duration of Participation	Because this trial is aimed at characterizing the safety, tolerability, and PK of MK-7762, it is designed to be descriptive and is not based on formal hypothesis testing. Therefore, this trial is not powered to detect any pre-specified differences in potential safety or PK data between treatment groups. A total of approximately 82 participants will be randomized (34 in Part 1 and 48 in Part 2), and a total of approximately 68 participants will be exposed to MK-7762 (32 from Part 1 and 36 from Part 2). All participants will undergo a screening period lasting up to 20 days (Day -21 to -2) followed by a confinement period in the CTU of varying length according to their assigned cohort. In Part 1, the maximum duration of participation, including the screening period, will be approximately 42 days for participants in Cohorts 1 and 2, approximately 28 days for participants in Cohort 3, and approximately 35 days for Cohort 4 participants. In Part 2, the maximum duration of participation, including the screening period, will be approximately 54 days for participants in Cohorts	• Because this trial is aimed at characterizing the safety, tolerability, and PK of MK-7762, it is designed to be descriptive and is not based on formal hypothesis testing. Therefore, this trial is not powered to detect any pre-specified differences in potential safety or PK data between treatment groups. A total of approximately 96 participants will be randomized (48 in Part 1 and 48 in Part 2), and a total of approximately 74 participants will be exposed to MK-7762 (38 in Part 1 and 36 in Part 2). • All participants will undergo a Screening period lasting up to 20 days (Day -21 to -2) followed by a confinement period in the CTU of varying length according to their assigned cohort. In Part 1, the maximum duration of participation, including the Screening period, will be up to approximately 30 days for participants in Cohorts 1 through 5 and approximately 38 days for participants in Cohort 6 (to be confirmed once washout period of at least 5 half-lives is determined). In Part 2, the maximum duration of

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	1-3. The duration of cohorts may be adjusted (increased or decreased) based on emerging PK data collected during the study.	participation, including the Screening period, will be up to approximately 54 days for participants in Cohorts 1-3. The duration of participants' participation may be adjusted (increased or decreased) based on emerging PK data collected during the study.
1.2 Schema	Previous schema demonstrating SAD crossover design in first two cohorts followed by Cohort 3 and then Cohort 4 (Food Effect)	• Schema updated to eliminate SAD crossover design and introduce 5 SAD cohorts and 1 Food Effect Cohort. Interim Review introduced demonstrating key activities before MAD can commence.
1.3 SoAs	Part 1, Cohorts 1-2 SoA (Table 3)	• Removed
	Part 1, Cohort 3 (Table 4)	• SoA Changed to apply to Part 1, Cohorts 1-5. • Sample collection for PGx screening added at Day -1 visit • Footnote 'k': added "Additional blood will be collected at the same time points for participants in Cohort 4 for storage for potential future qualitative analysis of any significant metabolites identified." • Footnote 'm': added "Samples will be collected and stored for potential pharmacogenetic (PGx) analysis (see Section 8.4.10)"
	Part 1, Cohort 4 (Table 5)	• SoA changed to apply to Part 1, Cohort 6 • Overall Day references from Period 2 removed • Sample collection for PGx screening added at Day -1 visit • Footnote 'a' updated to read: "Day 1 of Period 2 will not occur until at least five half-lives of MK-7762 have elapsed as determined by PK results from Cohorts 1-5." • Footnote 'l': added "Samples will be collected and stored for potential pharmacogenetic (PGx) analysis (see Section 8.4.10)"
	Part 2, Cohorts 1-3 (Table 6)	• Sample collection for PGx screening added at Day -1 visit • Footnote 'm': added "Samples will be collected and stored for potential pharmacogenetic (PGx) analysis (see Section 8.4.10)"

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2.6.1 Justification for Dose – Part 1 (SAD)	The highest possible dose to be tested (Part 1 Cohort 3, Period 5) is not pre-defined and will be determined following SRT review of evolving safety data (number, severity, and frequency of AEs) and available PK data from earlier cohorts. Given that MK-7762 administration to animals did not cause serious toxicities, the selected dose for Cohort 3 may produce exposures exceeding the NOEL levels… The wide dose range to be tested in healthy adults will cover the anticipated target exposures in TB patients. The safety and PK data from Part 1 will enable proceeding to Part 2 where multiple doses of MK-7762 will be administered.	The highest dose to be tested in Part 1 is not pre-defined and will be determined following SRT review of evolving safety data (number, severity, and frequency of AEs) and available PK data from earlier cohorts. The maximal exposure target will be below the NOAEL levels (AUC_{ss} 1040 μM·h and $C_{max,ss}$ of 66 μM). The wide dose range to be tested in healthy adults will cover the anticipated target exposures in TB patients. The safety and PK data from Part 1 will enable proceeding to Part 2 following the planned interim review (see Section 1.1.3.2) where multiple doses of MK-7762 will be administered.
2.6.2 Justification for Dose – Part 2 (MAD)	N/A	New paragraph added: “The highest possible dose to be tested in Part 2 may be modified following review of evolving safety data (number, severity, and frequency of AEs) and available PK data from earlier cohorts in Part 1. The steady state exposure target will be below the NOAEL levels (AUCss 1040 μM·h and Cmax,ss of 66 μM). The highest dose in Part 2 will not exceed the highest dose in Part 1.”
4 – Trial Design	A total of approximately 82 participants will be randomized (34 in Part 1 and 48 in Part 2), and a total of approximately 68 participants will be exposed to MK-7762 (32 from Part 1 and 36 from Part 2). … All participants will undergo a screening period lasting up to 20 days (Day -21 to -2) followed by a confinement period in the CTU of varying length according to their cohort. In Part 1, the maximum duration of participation, including the screening period, will be approximately 42 days for participants in Cohorts 1 and 2, approximately 28 days for participants in Cohort 3, and approximately 35 days for Cohort 4 participants. In Part 2, the maximum duration of participation, including the screening period, will be approximately 54 days for participants in Cohorts 1-3. The duration of cohorts may be adjusted (increased or decreased) based on emerging PK data collected during the study.	A total of approximately 96 participants will be randomized (48 in Part 1 and 48 in Part 2), and a total of approximately 74 participants will be exposed to MK-7762 (38 from Part 1 and 36 from Part 2). … All participants will undergo a Screening period lasting up to 20 days (Day -21 to -2) followed by a confinement period in the CTU of varying length according to their cohort. In Part 1, the maximum duration of participation, including the Screening period, will be approximately up to 30 days for participants in Cohorts 1 through 5, approximately 38 days for participants in Cohort 6 (to be confirmed once washout period of at least 5 half-lives is determined). In Part 2, the maximum duration of participation, including the Screening period, will be approximately up to 54 days for participants in Cohorts 1-3. The duration of cohorts may be adjusted (increased or decreased) based on emerging PK data collected during the study.

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4.1 – Part 1 – SAD and Food Effect	In Part 1 of the trial (SAD/FE), three sequential cohorts will be enrolled to evaluate five escalating single doses of MK-7762; participants in each cohort will be randomized to receive MK-7762 or placebo. A fourth cohort will evaluate the effect of food on PK of single doses of MK-7762. All participants in Part 1 will be confined at the trial site from Day -1 until their end of-trial visit. Cohorts 1 and 2 in Part 1 will have a crossover design. In the first dosing period of each cohort, nine participants will be randomized 2:1 to MK-7762 or placebo. For the second dosing period, Cohort 1 and 2 participants will cross over to receive a placebo or a higher single dose of MK 7762, respectively, following a washout period of approximately two weeks. That is, the six participants who receive MK-7762 in their first dosing period will be randomized 1:1 to receive a higher dose of MK-7762 or placebo in the second dosing period, while the three participants who receive placebo in their first dosing period will all receive the higher dose MK-7762 in the second dosing period. If all Cohort 1 and 2 participants complete both dosing periods, a total of 12 participants will receive both MK-7762 and placebo in a randomized crossover fashion. See Figure 2 and Table 8. If more than one participant from Cohort 1 or 2 is withdrawn from the trial after receiving their first dose but before receiving their second dose of study drug, additional participants will be randomized to replace them. No replacements are required if only one participant is withdrawn from either cohort before receiving the second dose of study drug. If more than one participant is withdrawn before the Day 18 (Day 4 of the second dosing period for Cohorts 1 and 2) trial assessments are completed, additional participants will be randomized to replace them.	In Part 1 of the trial (SAD/FE), five sequential cohorts will be enrolled to evaluate up to five escalating single doses of MK-7762; eight participants in each cohort will be randomized (3:1) to receive MK-7762 or placebo. A sixth cohort will evaluate the effect of food on PK of single doses of MK-7762 utilizing an open-label, single-dose cross-over design in 8 participants. The MK-7762 dose to be evaluated in the FE Cohort will be a dose demonstrated to be safe and well tolerated in previously completed SAD cohorts. All participants in Part 1 will be confined at the trial site from Day -1 until their end-of-trial visit (approximately 8 days for Cohorts 1-5 and 16 days for Cohort 6). Cohorts 1 through 4 are planned to evaluate the safety and PK of single oral doses of MK-7762 of 50 mg, 150 mg, 300 mg, and 600 mg. Cohort 5 may evaluate a dose of MK-7762 that will be selected based on the safety and PK data from previous cohorts. The dose of MK-7762 chosen for evaluation in Cohort 5 will not result in greater predicted exposure than that allowable based on the nonclinical toxicology NOAEL. For Cohort 6 (the FE Cohort), eight participants will be dosed with MK-7762 in both fasted and fed states with a between-dose washout period of at least 5 half-lives of MK-7762 determined by the SAD cohorts PK results. The MK-7762 dose to be evaluated in the FE Cohort will be a dose demonstrated to be safe and well-tolerated in a previously completed SAD cohort. Two sentinel participants in Cohort 6 will be dosed in the fed state first followed by the second dose in the fasted state after washout. The SRT will review safety data up to Day 4 and PK data up to Day 2 following completion of the dosing periods for the two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 6 will receive MK 7762 in fed and fasted states in a crossover manner employing the washout period previously determined. The FE Cohort may start following review of 4 days of safety data from Cohort 4, and 48-hour PK data from Cohort 3. The FE Cohort (Periods 6 and 7) may start before Cohort 5 if PK data from Cohorts 1-4 are sufficient for selecting the dose to be evaluated in the FE Cohort. The doses of MK-7762 to be administered in any of the cohorts following Cohort 1 may be modified based on accumulating safety,

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		tolerability, and PK data. The Protocol may be amended to enroll additional participants at any of the planned dose level(s) or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previously completed cohorts. If more than 1 participant from Cohort 6 is withdrawn from the trial after receiving the first dose but before receiving the second dose of study drug, additional participants will be enrolled to replace the withdrawn participants. No replacements are required if only one participant is withdrawn from Cohort 6 before receiving the second dose of study drug.
4.1 – Table 7 and Figure 2		Updated to reflect text changes
4.1 – Table 7 footnotes	All suggested doses may be adjusted downward based on evaluation of safety, tolerability, or PK data observed in previous participants. a Period 2 dosing will occur after review of safety data through at least Day 4 post dose administration from Period 1 (no PK data will be reviewed). b Period 3 dosing will occur approximately 2 weeks after Period 1 dosing, after review of safety data through at least Day 4 post dose administration from Period 2, and after review of 48-hour PK data from Period 1. c Period 4 dosing will occur approximately 2 weeks after Period 2 dosing, after review of safety data through at least Day 4 post dose administration from Period 3, and after review of 48-hour PK data from Period 2.	All suggested doses may be adjusted based on evaluation of safety, tolerability, or PK data observed in previous participants. a Cohort 2 dosing will occur after review of safety data through at least Day 4 post dose administration for all participants in Cohort 1 (no PK data will be reviewed). b Cohort 3 dosing will occur after review of safety data through at least Day 4 post dose administration for all participants in Cohort 2. Aggregated 48-hour PK data (mean) from Cohort 1 will be available for review. c Cohort 4 dosing will occur after review of safety data through at least Day 4 post dose administration for all participants in Cohort 3. Aggregated 48-hour PK data (mean) from Cohort 2 will be available for review.
4.1 – Text following Table 7	For Cohort 3, eight participants will be randomized 3:1 to MK-7762 or placebo (see Figure 3 and Table 9). If more than one participant from Cohort 3 is withdrawn from the trial before their Day 4 trial assessments are completed, additional participants will be randomized to replace them. No replacements are required if only one participant is withdrawn before Day 4.	Removed
4.1 – Table 8 and Figure 4		Updated to reflect text changes

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4.1 former Table 9, Figure 3, and Table 9 footnotes	Cohort 3 MK-7762 dose to be administered will be selected based on evaluation of safety, tolerability, or PK data observed in previous participants. a Period 5 dosing will occur after review of at least 4 days of safety and 48-hour PK data from Period 4.	All removed
4.1 Table 8 Footnotes	Cohort 4 MK-7762 dose to be administered will be selected based on evaluation of safety, tolerability, or PK data observed in previous participants. a Periods 6 and 7 will be conducted approximately 7 days apart, either consecutively or concurrently with other Periods, after PK data from the corresponding dose level to be used for FE Cohort has been reviewed.	Cohort 6 MK-7762 dose to be administered will be selected based on evaluation of safety, tolerability, or PK data observed in previous participants. a The second dose of MK-7762 will be administered no earlier than 5 half-lives of MK-7762 after PK data from prior dose levels are reviewed to determine half-life. Two sentinel participants will be dosed in the fed state first followed by the second dose in the fasted state after washout. The SRT will review safety data up to Day 4 and PK data up to Day 2 following completion of the dosing periods for the two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining six participants will receive doses of MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.
4.1.1 – Screening Period	Part 1 participants will undergo a screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 3, Table 4, and Table 5 in Section 1.3.	Part 1 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 3 for Cohorts 1 5 or Table 4 for Cohort 6 in Section 1.3. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will apply during the Screening period.
4.1.2 – Confinement Period	All Part 1 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 3, Table 4, and Table 5 in Section 1.3. Randomization will occur prior to dosing on Day 1 for all cohorts. Participants must have fasted for at least 8 hours prior to dosing. Cohort 1 and 2 participants will be admitted from Day -1 until Day 21 (±1 day; 22 days total) for their two dosing periods. In Cohort 3, participants will be admitted from Day -1 until Day 7 (±1 day; 8 days total) for their single dosing period. Participants in Cohort 4 (FE Cohort) will be admitted from Day -1 until Day 14 (±1 day; 15 days total) for their two dosing periods.	All Part 1 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 3 for Cohorts 1-5 or Table 4 for Cohort 6 in Section 1.3. Randomization will occur prior to dosing on Day 1 for all cohorts. Participants in Cohorts 1-5 must have fasted for at least 8 hours prior to dosing. Participants in Cohorts 1-5 will be admitted from Day -1 until Day 7 (±1 day; 8 days total) for the single dosing period. Participants in Cohort 6 (FE Cohort) will be admitted from Day -1 until Day 7 (±1 day) of the second dosing period. The exact duration of the confinement will be determined by the time required for an

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		adequate washout period of at least five half-lives to be determined by PK results from the SAD cohorts.
4.1.4 – Food Effect cohort	Participants will be randomized 1:1 to receive their first dose of MK-7762 fasting or fed on Day 1. Participants randomized to administration in fasting state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants randomized to administration in fed state will be provided the standard US FDA high fat breakfast after an 8-hour fast. The high-fat meal should be consumed within 30 minutes or less, with study drug administration occurring approximately 30 minutes after the start of the meal. Fasting will resume for 4 hours post-dose, at which time, a standardized meal will be provided.	Participants will receive open-label MK-7762. The first two participants in this cohort will be termed sentinel participants and will receive MK-7762 in a fed state and then, following a washout period of at least five half-lives, a second dose of MK-7762 will be administered in the fasted state. The SRT will review safety data up to Day 4 and PK data up to Day 2 following completion of the dosing periods for the two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining six participants in Cohort 6 will receive doses of MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined. Participants administered MK-7762 in the fasted state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants administered MK-7762 in the fed state will be provided the standard US FDA high fat breakfast, which should be consumed within 30 minutes or less, with MK-7762 administration occurring approximately 30 minutes after the start of the meal. In both the fed and fasted settings, fasting will resume for 4 hours post-dose, at which time, a standardized meal will be provided.
4.2 – Part 2 - MAD	In Part 2 of the trial (MAD), participants will be enrolled into three sequential cohorts to evaluate escalating once daily doses of MK-7762 or placebo for 28 days. Each of the three MAD cohorts will have sixteen participants randomized 3:1 to receive MK-7762 or placebo. See Figure 5 and Table 11. If more than two participants from a MAD cohort are withdrawn from the trial before their Day 29 visit assessments are completed, additional participants will be randomized to replace them. No replacements are required if two or fewer participants are withdrawn before their Day 29 visits. A fourth MAD cohort will be considered for subsequent enrolment after protocol amendment to evaluate once daily doses of MK-7762 or placebo for 91 days based on findings from the planned 4-month sub-chronic toxicology studies in rats and dogs.	Screening and enrollment of participants in Part 2 of the trial will not commence until after the planned interim review of data from Part 1 and any available additional nonclinical data, and Sponsor agreement to continue the trial after regulatory review and comment (see Section 1.1.3.2). In Part 2 of the trial (MAD), participants will be enrolled into three sequential cohorts to evaluate escalating once daily doses of MK-7762 or placebo for 28 days. Each of the three MAD cohorts will have sixteen participants randomized 3:1 to receive MK-7762 or placebo. See Figure 4 and Table 9. If more than two participants from a MAD cohort are withdrawn from the trial before the Day 29 visit assessments are completed, additional participants will be enrolled with blinded treatment assignment matching that of the withdrawn participants. No replacements are required if two or fewer participants are withdrawn before their Day 29 visits.

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		An additional MAD cohort may be considered for subsequent enrolment after protocol amendment to evaluate once daily doses of MK-7762 or placebo for 91 days based on findings from the planned 4-month sub-chronic toxicology studies in rats and dogs.
4.2.2 – Confinement Period	All Part 2 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 6 in Section 1.3. Randomization will occur prior to dosing on Day 1 for all cohorts. In Part 2, study drug may be dosed shortly after a meal (fed condition) or under fasting condition. PK data collected in the FE cohort will be considered in deciding how study drug will be administered. Additional information regarding how FE Cohort data will be used to decide how study drug will be dosed in the MAD component will be discussed in the SAP.	All Part 2 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 5 in Section 1.3. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will apply during the Screening period. Randomization will occur prior to dosing on Day 1 for all cohorts. In Part 2, the dosing of study drug in relation to a meal will be dependent on review of PK data collected from participants in the FE Cohort (Cohort 6) in Part 1 of the trial. Additional information regarding how FE Cohort data will be used to decide how study drug will be dosed in the MAD component will be discussed in the SAP.
4.3 – Trial Drug Administration	MK-7762 will be supplied as 10 mg, 100 mg, and 300 mg capsules and matching placebo for oral administration. The planned doses for each cohort in Part 1 are listed in the Table 2. The doses of SAD Cohorts 2-3 may be modified based on accumulating safety, tolerability, and PK data. Additional cohorts may be enrolled after protocol amendment to repeat a dose level or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previous cohorts. The dose for Cohort 4 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previous SAD cohorts. The doses for MAD Cohorts 1-3 will be selected after review of PK and safety data from Part 1.	MK-7762 will be supplied as 10 mg, 100 mg, and 300 mg capsules and matching placebo for oral administration. The planned doses for each cohort in Part 1 are listed in Table 2. All doses of MK-7762 and placebo will be administered with 240 mL (8 ounces) of water. The doses of SAD Cohorts 2-4 may be modified based on accumulating safety, tolerability, and PK data. Additional cohorts may be enrolled after protocol amendment to repeat a dose level or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previous cohorts. The dose for Cohort 6 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previous SAD cohorts. The MK-7762 doses for daily administration in MAD Cohorts 1-3 will be selected after a planned interim review of data from Part 1 and additional nonclinical data and Sponsor agreement to continue the study after regulatory review and comment (see Section 1.1.3.2)
4.5 – Dose Escalation Decisions and Safety Review Team	A SRT will be established as the team responsible for safety review and the dose escalation recommendations for the trial. Details on the membership of the SRT will be featured in a charter that will be developed for the SRT's review of blinded data and deliberation processes (including the format of data to be	A Safety Review Team (SRT) will be established as the team responsible for safety review and dose escalation recommendations during Part 1 and Part 2 of the trial. Details of the SRT will be contained in a charter that will describe the SRT review of blinded safety data and the deliberation processes (including the format of

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	reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment. In Part 1, Period 2 may start following review of safety data through Day 4 from Period 1 (no PK data review). Periods 3 and 4 may start following review of 4 days of safety data from Periods 2 and 3 respectively, and 48-hour PK data from Periods 1 and 2, respectively. Period 5 may start following review of 4 days of safety data and 48-hour PK data from the previous period. The FE Cohort may start following review of 4 days of safety data from Period 4, and 48-hour PK data from Period 3. The FE Cohort (Periods 6 and 7) may start before Cohort 3 (Period 5) if PK data from Cohorts 1 and 2 are sufficient for selecting the dose to be evaluated in the FE Cohort. In Part 2, Cohort 1 may start following review of 4 days of safety data and 48-hour PK data from Part 1 Period 3. Cohorts 2 and 3 in the MAD may start following a review of a minimum of 14 days of safety data and 7 days of PK data from MAD Cohorts 1 and 2, respectively.	data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment and when PK data are made available, only aggregated mean PK data will be provided. During Part 1 of the study, the SRT will convene after all participants in a specific cohort have completed 4 days of follow-up post-dosing and all safety data collected through Day 4 are available for review. Safety review will be conducted after completion of each of Cohorts 1, 2, 3, and 4 (see Section 1.1.3). The SRT will have access to available aggregated mean PK data during its meetings to consider escalation to Cohorts 3, 4, and 5. The SRT may recommend dose escalation to a subsequent planned cohort if no pausing rule is present. If dose escalation is recommended following completion of Cohort 1 (50 mg), the single dose to be evaluated in Cohort 2 is planned as 150 mg. If dose escalation is recommended following completion of Cohort 2, the dose to be evaluated in Cohort 3 is planned as 300 mg. If dose escalation to Cohort 4 is recommended following completion of Cohort 3, the dose to be evaluated in Cohort 4 is planned as 600 mg. The dose to be evaluated in Cohort 5 will be decided by analysis of the safety and PK data available from the previously completed Cohorts 1 through 4. As described in Section 1.1.3.2, an interim review of data from Part 1 will be conducted in an unblinded manner by the Sponsor. Any additional relevant nonclinical data will also be reviewed as part of this process. The results of the interim review are intended for regulatory submission and comment prior to initiation of Part 2 of the trial. After regulatory authority agreement and Sponsor approval to proceed to the MAD phase of the trial, MAD cohort 1 may be initiated with MK-7762 (low dose) to be administered once daily for 28 days (either with or without food depending on results of the FE evaluation results of SAD Cohort 6). The SRT will convene after all participants in MAD Cohort 1 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 2 (medium dose of MK-7762 administered once daily for 28 days) if no pausing rule is present.

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		The SRT will convene after all participants in MAD Cohort 2 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 3 (high dose of MK-7762 administered once daily for 28 days) if no pausing rule is present.
4.5.1 Trial Pausing Rules	The SRT must assess the data as showing no significant safety concerns before recommending proceeding with MK-7762 administration for the next highest dose group. Events necessitating a pause in enrollment and participant dosing, and, in turn, requiring an ad hoc SRT review, include: • At least one participant experiences a Grade 3 AE assessed as related to study drug by the Investigator or Sponsor. The qualifying AE should occur within 4 days of the last dose of study drug received (see Appendix 1 for the AE grading table to be used for the trial). The Investigator should assess clinical significance of safety laboratory abnormalities before reporting as an AE. • At least one participant experiences a SAE assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of the last dose of study drug received. • At least two participants experience Grade 2 AEs of a similar nature assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of the last dose of study drug received. • Any occurrence of anaphylaxis or Grade 4 hypersensitivity reaction. • Any other findings that, at the discretion of the Investigator, SRT, or Sponsor, indicate dose escalation should be paused.	The SRT must assess the data as showing no significant safety concerns before recommending proceeding with MK-7762 administration to participants in SAD and/or MAD cohorts to receive higher doses of MK-7762. Events necessitating a pause in enrollment and/or participant dosing in the study Part 1 (SAD and FE) or Part 2 (MAD), and, in turn, requiring an ad hoc SRT review, include: • At least one participant experiences a Grade ≥ 3 AE assessed as related to study drug by the Investigator or Sponsor. The qualifying AE should occur within 4 days of receipt of a dose of study drug (see Appendix 1 for the AE grading table to be used for the trial). The Investigator should assess clinical significance of safety laboratory abnormalities before reporting as an AE. • At least one participant experiences a SAE assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug. • At least two participants experience Grade ≥ 2 AEs of a similar nature assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug. • Any occurrence of anaphylaxis or Grade 4 hypersensitivity reaction. • Any other findings that, at the discretion of the Investigator, SRT, or Sponsor, indicate dose escalation should be paused.
4.6 – End of Trial Definition	A participant is considered to have completed the trial if they complete the final scheduled visit for their assigned cohort. If a participant has an AE that has not resolved by their final trial visit, it will be documented as “ongoing”, however, follow-up of a SAE or AESI must continue until resolved or the condition has stabilized. The end of the trial is defined as the date of the last	The end of the trial is defined as the date of the last visit of the last participant, last scheduled procedure shown in the SoA for the last participant, or early withdrawal visit if last participant is withdrawn early from the trial. Any participant withdrawn from the trial before their last scheduled trial visit will be asked to return for an early termination visit.

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	visit of the last participant or last scheduled procedure shown in the SoA for the last participant. Any participant withdrawn from the trial before their last scheduled trial visit will be asked to return for an early termination visit. Participants for whom trial treatment is permanently stopped or changed by the Investigator will be asked to undergo this early termination visit within 2 weeks of discontinuing trial treatment regardless of the reason for trial treatment discontinuation. Assessments to be conducted at the early termination visit are specified in Section 1.3. Participants with ongoing AEs at the time of the early termination visit should be followed up until the AEs have resolved or stabilized.	Participants for whom study drug is permanently stopped or changed by the Investigator will be asked to undergo this early termination visit within 2 weeks of discontinuing study drug regardless of the reason for study drug discontinuation. Assessments to be conducted at the early termination visit are specified in Section 1.3. An individual participant is considered to have completed the trial if he/she completes the final scheduled visit for their assigned cohort. If a participant has an AE that has not resolved or is not otherwise explained at the final trial visit, the AE will be documented as "ongoing". However, follow-up of a SAE or AESI must continue until the event is resolved or the condition has stabilized.
5 – Trial Population	Approximately 82 healthy adult participants…	Approximately 96 healthy adult participants…
5.1 – Inclusion Criteria 3	3. Can understand and comply with the trial procedures…	3. Can understand and comply with the trial and site procedures…
5.2 – Exclusion Criteria 2	2. Has history of or screening findings of abnormalities of vision, including corrected visual acuity worse than 20/25 in either eye based on screening assessment using Snellen chart and Rosenbaum pocket chart, color vision based on screening assessment using Ishihara plates, or optic neuropathy or retinopathy based on screening fundoscopy. Candidates with ametropia corrected to 20/25 or better do not have to be excluded.	2. Has history of or Screening findings of abnormalities of vision, including corrected visual acuity worse than 20/25 in either eye based on Screening assessment using Snellen chart and Rosenbaum pocket chart, or color vision impairment based on Screening assessment using Ishihara plates. Candidates with ametropia corrected to 20/25 or better do not have to be excluded.
6.2 – Study Drug Administration	In Part 1 (SAD), the first two sequential cohorts will be exposed to two escalating single oral doses of MK-7762 or placebo in a randomized fashion separated by a washout period. A subsequent third cohort will be exposed to one single oral dose of MK-7762 in a randomized fashion. Participants in a fourth cohort (FE Cohort) will be randomized to receive a single oral dose of MK-7762 in a fed or fasting state followed by a second oral dose of MK-7762 of the same strength in the opposite state after a washout period. …	In Part 1 (SAD), up to 5 sequential cohorts will be exposed to escalating single oral doses of MK-7762 or placebo in a randomized fashion. The first 2 participants in Cohort 6 (FE Cohort), termed sentinel participants, will receive open-label MK-7762 in a fed state and a second dose of MK-7762 in a fasting state after a washout period of at least 5 half-lives of MK-7762 as determined by PK data available from previously completed cohorts. After SRT review of safety and PK data from the two sentinel participants, the remaining 6 participants in Cohort 6 will be dosed fed and fasted in random manner with the washout period between doses as previously determined. After completion of Part 1 of the study, an interim review of safety and PK data as well as any additional nonclinical data available

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		will be conducted prior to a decision to commence Part 2 of the study (see Section 1.1.3.2). …
6.4.1 Randomization	Randomization will be based on a randomly generated sequence of participant identification (identifier) numbers (randomization schedule) using a validated Interactive Voice/Web Response System (IXRS). In Part 1, Cohorts 1 and 2 will randomize participants 2:1 to MK-7762 or placebo. Cohort 3 will randomize participants 3:1 to MK-7762 or placebo. Cohort 4 will randomize participants 1:1 to fed vs. fasting in their first dosing period (Period 6) with crossover in their second dosing period (Period 7) following washout. In Part 2, Cohorts 1-3 will randomize participants 3:1 to MK-7762 or placebo….	Randomization will be based on a randomly generated sequence of participant identification (identifier) numbers (randomization schedule) using a validated Interactive Voice/Web Response System (IXRS). In Part 1, participants in Cohorts 1 through 5 will be randomized 3:1 to MK 7762 or placebo. After the 2 sentinel participants in Cohort 6, the remaining 6 participants will be randomized 1:1 to fed vs fasting in their first dosing period with crossover in their second dosing period following washout. In Part 2, participants in Cohorts 1-3 will be randomized 3:1 to MK-7762 or placebo. …
8.4.3 Visual Assessment	A visual assessment will be conducted at screening to assess eligibility for all trial participants and repeated during the treatment period for Part 2 participants per the SoA to assess for possible signs of optic neuropathy toxicity from repeat dosing. During screening, the Investigator or their delegate will conduct a fundoscopic examination and assessments of visual acuity and color vision. At subsequent visits in Part 2, trial staff will conduct tests of visual acuity and color vision. Visual acuity will be assessed on each eye separately by means of a Snellen chart and Rosenbaum pocket chart. Color vision will be assessed on each eye separately using the Ishihara color plates. Investigators should refer participants with significant findings to an ophthalmologist for an evaluation to assist in their determination of eligibility or assessment of a treatment-emergent AE.	A visual assessment will be conducted at Screening to assess eligibility for all trial participants and repeated during the treatment period for Part 2 participants per the SoA to assess for possible signs of optic neuropathy toxicity from repeat dosing. During Screening, the Investigator or their delegate will conduct assessments of visual acuity and color vision. At subsequent visits in Part 2, trial staff will conduct tests of visual acuity and color vision. Visual acuity will be assessed on each eye separately by means of a Snellen chart and Rosenbaum pocket chart. Color vision will be assessed on each eye separately using the Ishihara color plates. Investigators should refer participants with significant findings to an ophthalmologist for an evaluation to assist in the assessment of potential treatment-emergent AEs.
8.4.9 – Pharmacokinetic Assessment	PK sampling will be performed per the SoAs in Section 1.3. Table 14 and Table 15 provide summaries of pharmacokinetic sampling timepoints for Part 1 and Part 2 participants. Additional blood will be collected from participants in Part 2, Cohort 3 at the same PK sampling timepoints for storage for possible future quantitative analysis of any significant metabolites identified. Urine collection for PK will only be conducted for Part 1, Cohort 3 and Part 2, Cohort 2. Details on plasma collection and processing procedures are provided in the Laboratory Manual.	PK sampling will be performed per the SoAs in Section 1.3. Table 12 and Table 13 provide summaries of pharmacokinetic sampling timepoints for Part 1 and Part 2 participants. Additional blood will be collected from participants in Part 1, Cohort 4 and Part 2, Cohort 3 at the same PK sampling timepoints for storage for possible future qualitative analysis of any significant metabolites identified. Urine collection for PK will only be conducted for Part 1, Cohort 4 and Part 2, Cohort 2. Details on sample collection and processing procedures are provided in the Laboratory Manual.

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8.4.10 – Pharmacogenetic Assessment (new section)	N/A (new section)	During the informed consent process, participants will be asked to provide consent for collecting a sample for pharmacogenetic analysis to look for genetic determinants of variability in drug metabolism of MK-7762 between participants. Participants who do not consent to collect a sample for pharmacogenetic analysis will remain eligible to participate in the trial. A pharmacogenomics sample will be collected on Day -1 from all participants providing consent for (potential) genetic analysis. PGx assessment will include an evaluation for potential associations of genetic polymorphisms with PK, and possibly, safety results. The samples will be stored, and the final list of blood samples and genes that may be investigated will be selected before analysis to allow new scientific information to inform it. PGx samples of participants not selected for the PGx analysis will be destroyed. PK (and safety) data summarized by genotypes will be presented based on data availability.
Table 12 – Plasma PK Sampling Timepoints for Part 1 (SAD)		Updated to reflect changes in SAD cohorts.
9 – Statistical Considerations	This section contains a brief summary of the statistical analyses to support the primary and secondary objectives of this trial. A full description of the statistical analyses will be presented in a SAP. When summary statistics are planned to be reported by treatment and dosing condition, this refers to summarizing as follows. • For Part 1 Cohorts 1 and 2, participants will be counted in each period according to the dose level (or placebo) received in that period. Pre-dose observations on Day 1 or Day -1 will be used as the baseline for the first dosing period, and similarly pre-dose observations on Day 15 or Day 14 will be used as the baseline for the second dosing period. • For Part 1 Cohort 3, participants will be counted once according to the dose level (or placebo) received. Pre-dose observations on Day 1 or Day -1 are used as the baseline. • For Part 1 Cohort 4 (FE Cohort), participants will be counted in each period according to the dosing condition (fed or fasted) in that period. Pre-dose observations on Day 1 or Day -1 will be used as the baseline for the first dosing period, and	This section contains a brief summary of the statistical analyses to support the primary and secondary objectives of this trial. A full description of the statistical analyses will be presented in a SAP. When summary statistics are planned to be reported by treatment and dosing condition, this refers to summarizing as follows. • For Part 1 Cohort 1-5, participants will be counted once according to the dose level (or placebo) received. Pre-dose observations on Day 1 or Day -1 are used as the baseline. • For Part 1 Cohort 6 (FE Cohort), participants will be counted in each period according to the dosing condition (fed or fasted) in that period. Pre-dose observations on Day 1 or Day -1 will be used as the baseline for both dosing periods. • For Part 2 Cohorts 1-3, participants will be counted once according to the dose level (or placebo) received. Observations on Day -1 or Day 1 before the first administration of study drug will be used as the baseline.

Section Number	Text in Version 1	Text in Version 2 (Amendment 1)
	similarly pre-dose observations on Day 8 or Day 7 will be used as the baseline for the second dosing period. • For Part 2 Cohorts 1-3, participants will be counted once according to the dose level (or placebo) received. Observations on Day -1 or Day 1 before the first administration of study drug will be used as the baseline.	
9.1 – Populations for Analysis	Intention to treat (ITT) Population: All participants randomly assigned to receive study intervention. Participants will be analyzed according to the intervention they were randomized to receive.	Removed
9.3.1 – Primary Analyses for Safety	For Part 1, the primary analysis will cover the time period from pre-dose on Day 1 to the end of each of the two dosing periods for Cohorts 1 and 2, to Day 7 for Cohort 3, and to Day 14 for Cohort 4 (Food Effect Cohort). For Part 2, the primary analysis will cover the time period from pre-dose on Day 1 to Day 33 for Cohorts 1-3. Safety summaries will be inclusive of all participants in the safety population, unless stated otherwise.	For Part 1, the primary analysis will cover the time period from pre-dose on Day 1 to Day 7 for Cohort 1-5, and Day 7 of each dosing period (fed or fasted) for Cohort 6 (Food Effect Cohort). For Part 2, the primary analysis will cover the time period from pre-dose on Day 1 to Day 33 for Cohort 1. Safety summaries will be inclusive of all participants in the safety population, unless stated otherwise.
9.3.1.1 – Treatment-emergent AEs, SAEs, AESIs	All AEs, inclusive of TEAEs, SAEs, and AESI will be recorded from screening through Day 21 for Cohorts 1 and 2, through Day 7 for Cohort 3, and through Day 14 for Cohort 4 (FE Cohort) for Part 1 and through Day 33 for Cohorts 1-3 in Part 2.	All AEs, inclusive of SAEs and AESI will be recorded from Screening through Day 7 for Cohorts 1-5, through Day 7 of the second dosing period for Cohort 6 (FE Cohort) for Part 1 and through Day 33 for Cohorts 1-3 in Part 2. Treatment-emergent AEs (TEAEs) are defined as AEs with onset after receipt of one or more doses of study drug through the end of study period for that participant (see Section 10.2.2).
9.3.1.4 – ECG Assessments	(second paragraph) Changes in these ECG parameters from the corresponding timepoint matched Day -1 ECG will also be presented for each post-dose ECG timepoint….	…Changes in these ECG parameters from the pre-dose ECGs will also be presented for each post-dose ECG timepoint…
9.4.1 – Pharmacokinetics	(last paragraph) In addition to calculating the PK parameters using Necessary Condition Analysis (NCA) methods	… In addition to calculating the PK parameters using Non-Compartment Analysis (NCA) methods
9.5 – Interim Analyses	No interim analyses are planned for the study, but blinded safety data will be monitored by the trial SRT at the conclusion of each dosing level to inform dose escalation decisions within the SAD and MAD components as well as progression from SAD to 28-day MAD component.	No interim analyses are planned for the study, but blinded safety data will be monitored by the trial SRT at the conclusion of each dosing level to inform dose escalation decisions within the SAD and MAD components (see Section 1.1.4.1). An unblinded review of safety and PK data will be conducted after Part 1 to inform progression to Part 2 (28-day MAD; see Section 1.1.3.2).

Section Number	Text in Version 1	Text in Version 2 (Amendment 1)
9.6 – Sample Size and Power	… Assuming all cohorts undergo treatment, 68 participants will be exposed to MK-7762 (32 from Part 1 and 36 from Part 2). With 68 participants across all doses of MK-7762 in Parts 1 and 2, there is 80% (90%) power to observe at least one AE in the study if the true AE rate due to MK-7762 is 2.4 % (3.4%).	… Assuming all cohorts receive MK-7762 treatment, 74 participants will be exposed to MK 7762 (38 from Part 1 and 36 from Part 2). With 74 participants across all doses of MK-7762 in Parts 1 and 2, there is 80% (90%) power to observe at least one AE in the study if the true AE rate due to MK-7762 is 2.2 % (3.1%).
10.1.2 – Trial Oversight	The Sponsor, the IRB/IEC, the institution… The Safety Review Team … • The SRT will review the blinded safety and tolerability data accumulated after at least 4 participants in SAD Cohorts 1-4 and 10 participants in MAD Cohorts 1-4 have completed follow-up based on details provided in Section 4. The SRT may request additional meetings as deemed appropriate…. • If a pausing event does not occur, the SRT may recommend that enrollment can continue. The SRT recommendation will be communicated to the Sponsor Chief Medical Officer for endorsement to proceed.	The Sponsor, the SRT, the IDMC, the IRB/IEC, the institution… The Safety Review Team … • The SRT will review the blinded safety and tolerability data accumulated from SAD and MAD cohorts (see Section 1.1.3.2 and Section 4.5). The SRT may request additional meetings as deemed appropriate…. • If a pausing event does not occur, the SRT may recommend that enrollment and/or dose escalation can continue….
10.1.4 – Informed Consent Process	Potential participants will be interviewed to ensure that they meet all entry criteria relating to history.	Removed
10.1.8 – Data Quality Assurance	All participant data relating to the trial will be recorded electronic CRFs	All participant data relating to the trial will be recorded in CRFs
10.1.9 – Source Documents	Data recorded on source documents will be transcribed in the Electronic CRFs	Data recorded on source documents will be transcribed in the CRFs
10.2.1 Definition of Adverse Event	• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.	• An AE is any untoward medical occurrence in a clinical study participant whether or not considered related to the study intervention. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) •NOTE: In this trial, any AE reported by a participant after signing of the informed consent form is to be recorded as an AE
10.2.2 – Definition of Treatment-emergent Adverse Event	N/A (new section)	A treatment-emergent adverse event (TEAE) is any AE that occurs after receipt of one or more doses of study drug through the end of study for that participant. All definitions of AEs as shown in Section 10.2.1 will apply to TEAEs.
10.2.9.2 – Reporting via paper CRF	If the Electronic CRF…	If the CRF…

Protocol Clarification Letter #1 (changes outlined in Summary of Changes for Version 3.0)

Modifications were outlined in the following sections:

- Protocol Section 5.1, Inclusion Criterion #14
- Protocol Sections 1.1.3.1, and 4.1 (Part 1 SAD and Food Effect (SAD/FE) and Section 4.5 (Dose Escalation and Safety Review Team)

Clarifications were outlined in the following sections:

- Table 12
- Section 5.1, Inclusion Criterion #13b
- Section 10.3 Contraceptive Guidance and Collection of Pregnancy Information
- Section 8.2 (Demography and Medical and Treatment History)
- Section 10.2.9.1 Reporting to Sponsor Delegate's (Contract Research Organization (CRO) Safety Team) Via the Electronic Data Capture (EDC) System
- Section 10.2.9.2. Reporting via paper CRF
- Footnotes of Protocol Tables 3, 4, and 5
- Protocol Section 4.1.1 Screening (Day -21 to -2)

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Memorandum to File – Protocol Modifications and Clarifications

Protocol title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with an Open Label (Single Dose) Food Effect Panel
Protocol number: Gates MRI-TBD09-101, Version 2.0, dated 19 December 2022
Sponsor name: Bill & Melinda Gates Medical Research Institute (Gates MRI)

From: [redacted] MD, MSc
Clinical Development Leader, Bill & Melinda Gates Medical Research Institute

The following protocol modifications and clarifications will be included in a protocol amendment. The Advarra IRB requested/approved the changes described as Modifications #1 and #2. Clarifications #1 through #8 were added at the request of Gates MRI and/or Celerion.

Modification #1

Protocol Section 5.1, Inclusion Criterion #14 states: "If individual is assigned male sex at birth, is not sterilized, and is sexually active with a female partner of childbearing potential, agrees to used condoms from Day -1 through 30 days after the last dose of study drug. They must also agree to not donate sperm during the trial and for 3 months (90 days) after receiving the last dose of study drug.

Protocol Section 5.1, Inclusion Criterion #14 will be **amended** to state: "If individual is assigned male sex at birth, is not sterilized, and is sexually active with a female partner of childbearing potential, agrees to used condoms from Day -1 through ***90*** days after the last dose of study drug. They must also agree to not donate sperm during the trial and for 3 months (90 days) after receiving the last dose of study drug. [amended text in ***italics***]

Modification #2

Protocol Sections 1.1.3.1, and 4.1 (Part 1 SAD and Food Effect (SAD/FE) and Section 4.5 (Dose Escalation and Safety Review Team) will be **amended** to include the following information within each of these sections. [new text in ***italics***]

The first two participants in Cohort 1 will be dosed as sentinel participants in a blinded manner, randomized 1:1 to MK-7762 or placebo. The SRT will review safety data up to Day 4 following dosing for these two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 1 will receive single doses of study drug (randomized 5:1; MK-7762:placebo).

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Clarification #1

Protocol Table 12, titled "Plasma PK Sampling Timepoints for Part 1 (SAD), notes that the timepoint (hours) for collection of the Day 7 PK sample for Cohorts 1-6 is '168' hours.

The timepoint of 168 hours is incorrect based on footnotes to Tables 3 and 4 regarding timepoints for collection of blood samples for PK analysis that state: "Day 7: Within ±1-hour time window of time of study drug administration on Day 1"

The Protocol Table 12 will be **amended** to specify that the Day 7 blood sample will be taken at **144** hours after the time of study drug administration on Day 1.

Clarification #2

Protocol Section 5.1, inclusion criterion #13.b. states: "Reports being surgically sterilized (i.e., tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy)" [amended text in ***italics***]
Inclusion criterion #13.b.will be **amended** to state: "Reports being surgically sterilized (i.e., tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy), ***and provides written documentation[(i.e., medical record(s)] to document such procedure(s) to the Principal Investigator".***

Clarification #3

Protocol Section 10.3 **Contraceptive Guidance and Collection of Pregnancy Information**

The third bullet under **Female of Childbearing Potential (FOCBP)** states 'For females with permanent infertility due to an alternate medical cause…(e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

The third bullet under **Female of Childbearing Potential (FOCBP)** will be **amended** to state 'For females with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), ***written documentation [i.e., medical record(s)] to document such condition(s) should be provided to the Principal Investigator".*** [amended text in ***italics***]

In Section 10.3 under **Collection and Reporting Pregnancy Information,** the first bullet will be amended to remove the requirement for use of a specific EDC page to report pregnancy. The first bullet will appear as follows:

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The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the Pregnancy Form and submitted to the Sponsor by email or facsimile within 24 hours of learning of a participant's pregnancy.

Clarification #4

Protocol Section 8.2 (Demography and Medical and Treatment History) will remove reference to 'place of birth', 'occupation', 'sex assigned at birth', and 'number of children' and the first sentence of this section will be amended as follows (final text in ***italics***):

Information on demographic characteristics (e.g., age, date of birth, sex/gender, ethnicity, and race) will be obtained and a medical and treatment history will be conducted during the Screening period to assess eligibility.

Clarification #5

Protocol Section 10.2.9.1 will be amended to specify that the reporting of Adverse Events of Special Interest (AESI) will be via the EDC system, as follows (amended text in ***italics***):

10.2.9.1 Reporting to Sponsor Delegate's (Contract Research Organization (CRO) Safety Team) Via the Electronic Data Capture (EDC) System

Reporting to Sponsor Delegate's (CRO Safety Team) Via the Electronic Data Collection Tool
The primary mechanism for reporting a SAE ***or an AESI*** and other immediately reportable events (e.g., Pregnancy; see Section 10.2.9.3) by the Investigator to the Sponsor or delegate will be the EDC system. The Investigator will complete the ***SAE, AESI*** and/or Pregnancy CRF, as appropriate with all the current information. All initial and follow-up ***SAEs or AESIs*** (regardless of assessment of causal relationship to the study intervention) and pregnancies will be reported to the Sponsor delegate (PPD) within 24 hours of discovery or notification at the clinical site. ***Any SAE or AESI that is attributable to study treatment by the Investigator*** will be reported even after the trial is over if the Sponsor, Medical Monitor, or Investigator becomes aware of them. Information not available at the time of the initial report must be documented in a follow-up report or CRF. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested. For hospitalizations, all attempts to obtain the hospital record should be documented in the source documents.

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The Investigator is responsible for expedited safety report submission to the Sponsor delegate and the Sponsor delegate reports to the national regulatory authority(ies) within specific time periods of being notified of the event. Therefore, it is important that the Investigator submit additional information requested as soon as it becomes available. If the electronic system is unavailable, the site may use the paper data collection tool (see Section 10.2.9.2 instead of the EDC, in order to report the event within 24 hours of becoming aware. If a site receives a report of a new SAE ***or AESI*** from a trial participant or receives updated data on a previously reported SAE ***or AESI*** after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE***/AESI*** form (see Section 10.2.9.2). Contacts for SAE ***and AESI*** reporting and for all safety personnel are contained in the Team Contact List which will be stored on-site in the Site Regulatory Binder and maintained by the Sponsor.

Clarification #6

Protocol Section 10.2.9.2 will be amended to specify that the reporting of Adverse Events of Special Interest (AESI) should be via paper CRF (amended text in ***italics***):

10.2.9.2. Reporting via paper CRF

Reporting via Paper CRF
If the CRF cannot be completed, the paper SAE, ***AESI*** and/or Pregnancy form should be completed by the Investigator or their designee, and scanned and emailed, or faxed to the Sponsor's Pharmacovigilance CRO within 24 hours of discovery. The Investigator is responsible for ensuring an adequate transmission of the fax and will store the distribution confirmation in the trial file. At a minimum, the following information should be included in an initial report: Protocol number Name and contact number of the Investigator Site and participant identification number Date(s) participant received study intervention Event term [with a brief summary of the event(s) and causality assessment]

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In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE ***or AESI*** report form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE, ***AESI*** and/or Pregnancy CRF pages within the designated reporting time frames.

Clarification #7

Certain footnotes of Protocol Tables 3, 4, and 5 will be amended to provide additional instructions for assessments and/or windows as follows (amended text in ***italics***):

Table 3

c: A continuous ECG recording will be performed for 25 hours, starting one hour pre-dose on Day 1, in all dose groups in which participants receive MK-7762 or placebo in the fasted state. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: at 3 time points within one hour prior to dosing (e.g., -45, -30 and -15 minutes) and at one time point each at approximately 1, 2, 3,4, 5, 6-, 8-, 12--, and 24-hours post-dose. Participants will be supinely resting for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ***safety*** ECGs then vital signs, ***except ECG extractions may occur before blood sample collection.***

d. Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and pre-dose on Day 1 within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times:

- Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (± ***30*** minutes).
- Day 2: 24 and 36 hours (± ***30*** minutes) post-dose.
- Day 3: 48 hours (± ***30*** minutes)post-dose
- Day 4: 72 hours (± ***30*** minutes) post-dose
- End-of-trial (Day 7) visit: ± 30 minutes of time of Day 1 dose administration.

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Table 4.

d. Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and pre-dose on Day 1 within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times:

- Day 1 and Day 8: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (± ***30*** minutes).
- Day 2 and Day 9: 24 and 36 hours (± ***30*** minutes) post-dose.
- Day 3 and Day 10: 48 hours (± ***30*** minutes)post-dose
- Day 4 and Day 11: 72 hours (± ***30*** minutes) post-dose
- Day 7 trial visit: ±30 minutes of time of Day 1 dose administration
- End-of-trial/follow up visit (Day 14): ± 30 minutes of time of Day 8 dose administration.

Table 5.

a. Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and Day 1 pre-dose within 60 minutes prior to dosing. Blood pressure and heart rate only will be measured at the following times :
   - Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (± ***30*** minutes)
   - Day 2-3: predose and 12 hours (± ***30*** minutes) post-dose
   - Day 7, 14, 21, and 28: predose (± ***30*** minutes) (blood pressure, heart rate, and temperature should be measured)
   - Day 28: 12 hours(± ***30*** minutes) post-dose
   - Day 29: 24 hours after Day 28 dose (± ***30*** minutes)
   - Day 33 end-of-trial visit (blood pressure, heart rate, and temperature should be measured): ± 30 minutes from time of last dose administration on Day 28.

g. Continuous ECG recordings will be performed for 25 hours, starting one hour pre-dose on Day 1 and Day 28. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: At 3 time points within one hour prior to dosing (e.g., -45, -30 and -15 minutes) and at one time point each at approximately 1, 2, 3,4, 5, 6-, 8-, 12--, and 24-hours post-dose. Participants will be supinely resting for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ***safety*** ECGs then vital signs, ***except ECG extractions may occur before blood sample collection.***

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Clarification #8

Protocol Section 4.1.1 **Screening (Day -21 to -2)** will be amended to clarify that screening assessments for Part 1 may be performed in any order/sequence. The paragraph in this section will be amended as follows (new text in ***italics***):

Part 1 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 3 for Cohorts 1-5 or Table 4 for Cohort 6 in Section 1.3. ***There is no stipulated order or sequence of the conduct of Screening assessments.*** Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will apply during the Screening period.

Protocol Section 4.2.1 **Screening (Day -21 to -2)** will be amended to clarify that screening assessments for Part 2 may be performed in any order/sequence. The paragraph in this section will be amended as follows (new text in ***italics):***

Part 2 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 5 in Section 1.3. ***There is no stipulated order or sequence of the conduct of Screening assessments.***

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Protocol Clarification Letter #2 (changes outlined in Summary of Changes for Version 3.0)

Modifications were outlined in the following sections:

- Section 10.2.7.1: Assessment of AE Intensity (Severity)
- Section 10.2.7.4: Assessment of AE Outcome
- Section 1, Table 5 (Schedule of Activities for Part 2, MAD Cohorts 1-3)
- Section 10.2.9.1, Reporting to Sponsor and/or Pharmacovigilance Service Provider

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Protocol Clarification Letter

March 2, 2023

Memorandum: Provision of minor modifications to trial protocol

Protocol title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with an Open Label (Single Dose) Food Effect Panel
Protocol number: Gates MRI-TBD09-101, Version 2.0, 19 December 2022
Sponsor name: Bill & Melinda Gates Medical Research Institute (Gates MRI)

The following modifications to the protocol are provided and will be made in a forthcoming protocol amendment:

Modification #1
Section 10.2.7.1: Assessment of AE Intensity (Severity)
The current language for Grade 5 is "Death related to AE," but is changed to "Fatal."

Modification #2
Section 10.2.7.4: Assessment of AE Outcome
The current language specifies "Ongoing" as one of 4 possible AE outcomes. "Ongoing" is replaced by "Not Resolved/Not Recovered" and "Resolving/Recovering." This terminology change also applies to "ongoing" in the third paragraph of Section 4.6 and the penultimate bullet in Section 10.2.7.

Also, "Death" is changed to "Fatal" in this list in Section 10.2.7.4.

Modification #3
Section 1, Table 5 (Schedule of Activities for Part 2, MAD Cohorts 1-3)
Footnote 'a', 6th bullet: Respiratory rate is removed from the list of vital signs that should be measured at the Day 33 end-of-trial visit.

Modification #4
Section 10.2.9.1
The section is renamed "Reporting to Sponsor and/or Pharmacovigilance Service Provider" from "Reporting to Sponsor Delegate's (Contract Research Organization (CRO) Safety Team) Via the Electronic Data Capture (EDC) System."

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The primary mechanism for reporting SAE, AESI, and other immediately reportable events (e.g., pregnancy) is changed effective immediately to completion of paper reporting forms and submission via email or fax to the Sponsor's Pharmacovigilance Service Provider.

Sincerely,

[redacted]
Clinical Development Leader
Bill & Melinda Gates Medical Research Institute

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Changes in Version 3.0:

Content-related changes are summarized in the table below. The amendment has been classified as an "Other Amendment" according to the Sponsor's relevant standard operating procedure.

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
Overall Document		Updated formatting, grammar, and style for consistency
Title Page	N/A	Added Amendment number and date
Section 1.1.3.1 – Part 1 -SAD and Food Effect (SAD/FE) and Section 1.1.4.2 Pausing Rules	N/A The SRT will review safety data up to Day 4 and PK data up to Day 2 ~~following completion of the dosing periods~~ for the two sentinel participants.	Added: **The first two participants in Cohort 1 will be dosed as sentinel participants in a blinded manner, randomized 1:1 to MK-7762 or placebo. The Safety Review Team (SRT) will review safety data up to Day 4 following dosing for these two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 1 will receive single doses of study drug (randomized 5:1; MK-7762:placebo).** *Updated the following within Sections:* The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants **from the fed state dosing period**.
Table 3 – Schedule of Activities for Part 1, Cohort 1-5	Footnote c: When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs. Footnote d: • Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (±20 minutes). • Day 2: 24 and 36 hours (±20 minutes) post-dose. • Day 3: 48 hours (±20 minutes) post-dose. • Day 4: 72 hours (±20 minutes) post-dose i: For Cohort 3 a single dose of MK-7762 or placebo will be administered.	Footnote c: When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by **safety** ECGs then vital signs, **except ECG extractions may occur before blood sample collection.** Footnote d: • Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (**±30** minutes). • Day 2: 24 and 36 hours (**±30** minutes) post-dose. • Day 3: 48 hours (**±30** minutes) post-dose. • Day 4: 72 hours (**±30** minutes) post-dose Removed: ~~i: For Cohort 3 a single dose of MK-7762 or placebo will be administered.~~ *Subsequent footnote lettering was updated*
Table 4 – Schedule of Activities for Part	Footnote d:	Footnote d:

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
1, Cohort 6 (Food Effect)	• Day 1 and Day 8: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (~~±20~~ minutes). • Day 2 and Day 9: 24 and 36 hours (~~±20~~ minutes) post-dose. • Day 3 and Day 10: 48 hours (~~±20~~ minutes) post-dose. • Day 4 and Day 11: 72 hours (~~±20~~ minutes) post-dose	• Day 1 and Day 8: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (**±30** minutes). • Day 2 and Day 9: 24 and 36 hours (**±30** minutes) post-dose. • Day 3 and Day 10: 48 hours (**±30** minutes) post-dose. • Day 4 and Day 11: 72 hours (**±30** minutes) post-dose
Table 5- Schedule of Activities for Part 2, MAD Cohorts 1-3	Footnote a: • Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (~~±20~~ minutes). • Day 2-3: predose and 12 hours (~~±20~~ minutes) post-dose. • Day 7, 14, 21, and 28: predose (~~±20~~ minutes) (blood pressure, heart rate, and temperature should be measured) • Day 28: 12 hours (~~±20~~ minutes) post-dose • Day 29: 24 hours after Day 28 dose (~~±20~~ minutes) • Day 33 end-of-trial visit (blood pressure, heart rate, respiratory rate, and temperature should be measured): ±30 minutes from time of last dose administration on Day 28 Footnote g: When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs. Footnote i: For Cohort 1-3 a daily dose of MK-7762 or placebo will be administered for 28 days at the same time of the day.	Footnote a: • Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (**±30** minutes). • Day 2-3: predose and 12 hours (**±30** minutes) post-dose. • Day 7, 14, 21, and 28: predose (**±30** minutes) (blood pressure, heart rate, and temperature should be measured) • Day 28: 12 hours (**±30** minutes) post-dose • Day 29: 24 hours after Day 28 dose (**±30** minutes) • Day 33 end-of-trial visit (blood pressure, heart rate, ~~respiratory rate,~~ and temperature should be measured): ±30 minutes from time of last dose administration on Day 28 Footnote g: When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by **safety** ECGs then vital signs, **except ECG extractions may occur before blood sample collection.** Footnote i: For Cohort 1-3 a daily dose of MK-7762 or placebo will be administered for 28 days at the **same time (+/- 1 hour)** of the day.
Section 4.1 Part 1 – SAD and Food Effect (SAD/FE)	The SRT will review safety data up to Day 4 and PK data up to Day 2 ~~following completion of the dosing periods~~ for the two sentinel participants.	The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants **from the fed state dosing period**.
Table 8 - Single Ascending Dose (Part 1) - Planned Dose Cohort 6	Footnote: The SRT will review safety data up to Day 4 and PK data up to Day 2 ~~following completion of the dosing periods~~ for the two sentinel participants.	Footnote: The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants **from the fed state dosing.**

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
(Food Effect Cohort)		
Section 4.1.1 Screening (Day -21 to -2)	N/A	Added: **There is no stipulated order or sequence of the conduct of Screening assessments.**
Section 4.1.4 Food Effect Cohort (Cohort 6)	The SRT will review safety data up to Day 4 and PK data up to Day 2 ~~following completion of the dosing periods~~ for the two sentinel participants.	The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants **from the fed state dosing.**
Section 4.2.1 Screening (Day -21 to -2)	N/A	**There is no stipulated order or sequence of the conduct of Screening assessments.**
Section 4.5 Dose Escalation Decisions and Safety Review Team	N/A	Added: **The first two participants in Cohort 1 will be dosed as sentinel participants in a blinded manner, randomized 1:1 to MK-7762 or placebo. The SRT will review safety data up to Day 4 following dosing for these two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 1 will receive single doses of study drug (randomized 5:1; MK-7762:placebo).**
Section 4.5.1 Trial Pausing Rules	Events necessitating a pause in enrollment and/or participant dosing in the study Part 1 (SAD and FE) or Part 2 (MAD), and, in turn, requiring an ad hoc ~~SRT~~ review, include:	Events necessitating a pause in enrollment and/or participant dosing in the study Part 1 (SAD and FE) or Part 2 (MAD), and, in turn, requiring an ad hoc **IDMC** review, include:
Section 4.6 End of Trial Definition, Participant Completion of Trial, and Follow up of Adverse Events	If a participant has an AE that has not resolved or is not otherwise explained at the final trial visit, the AE will be documented as ~~"ongoing"~~.	If a participant has an AE that has not resolved or is not otherwise explained at the final trial visit, the AE will be documented as **either "Not Resolved/Not Recovered" or "Resolving/ Recovering".**
Section 5.1 Inclusion Criteria	13b. Reports being surgically sterilized (i.e., tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy) 14. If individual is assigned male sex at birth, is not sterilized, and is sexually active with a female partner of childbearing potential, agrees to use condoms from Day -1 through ~~30~~ days after the last dose of study drug.	13b. Reports being surgically sterilized (i.e., tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy), **and provides written documentation (i.e., medical record(s) to document such procedure(s) to the Principal Investigator.** 14. If individual is assigned male sex at birth, is not sterilized, and is sexually active with a female partner of childbearing potential, agrees to use condoms from Day -1 through **90** days after the last dose of study drug.

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
Section 6.4.1 Randomization	~~After the 2 sentinel participants in Cohort 6~~, the remaining 6 participants will be randomized 1:1 to fed vs fasting in their first dosing period with crossover in their second dosing period following washout.	**All participants in Cohort 6 will receive open-label MK-7762. The 2 sentinel participants in Cohort 6 will receive open-label MK-7762 in the fed state in the first dosing period with open-label dosing of MK-7762 in the fasted state in the second dosing period. After the 2 sentinel participants are dosed in the fed state,** the remaining 6 participants will be randomized 1:1 to fed vs fasting in their first dosing period with crossover in their second dosing period following washout.
Section 8.2 Demography and Medical and Treatment History	Information on demographic characteristics (e.g., age, ~~sex assigned at birth~~, gender, ~~place~~ of birth, ~~occupation, number of children~~) will be obtained and a medical and treatment history will be conducted during the Screening period to assess eligibility.	Information on demographic characteristics (e.g., age, **date of** birth, **sex/gender, ethnicity, and race**) will be obtained and a medical and treatment history will be conducted during the Screening period to assess eligibility.
Table 12 Plasma PK Sampling Timepoints for Part 1 (SAD)	Hour ~~168~~	Hour **144**
Section 10.1.2 Trial Oversight	• The operational details of the SRT, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to the first participant is enrolled. • The operational details of the IDMC, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to the first participant is enrolled.	• The operational details of the SRT, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to **the time that** the first participant is enrolled. • The operational details of the IDMC, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior **to the time that** the first participant is enrolled.
Section 10.1.5.1 Informed Consent for Trial Participation	If there is a change to the ICF during the conduct of the trial, participants will be re-consented to the most current version of the ICF.	If there is a change to the ICF during the conduct of the trial, **actively enrolled** participants will be re-consented to the most current version of the ICF.
Section 10.1.7 Dissemination of Clinical Trial Data	~~Summaries of the results of the trial will also be posted on the same websites.~~	Sentence deleted

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
Section 10.2.7 Recording and Follow-up of AEs (including SAEs and AESIs)	If the event has not resolved by the final trial visit, it will be documented as ~~"ongoing"~~ on the eCRF, however, follow-up of a SAE must continue until resolved or the condition has stabilized.	If the event has not resolved by the final trial visit, it will be documented as **either "Not Resolved/Not Recovered" or "Resolving/Recovering"** on the eCRF, however, follow-up of a SAE must continue until resolved or the condition has stabilized.
Section 10.2.7.1 Assessment of AE Intensity (Severity)	**Grade 5:** ~~Death related to AE~~	**Grade 5: Fatal**
Section 10.2.7.4 Assessment of AE Outcome	The outcome of each AE must be reported to the Sponsor. The outcome of all AEs will be classified as one of the following: • Resolved • Resolved with sequelae • ~~Ongoing~~ • ~~Death~~	The outcome of each AE must be reported to the Sponsor. The outcome of all AEs will be classified as one of the following: • Resolved • Resolved with Sequelae • **Not Resolved/Not Recovered** • **Resolving/Recovering** • **Fatal**
Section 10.2.9.1 Reporting to Sponsor Delegate's (Contract Research Organization (CRO) Safety Team) Via the Electronic Data Capture (EDC) System	~~**Reporting to Sponsor Delegate's (Contract Research Organization (CRO) Safety Team) Via the Electronic Data Capture (EDC) System**~~ ~~**Reporting to Sponsor Delegate's (CRO Safety Team) Via the Electronic Data Collection Tool**~~ ~~The primary mechanism for reporting an SAE (including AESI and ADR) and other immediately reportable events (e.g., Pregnancy; see Section 10.2.9.3) by the Investigator to the Sponsor or delegate will be the EDC system. The Investigator will complete the AE, SAE, and/or Pregnancy CRF, as appropriate with all the current information.~~ ~~All initial and follow-up SAEs (regardless of assessment of causal relationship to the study intervention) and pregnancies will be reported to the Sponsor delegate (PPD) within 24 hours of discovery or notification at the clinical site.~~ ~~Serious ADRs are reported even after the trial is over if the Sponsor, Medical Monitor, or Investigator become aware of them.~~ ~~Information not available at the time of the initial report must be documented in a follow-up report or CRF. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested. For~~	**Reporting to Sponsor and/or Pharmacovigilance Service Provider** **There are two required methods for reporting an SAE and/or AESI by the Investigator to the Sponsor and the Sponsor's safety delegate.** **3) <u>Sponsor Pharmacovigilance Service Provider (PPD) Notification</u>: The first step of reporting an SAE or AESI by the Investigator to the Sponsor Pharmacovigilance Service Provider will be using paper CRFs (see Section 10.2.9.2). This report must be sent to PPD within 24 hours of discovery or notification at the clinical site.** **4) <u>Sponsor Notification</u>: The second step of reporting an SAE or AESI by the Investigator to the Sponsor will be the EDC system. The Investigator will complete the electronic SAE/AESI, CRF, as appropriate with all the current information.** **All initial and follow-up SAEs or AESIs (regardless of assessment of causal relationship to the study intervention) will require following the two methods of reporting detailed above. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be**

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
	~~hospitalizations, all attempts to obtain the hospital record should be documented in the source documents.~~ ~~The Investigator is responsible for expedited safety report submission to the Sponsor delegate and the Sponsor delegate reports to the national regulatory authority(ies) within specific time periods of being notified of the event. Therefore, it is important that the Investigator submit additional information requested as soon as it becomes available.~~ ~~If the electronic system is unavailable, the site may use the paper data collection tool (see instead of the EDC, in order to report the event within 24 hours of becoming aware.~~ ~~If a site receives a report of a new SAE from a trial participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see Section 10.2.9.2).~~ ~~Contacts for SAE reporting and for all safety personnel are contained in the Team Contact List which will be stored on-site in the Site Regulatory Binder and maintained by the Sponsor.~~	**requested. For hospitalizations, all attempts to obtain the hospital record should be documented in the source documents.** **Any SAE or AESI that is attributable to study treatment by the Investigator will be reported even after the trial is over if the Sponsor, Medical Monitor, or Investigator become aware of them.** **Contacts for SAE and AESI reporting and for all safety personnel are contained in the Team Contact List which will be stored on-site in the Site Regulatory Binder and maintained by the Sponsor.** **The Investigator is responsible for ensuring an adequate transmission of the fax or ema-mail and will store the distribution confirmation in the trial file.** **At a minimum, the following information should be included in an initial report:** • **Protocol number** • **Name and contact number of the Investigator** • **Site and participant identification number** • **Date(s) participant received study intervention** • **Event term [with a brief summary of the event(s) and causality assessment]** **Pregnancy reports (initial and follow up) must be sent to the Sponsor PV Service Provider (PPD) within 24 hours of discovery or notification at the clinical site by scanning and emailing the forms or faxing the completed paper forms.** **In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE/AESI or Pregnancy form(s) sent by overnight mail or courier service.** **Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE/AESI, and/or Pregnancy paper forms within the designated reporting time frames.**
Section 10.2.9.2 Reporting via Paper CRF	~~In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE report form sent by overnight mail or courier service.~~	Section deleted.

Section Number	Text in Version 2 (Amendment 1)	Text in Version 3 (Amendment 2)
	~~Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE and/or Pregnancy CRF pages within the designated reporting time frames.~~	
Section 10.2.9.3 Other Events Requiring Immediate Reporting	Section 10.2.9.~~3~~ The following events also require immediate reporting to the Sponsor or Sponsor's Pharmacovigilance ~~CRO~~ (PPD) within 24 hours of learning of the event: • Pregnancy	Section 10.2.9.**2** The following events also require immediate reporting to the Sponsor or Sponsor's Pharmacovigilance **Service Provider** (PPD) within 24 hours of learning of the event: • Pregnancy **(see Section 10.2.9.1)**
Section 10.3 Contraceptive Guidance and Collection of Pregnancy Information	• For females with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), ~~Investigator discretion should be applied to determining study entry~~. • The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the ~~appropriate form/EDC section~~ and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy ~~through specific EDC page or emailed/faxed Pregnancy Form is EDC is not available~~.	• For females with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), **written documentation [i.e., medical record(s)] to document such condition(s) should be provided to the Principal Investigator.** • The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the **Pregnancy Form** and submitted to the Sponsor **Pharmacovigilance Service Provider (PPD) by email or facsimile** within 24 hours of learning of a participant's pregnancy **(see Section 10.2.9.2).**

Protocol Clarification Memo (dated 10 February 2023)

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Memorandum to File – Protocol Modifications and Clarifications

Protocol title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with an Open Label (Single Dose) Food Effect Panel
Protocol number: Gates MRI-TBD09-101, Version 2.0, dated 19 December 2022
Sponsor name: Bill & Melinda Gates Medical Research Institute (Gates MRI)

From: [redacted] MD, MSc
Clinical Development Leader, Bill & Melinda Gates Medical Research Institute

The following protocol modifications and clarifications will be included in a protocol amendment. The Advarra IRB requested/approved the changes described as Modifications #1 and #2. Clarifications #1 through #8 were added at the request of Gates MRI and/or Celerion.

Modification #1

Protocol Section 5.1, Inclusion Criterion #14 states: "If individual is assigned male sex at birth, is not sterilized, and is sexually active with a female partner of childbearing potential, agrees to used condoms from Day -1 through 30 days after the last dose of study drug. They must also agree to not donate sperm during the trial and for 3 months (90 days) after receiving the last dose of study drug.

Protocol Section 5.1, Inclusion Criterion #14 will be **amended** to state: "If individual is assigned male sex at birth, is not sterilized, and is sexually active with a female partner of childbearing potential, agrees to used condoms from Day -1 through ***90*** days after the last dose of study drug. They must also agree to not donate sperm during the trial and for 3 months (90 days) after receiving the last dose of study drug. [amended text in ***italics***]

Modification #2

Protocol Sections 1.1.3.1, and 4.1 (Part 1 SAD and Food Effect (SAD/FE) and Section 4.5 (Dose Escalation and Safety Review Team) will be **amended** to include the following information within each of these sections. [new text in ***italics***]

The first two participants in Cohort 1 will be dosed as sentinel participants in a blinded manner, randomized 1:1 to MK-7762 or placebo. The SRT will review safety data up to Day 4 following dosing for these two sentinel participants. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 1 will receive single doses of study drug (randomized 5:1; MK-7762:placebo).

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Clarification #1

Protocol Table 12, titled "Plasma PK Sampling Timepoints for Part 1 (SAD), notes that the timepoint (hours) for collection of the Day 7 PK sample for Cohorts 1-6 is '168' hours.

The timepoint of 168 hours is incorrect based on footnotes to Tables 3 and 4 regarding timepoints for collection of blood samples for PK analysis that state: "Day 7: Within ±1-hour time window of time of study drug administration on Day 1"

The Protocol Table 12 will be **amended** to specify that the Day 7 blood sample will be taken at **144** hours after the time of study drug administration on Day 1.

Clarification #2

Protocol Section 5.1, inclusion criterion #13.b. states: "Reports being surgically sterilized (i.e., tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy)" [amended text in ***italics***]
Inclusion criterion #13.b.will be **amended** to state: "Reports being surgically sterilized (i.e., tubal ligation, hysterectomy, bilateral oophorectomy/salpingectomy), ***and provides written documentation[(i.e., medical record(s)] to document such procedure(s) to the Principal Investigator".***

Clarification #3

Protocol Section 10.3 **Contraceptive Guidance and Collection of Pregnancy Information**

The third bullet under **Female of Childbearing Potential (FOCBP)** states 'For females with permanent infertility due to an alternate medical cause…(e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

The third bullet under **Female of Childbearing Potential (FOCBP)** will be **amended** to state 'For females with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity), ***written documentation [i.e., medical record(s)] to document such condition(s) should be provided to the Principal Investigator".*** [amended text in ***italics***]

In Section 10.3 under **Collection and Reporting Pregnancy Information,** the first bullet will be amended to remove the requirement for use of a specific EDC page to report pregnancy. The first bullet will appear as follows:

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The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the Pregnancy Form and submitted to the Sponsor by email or facsimile within 24 hours of learning of a participant's pregnancy.

Clarification #4

Protocol Section 8.2 (Demography and Medical and Treatment History) will remove reference to 'place of birth', 'occupation', 'sex assigned at birth', and 'number of children' and the first sentence of this section will be amended as follows (final text in ***italics***):

Information on demographic characteristics (e.g., age, date of birth, sex/gender, ethnicity, and race) will be obtained and a medical and treatment history will be conducted during the Screening period to assess eligibility.

Clarification #5

Protocol Section 10.2.9.1 will be amended to specify that the reporting of Adverse Events of Special Interest (AESI) will be via the EDC system, as follows (amended text in ***italics***):

10.2.9.1 Reporting to Sponsor Delegate's (Contract Research Organization (CRO) Safety Team) Via the Electronic Data Capture (EDC) System

Reporting to Sponsor Delegate's (CRO Safety Team) Via the Electronic Data Collection Tool
The primary mechanism for reporting a SAE ***or an AESI*** and other immediately reportable events (e.g., Pregnancy; see Section 10.2.9.3) by the Investigator to the Sponsor or delegate will be the EDC system. The Investigator will complete the ***SAE, AESI*** and/or Pregnancy CRF, as appropriate with all the current information. All initial and follow-up ***SAEs or AESIs*** (regardless of assessment of causal relationship to the study intervention) and pregnancies will be reported to the Sponsor delegate (PPD) within 24 hours of discovery or notification at the clinical site. ***Any SAE or AESI that is attributable to study treatment by the Investigator*** will be reported even after the trial is over if the Sponsor, Medical Monitor, or Investigator becomes aware of them. Information not available at the time of the initial report must be documented in a follow-up report or CRF. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested. For hospitalizations, all attempts to obtain the hospital record should be documented in the source documents.

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The Investigator is responsible for expedited safety report submission to the Sponsor delegate and the Sponsor delegate reports to the national regulatory authority(ies) within specific time periods of being notified of the event. Therefore, it is important that the Investigator submit additional information requested as soon as it becomes available. If the electronic system is unavailable, the site may use the paper data collection tool (see Section 10.2.9.2 instead of the EDC, in order to report the event within 24 hours of becoming aware. If a site receives a report of a new SAE ***or AESI*** from a trial participant or receives updated data on a previously reported SAE ***or AESI*** after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE***/AESI*** form (see Section 10.2.9.2). Contacts for SAE ***and AESI*** reporting and for all safety personnel are contained in the Team Contact List which will be stored on-site in the Site Regulatory Binder and maintained by the Sponsor.

Clarification #6

Protocol Section 10.2.9.2 will be amended to specify that the reporting of Adverse Events of Special Interest (AESI) should be via paper CRF (amended text in ***italics***):

10.2.9.2. Reporting via paper CRF

Reporting via Paper CRF
If the CRF cannot be completed, the paper SAE, ***AESI*** and/or Pregnancy form should be completed by the Investigator or their designee, and scanned and emailed, or faxed to the Sponsor's Pharmacovigilance CRO within 24 hours of discovery. The Investigator is responsible for ensuring an adequate transmission of the fax and will store the distribution confirmation in the trial file. At a minimum, the following information should be included in an initial report: Protocol number Name and contact number of the Investigator Site and participant identification number Date(s) participant received study intervention Event term [with a brief summary of the event(s) and causality assessment]

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In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE ***or AESI*** report form sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE, ***AESI*** and/or Pregnancy CRF pages within the designated reporting time frames.

Clarification #7

Certain footnotes of Protocol Tables 3, 4, and 5 will be amended to provide additional instructions for assessments and/or windows as follows (amended text in ***italics***):

Table 3

c: A continuous ECG recording will be performed for 25 hours, starting one hour pre-dose on Day 1, in all dose groups in which participants receive MK-7762 or placebo in the fasted state. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: at 3 time points within one hour prior to dosing (e.g., -45, -30 and -15 minutes) and at one time point each at approximately 1, 2, 3,4, 5, 6-, 8-, 12--, and 24-hours post-dose. Participants will be supinely resting for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ***safety*** ECGs then vital signs, ***except ECG extractions may occur before blood sample collection.***

d. Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and pre-dose on Day 1 within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times:

- Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (± ***30*** minutes).
- Day 2: 24 and 36 hours (± ***30*** minutes) post-dose.
- Day 3: 48 hours (± ***30*** minutes)post-dose
- Day 4: 72 hours (± ***30*** minutes) post-dose
- End-of-trial (Day 7) visit: ± 30 minutes of time of Day 1 dose administration.

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Table 4.

d. Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and pre-dose on Day 1 within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times:

- Day 1 and Day 8: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (± ***30*** minutes).
- Day 2 and Day 9: 24 and 36 hours (± ***30*** minutes) post-dose.
- Day 3 and Day 10: 48 hours (± ***30*** minutes)post-dose
- Day 4 and Day 11: 72 hours (± ***30*** minutes) post-dose
- Day 7 trial visit: ±30 minutes of time of Day 1 dose administration
- End-of-trial/follow up visit (Day 14): ± 30 minutes of time of Day 8 dose administration.

Table 5.

a. Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and Day 1 pre-dose within 60 minutes prior to dosing. Blood pressure and heart rate only will be measured at the following times :
   - Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (± ***30*** minutes)
   - Day 2-3: predose and 12 hours (± ***30*** minutes) post-dose
   - Day 7, 14, 21, and 28: predose (± ***30*** minutes) (blood pressure, heart rate, and temperature should be measured)
   - Day 28: 12 hours(± ***30*** minutes) post-dose
   - Day 29: 24 hours after Day 28 dose (± ***30*** minutes)
   - Day 33 end-of-trial visit (blood pressure, heart rate, and temperature should be measured): ± 30 minutes from time of last dose administration on Day 28.

g. Continuous ECG recordings will be performed for 25 hours, starting one hour pre-dose on Day 1 and Day 28. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: At 3 time points within one hour prior to dosing (e.g., -45, -30 and -15 minutes) and at one time point each at approximately 1, 2, 3,4, 5, 6-, 8-, 12--, and 24-hours post-dose. Participants will be supinely resting for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ***safety*** ECGs then vital signs, ***except ECG extractions may occur before blood sample collection.***

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Clarification #8

Protocol Section 4.1.1 **Screening (Day -21 to -2)** will be amended to clarify that screening assessments for Part 1 may be performed in any order/sequence. The paragraph in this section will be amended as follows (new text in ***italics***):

Part 1 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 3 for Cohorts 1-5 or Table 4 for Cohort 6 in Section 1.3. ***There is no stipulated order or sequence of the conduct of Screening assessments.*** Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will apply during the Screening period.

Protocol Section 4.2.1 **Screening (Day -21 to -2)** will be amended to clarify that screening assessments for Part 2 may be performed in any order/sequence. The paragraph in this section will be amended as follows (new text in ***italics):***

Part 2 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 5 in Section 1.3. ***There is no stipulated order or sequence of the conduct of Screening assessments.***

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Protocol Clarification Memo (dated 02 March 2023)

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Protocol Clarification Letter

March 2, 2023

Memorandum: Provision of minor modifications to trial protocol

Protocol title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with an Open Label (Single Dose) Food Effect Panel
Protocol number: Gates MRI-TBD09-101, Version 2.0, 19 December 2022
Sponsor name: Bill & Melinda Gates Medical Research Institute (Gates MRI)

The following modifications to the protocol are provided and will be made in a forthcoming protocol amendment:

Modification #1
Section 10.2.7.1: Assessment of AE Intensity (Severity)
The current language for Grade 5 is "Death related to AE," but is changed to "Fatal."

Modification #2
Section 10.2.7.4: Assessment of AE Outcome
The current language specifies "Ongoing" as one of 4 possible AE outcomes. "Ongoing" is replaced by "Not Resolved/Not Recovered" and "Resolving/Recovering." This terminology change also applies to "ongoing" in the third paragraph of Section 4.6 and the penultimate bullet in Section 10.2.7.

Also, "Death" is changed to "Fatal" in this list in Section 10.2.7.4.

Modification #3
Section 1, Table 5 (Schedule of Activities for Part 2, MAD Cohorts 1-3)
Footnote 'a', 6th bullet: Respiratory rate is removed from the list of vital signs that should be measured at the Day 33 end-of-trial visit.

Modification #4
Section 10.2.9.1
The section is renamed "Reporting to Sponsor and/or Pharmacovigilance Service Provider" from "Reporting to Sponsor Delegate's (Contract Research Organization (CRO) Safety Team) Via the Electronic Data Capture (EDC) System."

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The primary mechanism for reporting SAE, AESI, and other immediately reportable events (e.g., pregnancy) is changed effective immediately to completion of paper reporting forms and submission via email or fax to the Sponsor's Pharmacovigilance Service Provider.

Sincerely,

[redacted]
Clinical Development Leader
Bill & Melinda Gates Medical Research Institute

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Protocol Memo (dated 04 May 2023)

Memo Protocol_TBD09-101_C5 + 6 Dose Clarifications 04May2023_final
Vault eTMF Document Number: VV-TMF-39686 | 1.0

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May 04, 2023

Memorandum to File – Protocol Clarifications for SAD Cohorts 5 and 6 Dose Selections

Protocol title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with an Open Label (Single Dose) Food Effect Panel
Protocol number: Gates MRI-TBD09-101, Version 3.0, dated 04 April 2023
Sponsor name: Bill & Melinda Gates Medical Research Institute (Gates MRI)

After review of the (blinded) safety and PK data from participants enrolled in Cohorts 1-3, the following doses have been selected for evaluation in Cohorts 5 and 6:

- Cohort 5: 1200 mg (one single dose)
- Cohort 6 (Food Effect): 300mg (two single doses separated by an 8-day washout period)

The projected safety margins for the 1200mg dose to be evaluated in Cohort 5 with reference to the no observed adverse effect level (NOAEL) established in the 1-month GLP toxicology study are 2.29x for Cmax and 1.64x for AUC.

These dose selections and the washout period between single doses for participants in Cohort 6 will be reflected in the protocol clarifications detailed on the following pages, which will be included in a future protocol amendment.

With Regards,

[redacted] MD, MSc
Clinical Development Leader
Bill & Melinda Gates Medical Research Institute

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Clarification #1
Protocol Section 1.1.3.1. (Part 1 – SAD and Food Effect (SAD/FE)

The 3rd sentence of paragraph 1 currently states:

"The MK-7762 dose to be evaluated in the FE cohort will be a dose demonstrated to be safe and well-tolerated in a previously completed SAD cohort."

This sentence will be **amended** to state:

"The MK-7762 dose to be evaluated in the FE cohort will be 300mg, which has been demonstrated to be safe and well-tolerated in a previously completed SAD cohort."

Clarification #2
Protocol Section 1.1.3.1. (Part 1 – SAD and Food Effect (SAD/FE)

The 5th and 6th sentences of paragraph 2 currently states:

"Cohort 5 may evaluate a dose of MK-7762 that will be selected based on the safety and PK data from previous cohorts. The dose of MK-7762 chosen for evaluation in Cohort 5 will not result in predicted exposure higher than that allowable based on the nonclinical toxicology no observed adverse effect level (NOAEL)."

The 5th and 6th sentences will be **amended** to state:

"Cohort 5 will evaluate a 1200mg dose of MK-7762 that has been selected based on the safety and PK data from previous cohorts. This 1200mg dose of MK-7762 for evaluation in Cohort 5 is projected to result in exposures below those observed at the nonclinical toxicology no observed adverse effect level (NOAEL)."

Clarification #3
Protocol Section 1.1.3.1. (Part 1 – SAD and Food Effect (SAD/FE)

The 1st and 2nd sentences of paragraph 3 currently states:

"For Cohort 6 (the FE Cohort) eight participants will be dosed with MK-7762 in both fasted and fed states with a between-dose washout period of at least 5 half-lives of MK-7762 as determined by the PK results from previous SAD cohorts. The MK-7762 dose to be evaluated in the FE cohort will be a dose demonstrated to be safe and well-tolerated in a previously completed SAD cohort.

The 1st and 2nd sentences will be **amended** to state:

"For Cohort 6 (the FE Cohort) eight participants will be dosed with MK-7762 in both fasted and fed states with a between-dose washout period of 8 days when the concentration of MK-7762 is

projected to be below the lower limit of quantification as determined by the PK results from previous SAD cohorts. The MK-7762 dose to be evaluated in the FE cohort will be 300mg, which has been demonstrated to be safe and well-tolerated in a previously completed SAD cohort."

Clarification #4
Protocol Section 1.1.3.1. (Part 1 – SAD and Food Effect (SAD/FE)

The 3rd sentence of paragraph 3 currently states:

"Two sentinel participants in Cohort 6 will be dosed in the fed state first followed by the second dose in the fasted state after washout."

The 3rd sentence of paragraph 3 will be **amended** to state:

"Two sentinel participants in Cohort 6 will be dosed in the fed state first."

Clarification #5
Protocol Section 1.1.3.1. (Part 1 – SAD and Food Effect (SAD/FE)

The 5th sentence of paragraph 4 currently states:

"If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined."

The 5th sentence of paragraph 3 will be **amended** to state:

"If recommended by the SRT and approved by the Sponsor, the two sentinel participants will be dosed with MK-7762 in the fasted state after the washout period previously determined and the remaining 6 participants in Cohort 6 will be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined."

Clarification #6
Protocol Section 1.1.3.1. (Part 1 – SAD and Food Effect (SAD/FE)
Food Effect Cohort (Cohort 6)

The 2nd sentence of paragraph #9 currently states:

"The first two participants in this cohort will be termed sentinel participants and will receive MK-7762 in a fed state and then, following a washout period of at least five half-lives, a second dose of MK-7762 will be administered in the fasted state."

The 2nd sentence of paragraph #9 will be **amended** to state:

"The first two participants in this cohort will be termed sentinel participants and will receive MK-7762 in a fed state and then, following a washout period of 8 days, a second dose of MK-7762 will be administered in the fasted state."

Clarification #7
Protocol Section 1.1.4 Study Drug Administration

The 5th sentence of paragraph 1 currently states:

"The dose for Cohort 5 will be determined after review of cumulative safety and PK data from the previously completed cohorts."

This sentence will be **amended** to state:

"Cohort 5 will evaluate a 1200mg dose of MK-7762 that has been selected based on the safety and PK data from previous cohorts."

Clarification #8
Protocol Section 1.1.4 Study Drug Administration

The 7th sentence of paragraph 1 currently states:

"The dose for Cohort 6 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previously completed SAD cohorts."

This 7th sentence will be **amended** to state:

"The MK-7762 dose to be evaluated in Cohort 6 in Part 1 (FE Cohort) will be 300mg, which has been demonstrated to be safe and well-tolerated in a previously completed SAD cohort."

Clarification #9
Protocol Section 1.1.4 Study Drug Administration

Table 2 contains the following information:

Part	Cohort	Period	Drug	Dose	Dose Strength	Dose Frequency
1 (SAD)	5	NA	MK-7762	TBD	10mg, 100mg and/or 300mg	Single Dose
			Placebo	NA	NA	Single Dose
	6 (FE)	1	MK-7762	TBD	10mg, 100mg and/or 300mg	Single Dose, fed or fasted
		2	MK-7762	TBD	10mg, 100mg and/or 300mg	Single Dose, fed or fasted

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Table 2 will be **amended** to contain the following information:

Part	Cohort	Period	Drug	Dose	Dose Strength	Dose Frequency
1 (SAD)	5	NA	MK-7762	1200mg	10mg, 100mg and/or 300mg	Single Dose
			Placebo	NA	NA	Single Dose
	6 (FE)	1	MK-7762	300mg	10mg, 100mg and/or 300mg	Single Dose, fed or fasted
		2	MK-7762	300mg	10mg, 100mg and/or 300mg	Single Dose, fed or fasted

Clarification #10
Protocol Section 1.1.4.1 Safety Review and Dose Escalation Decisions

The last sentence of 2nd paragraph 1 currently states:

"The dose to be evaluated in Cohort 5 will be decided by analysis of the safety and PK data available from previous cohorts."

The last sentence of the 2nd paragraph will be **amended** to state:

"Cohort 5 will evaluate a 1200mg dose of MK-7762 that has been selected based on the safety and PK data from previous cohorts."

Clarification #11
Protocol Section 1.2 Schema / Figure 1 Study Schema

The Part 1 SAD + FE schema for Cohort 5 and for Cohort 6 currently states that the doses of MK-7762 are 'TBD mg', respectively.

The Part 1 SAD + FE schema will be **amended** for Cohort 5 to state the MK-7762 dose is 1200mg and for Cohort 6 to state the MK-7762 dose is 300mg.

Clarification #12
Protocol Section 1.3 Schedule of Activities (SoA)
Table 4 Schedule of Activities for Part 1, Cohort 6 (Food Effect Cohort)

The following six (6) footnotes to Table 4 will be amended as follows:

Footnote 'a' currently states:
"Day 1 of Period 2 will not occur until at least 5 half-lives of MK-7762 have elapsed as determined by PK results from Cohorts 1-5."

Footnote 'a' will be **amended** to state:

"Day 1 of Period 2 (Day 9 of study for participants) will not occur until a washout period of 8 days has elapsed inclusive of Day 1 in Period 1."

Footnote 'c' will be **amended** to specify: (1) that the end of the trial for participants in Cohort 6 will be Day 15 (not Day 14); (2) that Day 1 of Period 2 will be Day 9 (not Day 8) of Period 1; and that ECGs scheduled to be performed on Day 14 will be performed on Day 15.

Footnote 'd' concerning the timing of vital signs assessments on certain days will be **amended** to reflect the following:

Day 8 will be changed to Day 9
Day 9 will be changed to Day 10
Day 10 will be changed to Day 11
Day 11 will be changed to Day 12

In addition:

"Day 7 trial visit: ±30 minutes of time of Day 1 dose administration" will be changed to:

"Period 1 – Day 8 trial visit: ±30 minutes of time of Day 1 dose administration"
"Period 2 – Day 14 trial visit: ±30 minutes of time of Day 9 dose administration"

In addition:

"End-of-trial/follow up visit (Day 14): ±30 minutes of time of Day 8 dose administration" will be changed to:

"End-of-trial/follow up visit (Day 15): ±30 minutes of time of Day 9 dose administration"

Footnote 'j' concerning the timing of collection of safety laboratory assessments will be **amended** to change Day 8 to Day 9.

Footnote 'k' concerning the timing of collection of PK samples will be **amended** to incorporate the following:

Day 8 will be changed to Day 9
Day 9 will be changed to Day 10
Day 10 will be changed to Day 11
Day 11 will be changed to Day 12
Day 14 will be changed to Day 15

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Footnote 'm' concerning the length of confinement in the CTU will be **amended** to specify that participants will stay in the CTU through Day 15 and will be discharged following Day 15 end of trial evaluations.

Clarification #13
Protocol Section 4.1 Part 1 – SAD and Food Effect (SAD/FE)

The 2nd sentence of paragraph 2 currently states:

"Cohort 5 may evaluate a dose of MK-7762 that will be selected based on the safety and PK data from previous cohorts."

The 2nd sentence of paragraph 2 will be **amended** to state:

"Cohort 5 will evaluate a 1200mg dose of MK-7762 selected based on the safety and PK data from previous cohorts."

Clarification #14
Protocol Section 4.1 Part 1 – SAD and Food Effect (SAD/FE)

The 2nd sentence of paragraph 3 currently states:

"The MK-7762 dose to be evaluated in the FE Cohort will be a dose demonstrated to be safe and well-tolerated in a previously completed SAD cohort."

The 2nd sentence of paragraph 3 will be **amended** to state:

"The MK-7762 dose to be evaluated in the FE Cohort will be 300mg, which has been demonstrated to be safe and well-tolerated in a previously completed SAD cohort."

Clarification #15
Protocol Section 4.1 Part 1 – SAD and Food Effect (SAD/FE)
Figure 2 Schema of Cohorts 1-5, Part 1

The Part 1 SAD schema for Cohort 5 currently states that the dose of MK-7762 is 'TBD mg'.

The Part 1 SAD schema will be **amended** for Cohort 5 to state the MK-7762 dose is 1200mg.

Clarification #16
Protocol Section 4.1 Part 1 – SAD and Food Effect (SAD/FE)
Table 7 Single Ascending Dose (Part 1) – Planned Dose Cohort 1-5

In Table 7, the dose of MK-7762 to be administered in Cohort 5 is stated as 'TBD mg'.

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Table 7 will be **amended** to state that the dose of MK-7762 to be administered in Cohort 5 is 1200mg.

Clarification #17
Protocol Section 4.1 Part 1 – SAD and Food Effect (SAD/FE)
Figure 3 Schema of Cohort 6/FE, Part 1

The Part 1 SAD/FE schema for Cohort 6 currently states that the dose of MK-7762 is 'TBD mg'.

The Part 1 SAD/FE schema will be **amended** for Cohort 6 to state that the MK-7762 dose is 300mg.

Clarification #18
Protocol Section 4.1 Part 1 – SAD and Food Effect (SAD/FE)
Table 8 Single Ascending Dose (Part 1) – Planned Dose Cohort 6 (Food Effect Cohort)

In Table 8, the dose of MK-7762 to be administered in Cohort 6 is stated as 'TBD mg'.

Table 8 will be **amended** to state that the dose of MK-7762 to be administered in Cohort 6 is 300 mg.

Clarification #19
Protocol Section 4.3 Trial Drug Administration

The 5th sentence of paragraph 1 currently states:

"The dose for Cohort 6 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previous SAD cohorts."

The 5th sentence of paragraph 1 will be **amended** to state:

"The MK-7762 dose to be evaluated in Cohort 6 in Part 1 (FE Cohort) will be 300mg, which has been demonstrated to be safe and well-tolerated in a previously completed SAD cohort."

Clarification #20
Protocol Section 4.5 Dose Escalation Decisions and Safety Review Team

The 7th (last) sentence of paragraph 3 currently states:

"The dose to be evaluated in Cohort 5 will be decided by analysis of the safety and PK data available from the previously completed Cohorts 1 through 4."

The 7th (last) sentence of paragraph 3 will be **amended** to state:

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"The dose to be evaluated in Cohort 5 will be 1200 mg, as decided by analysis of the safety and PK data available from previously completed cohorts."

Clarification #21

Protocol Section 6.1 Study Drug Administration

The 2nd sentence of paragraph 1 currently states:

"The first 2 participants in Cohort 6 (FE Cohort), termed sentinel participants, will receive open-label MK-7762 in a fed state and a second dose of MK-7762 in a fasting state after a washout period of at least 5 half-lives of MK-7762 as determined by PK data available from previously completed cohorts."

The 2nd sentence of paragraph 1 will be **amended** to state:

"The first 2 participants in Cohort 6 (FE Cohort), termed sentinel participants, will receive MK-7762 in a fed state and a second dose of MK-7762 in a fasting state after a washout period of 8 days as determined by PK data available from previously completed cohorts."

Clarification #22

Protocol Section 8.4.9

Table 12 Plasma PK Sampling Timepoints for Part 1 (SAD)

In Table 12 column headings:

Day 8 – Cohort 6 will be changed to Day 9 –Cohort 6

Day 9 – Cohort 6 will be changed to Day 10 – Cohort 6

Day 10 –Cohort 6 will be changed to Day 11 – Cohort 6

Day 11 – Cohort 6 will be changed to Day 12 – Cohort 6

Day 14 – Cohort 6 will be changed to Day 15 – Cohort 6

The footnote 'a' of Table 12 will be **amended** to state:

a: Start of second dosing period for Cohort 6 (FE Cohort) will be Day 9 to provide an 8-day washout period between single doses of MK-7762.

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Memo Protocol_TBD09-101_C5 + 6 Dose Clarifications 04May2023_final
Vault eTMF Document Number: VV-TMF-39686 | 1.0

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Reason for signing: Approved	Name: [redacted] Role: Clinical Development Date of signature: 04-May-2023 18:51:06 GMT+0000

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Protocol Memo (dated 23 May 2023)

Memo Protocol_TBD09-101_Clarifications Table 4 footnote 'k' and Table 12 final 23May2023
Vault eTMF Document Number: VV-TMF-40651 | 1.0

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23 May 2023

Memorandum to File – Protocol Clarifications

Protocol title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose and Multiple Ascending Dose Trial in Healthy Adult Participants to Evaluate the Safety, Tolerability, and Pharmacokinetics of MK-7762 with an Open Label (Single Dose) Food Effect Panel
Protocol number: Gates MRI-TBD09-101, Version 3.0, dated 04 April 2023
Sponsor name: Bill & Melinda Gates Medical Research Institute (Gates MRI)

The following protocol clarifications will be included in a subsequent protocol amendment.

Clarification #1

Protocol Section 1.3 Schedule of Activities (SoA)
Table 4 Schedule of Activities for Part 1, Cohort 6 (Food Effect Cohort)

Note: this Clarification #1 supercedes a portion of Clarification # 12 in PCL issued on 04 May 2023 that concerned changes to footnote 'k'.

In Protocol version 3.0, the footnote 'k' to Table 4 currently states:

k: Blood samples for PK analysis will be collected in each period at the following times:

- Day 1 and Day 8: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2 and Day 9).
- Day 3 and Day 10: 48 hours (±10 minutes) post-dose
- Day 4 and Day 11: 72 hours (±10 minutes) post-dose
- Day 7 and Day 14: within ±1-hour time window of time of study drug administration on Day 1 and Day 8, respectively

Footnote 'k' will be **amended** to state:

k: Blood samples for PK analysis **in Period 1** will be collected at the following times:

- Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2).
- Day 3: 48 hours (±10 minutes) post-dose
- Day 4: 72 hours (±10 minutes) post-dose

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Memo Protocol_TBD09-101_Clarifications Table 4 footnote 'k' and Table 12 final 23May2023
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- Day 7: within ±1-hour time window of time of study drug administration on Day 1

[note: No PK sample is collected on Day 8]

Blood samples for PK analysis **in Period 2** will be collected at the following times:

- Day 9: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 10).
- Day 11: 48 hours (±10 minutes) post-dose
- Day 12: 72 hours (±10 minutes) post-dose
- Day 15: within ±1-hour time window of time of study drug administration on Day 9

Clarification #2

Protocol Section 8.4.9 Pharmacokinetic Assessment
Table 12 Plasma PK Sampling Timepoints for Part 1 (SAD)

The header row for Table 12 currently shows:

Timepoint (day)	Day 1 -Cohorts 1-6 Day 8[a] – Cohort 6	Day 2 -Cohorts 1-6 Day 9[a] – Cohort 6	Day 3 -Cohorts 1-6 Day 10[a] – Cohort 6	Day 4 -Cohorts 1-6 Day 11[a] – Cohort 6	Day 7 -Cohorts 1-6 Day 14[a] – Cohort 6	ET

The header row for Table 12 will be **amended to** show that Day 1 of Period 2 is Day 9 (changes are bolded) :

Timepoint (day)	Day 1 -Cohorts 1-6 **Day 9[a]** – Cohort 6	Day 2 -Cohorts 1-6 **Day 10[a]** – Cohort 6	Day 3 -Cohorts 1-6 **Day 11[a]** – Cohort 6	Day 4 -Cohorts 1-6 **Day 12[a]** – Cohort 6	Day 7 -Cohorts 1-6 **Day 15[a]** – Cohort 6	ET

The timepoints of PK samples in rows 2 and 3 of Table 12 are unchanged.

In addition, the footnote 'a' of Table 12 will be **amended** to state:

a: Start of second dosing period for Cohort 6 (FE Cohort) will be Day 9 to provide an 8-day washout period between single doses of MK-7762.

With Regards,

[redacted] MD, MSc
Clinical Development Leader
Bill & Melinda Gates Medical Research Institute

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Memo Protocol_TBD09-101_Clarifications Table 4 footnote 'k' and Table 12 final 23May2023
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Reason for signing: Approved	Name: [redacted] Role: Clinical Development Date of signature: 23-May-2023 12:58:40 GMT+0000

Signature Page for VV-TMF-40651 v1.0

Changes in Version 4.0:

The protocol has been modified to include the following:

- Inclusion of Part 1, Summary: Data from SAD Cohorts 1-5 and FE Cohort 6
- Update to Part 2 to include FE Cohort 7 and MAD Cohorts 8-10 and to include the following:
  - Justification for doses
  - Trial Design
  - Human Efficacious Concentration Prediction
- Addition of genotoxicity study data
- Clarification for criteria for discontinuation of study drug for individual participants and hematological parameters (For Part 2 Only)
- Protocol clarifications consistent with the Memoranda to File from 4 May 2023 and 23 May 2023
- Inclusion of administrative changes and minor clarifications throughout
- The amendment has been classified as an “Other Amendment” according to the Sponsor’s relevant standard operating procedure.

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
Title Page	N/A	Added Amendment number and date Added IND number
Sponsor Signatory Page	[redacted] MD Clinical Development Leader Bill & Melinda Gates Medical Research Institute	[redacted], MD, PhD Clinical Development Leader Bill & Melinda Gates Medical Research Institute
List of Abbreviations	%w/w- Percent weight by weight API-Active pharmaceutical ingredient B-Bedaquiline BT-Body temperature BUN-Blood urea nitrogen CFR-Code Federal Regulations CNS-central nervous system CONSORT- Consolidated standards of Reporting Trials C_{trough}-Predose concentration levels CV-Coefficient of variation EMA-European Medicines Agency HDL-High density lipoprotein HIPAA-Health Insurance Portability and Accountability Act HPMC-Hydroxypropyl methylcellulose HRZE- Isoniazid, rifampin, pyrazinamide, and ethambutol IND-Investigational new drug ITT-Intent-to-treat IVRS- Interactive voice response system IWRS-Interactive web response system L-linezolid MedDRA- Medical Dictionary for Regulatory Activities MRSD- Maximum recommended starting dose NCA-Necessary condition analysis PA-Pretomanid PCP-Phencyclidine PP-Per protocol PT-Preferred term RBC-Red blood cell RNA-Ribonucleic acid SOC-System organ class	~~%w/w- Percent weight by weight~~ ~~API-Active pharmaceutical ingredient~~ ~~B-Bedaquiline~~ ~~BT-Body temperature~~ ~~BUN-Blood urea nitrogen~~ ~~CFR-Code Federal Regulations~~ ~~CNS-central nervous system~~ ~~CONSORT- Consolidated standards of Reporting Trials~~ ~~C_{trough}-Predose concentration levels~~ ~~CV-Coefficient of variation~~ ~~EMA-European Medicines Agency~~ ~~HDL-High density lipoprotein~~ ~~HIPAA-Health Insurance Portability and Accountability Act~~ ~~HPMC-Hydroxypropyl methylcellulose~~ ~~HRZE- Isoniazid, rifampin, pyrazinamide, and ethambutol~~ ~~IND-Investigational new drug~~ ~~ITT-Intent-to-treat~~ ~~IVRS- Interactive voice response system~~ ~~IWRS-Interactive web response system~~ ~~L-linezolid~~ ~~MedDRA- Medical Dictionary for Regulatory Activities~~ ~~MRSD- Maximum recommended starting dose~~ ~~NCA-Necessary condition analysis~~ ~~PA-Pretomanid~~ ~~PCP-Phencyclidine~~ ~~PP-Per protocol~~ ~~PT-Preferred term~~ ~~RBC-Red blood cell~~ ~~RNA-Ribonucleic acid~~ ~~SOC-System organ class~~ **Added:** **BPaL- Bedaquiline, pretomanid and linezolid** **IxRS- Interactive voice response system/Interactive web response system** **PKPD-Pharmacokinetics/Pharmacodynamics**

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
Section 1.1.2 - Rationale	The effect of food on the rate and extent of absorption of a single oral dose of MK-7762 will also be evaluated.	The effect of food on the rate and extent of absorption of **two different** single oral doses of MK-7762 will also be evaluated.
Table 1	Primary For Parts 1 and 2 • Part 1, Cohorts 1 through 5: Day 1 through Day 7 • Part 1, Cohort 6 (Food Effect): Day 1 through last day of washout period for first dosing period; Day 1 of second dosing period through Day 7 of second dosing period. • Part 2, Cohorts 1-3: Day 1 through Day 33 Secondary For Parts 1 and 2 • To evaluate the impact of food on the PK of MK-7762 in plasma **For Part 1** Only • **Treatment:** 1) MK-7762 in escalating single doses or placebo (Part 1, Cohorts 1-5) and 2); MK-7762 under fasted or fed conditions (Part 1, Cohort 6) • To determine the PK of multiple doses of MK-7762 in plasma. **For Part 2 Only** • Treatment: MK-7762 in escalating multiple doses or placebo (Part 2, Cohorts 1-3) • Participant-level endpoints **Day 28 (Cohorts 1-3):** Cohorts 1-3: Day 28 vs Day 1	Primary For Parts 1 and 2 **(All Cohorts)** • Part 1, **SAD** Cohorts 1 - 5: Day 1 through Day 7 • Part 1, **Food Effect (FE) Cohort 6:** Day 1 through last day of washout period for first dosing period; Day 1 of second dosing period through Day 7 of second dosing period • **Part 2, FE Cohort 7: Day 1 through last day of washout period for first dosing period; Day 1 of second dosing period through last day of washout period for second dosing period; Day 1 of third dosing period through Day 7 of third dosing period** • **Part 2, MAD Cohorts 8-10: Day 1 through Day 36** Secondary **For Part 1 (SAD Cohorts 1-5)** • To evaluate the impact of food on the PK of **single doses** of MK-7762 in plasma For Part 1 **(FE Cohort 6)** **Added: For Part 2 (FE Cohort 7)** • **Treatment:** 1) MK-7762 in escalating single doses or placebo (Part 1, SAD Cohorts 1-5) and 2); MK-7762 under fasted or fed conditions **(Part 1, FE Cohort 6) and 3) MK-7762 under fasted or fed conditions (Part 2, FE Cohort 7)** • To determine the PK of multiple doses of MK-7762 in plasma **in fed and fasted states.** For Part 2 **(MAD Cohorts 8-10)** • **Treatment:** MK-7762 in escalating multiple doses or placebo (Part 2, **MAD Cohorts 8-10)** • Participant-level endpoints **(all endpoints will be assessed in fed and fasted states):** **Day 28 ~~(Cohorts 1-3):~~** ~~Cohorts 1-3:~~ Day 28 vs Day 1

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	Exploratory For Parts 1 and 2 • For each of (a) and (b), the descriptive statistics for the laboratory parameter in participants who meet the criterion • For each of (c) and (d), descriptive statistics for the percent decrease in the laboratory parameter in participants who meet the criterion For Part 2 Only • For eye symptom assessment for each eye o Proportion of participants with a reported new post-baseline eye symptom in either eye (overall and by severity grade) For Parts 1 and 2	Exploratory For Part 1 **(Cohort 4)** and **Part** 2 **(Cohort 9)** For Part 1 **(Cohort 4)** and **Part 2 (Cohort 10)** For Parts 1 and 2 **(All Cohorts)** ~~• For each of (a) and (b), the descriptive statistics for the laboratory parameter in participants who meet the criterion~~ ~~• For each of (c) and (d), descriptive statistics for the percent decrease in the laboratory parameter in participants who meet the criterion~~ **For Part 2 (MAD Cohorts 8-10)** ~~• For eye symptom assessment for each eye~~ ~~o Proportion of participants with a reported new post-baseline eye symptom in either eye (overall and by severity grade)~~ **For Parts 1 and 2 (All Cohorts)**
Section 1.1.3 Study Design	This is a first-in-human (FIH) trial of MK-7762, administered to healthy adults. It is a randomized, double-blind, placebo-controlled, two-part trial.	This is a first-in-human (FIH) trial of MK-7762, administered **orally** to healthy adults. It is a randomized, double-blind, placebo-controlled, two-part trial, **evaluating participants in SAD cohorts who are administered single ascending oral doses in the fasted state and participants in MAD cohorts who are administered daily doses for 28 days in either the fed or fasted state. Treatment will be blinded for participants in Part 1, SAD Cohorts 1-5, and in Part 2, MAD Cohorts 8-10. Two open-label food effect cohorts will be enrolled (Part 1, FE Cohort 6, and Part 2, FE Cohort 7).** Added: **Part 2 includes an open-label, three-period food effect cohort (FE Cohort 7) evaluating 9 participants who receive a single MK-7762 dose in the fasting state and after a standard meal breakfast and after a high-fat meal breakfast. Part 2 also consists of a multiple ascending dose (MAD) double-blind, placebo-controlled cohorts**

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		(MAD Cohorts 8-10, N=60), evaluating 3 dose levels of MK-7762 administered once-daily for 28 days. Added: **Gates MRI-TBD09-101, Amendment 3 (Version 4.0)** **Part 1 of this trial has been completed. See Section 2.3.2 for results from Part 1.** • **The dose of MK-7762 for SAD Cohort 5 was 1200 mg.** • **The dose of MK-7762 for FE Cohort 6 was 300 mg.** • **The washout period between doses in FE Cohort 6 was 8 days.**
	Cohorts 1 through 4 will evaluate the safety and PK of single oral doses of MK-7762 of 50 mg, 150 mg, 300 mg, and 600 mg. Two sentinel participants in Cohort 6 will be dosed in the fed state first followed by the second dose in the fasted state after washout. If recommended by the SRT and approved by the Sponsor, the remaining 6 participants in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined. In Cohorts 1-5…. Participants will receive open-label MK-7762. The first two participants in this cohort will be termed sentinel participants and will receive MK-7762 in a fed state and then, following a washout period of at least five half-lives, a second dose of MK-7762 will be administered in the fasted state. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing period. If recommended by the SRT and approved by the Sponsor, the remaining six participants in Cohort 6 will receive doses of MK-7762 in fed and fasted states in a	SAD Cohorts 1 through -4 will evaluate the safety and PK of single oral doses of MK-7762 of 50 mg, 150 mg, 300 mg, and 600 mg. Two sentinel participants in Cohort 6 will be dosed in the fed state first ~~followed by the second dose in the fasted state after washout.~~ If recommended by the SRT and approved by the Sponsor, the **two sentinel** participants **will be dosed with MK-7762 in the fed state after the washout period previously determined, and the remaining 6 participants** in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined. In **SAD** Cohorts 1-5 ~~Participants will receive open-label MK-7762. The first two participants in this cohort will be termed sentinel participants and will receive MK-7762 in a fed state and then, following a washout period of at least five half-lives, a second dose of MK-7762 will be administered in the fasted state. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing period. If recommended by the SRT and approved by the Sponsor, the remaining six participants in Cohort 6 will receive doses of MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.~~

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	crossover manner employing the washout period previously determined.	
Section 1.1.3.2 Interim Review of Data from Part 1	Following completion of Part 1, a comprehensive interim review of cumulative clinical and PK data will be conducted in an unblinded manner by the Sponsor to guide selection of appropriate doses to be evaluated in Part 2 The results of the interim review are intended for regulatory submission and comment prior to initiation of Part 2 of the trial.	Following completion of Part 1, a comprehensive interim review of cumulative clinical **safety** and PK data **for Cohorts 1-6** will be conducted in an unblinded manner by the Sponsor to guide selection of appropriate doses to be evaluated in Part 2. The results of the interim review are intended for regulatory submission, **comment and regulatory agreement to proceed prior to the Sponsor's agreement to initiate Part 2 of the trial. In the current amendment of the Protocol (Amendment 3, Version 4.0), the preliminary results from Part 1 are included in the current amendment of the Protocol, (Section 2.3.2) and Part 2 has been updated to reflect the results of the interim review.**
Section 1.1.3.3 Part 2-Food Effect and MAD (FE/MAD)	In Part 2 of the trial, participants will be enrolled into three sequential cohorts to evaluate escalating once daily doses of MK-7762 or placebo for 28 days. Each of the three MAD cohorts will enroll sixteen participants randomized 3:1 to receive MK-7762 or placebo. All participants in Part 2 will be confined at the trial site from Day -1 until their end-of-trial visit (approximately 34 days for MAD Cohorts 1-3). Subsequently, a fourth MAD cohort may be considered to evaluate once daily doses of MK-7762 or placebo for 91 days, in the event of acceptable findings from the planned 4-month sub-chronic toxicology studies in rats and dogs. *Screening (Day -21 to -2)* Potential participants in Part 2 will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 5 in Section 1.3. *Confinement Period* All Part 2 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 5 in Section 1.3. Randomization will occur prior to dosing on Day 1 for all cohorts. In Part 2, MK-7762 will be dosed either shortly after a meal (fed condition) or under fasting conditions depending on the PK results of the FE evaluation in Part 1.	In Part 2, **an open-label, three-period food effect cohort (FE Cohort 7) will be enrolled to evaluate a single dose of MK-7762 600 mg in the fasted state, after ingestion of a standard meal breakfast, and after ingestion of a high-fat meal breakfast, in random fashion (Table 5). FE Cohort 7 will enroll a sufficient number of participants to ensure that 9 participants complete each of the three dosing periods.** All participants in FE **Cohort 7** will be confined at the trial site from Day -1 until their end-of-trial visit on Day 8 of **Period 3.** **In MAD Cohorts 8-10, 3 dose levels of MK-7762 will be administered daily for 28 days in a placebo-controlled, multiple ascending dose (MAD) design (N=60) (see Section 1.1.3.1). MAD Cohort 8 will enroll in parallel with FE Cohort 7. The MAD doses in Part 2 were selected based on data from Part 1: MAD Cohort 8 will evaluate MK-7762 100 mg once daily (QD), MAD Cohort 9 will evaluate MK-7762 300 mg QD. The anticipated MK-7762 QD dose to be evaluated in MAD Cohort 10 is 500 mg. This may be modified through a protocol amendment after review of PK and safety data from FE Cohort 7 and MAD Cohorts 8 and 9. The dose in MAD Cohort 10 will not exceed 600 mg QD (See Section 2.6 for Justification for Dose).** **Each of the three MAD cohorts will enroll approximately 20 participants randomized 4:4:1:1 to receive MK-7762 in fasted state, MK-7762 in fed state after a standard meal breakfast, placebo in fasted state, or placebo in fed state after a standard meal breakfast, respectively. All participants in Part 2 MAD Cohorts 8-10**

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	Part 2 participants in Cohorts 1-3 will remain in the CTU until Day 33 (±2 days; 34 days total). Clinical and safety laboratory assessments will be performed throughout the confinement period as per Table 5 for MAD Cohorts 1-3.	**will be confined at the trial site from Day -1 until their end-of-trial visit on Day 36.** Subsequently, a fourth MAD cohort may be considered to evaluate once daily doses of MK-7762 or placebo for **up to** 91 days, in the event of acceptable **findings in the ongoing 4-month** sub-chronic toxicology studies in rats and dogs. *Screening (Day -21 to -2)* Potential participants in Part 2 will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 5 and Table 6 in Section 1.3. *Confinement Period* **Participants in FE Cohort 7 will be admitted from Day -1 prior to first dosing period with confirmation of eligibility and baseline assessments performed** as per Table 5 in Section 1.3. Randomization will occur prior to dosing on Day 1. **They will remain in the CTU until Day 8 of the third dosing period. All MAD Cohort 8-10 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 6 in Section 1.3. Randomization will occur prior to dosing on Day 1 for all cohorts. They will remain in the CTU until Day 36.** ***Food Effect Cohort 7*** **Participants will receive open-label MK-7762 600 mg utilizing a 3-period design. Participants will be randomized to one of the following 3 sequences:** • **Fasted, standard meal, high-fat meal** • **Standard meal, high-fat meal, fasted** • **High-fat meal, fasted, standard meal** **Between doses, there will be a washout period of at least 8 days, consistent with at least 5 half-lives. Participants administered MK-7762 in the fasted state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants administered MK-7762 in the standard meal fed state will be provided with a standard meal breakfast, which should be consumed within 30 minutes or less, with MK-7762 administration occurring approximately 30 minutes after the start of the meal. Participants administered MK-7762 in the high-fat meal fed state will be provided with a high-fat meal breakfast, which should be consumed within 30 minutes or less, with MK-7762**

<table>
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<tr><td></td><td></td><td>administration occurring approximately 30 minutes after the start of the meal. In both the fed and fasted settings, fasting will resume for at least 4 hours post-dose.
FE Cohort 7 clinical and safety laboratory assessments will be performed as per Table 5.
MAD Cohorts 8-10
Participants in the MAD cohorts will be randomized 4:4:1:1 to receive MK-7762 in fasted state, MK-7762 in fed state after a standard meal breakfast, placebo in fasted state, or placebo in fed state after a standard meal breakfast, respectively. Dosing in the fasted state or after standard breakfast meal will follow same procedures as FE Cohort 7 described above.
Clinical and safety laboratory assessments will be performed as per Table 6 for MAD Cohorts 8-10.</td></tr>
<tr><td>Section 1.1.4 Study Drug Administration</td><td>Capsules containing MK-7762 will be supplied as 10 mg (size 3), 100 mg (size 0), and 300 mg capsules (size 00) with matching placebo capsules for oral administration. The planned doses for each cohort in Part 1 are listed in Table 2 below. All doses of MK-7762 and placebo will be administered with 240 mL (8 ounces) of water. The doses of MK-7762 for Part 1 Cohorts 2 through 4 may be modified based on accumulating safety, tolerability, and PK data. The dose for Cohort 5 will be determined after review of cumulative safety and PK data from the previously completed cohorts. Additional cohorts may be enrolled after protocol amendment to enroll additional participants at any of the planned dose level(s) or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previously completed cohorts. The dose for Cohort 6 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previously completed SAD cohorts. The MK-7762 doses for daily administration in MAD Cohorts 1-3 will be selected after the interim review described above (see Section 1.1.3.2).</td><td>Capsules containing MK-7762 will be supplied as 10 mg (size 3), 100 mg (size 0), and 300 mg capsules (size 00) with matching placebo capsules for oral administration. The planned doses for each cohort evaluated in Part 1 and planned for Part 2 are listed in Table 2 below. See Section 2.6 for rationale for doses selected. All doses of MK-7762 and placebo will be administered with 240 mL (8 ounces) of water. ~~The doses of MK-7762 for Part 1 Cohorts 2 through 4 may be modified based on accumulating safety, tolerability, and PK data. The dose for Cohort 5 will be determined after review of cumulative safety and PK data from the previously completed cohorts. Additional cohorts may be enrolled after protocol amendment to enroll additional participants at any of the planned dose level(s) or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previously completed cohorts. The dose for Cohort 6 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previously completed SAD cohorts. The MK-7762 doses for daily administration in MAD Cohorts 1-3 will be selected after the interim review described above (see Section 1.1.3.2).~~</td></tr>
<tr><td>Table 2</td><td>1 (SAD)</td><td>1 (SAD and FE)
Added: Cohort 7 (FE) 1, 2, 3
<table>
<tr><th>Period</th><th>Drug</th><th>Dose</th><th>Dose Strength</th><th>Dose Frequency</th></tr>
<tr><td>1</td><td>MK-7762</td><td>600 mg</td><td>100 mg and/or 300 mg</td><td>Single Dose, fed or fasted[2]</td></tr>
</table></td></tr>
</table>

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		2 | MK-7762 | 600 mg | 100 mg and/or 300 mg | Single Dose, fed or fasted[1] 3 | MK-7762 | 600 mg | 100 mg and/or 300 mg | Single Dose, fed or fasted[2]
	Cohort 1, 2, 3 = Dose: TBD Once daily, 28 days	Cohort 8, 9, 10 = Dose: 10, 30, 50 mg, respectively Once daily, 28 days **fed or fasted** Added footnotes: **Abbreviations: NA = not applicable; TBD = to be determined** **1 Cohort 5: 1200 mg; Cohort 6: 300 mg (see Section 2.3.2)** **2 The fed state in FE Cohort 7 will be a standard breakfast meal or a high-fat breakfast meal** **3 The fed state in MAD Cohorts 8-10 will be a standard breakfast meal**
Section 1.1.4.1 Safety Review and Dose Escalation Decisions	A Safety Review Team (SRT) will be established as the team responsible for safety review and dose escalation recommendations during Part 1 and Part 2 of the trial. Details on the membership of the SRT will be contained in a charter that will describe the SRT review of blinded safety and PK data and the deliberation processes (including the format of data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment and, if PK data are available, only aggregated mean PK data will be provided. During Part 1 of the study, the SRT will convene after all participants in a specific cohort have completed 4 days of follow-up post-dosing and all safety data collected through Day 4 are available for review. Safety review will be conducted after completion of each of Cohorts 1, 2, 3, and 4 (see Figure 1). The SRT will have access to available aggregated mean PK data during its meetings to consider progression to Cohorts 3, 4, and 5. The SRT may recommend dose escalation to a subsequent planned cohort if no pausing rule is present. If dose escalation is recommended following completion of Cohort 1 (50 mg), the single dose to be evaluated in Cohort 2 is planned as 150 mg. If dose escalation is recommended following completion of Cohort 2, the dose to be evaluated in Cohort 3 is planned as 300 mg. If dose escalation to Cohort 4 is recommended following completion of Cohort 3, the dose to be evaluated in Cohort 4	A Safety Review Team (SRT) will be established as the team responsible for safety review and dose escalation recommendations during Part 1 and Part 2 of the trial. Details on the membership of the SRT will be contained in a charter that will describe the SRT review of blinded safety and PK data and the deliberation processes (including the format of data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment and, if PK data are available, only aggregated mean PK data will be provided. **See Section 4.4 for further details, including the pausing rules for which the SRT will monitor.** ~~During Part 1 of the study, the SRT will convene after all participants in a specific cohort have completed 4 days of follow-up post-dosing and all safety data collected through Day 4 are available for review. Safety review will be conducted after completion of each of Cohorts 1, 2, 3, and 4 (see Figure 1). The SRT will have access to available aggregated mean PK data during its meetings to consider progression to Cohorts 3, 4, and 5. The SRT may recommend dose escalation to a subsequent planned cohort if no pausing rule is present. If dose escalation is recommended following completion of Cohort 1 (50 mg), the single dose to be evaluated in Cohort 2 is planned as 150 mg. If dose escalation is recommended following completion of Cohort 2, the dose to be evaluated in Cohort 3 is planned as 300 mg. If dose escalation to Cohort 4 is recommended following completion of Cohort 3, the dose to be evaluated in Cohort 4 is planned as 600 mg. The dose to be evaluated in Cohort 5 will be decided by analysis of the safety and PK data available from the previous cohorts.~~ ~~As described in Section 1.1.3.2, an interim review will be conducted following completion of Part 1 and prior to any activities of Part 2. After~~

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	is planned as 600 mg. The dose to be evaluated in Cohort 5 will be decided by analysis of the safety and PK data available from the previous cohorts. As described in Section 1.1.3.2, an interim review will be conducted following completion of Part 1 and prior to any activities of Part 2. After regulatory authority agreement and Sponsor approval to proceed to the Part 2, MAD Cohort 1 may be initiated with MK-7762 (low dose) to be administered once daily for 28 days (either with or without food depending on results of the FE evaluation results of Part 1 Cohort 6). The SRT will convene after all participants in MAD Cohort 1 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 2 (medium dose of MK-7762 administered once daily for 28 days) if no pausing rule is present. The SRT will convene after all participants in MAD Cohort 2 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 3 (high dose of MK-7762 administered once daily for 28 days) if no pausing rule is present. 1.1.4.2 Pausing Rules The SRT must assess the data as showing no significant safety concerns before recommending proceeding with MK-7762 administration to participants in SAD and/or MAD cohorts scheduled to receive higher doses of MK-7762. Events necessitating a pause in enrollment and/or participant dosing in both parts of the trial, and, in turn, requiring an ad hoc IDMC review, include: • At least one participant experiences a Grade ≥ 3 AE assessed as related to study drug by the Investigator or Sponsor. The qualifying AE should occur within 4 days of receipt of a dose of study drug (see Appendix 1 for the AE grading table to be used for the trial). The Investigator	~~regulatory authority agreement and Sponsor approval to proceed to the Part 2, MAD Cohort 1 may be initiated with MK-7762 (low dose) to be administered once daily for 28 days (either with or without food depending on results of the FE evaluation results of Part 1 Cohort 6).~~ ~~The SRT will convene after all participants in MAD Cohort 1 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 2 (medium dose of MK-7762 administered once daily for 28 days) if no pausing rule is present.~~ ~~The SRT will convene after all participants in MAD Cohort 2 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 3 (high dose of MK-7762 administered once daily for 28 days) if no pausing rule is present.~~ ~~1.1.4.2 Pausing Rules~~ ~~The SRT must assess the data as showing no significant safety concerns before recommending proceeding with MK-7762 administration to participants in SAD and/or MAD cohorts scheduled to receive higher doses of MK-7762. Events necessitating a pause in enrollment and/or participant dosing in both parts of the trial, and, in turn, requiring an ad hoc IDMC review, include:~~ ~~• At least one participant experiences a Grade ≥ 3 AE assessed as related to study drug by the Investigator or Sponsor. The qualifying AE should occur within 4 days of receipt of a dose of study drug (see Appendix 1 for the AE grading table to be used for the trial). The Investigator should assess clinical significance of safety laboratory abnormalities before reporting as an AE.~~ ~~• At least one participant experiences a SAE assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug.~~ ~~• At least two participants within any of the cohorts (SAD or MAD) experience Grade ≥ 2 AEs of a similar nature assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug.~~ ~~• Any occurrence of anaphylaxis or Grade 4 hypersensitivity reaction.~~ ~~Any other findings that, at the discretion of the Investigator, SRT, or Sponsor, indicate dose escalation should be paused.~~

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	should assess clinical significance of safety laboratory abnormalities before reporting as an AE. • At least one participant experiences a SAE assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug. • At least two participants within any of the cohorts (SAD or MAD) experience Grade ≥ 2 AEs of a similar nature assessed as related to study drug by the Investigator or Sponsor. The qualifying event should occur within 4 days of receipt of a dose of study drug. • Any occurrence of anaphylaxis or Grade 4 hypersensitivity reaction. • Any other findings that, at the discretion of the Investigator, SRT, or Sponsor, indicate dose escalation should be paused.	
Section 1.1.4.2 IDMC		Added: **See Section 4.4.2 for further details on the trial IDMC.**
Section 1.1.5 Rules for Discontinuation of Study Drug for Individual Participants in Part 2 2, **MAD Cohorts 8-10**	Treatment will be discontinued for participants in Part 2 that experience one or more of the following safety laboratory abnormalities at any time from Day 1 through the end of their dosing period: • Hemoglobin < 9.0 g/dL for males and < 8.5 g/dL for females • Total WBC count < 1,500 cells/mm^3 • ANC < 600 cells/mm^3 • Platelet count < 50,000 cells/mm^3 Part 2 participants with a safety laboratory result meeting one of these criteria should have the relevant test repeated to confirm the finding before discontinuation of treatment. Treatment will be discontinued for participants in Part 2 that experience any of the following clinical AEs at any time from Day 1 through the end of their dosing period: • Grade 2 or higher peripheral neuropathy • Optic neuritis of any grade confirmed by an ophthalmologist	Treatment will be discontinued for participants in Part 2, **MAD Cohorts 8-10,** that experience one or more of the following safety laboratory abnormalities at any time from Day 1 through the end of their dosing period: • Hemoglobin **<11.5 g/dL** for males and **<10.0 g/dL** for females **or >2 g/dL decrease from Day -1 for both males and females** • Total WBC count **<2,000** cells/mm^3 • ANC **<1,200** cells/mm^3 • Platelet count **<100,000** cells/mm^3 or **>50% decrease from Day -1** • **Alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal** Part 2, **MAD Cohort 8-10, participants** with a safety laboratory result meeting one of these criteria should have the relevant test repeated to confirm the finding before discontinuation of treatment. Treatment will be discontinued for participants in Part 2, **MAD Cohorts 8-10**, that experience any of the following clinical AEs at any time from Day 1 through the end of their dosing period: • Grade 2 or higher peripheral neuropathy • Optic neuritis of any grade confirmed by an ophthalmologist

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		Study treatment discontinuation in one or more MAD Cohorts 8-10 participants does not require a pause in trial enrollment or in dosing for all currently enrolled participants (see Section 4.4.1). Individual participant study treatment discontinuations will be considered by the SRT during MAD dose escalation review meetings.
Section 1.1.6 Number of Participants and Duration of Participation	A total of approximately 96 participants will be randomized (48 in Part 1 and 48 in Part 2), and a total of approximately 74 participants will be exposed to MK-7762 (38 in Part 1 and 36 in Part 2). In Part 1, the maximum duration of participation, including the Screening period, will be up to approximately 30 days for participants in Cohorts 1 through 5 and approximately 38 days for participants in Cohort 6 (to be confirmed once washout period of at least 5 half-lives is determined). In Part 2, the maximum duration of participation, including the Screening period, will be up to approximately 54 days for participants in Cohorts 1-3. **Blinding:** The trial has a double-blind design in which participants and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at the trial site who will prepare the oral doses of MK-7762 and placebo appropriately masked for site personnel who are authorized to administer treatment.	A total of approximately **117 participants** will be randomized (**48** in Part 1 and **69** in Part 2), and a total of approximately **95** participants will be exposed to MK-7762 (38 in Part 1 and **57** in Part 2). In Part 1, the maximum duration of participation, including the Screening period, will be up to approximately 30 days for participants in **Part 1**, SAD Cohorts 1-5 and approximately 38 days for participants in **FE** Cohort 6 (to be confirmed once washout period of at least 5 half-lives is determined). **The duration of participation for participants in Part 2, FE Cohort 7, will be up to approximately 44 days, which includes a washout period of at least 8 days between the open-label doses of MK-7762**. In Part 2, MAD Cohorts 8-10, the maximum duration of participation, including the Screening period, will be up to approximately 54 days for participants~~. in Cohorts 1-3~~. **Blinding:** The trial has a double-blind design in which participants **in SAD Cohorts 1-5 and MAD Cohorts 8-10** and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at the trial site who will prepare the oral doses of MK-7762 and placebo appropriately masked for site personnel who are authorized to administer treatment. **All doses of MK-7762 administered to all participants in Part 1 FE Cohort 6 and in Part 2 FE Cohort 7 will be open-label.**

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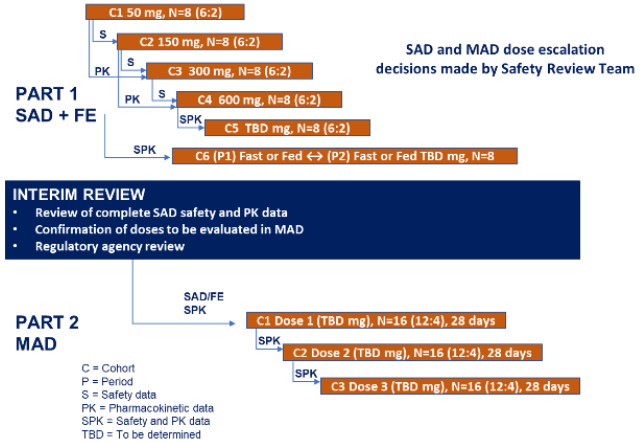
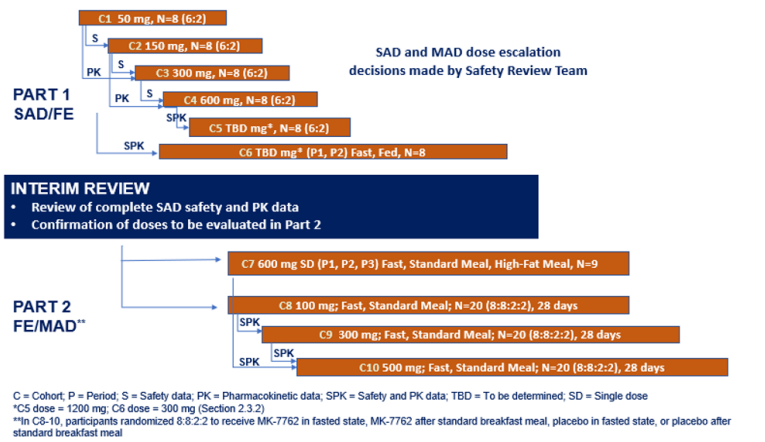
Section 1.2 Schema		
Table 3	Title: Schedule of Activities for Part 1, Cohorts 1-5 Footnotes: g: Screening labs include Hep B, C, & HIV h: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range. i: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. Blood and urine for post-dose safety laboratory assessments should be collected within a ±2-hour time window from the same time of day as study drug administration on Day 1. j: Blood samples for PK analysis will be collected at the following times: • Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2). • Day 3: 48 hours (±10 minutes) post-dose	Title: Schedule of Activities for Part 1, **SAD** Cohorts 1-5 Footnotes: **g: Screening labs include Hep B, C, & HIV** **h: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.** ~~g: Screening labs include Hep B, C, & HIV~~ ~~h: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.~~ i: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. Blood and urine for post-dose safety laboratory assessments should be collected within a ±2-hour time window from the same time of day as study drug administration on Day 1. **j: Blood samples for PK analysis will be collected at the following times:** • **Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours**

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	• Day 4: 72 hours (±10 minutes) post-dose • Day 7: Within ±1-hour time window of time of study drug administration on Day 1 Additional blood will be collected at the same time points for participants in Cohort 4 for storage for potential future qualitative and/or quantitative analysis of any significant metabolites identified. k: Urine will be collected for PK analysis at the following times from Cohort 4 only: • Pre-dose (spot check) collected as first morning void • Day 1: 0-4, 4-8, 8-12, 12-24 hours • Day 2: 24-36 and 36-48 hours • Day 3: 48-72 hours l: Samples will be collected and stored for potential pharmacogenetic (PGx) analysis (see Section 8.4.10) m: Adverse events will be collected from the time of signed informed consent	**(±5 minutes) postdose and 24 and 36 hours** (±10 minutes) postdose (Day 2). • Day 3: 48 hours (±10 minutes) post-dose • Day 4: 72 hours (±10 minutes) post-dose • Day 7: Within ±1-hour time window of time of study drug administration on Day 1 Additional blood will be collected at the same time points for participants in Cohort 4 for storage for potential future qualitative and/or quantitative analysis of any significant metabolites identified. k: Urine will be collected for PK analysis at the following times from Cohort 4 only: • **Pre-dose (spot check) collected as first morning void** • Day 1: 0-4, 4-8, 8-12, 12-24 hours • Day 2: 24-36 and 36-48 hours • Day 3: 48-72 hours l: Samples will be collected and stored for potential pharmacogenetic (PGx) analysis (see Section 8.4.10) **m**: **Adverse events will be collected from the time of signed informed consent**
Table 4	Title: Title: Schedule of Activities for Part 1, Cohort 6 Footnotes: a: Day 1 of Period 2 will not occur until at least five half-lives of MK-7762 have elapsed as determined by PK results from Cohorts 1-5. b: In the event of a participant's early withdrawal, efforts will be made to perform end-of-trial procedures at the time of participant withdrawal. c: 12-lead safety ECG for on-site evaluation will be recorded at Screening, on Days -1, 1, 2, 7, 8 and 9, and at the end of the trial (Day 14). The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with at	Added: Gates MRI-TBD09-101, Amendment 3 (Version 4.0) Part 1 of this trial has been completed. See Section 2.3.2 for results from Part 1. • The washout period between doses in FE Cohort 6 was 8 days. Title: Schedule of Activities for **Part 1, FE Cohort 6** Footnotes: a: Day 1 of Period 2 will not occur until at least five half-lives of MK-7762 have elapsed as determined by PK results from Cohorts 1-5. b: In the event of a participant's early withdrawal, efforts will be made to perform end-of-trial procedures at the time of participant withdrawal. c: 12-lead safety ECG for on-site evaluation will be recorded at Screening, on **Days -1, 1, 2, 8, 9, and 10, and** at the end of the trial (Day 15). The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with at least 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on **Day 1 Period 1 and Day 1 Period 2** should be collected within 120 minutes prior to dosing and

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	least 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 and Day 8 (Day 1 Period 2) should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Day 2, Day 7, Day 9, and Day 14 should be taken at approximately the same time as the study drug was administered. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator. When safety ECGs coincide with vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs. d: Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and pre-dose on Day 1 and Day 8 within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times: • Day 1 and Day 8: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (±30 minutes). • Day 2 and Day 9: 24 and 36 hours (±30 minutes) post-dose. • Day 3 and Day 10: 48 hours (±30 minutes) post-dose. • Day 4 and Day 11: 72 hours (±30 minutes) post-dose • Day 7 trial visit: ±30 minutes of time of Day 1 dose administration • End-of-trial/follow up visit (Day 14): ±30 minutes of time of Day 8 dose administration. e: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool. f: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates g: Screening labs include Hep B, C, & HIV h: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range. i: Participants will receive a single dose in 2 treatment periods: one after a high fat, high calorie breakfast (fed) and the second treatment period under fasted conditions (or the opposite order). The fed and fasted treatment periods will be separated by a washout period of at least five half-lives. See Section 4.1.4.	at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Day 2, Day 7, Day 9, and Day 14 **of Periods 1and 2 should** be taken at approximately the same time as the study drug was administered. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator. When safety ECGs coincide with vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs. d: Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and pre-dose on Day 1 and **Day 9** within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times: • **Day 1 of Periods 1 and 2:** 30 minutes (±10 minutes) post-dose and then at each PK sample timepoint (±30 minutes). • **Day 2 of Periods 1 and 2:** 24 and 36 hours (±30 minutes) post-dose. • **Day 3 of Periods 1 and 2**: 48 hours (±30 minutes) post-dose. • **Day 4 of Periods 1 and 2:** 72 hours (±30 minutes) post-dose • **Day 8 of Period 1 (Day -1 Period 2):** ± 30 minutes of time of **Day 1 Period 1** dose administration • **Day 7 of Period 2 end of trial:** ±30 minutes of time of **Day 1 Period 2** dose administration e: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool. f: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates. **g**: **Screening labs include Hep B, C, & HIV** **h: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.** ~~g: Screening labs include Hep B, C, & HIV~~ i: Participants will receive a single dose in 2 treatment periods: one after a high fat, high calorie breakfast (fed) and the second treatment period under fasted conditions (or the opposite order). The fed and fasted treatment periods will be separated by a washout period of at least five half-lives. See Section 4.1.4. j: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. Blood and urine for post-dose safety laboratory assessments should be collected within a ±2-hour time window from the same time of day as study drug administration on **Day 1Period 1** or **Day 1 Period 2,** accordingly. k: Blood samples for PK analysis in Period 1 will be collected in each period at the following times:

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	j: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. Blood and urine for post-dose safety laboratory assessments should be collected within a ±2-hour time window from the same time of day as study drug administration on Day 1 or 8, accordingly. k: Blood samples for PK analysis will be collected in each period at the following times: • Day 1 and Day 8: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2 and Day 9). • Day 3 and Day 10: 48 hours (±10 minutes) post-dose • Day 4 and Day 11: 72 hours (±10 minutes) post-dose • Day 7 and Day 14: within ±1-hour time window of time of study drug administration on Day 1 and Day 8, respectively l: Blood samples will be collected and stored for potential PGx analysis (see Section 8.4.10) m: Participants will stay in the CTU through Day 14 and will be discharged following Day 14 end of trial evaluations. n: Adverse events will be collected from the time of signed informed consent	• **Day 1:** Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (**Day 2).** • **Day 3:** 48 hours (±10 minutes) post-dose • **Day 4:** 72 hours (±10 minutes) post-dose • **Day 7:** within ±1-hour time window of time of study drug administration on Day 1 **NOTE: No PK sample is collected on Day 8 Period 1** **Blood samples for PK analysis in Period 2 will be collected at the following times:** • **Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 3, 4, 5, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2 Period 2).** • **Day 3: 48 hours (±10 minutes) post-dose** • **Day 4: 72 hours (±10 minutes) post-dose** • **Day 7: within ±1-hour time window of time of study drug administration on Day 1 Period 2** l: Blood samples will be collected and stored for potential PGx analysis (see Section 8.4.10) m: Participants will stay in the CTU through **Day 7 of Period 2** and will be discharged **following the end of trial evaluations.** n: Adverse events will be collected from the time of signed informed consent
Table 5	Title: Schedule of Activities for Part 2, MAD Cohorts 1-3 Footnotes: For abbreviations, see List of Abbreviations a: Blood pressure, heart rate, and temperature will be measured with participant in supine position at Screening, Day -1 check-in, and Day 1 pre-dose within 60 minutes prior to dosing. Blood pressure and heart rate only will be measured at the following times: • Day 1: 30 minutes (± 10 minutes) post-dose and then at each PK sample timepoint (±30 minutes). • Day 2-3: predose and 12 hours (±30 minutes) post-dose. • Day 7, 14, 21, and 28: predose (±30 minutes) (blood pressure, heart rate, and temperature should be measured)	Title: Schedule of Activities for Part 2, **FE Cohort 7** **MADE MULTIPLE REVISIONS TO SOA** Footnotes: For abbreviations, see List of Abbreviations **a: Day 1 of Period 2 and 3 will not occur until at least 8 days have elapsed since Day 1 of Period 1 and 2, respectively.** **b: In the event of a participant's early withdrawal, efforts will be made to perform end-of-trial procedures at the time of participant withdrawal.** **c: 12-lead safety ECG for on-site evaluation will be recorded at Screening, on Days -1, 1, 2, and 7 for each Period and at the end of the trial (Day 7 of Period 3). The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with approximately 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 Period 1, on Day 1 Period 2 and Day 1 Period 3 should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Day 2, and Day 7 should be taken at approximately the same time as the**

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	• Day 28: 12 hours (±30 minutes) post-dose • Day 29: 24 hours after Day 28 dose (±30 minutes) • Day 33 end-of-trial visit (blood pressure, heart rate, and temperature should be measured): ±30 minutes from time of last dose administration on Day 28 b: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool. The assessments should be conducted within ±3 hours of that day's dose when scheduled on a study day after Day 1. c: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates. The assessments should be conducted within ±3 hours of that day's dose when scheduled on a study day after Day 1. d: Screening labs include Hep B, C, & HIV e: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.	**study drug was administered. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator. When safety ECGs coincide with vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs**. d: Blood pressure, heart rate, and temperature will be measured with participant in supine position **after resting for ≥3 minutes** at Screening, Day -1 check-in, and **pre-dose on Day 1 of each period** within 60 minutes prior to dosing. Supine blood pressure and heart rate only will be measured at the following times: • Day 1 **of Periods 1, 2, and 3**: 30 minutes (±10 minutes) post-dose and then at each PK sample timepoint (±30 minutes). • **Day 2 of Periods 1, 2, and 3: 24 and 36 hours (±30 minutes) post-dose.** • Day 3 of Periods 1, 2, and 3: 48 hours (±30 minutes) post-dose. • **Day 4 of Periods 1, 2, and 3: 72 hours (±30 minutes) post-dose** • **Day 8 of Periods 1, 2 and 3: ±30 minutes of time of Day 1 dose administration of Period 1, Period 2 or Period 3, respectively** e: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool.~~The assessments should be conducted within ±3 hours of that day's dose when scheduled on a study day after Day 1.~~ f: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates~~The assessments should be conducted within ±3 hours of that day's dose when scheduled on a study day after Day 1.~~ g: **Performed at Period 1 only.** h: **Screening** labs include Hep B, C, & HIV i: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range. **j: Participants will receive a single dose in 3 periods: one after a high fat, high calorie breakfast, one after a standard breakfast, and under fasted conditions separated by a washout period of at least 8 days. See Section 4.2.** **k: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. Blood and urine for post-dose safety laboratory assessments should be collected within a ±2-hour time window from the same time of day as study drug administration on Day 1 of each dosing period.** **l. Blood samples for PK analysis will be collected in each of the three periods at the following times:**

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		• **Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 4, 6, 8, and 12 hours (±5 minutes) postdose and 24 and 36 hours (±10 minutes) postdose (Day 2).** • **Day 3: 48 hours (±10 minutes) post-dose** • **Day 4: 72 hours (±1 hour) post-dose** • **Day 5: 96 hours (±1 hour) post-dose** • **Day 6: 120 hours (±1 hour) post-dose** • **Day 7: 144 hours (±1 hour) post-dose** • **Day 8: 168 hours (±1 hour) post-dose** **m: Blood samples will be collected and stored for potential PGx analysis (see Section 8.4.10)** **n: Participants will stay in the CTU through Day 7 of Period 3 and will be discharged following end of trial evaluations.** **o: Adverse events will be collected from the time of signed informed consent**
Table 6		Added: "X" on Day 29 for vital signs Added: NEW TABLE with Title, **Schedule of Activities for Part 2, MAD Cohorts 8-10** **For abbreviations, see List of Abbreviations** **a: Blood pressure, heart rate, and temperature will be measured with participant in supine position after resting for ≥3 minutes at Screening, Day -1 check-in, and Day 1 pre-dose within 60 minutes prior to dosing. Blood pressure and heart rate only will be measured at the following times:** • **Day 1: 30 minutes (±10 minutes) post-dose and then at each PK sample timepoint (±30 minutes).** • **Day 2-3: predose and 12 hours (±60 minutes) post-dose.** • **Day 7, 14, 21, and 28: predose (±60 minutes) (blood pressure, heart rate, and temperature should be measured)** • **Day 28: 12 hours (±30 minutes) post-dose** • **Day 29: 24 hours after Day 28 dose (±3 hours)** • **Day 31: 72 hours after Day 28 dose (±3 hours)** • **Day 33: 120 hours after Day 28 dose (±3 hours)** • **Day 36: 168 hours after Day 28 dose (±3 hours) (end-of-trial visit) (blood pressure, heart rate, and temperature should be measured)** **b: Neurologic assessments will consist of assessments for peripheral sensory neuropathy using the Brief Peripheral Neuropathy Screening (BPNS) tool. The assessments should be conducted within**

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		±3 hours of that day's dose when scheduled on a study day after Day 1. **c: Ophthalmologic assessments will consist of assessments of visual acuity using Snellen chart and Rosenbaum pocket chart and color vision using Ishihara plates. The assessments should be conducted within ±3 hours of that day's dose when scheduled on a study day after Day 1.** **d: Screening labs include Hep B, C, & HIV** **e: Females who are not surgically sterilized must be amenorrheic for ≥12 months in absence of any exogenous hormonal treatments and have a Screening follicle stimulating hormone level in the laboratory-defined postmenopausal range.** **f: 12-lead safety ECG for on-site evaluation will be recorded at Screening, Day -1, Days 1-3, 7, 14, 21, 28, 29, and 36. The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with approximately 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 and Day 28 should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Days 2, 3, 7, 14, and 21 should be taken within 60 minutes prior to dosing on that day. Day 29 and Day 36 ECGs should be taken at approximately the same time as the study drug was administered on Day 28. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator or designee** **g: Continuous ECG recordings will be performed for 25 hours, starting one hour pre-dose on Day 1 and Day 28. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: At 3 time points within one hour prior to dosing (eg, -75, -60 and -45 minutes) and at one time point each at approximately 1, 2, 4, 6-, 8-, 12-, and 24-hours post-dose. Participants will be supinely resting for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by safety ECGs then vital signs, except ECG extractions may occur before blood sample collection.** **h: Participants will be admitted to the CTU from Day -1 until Day 36.**

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		i: For Cohort 8-10 a daily dose of MK-7762 or placebo will be administered for 28 days at the same time (+/- 1 hour) of the day either fasted or within 30 min of a standard breakfast meal. **j: Safety laboratory assessments will include complete blood count with hemoglobin, platelets, and white blood cell count with differential, reticulocyte count, chemistry panel, liver function panel, lipid profile, coagulation profile, creatine kinase, and urinalysis. From Day 4 to 27, safety laboratory assessments will be performed on Days 4, 7, 10, 14, 17, 21, and 24. Blood and urine for safety laboratory assessments should be collected within a ±2-hour window from that day's dosing.** **k: Blood samples for PK analysis will be collected at the following times:** • **Day 1: Within 120 minutes before dosing (pre-dose, defined as the 0-hour sample), and at 1, 2, 4, 6, 8, and 12 hours (±5 minutes) postdose** • **Days 2-27: pre-dose within 60 minutes of that day's dose** • **Days 7,14 and 21: 8 hours ± 2 hours post dose** • **Day 28: Within 60 minutes of that day's dose, and at 1, 2, 4, 6, 8, and 12 hours (±5 minutes) postdose** • **Day 29: 24 hours (±30 minutes) after the Day 28 dose** • **Days 30-36 (±1 day) within ±3-hour time window of time of last study drug administration on Day 28** **Additional blood will be collected at the same time points for participants in MAD Cohort 10 for storage for potential future qualitative and/or quantitative analysis of any significant metabolites identified.** **l: Urine will be collected for PK analysis at the following times only from MAD Cohort 9:** • **Day 28: Pre-dose (spot check collected as first morning void) and 0-4, 4-8, 8-12, 12-24-, and 24-48-hours post dose.** **m:Blood samples will be collected and stored for potential PGx analysis (see Section 8.4.10)** **n: Adverse events will be collected from the time of signed informed consent and continuously while in CRU.**
Section 2.3.1		Added: **Additional studies to assess the mutagenic potential of MK-7762 in mammalian cells concluded that the compound did not induce**

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		mutation at the *hprt* locus of Chinese hamster ovary (CHO) cells when tested up to the maximum concentration required by regulatory guidelines. The overall conclusion from the submitted genotoxicity package, and the additional studies, was that MK-7762 was not genotoxic.
New Section 2.3.2 Clinical Development of MK-7762 - Results from Part 1		**TBD09-101 Part 1 was completed on July 18, 2023. A comprehensive interim review of the unblinded clinical safety and PK data for Cohorts 1 through 6 is summarized herein.** **The highest dose tested in Part 1 was 1200 mg following SRT review of cumulative safety and mean PK results from earlier cohorts. The maximal exposure produced by a single 1200 mg dose was predicted to be below the NOAEL levels established in the 28-day GLP toxicology study (AUC_{ss} 1040 µM·h and $C_{max,ss}$ of 66 µM; see Table 7).** **The dose selected to be administered to the FE Cohort (Part 1, Cohort 6) was300 mg based on the Sponsor's review of the available MK-7762 safety and PK data collected from earlier cohorts. The washout period was established as at least 8 days, consistent with 5 half-lives of MK-7762 determined by the SAD cohorts' PK results.**
New Section 2.3.2.1 Phase 1 Safety Results		**Overall, in Part 1, 48 participants were enrolled with 10 receiving placebo and 38 receiving MK-7762. In SAD Cohorts 1-5,40 participants were enrolled with 10 receiving placebo and 30 receiving MK-7762 (6 participants in each cohort received 50 mg, 150 mg, 300 mg, 600 mg, or 1200 mg). In FE Cohort 6,8 participants received a single dose of 300 mg MK-7762 in a randomized crossover design evaluating both fasted and fed states. Across all cohorts, all participants received the assigned treatment and completed the trial.** **In Part 1, MK-7762 was generally well-tolerated with an acceptable safety profile. TEAEs in the Safety Population were observed in 4 participants (11%) who received MK-7762 at any dose and 2 participants (20%) in the placebo group. Of the 4 participants who received MK-7762 and reported any TEAE, 3 had a maximal severity of Grade 1 (mild) and 1 had a maximal severity of Grade 2 (moderate). Of the 4 participants who received MK-7762 and experienced a TEAE, 2 participants (5%) experienced TEAEs considered to be related to study drug. Among the 10 participants who received placebo, 2 (20%) reported any TEAE (1 was Grade 1 and 1 was Grade 2). No TEAEs led to trial discontinuation. There were no Grade 3 (severe) or 4 (potentially life-threatening) TEAEs.**

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		There were no SAEs, AESIs or deaths in Part 1 of the trial. There was no TEAE reported by more than 1 participant receiving MK-7762. Two participants in FE Cohort 6 had a Grade 3 elevated low-density lipoprotein (LDL) cholesterol laboratory abnormality (neither reported as an AE). There were no Grade 4 laboratory abnormalities and no clinically significant trends in the laboratory results (including hematologic parameters), vital signs, or ECGs.
Section 2.3.2.2 Part 1 PK Results New Table 7		**Table 7 summarizes the observed mean PK results from Part 1 of the trial. Review of the time versus concentration profiles for all Part 1 participants suggests that plasma levels notably increased for all participants within several hours after dosing. Dose proportional increases in exposure were observed up through 300 mg after which plateauing of C_{max} occurred and non-linear increases in AUC_{last} were seen. The observed half-life was 20-27 hours across all cohorts, notably longer than the 12-hour half-life projected from animal studies (see Section 2.3.1). Ingestion of a high-fat, high-calorie meal prior to MK-7762 administration resulted in a 56% and 12% increase in mean C_{max} and $AUC_{0\text{-inf}}$, respectively, compared to administration in the fasted state.** **Added Table 7**

<table>
<tr><th>Section Number</th><th>Text in Version 3</th><th>Text in Version 4 (Amendment 3)</th></tr>
<tr><td></td><td></td><td>
Table 7 MK-7762 Mean PK Parameters in µM Following a Single Dose Administration of MK-7762 – Cohorts 1 to 6 (Part 1)
<table>
<tr><th></th><th colspan="8">Cohort</th></tr>
<tr><th></th><th>1 – SAD</th><th>2 – SAD</th><th>3 – SAD</th><th>4 – SAD</th><th>5 – SAD</th><th colspan="3">6 – FE[c]</th></tr>
<tr><th></th><th>50 mg MK-7762</th><th>150 mg MK-7762</th><th>300 mg MK-7762</th><th>600 mg MK-7762</th><th>1200 mg MK-7762</th><th>300 mg MK-7762 (fasted)</th><th>300 mg MK-7762 (fed)</th><th>Geometric Mean Ratio (fed:fasted)</th></tr>
<tr><th>PK Parameter (Unit)</th><th>N = 6</th><th>N = 6</th><th>N = 6</th><th>N = 6</th><th>N = 6</th><th>N = 8</th><th>N = 8</th><th>N = 8</th></tr>
<tr><td>$AUC_{0\text{-}24}$ (h*µM)</td><td>25.80 (19.6)</td><td>71.40 (21.5)</td><td>136.0 (25.4)</td><td>143.0 (29.6)</td><td>128.0 (18.1)</td><td>119.0 (19.9)</td><td>164.0 (17.3)</td><td>1.378</td></tr>
<tr><td>$AUC_{0\text{-}72}$ (h* µM)</td><td>44.10 (30.0)</td><td>166.0 (13.8)</td><td>284.0 (28.4)</td><td>399.0 (27.2)</td><td>441.0 (20.2)</td><td>293.0 (23.2)</td><td>339.0 (21.2)</td><td>1.157</td></tr>
<tr><td>AUC_{last} (h* µM)</td><td>43.90 (30.8)</td><td>184.0 (21.2)</td><td>309.0 (34.0)</td><td>473.0 (30.5)</td><td>676.0 (41.0)</td><td>341.0 (33.5)</td><td>394.0 (26.8)</td><td>1.155</td></tr>
<tr><td>$AUC_{0\text{-}inf}$ (h* µM)</td><td>50.50 (29.8)</td><td>215.0 (11.8)[a]</td><td>326.0 (32.3)</td><td>490.0 (30.0)</td><td>486.0 (11.3)[b]</td><td>362.0 (30.2)</td><td>406.0 (27.0)</td><td>1.121</td></tr>
<tr><td>C_{max} (µM)</td><td>1.440 (15.5)</td><td>3.590 (22.1)</td><td>7.310 (30.0)</td><td>7.240 (27.2)</td><td>7.770 (19.1)</td><td>6.190 (20.0)</td><td>9.680 (17.0)</td><td>1.564</td></tr>
<tr><td>C_{24} (µM)</td><td>0.812 (30.8)</td><td>3.140 (13.1)</td><td>5.470 (32.0)</td><td>7.060 (24.6)</td><td>6.650 (18.3)</td><td>5.580 (18.9)</td><td>6.590 (21.6)</td><td>1.181</td></tr>
<tr><td>t_{max} (hours)</td><td>4.50 (3.00 – 8.00)</td><td>10.00 (5.00 – 24.00)</td><td>10.02 (6.00 – 24.00)</td><td>24.00 (8.00 – 36.00)</td><td>30.01 (8.01 – 72.1)</td><td>18.00 (6.00 – 24.00)</td><td>7.00 (5.00 – 24.00)</td><td>-11[d]</td></tr>
<tr><td>$t_{1/2}$ (hours)</td><td>20.3 (15.6)</td><td>27.4 (9.4)[a]</td><td>21.2 (19.7)</td><td>21.7 (13.9)</td><td>22.2 (14.3)[b]</td><td>25.3 (20.0)</td><td>24.8 (22.9)</td><td>NA</td></tr>
</table>
AUC=Area under the curve; C_{max}=Maximum concentration, NA=Not applicable
Note: All values were presented as geometric mean (geometric coefficient of variation (CV)(%) except for t_{max} which is presented as median (min-max)
[a] N = 5 due to AUC Extrapolation >20% (i.e., terminal phase unreliable)
[b] N = 3 due to AUC Extrapolation >20% (i.e., terminal phase unreliable)
[c] Food effect following a high fat meal.
[d] Absolute change in the T_{max} of fed vs fasted
</td></tr>
<tr><td>Section 2.5</td><td>The potency of MK-7762 against Mtb H37Rv was determined as 0.93 µM and the MIC_{90} was determined for a panel of 50 clinical isolate strains as 0.78 µM. Given the protein binding in human plasma is approximately 30%, the estimated efficacy target in total plasma is 1.1 µM. Therefore, the following exposure thresholds are identified:</td><td>The minimum acceptable PK threshold for MK-7762 is considered to be one that matches the efficacious concentrations of linezolid, another oxazolidinone with the same mechanism of action. The potency of MK-7762 against Mtb H37Rv was determined as 0.93 µM and the MIC_{90} (i.e., the concentration required for complete growth inhibition of 90% (MIC_{90}) was determined for a panel of 50 clinical Mtb isolate strains) as 0.78 µM. Given that protein binding in human plasma is approximately 30%, the estimated linezolid-equivalent efficacy target in total plasma is 1.1 µM. Therefore, the following efficacy exposure thresholds based on MIC_{90} were identified:

Added:
To further understand the predicted efficacy of MK-7762, a recognized mouse-to-human translational platform was used (Ernest et al, 2023). This platform, previously verified with clinical early bactericidal activity (EBA) data from other anti-TB drugs, utilizes preclinical in vivo mice pharmacokinetic-pharmacodynamic (PKPD) data in combination with a model-centric translational pharmacology method to predict the clinical bactericidal activity of MK-7762.</td></tr>
</table>

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		This translational platform was developed using an exhaustive preclinical and clinical data repository on PK, PD, and initial bacterial growth for a collection of ten anti-TB drugs, including linezolid (Ernest et al, 2023). These drugs, which were instrumental in the creation and validation of the platform, include a bacteriostatic antibiotic (ethambutol), five bactericidal antibiotics (isoniazid, delamanid, pretomanid, linezolid, and moxifloxacin), as well as four sterilizing antibiotics (rifampin, rifapentine, pyrazinamide, and bedaquiline). The translational model has been shown to accurately predict clinical efficacy as measured by the observed daily decreases of CFU in the first 2 days of treatment and between day 2 and day 14 in the clinical EBA trials previously conducted for these ten drugs. **For MK-7762, mouse PK and PKPD models were established to identify an exposure-response relationship and used to make predictive translations of bactericidal activity of MK-7762 administered as monotherapy and in combination with bedaquiline and pretomanid in a Phase 2a EBA study. The estimated effective trough MK-7762 concentrations predicted to achieve 50% (EC_{50}), 80% (EC_{80}), and 90% (EC_{90}) of maximum response when administered alone (monotherapy) were 11.15 µM, 23.32 µM, and 35.87 µM (data on file). The estimated effective trough MK-7762 concentrations predicted to achieve 50% (EC_{50}), 80% (EC_{80}), and 90% (EC_{90}) of maximum response when administered in combination with bedaquiline and pretomanid were 4.08 µM, 16.36 µM, and 36.77 µM, respectively (data on file).** **The human efficacious concentrations predicted from the in vitro MIC_{90} were used to select the range of doses to be evaluated in Part 1 (SAD/FE). Both the in vitro MIC_{90} and the in vivo translational PKPD model were used to select the doses to be evaluated in Part 2 (MAD/FE) along with the Part 1 safety and PK data (see Section 2.3.2).**
Section 2.6.1 Part 1 (SAD/FE)	Section title: Section 2.6.1 Part 1 (SAD)	Section title: Section 2.6.1 Part 1 (SAD/**FE**)
Section 2.6.2 Part 2 (MAD)	Section title: Section 2.6.2 Part 2 (MAD) The goal of Part 2 is to characterize the safety of multiple doses of MK-7762 and identify a maximal tolerated dose. The doses tested in the MAD should ideally generate steady-	Section title: Section 2.6.2 Part 2 ~~(MAD)~~ **2.6.2.1 Food Effect Cohort 7** **The goal of FE Cohort 7 is to describe the variability in exposure caused by the two different meal types to further investigate the**

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	state exposures at and above the efficacy target following multiple dose administration (minimal [trough] concentrations at steady-state [$C_{min,ss}$] □ 1.1 □M and area under the concentration curve at steady-state [AUC_{ss}]/MIC □80) that are well-tolerated. Three dose levels are planned to be tested in the 28-day MAD cohorts in Part 2. Dose selections will be made by the Sponsor and will be informed by available MK-7762 PK data collected from earlier SAD and MAD cohorts. The highest possible dose to be tested in Part 2 may be modified following review of evolving safety data (number, severity, and frequency of AEs) and available PK data from earlier cohorts in Part 1. The steady state exposure target will be below the NOAEL levels (AUC_{ss} 1040 µM·h and $C_{max,ss}$ of 66 µM). The highest dose in Part 2 will not exceed the highest dose in Part 1. The proposed duration for Cohorts 1-3 is 28 days of daily dosing. In short term studies (21 to 28 days) of linezolid and other oxazolidinones (tedizolid and delpazolid), hematologic changes were observed in some participants within 14-28 days (Gerson et al, 2002; Lodise et al, 2016; Choi et al, 2018). While steady-state plasma levels of MK-7762 are expected to be reached in less than a week based on the estimated $t_{½}$ of 12 hours, the 28-day dosing period of MK-7762 in the multiple ascending dose part of this trial is designed to evaluate the potential hematologic effects of MK-7762 based on this known class effect.	**increase in mean exposure observed after administration of 300 mg of MK-7762 in FE Cohort 6 with a high-fat, high-calorie meal (see Table 8). A dose of 600 mg was selected for evaluation in FE Cohort 7 based on the overall safety analysis in Part 1, in which single doses were administered up to 1200 mg in the fasted state and 300 mg in the fed state (high-fat meal) and where a non-linear increase in exposure was observed above 300 mg in Part 1. MAD participants will be randomized to receive MK-7762 or placebo in the fasted or fed state after a standard breakfast, and the safety and PK results of FE Cohort 7 will inform selection of the MK-7762 dose to be evaluated in MAD Cohort 10.** **2.6.2.1 MAD Cohorts 8-10** **The goal of the MAD portion of Part 2 is to characterize the safety of multiple dose levels of MK-7762 administered once daily for 28 days that generate steady-state exposures at and/or above the efficacy targets (see Section 2.5). Three dose levels are planned to be tested in the 28-day MAD cohorts in Part 2: MAD Cohort 8 will evaluate MK-7762 100 mg once daily (QD); MAD Cohort 9 will evaluate MK-7762 300 mg QD; and the anticipated MK-7762 QD dose to be evaluated in MAD Cohort 10 is 500 mg, which may be modified through a protocol amendment after review of PK and safety data from FE Cohort 7 and MAD Cohorts 8 and 9. The dose in MAD Cohort 10 will not exceed 600 mg QD. These doses are selected based on the range of doses evaluated in Part 1 and the safety profile associated with the observed exposures. In addition, these doses are projected to result in efficacious concentrations in patients.** **In Part 1, healthy participants received single doses of MK-7762 50 mg – 1200 mg administered in the fasted state and 300 mg in the fed state after a high fat meal. The detailed PK results are included in Section 2.3.2.2. Across the dose range and observed exposures, MK-7762 was generally well-tolerated and had an acceptable safety profile (Section 2.3.2.1). The greatest observed $C_{max,ss}$ observed in Part 1 was 9.7 µM with 300 mg (fed) in FE Cohort 6 and the greatest observed AUC_{ss} was 676 µM*hr with 1200 mg (fasted) in SAD Cohort 5.** **A population PK model was developed to describe the concentration time profiles from Part 1 of the trial (SAD+FE). This model was used in a simulation mode to predict steady state exposures following various multiple dose scenarios (Population PK Report). The**

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		predicted mean (95% CI) steady state exposures at the planned doses for MAD Cohorts 8-10 are shown in Table 9.

Table 9 Predicted Multi-Dose Steady State Exposures

PK Parameter	Fasted			Fed (high fat meal)		
	100 mg QD	300 mg QD	500 mg QD	100 mg QD	300 mg QD	500 mg QD
$C_{max,ss}$ (µM)	5.97 (4.16, 8.80)	17.2 (11.3, 30.2)	21.9 (13.8, 43.0)	7.26 (5.06, 10.7)	21.0 (13.7, 36.7)	26.7 (16.7, 52.3)
$C_{min,ss}$ (µM)	4.21 (2.84, 6.47)	9.98 (6.46, 16.6)	14.9 (8.68, 28.3)	5.13 (3.45, 7.87)	12.2 (7.86, 20.1)	18.1 (10.6, 34.4)
AUC_{ss} (µM*hr)	121 (84.9, 176)	316 (213, 494)	444 (283, 790)	147 (103, 215)	385 (259, 601)	540 (345, 962)

Source: Population PK Report

The low dose in the first MAD cohort, 100 mg QD, is predicted to have a mean $C_{max,ss}$ of 5.97 µM in the fasted state and 7.26 µM in the fed state, which is below the highest exposure observed in Part 1 (9.7 µM). The predicted mean $C_{max,ss}$ for all planned doses in Part 2 are less than the MPS inhibition threshold (50 µM) and below the NOEL/NOAEL observed in the safety pharmacology and 28-day pivotal GLP studies. The predicted mean AUCss for all 3 planned doses are less than the highest exposure observed in Part 1 (676 h*µM) and are also below the NOAEL observed in 28-day pivotal GLP studies (1040 h*µM).

The proposed duration for MAD Cohorts 8-10 is 28 days of daily dosing. In short term studies (21 to28 days) of linezolid and other oxazolidinones (tedizolid and delpazolid), hematologic changes were observed in some participants within 14-28 days (Gerson et al, 2002; Lodise et al, 2016; Choi et al, 2018). While steady-state plasma levels of MK-7762 are expected to be reached in 7 days based on the population PK model predictions, the 28-day dosing period of MK-7762 in the multiple ascending dose part of this trial is designed to evaluate the potential hematologic effects of MK-7762 based on this known class effect.

Lastly, with regard to safety, all participants in Part 2 will be admitted to the CTU for close monitoring during dosing and until 1 week post dosing (Section 1.1.3.3). Enrollment of the MAD cohorts will be sequential and safety and PK data from each cohort will be reviewed prior to enrollment of higher doses (Section 4.4).

Additionally, the planned doses provide a range of concentrations across which MK-7762 may be efficacious as predicted by various methodologies (Section 2.5). All3 doses of MK-7762 are projected to produce mean minimal (trough) concentrations at steady-state

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		($C_{min,ss}$) which are more than 2-fold greater than the efficacy exposure threshold of 1.1 μM based on MIC_{90} and also result in a daily exposure more than 80 times the MIC90 (area under the concentration curve at steady-state AUC_{ss}/MIC_{90} ratios). The projected $C_{min,ss}$ for MK-7762 100 mg (4.21 μM and 5.13 μM in the fasted and fed states, respectively) and for MK-7762 300 mg (9.98 μM and 12.2 μM in the fasted and fed states, respectively) are in the range of the predicted EC_{50} (4.08 uM) using the in vivo translational PKPD model for MK-7762 when administered with bedaquiline and pretomanid. Similarly, the projected $C_{min,ss}$ for MK-7762 500 mg (14.9 μM and 18.1 μM in the fasted and fed states, respectively) is in the range of the EC_{80} (16.36 μM). **In summary, the doses selected for the Part 2 MAD cohorts are expected to be safe and well tolerated by participants and below the NOAEL observed in the 28-day pivotal GLP studies. The low dose is predicted to result in exposures below the highest exposure observed in Part 1, and, during dose escalations, participants will be confined to clinic and closely monitored for safety during the dose escalations. Additionally, the planned doses will provide a range of exposures across which MK-7762 may be efficacious as predicted by various methodologies, which will help to inform dose selection in future studies of bactericidal effects and efficacy of MK-7762.**
Section 4 Trial Design	The trial will be conducted in two parts: Part 1 – a SAD and FE part (N=48) and Part 2 – a MAD part (N=48). Because this trial is aimed at characterizing the safety, tolerability, and PK of MK-7762, it is designed to be descriptive and is not based on formal hypothesis testing. Therefore, this trial is not powered to detect any pre-specified differences in potential safety or PK data between treatment groups. A total of approximately 96 participants will be randomized (48 in Part 1 and 48 in Part 2), and a total of approximately 74 participants will be exposed to MK-7762 (38 from Part 1 and 36 from Part 2). The trial has a double-blind design in which participants and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at	The trial will be conducted in two parts: **Part 1 –5 SAD cohorts (double-blind, placebo-controlled) (N=40) and a FE cohort (open-label) enrolling 8 participants and Part 2 –3 MAD cohorts (double-blind, placebo-controlled) (N=60) and a FE cohort (open-label) enrolling 8 participants**. Because this trial is aimed at characterizing the safety, tolerability, and PK of MK-7762, it is designed to be descriptive and is not based on formal hypothesis testing. Therefore, this trial is not powered to detect any pre-specified differences in potential safety or PK data between treatment groups. A total of **approximately 117** participants will be randomized (48 in Part 1 and **69** in Part 2), and a total of approximately **95** participants will be exposed to MK-7762 (38 from Part 1 and **57** from Part 2). The trial has a double-blind design in which **all** participants **in SAD Cohorts 1-5 and MAD Cohorts 8-10** and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at the trial site who will prepare oral doses of MK-7762

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	the trial site who will prepare oral doses of MK-7762 and placebo appropriately masked for site personnel who are authorized to administer treatment. All participants will undergo a Screening period lasting up to 20 days (Day -21 to -2) followed by a confinement period in the CTU of varying length according to their cohort. In Part 1, the maximum duration of participation, including the Screening period, will be approximately up to 30 days for participants in Cohorts 1 through 5, approximately 38 days for participants in Cohort 6 (to be confirmed once washout period of at least 5 half-lives is determined). In Part 2, the maximum duration of participation, including the Screening period, will be approximately up to 54 days for participants in Cohorts 1-3. The duration of cohorts may be adjusted (increased or decreased) based on emerging PK data collected during the study.	and placebo appropriately masked for site personnel who are authorized to administer treatment. All ~~participants will undergo a Screening period lasting up~~**doses of MK-7762 administered** to ~~20 days (Day -21 to -2) followed by a confinement period in the CTU of varying length according to their cohort. In Part 1, the maximum duration of participation, including the Screening period, will be approximately up to 30 days for~~**all** participants in ~~Cohorts 1 through 5, approximately 38 days for participants in~~**FE Cohort 6** ~~(to be confirmed once washout period of at least 5 half-lives is determined). In Part 2, the maximum duration of participation, including the Screening period, will be approximately up to 54 days for participants in Cohorts 1-3. The duration of cohorts may be adjusted (increased or decreased) based on emerging PK data collected during the study.~~ **and FE Cohort 7 will be open-label.**

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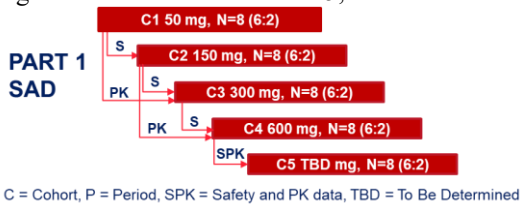
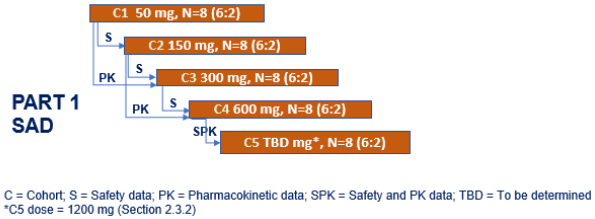
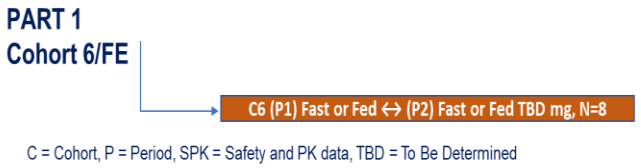
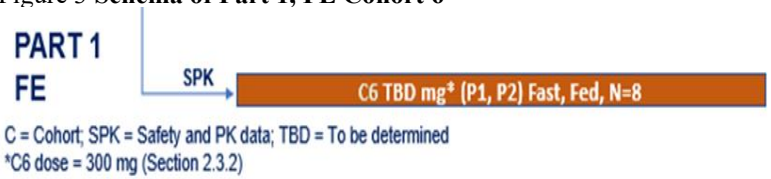
Section 4.1 Part 1- SAD and Food Effect (SAD/FE)		Added: **Gates MRI-TBD09-101, Amendment 3 (Version 4.0)** **Part 1 of this trial has been completed. See Section 2.3.2 for results from Part 1.** • **The dose of MK-7762 for SAD Cohort 5 was 1200 mg.** • **The dose of MK-7762 for FE Cohort 6 was 300 mg.** • **The washout period between doses in FE Cohort 6 was 8 days.**
	In Part 1 of the trial (SAD/FE), five sequential cohorts will be enrolled to evaluate up to five escalating single doses of MK-7762; eight participants in each cohort will be randomized (3:1) to receive MK-7762 or placebo. Figure 2 Schema of Cohorts 1-5, Part 1  	In Part 1 of the trial (SAD/FE), five sequential cohorts will be enrolled to evaluate **5** escalating single doses of MK-7762; eight participants in each cohort will be randomized (3:1) to receive MK-7762 or placebo. Figure 2 Schema of **Part 1**, Cohorts 1-5~~, Part 1~~ 
	Table 7	• Table 10 • Added: [d] **Cohort 5 dosing will occur after review of safety data through at least Day 4 post dose administration for all participants in Cohort 4. Aggregated 48-hour PK data (mean) from Cohort 4 will be available for review.** [e] **TBD = 1200 mg (see Section 2.3.2)**
	Figure 3 Schema of Cohort 6/FE, Part 1  	Figure 3 **Schema of Part 1, FE Cohort 6** 
	Figure 8 = n =2, n=6	Figure 11 = n =3, n=5; added: [b] **TBD = 300 mg (see Section 2.3.2)**

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Section 4.1.1 Screening (Day -21 to -2)	Part 1 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 3 for Cohorts 1-5 or Table 4 for Cohort 6 in Section 1.3. There is no stipulated order or sequence of the conduct of Screening assessments. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will apply during the Screening period.	Deleted: ~~Part 1 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 3 for Cohorts 1-5 or Table 4 for Cohort 6 in Section 1.3. There is no stipulated order or sequence of the conduct of Screening assessments. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will apply during the Screening period.~~ Added: **See Section 1.1.3.1 for details of the screening and confinement periods for all Part 1 participants (SAD Cohorts 1-5 and FE Cohort 6).**
Section 4.1.2 Confinement Period	All Part 1 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 3 for Cohorts 1-5 or Table 4 for Cohort 6 in Section 1.3. Randomization will occur prior to dosing on Day 1 for all cohorts. Participants in Cohorts 1-5 must have fasted for at least 8 hours prior to dosing. Participants in Cohorts 1-5 will be admitted from Day -1 until Day 7 (±1 day; 8 days total) for the single dosing period. Participants in Cohort 6 (FE Cohort) will be admitted from Day -1 until Day 7 (±1 day) of the second dosing period. The exact duration of the confinement will be determined by the time required for an adequate washout period of at least five half-lives to be determined by PK results from the SAD cohorts.	Deleted: ~~All Part 1 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 3 for Cohorts 1-5 or Table 4 for Cohort 6 in Section 1.3. Randomization will occur prior to dosing on Day 1 for all cohorts. Participants in Cohorts 1-5 must have fasted for at least 8 hours prior to dosing.~~ ~~Participants in Cohorts 1-5 will be admitted from Day -1 until Day 7 (±1 day; 8 days total) for the single dosing period. Participants in Cohort 6 (FE Cohort) will be admitted from Day -1 until Day 7 (±1 day) of the second dosing period. The exact duration of the confinement will be determined by the time required for an adequate washout period of at least five half-lives to be determined by PK results from the SAD cohorts.~~
Section 4.1.3 Fasted Cohorts (Cohorts 1-5)	Dose administration will occur after an 8-hour overnight fast on the morning of Day 1. Fasting will continue until 4 hours post-dose at which time a standardized meal will be provided. Clinical and safety laboratory assessments will be performed throughout the confinement period as per Table 3 for Cohorts 1-5.	Deleted: ~~Dose administration will occur after an 8-hour overnight fast on the morning of Day 1. Fasting will continue until 4 hours post-dose at which time a standardized meal will be provided. Clinical and safety laboratory assessments will be performed throughout the confinement period as per Table 3 for Cohorts 1-5.~~
Section 4.1.4 Food Effect	Participants will receive open-label MK-7762. The first two participants in this cohort will be termed sentinel participants and will receive MK-7762 in a fed state and then, following a washout period of at least five half-lives, a second dose of MK-7762 will be administered in the fasted state. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing	Deleted: ~~Participants will receive open-label MK-7762. The first two participants in this cohort will be termed sentinel participants and will receive MK-7762 in a fed state and then, following a washout period of at least five half-lives, a second dose of MK-7762 will be administered in the fasted state. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing period. If recommended by the SRT and approved by the Sponsor, the~~

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	period. If recommended by the SRT and approved by the Sponsor, the remaining six participants in Cohort 6 will receive doses of MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined. Participants administered MK-7762 in the fasted state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants administered MK-7762 in the fed state will be provided the standard US FDA high fat breakfast, which should be consumed within 30 minutes or less, with MK-7762 administration occurring approximately 30 minutes after the start of the meal. In both the fed and fasted settings, fasting will resume for 4 hours post-dose, at which time, a standardized meal will be provided.	~~remaining six participants in Cohort 6 will receive doses of MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.~~ ~~Participants administered MK-7762 in the fasted state will be dosed after an 8-hour overnight fast on the morning of Day 1. Participants administered MK-7762 in the fed state will be provided the standard US FDA high fat breakfast, which should be consumed within 30 minutes or less, with MK-7762 administration occurring approximately 30 minutes after the start of the meal. In both the fed and fasted settings, fasting will resume for 4 hours post-dose, at which time, a standardized meal will be provided.~~
Section 4.2 Part 2 - Food Effect-MAD (FE/MAD)	Screening and enrollment of participants in Part 2 of the trial will not commence until after the planned interim review of data from Part 1 and any available additional nonclinical data, and Sponsor agreement to continue the trial after regulatory review and comment (see Section 1.1.3.2). In Part 2 of the trial (MAD), participants will be enrolled into three sequential cohorts to evaluate escalating once daily doses of MK-7762 or placebo for 28 days. Each of the three MAD cohorts will have sixteen participants randomized 3:1 to receive MK-7762 or placebo. See Figure 4 and Table 9. If more than two participants from a MAD cohort are withdrawn from the trial before the Day 29 visit assessments are completed, additional participants will be enrolled with blinded treatment assignment matching that of the withdrawn participants. No replacements are required if two or fewer participants are withdrawn before their Day 29 visits. An additional MAD cohort may be considered for subsequent enrolment after protocol amendment to evaluate	Screening and enrollment of participants in Part 2 of the trial will not commence until after the planned interim review of data from Part 1 and any available additional nonclinical data, and Sponsor agreement to continue the trial after regulatory review and **approval** (see Section 1.1.3.2). Part 2 of the trial will **consist of a food effect cohort and** three sequential cohorts to evaluate escalating once daily doses of MK-7762 or placebo for 28 days. **FE Cohort 7 will be an open-label, three-period evaluation of 600 mg of MK-7762 in at least 9 participants who will complete each of the three dosing periods. See Figure 4 and Table 12. Within each MAD cohort, half of the participants will be dosed in the fasted state and half of the participants will be dosed after a standard breakfast meal.** Each of the three MAD cohorts will have **approximately 20** participants randomized 4:4:1:1 to receive MK-7762 **in fasted state, MK-7762 after standard breakfast meal, placebo in fasted state, or placebo after standard breakfast meal. See Figure 5 and Table 10.** If more than two participants from a MAD cohort are withdrawn from the trial before the Day 29 visit assessments are completed, additional participants will be enrolled with blinded treatment assignment matching that of the withdrawn participants. **No replacement**

<table>
<tr><th>Section Number</th><th>Text in Version 3</th><th>Text in Version 4 (Amendment 3)</th></tr>
<tr><td></td><td>once daily doses of MK-7762 or placebo for 91 days based on findings from the planned 4-month sub-chronic toxicology studies in rats and dogs.

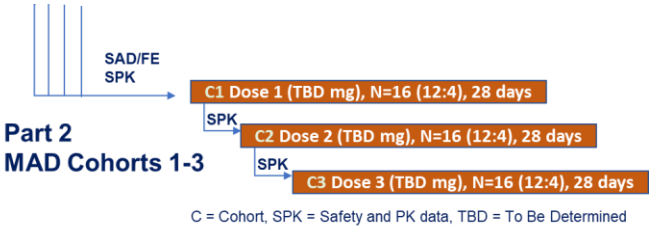
Figure 4 Schema of MAD Cohorts 1-3, Part 2
 

Table 9 Multiple Ascending Dose (Part 2) – Planned Cohorts
<table>
<tr><td></td><td colspan="3">Dosing Period Duration</td></tr>
<tr><td></td><td colspan="3">28 Days QD</td></tr>
<tr><td>Cohort 1</td><td>Low dose TBD</td><td></td><td></td></tr>
<tr><td>Cohort 2</td><td></td><td>Medium dose TBD</td><td></td></tr>
<tr><td>Cohort 3</td><td></td><td></td><td>High dose TBD</td></tr>
<tr><td colspan="4">QD = Once Daily, TBD = To Be Determined</td></tr>
</table></td><td>participants are required if two or fewer participants are withdrawn from a cohort before their Day 29 visit.

An additional MAD cohort may be considered for subsequent enrolment after protocol amendment to evaluate once daily doses of MK-7762 or placebo for up to 91 days based on findings from the 28-day MAD cohorts and the ongoing 4-month sub-chronic toxicology studies in rats and dogs.

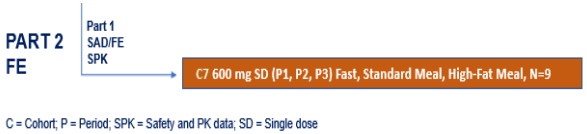
Figure 4 Schema of Part 2 FE, Cohort 7
 

Table 12 Single Ascending Dose (Part 1) – Planned Dose Cohort 6 (Food Effect Cohort)
<table>
<tr><th>Cohort</th><th>Sequence</th><th>Period 1</th><th>Period 2</th><th>Period 3</th></tr>
<tr><td rowspan="3">7 (FE)</td><td>1</td><td>600 mg fasted</td><td>600 mg fed-standard meal</td><td>600 mg fed-high-fat meal</td></tr>
<tr><td>2</td><td>600 mg fed-standard meal</td><td>600 mg fed-high-fat meal</td><td>600 mg fasted</td></tr>
<tr><td>3</td><td>600 mg fed-high-fat meal</td><td>600 mg fasted</td><td>600 mg fed-standard meal</td></tr>
</table></td></tr>
<tr><td>Section 4.2.1 Screening (Day -21 to -2)</td><td>Part 2 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 5 in Section 1.3. There is no stipulated order or sequence of the conduct of Screening assessments.</td><td>Deleted: ~~Part 2 participants will undergo a Screening period of up to 20 days from Day -21 to Day -2 to ensure participant eligibility. Eligibility assessments will be performed per Table 5 in Section 1.3. There is no stipulated order or sequence of the conduct of Screening assessments.~~

•</td></tr>
<tr><td>Section 4.2.2 Confinement Period</td><td>All Part 2 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 5 in Section 1.3. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will apply</td><td>Deleted: ~~All Part 2 participants will be admitted to the CTU on Day -1 with confirmation of eligibility and baseline assessments performed as per Table 5 in Section 1.3. Inclusion and exclusion criteria (Section 5.1 and Section 5.2) will apply during the Screening period. Randomization will occur prior to dosing on Day 1 for all cohorts.~~</td></tr>
</table>

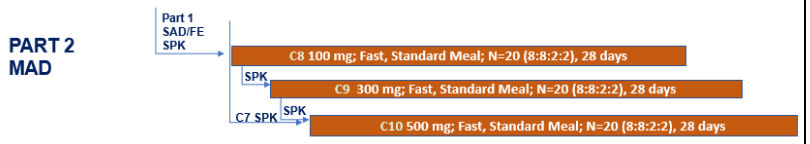
<table>
<tr><th>Section Number</th><th>Text in Version 3</th><th>Text in Version 4 (Amendment 3)</th></tr>
<tr><td></td><td>during the Screening period. Randomization will occur prior to dosing on Day 1 for all cohorts.

In Part 2, the dosing of study drug in relation to a meal will be dependent on review of PK data collected from participants in the FE Cohort (Cohort 6) in Part 1 of the trial. Additional information regarding how FE Cohort data will be used to decide how study drug will be dosed in the MAD component will be discussed in the SAP.

Participants in MAD Cohorts 1-3 will be admitted on Day -1 until Day 33 (±2 days; 34 days total).

Clinical and safety laboratory assessments will be performed throughout the confinement period as per Table 5 for MAD Cohorts 1-3.</td><td><s>In Part 2, the dosing of study drug in relation to a meal will be dependent on review of PK data collected from participants in the FE Cohort (Cohort 6) in Part 1 of the trial. Additional information regarding how FE Cohort data will be used to decide how study drug will be dosed in the MAD component will be discussed in the SAP.</s>

<s>Participants in MAD Cohorts 1-3 will be admitted on Day -1 until Day 33 (±2 days; 34 days total).</s>

<s>Clinical and safety laboratory assessments will be performed throughout the confinement period as per Table 5 for MAD Cohorts 1-3.</s>
New Figure 5 Schema of MAD Cohorts 8-10, Part 2
 

C = Cohort; SPK = Safety and PK data
*In C8-10, participants randomized 8:8:2:2 to receive MK-7762 in fasted state, MK-7762 after standard breakfast meal, placebo in fasted state, or placebo aft standard breakfast meal

New Table 13 – Multiple Ascending Dose (Part 2) – Planned Cohorts

Table 13 Multiple Ascending Dose (Part 2) – Planned Cohorts
<table>
<tr><th>Cohort</th><th>n</th><th colspan="3">Dose Levels</th></tr>
<tr><td rowspan="4">8</td><td>8</td><td>100 mg (fast)</td><td></td><td></td></tr>
<tr><td>8</td><td>100 mg (standard meal)</td><td></td><td></td></tr>
<tr><td>2</td><td>PBO (fast)</td><td></td><td></td></tr>
<tr><td>2</td><td>PBO (standard meal)</td><td></td><td></td></tr>
<tr><td rowspan="4">9[a]</td><td>8</td><td></td><td>300 mg (fast)</td><td></td></tr>
<tr><td>8</td><td></td><td>300 mg (standard meal)</td><td></td></tr>
<tr><td>2</td><td></td><td>PBO (fast)</td><td></td></tr>
<tr><td>2</td><td></td><td>PBO (standard meal)</td><td></td></tr>
<tr><td rowspan="4">10[b]</td><td>8</td><td></td><td></td><td>500 mg (fast)</td></tr>
<tr><td>8</td><td></td><td></td><td>500 mg (standard meal)</td></tr>
<tr><td>2</td><td></td><td></td><td>PBO (fast)</td></tr>
<tr><td>2</td><td></td><td></td><td>PBO (standard meal)</td></tr>
</table>
PBO = placebo
All suggested doses may be adjusted based on evaluation of safety, tolerability, or PK data observed in previous participants.
[a] Cohort 9 dosing will occur after review of all safety data collected through Day 28 and PK data through Day 14 in Cohort 8 are available for review.
[b] Cohort 10 dosing will occur after review of all safety data collected through Day 28 and PK data through Day 14 in Cohort 9 are available for review.</td></tr>
<tr><td>Section 4.2.1 Screening and Confinement Period</td><td>Section 4.3 Drug Administration

MK-7762 will be supplied as 10 mg, 100 mg, and 300 mg capsules and matching placebo for oral administration. The planned doses for each cohort in Part 1 are listed in Table 2.</td><td>Section 4.2.1 Screening and Confinement Period See Section 1.1.3.3 for details of the screening, confinement, and post-discharge follow-up periods for all Part 2 participants (Cohort 7 FE and MAD Cohorts 8-10).</td></tr>
</table>

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
	All doses of MK-7762 and placebo will be administered with 240 mL (8 ounces) of water. The doses of SAD Cohorts 2-4 may be modified based on accumulating safety, tolerability, and PK data. Additional cohorts may be enrolled after protocol amendment to repeat a dose level or to study another dose level if the Sponsor determines that it is necessary based on emerging safety and PK data from previous cohorts. The dose for Cohort 6 in Part 1 (FE Cohort) will be selected after review of PK and safety data from previous SAD cohorts. The MK-7762 doses for daily administration in MAD Cohorts 1-3 will be selected after a planned interim review of data from Part 1 and additional nonclinical data and Sponsor agreement to continue the study after regulatory review and comment (see Section 1.1.3.2)	
New Section 4.3 Trial Drug Administration		**See Section 1.1.4 and Table 2** for details regarding study drug administration. See the Schedule of Activities in Section 1.3 and Section 8 for details of assessments to be conducted and the schedules.
Section 4.5 Dose Escalation Decisions and Safety Review Team	Details of the SRT will be contained in a charter that will describe the SRT review of blinded safety data and the deliberation processes (including the format of data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment and when PK data are available, only aggregated mean PK data will be provided. The results of the interim review are intended for regulatory submission and comment prior to initiation of Part 2 of the trial.	Details of the SRT will be contained in a charter that will describe the SRT review of blinded safety data and the deliberation processes (including the format of data to be reviewed and the cadence of meetings). SRT members will be blinded to treatment assignment **(for SAD Cohorts 1-5 and MAD Cohorts 8-10),** and when PK data are available, only aggregated mean PK data will be provided. Added: **In Cohort 6, two sentinel participants in Cohort 6 will be dosed in the fed state first followed by the second dose in the fasted state after washout. The SRT will review safety data up to Day 4 and PK data up to Day 2 for the two sentinel participants from the fed state dosing period. If recommended by the SRT and approved by the Sponsor, the two sentinel participants will be dosed with MK-7762 in the fed state after the washout period previously determined and the remaining 6 participants in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.** The results of the interim review are intended for regulatory submission and comment **and agreement** prior to ~~initiation of~~ Part 2 of the trial.

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
	After regulatory authority agreement and Sponsor approval to proceed to the MAD phase of the trial, MAD cohort 1 may be initiated with MK-7762 (low dose) to be administered once daily for 28 days (either with or without food depending on results of the FE evaluation results of SAD Cohort 6). The SRT will convene after all participants in MAD Cohort 1 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 2 (medium dose of MK-7762 administered once daily for 28 days) if no pausing rule is present. The SRT will convene after all participants in MAD Cohort 2 have completed at least 14 days of dosing and all safety data collected through Day 14 and PK data through Day 7 are available for review. The SRT may recommend dose escalation to MAD Cohort 3 (high dose of MK-7762 administered once daily for 28 days) if no pausing rule is present.	After regulatory authority agreement and Sponsor approval to proceed to **Part 2 of the trial, there will be approximately concurrent initiation of FE Cohort 7 and MAD Cohort** 8. The SRT will convene after all participants in MAD **Cohorts 8** have completed **28** days of dosing and all safety data collected through **Day 28** and PK data through **Day 14** are available for review. **If no pausing rule is present, the** SRT may recommend dose escalation to MAD Cohort~~(medium dose of MK-7762 administered once daily for 28 days) if no pausing rule is present.~~ **Data from FE Cohort 7 is not required for the SRT's dose escalation recommendation from MAD Cohort 8 to MAD Cohort 9. The SRT** will convene after all participants in MAD **Cohort 9** have completed **28** days of dosing and all safety data collected through **Day 28** and PK data through **Day 14** are available for review. ~~The SRT may recommend dose escalation to MAD Cohort 3 (high dose of MK-7762 administered once daily for 28 days) if~~ no pausing rule is present, t**he SRT may recommend dose escalation to MAD Cohort 10. The anticipated MK-7762 dose in MAD Cohort 10 may be modified though a protocol amendment after review of PK and safety data from FE Cohort 7 and MAD Cohorts 8 and 9.**
Section 4.5.1 Trial Pausing rules	Events necessitating a pause in enrollment and/or participant dosing in the study Part 1 (SAD and FE) or Part 2 (MAD), and, in turn, requiring an ad hoc IDMC review, include:	Events necessitating a pause in enrollment and/or participant dosing in the study Part 1 (SAD and FE) or Part 2 (MAD **and FE**), and, in turn, requiring an ad hoc IDMC review, include: Added: **Note: A qualifying AE for meeting a trial pausing rule can be either a clinical AE or a safety laboratory abnormality.**
Section 4.5.3 Rules for Discontinuation of Treatment of Individual Participants in Part 2 MAD Cohorts	Study drug will be discontinued for participants that experience one or more of the following safety laboratory abnormalities at any time from Day 1 through the end of study participation (MAD cohorts): • Hemoglobin < 9.0 g/dL for males and < 8.5 g/dL for females • Total WBC count < 1,500 cells/mm^3 • ANC < 600 cells/mm^3 • Platelet count < 50,000 cells/mm^3 Participants with a safety laboratory result meeting one of these criteria should have the relevant test repeated to confirm the finding before discontinuation of study drug.	**See Section 1.1.5 for rules for discontinuing study treatment for individual participants.**

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
	Study drug will be discontinued for participants that experience any of the following clinical AEs at any time from Day 1 through the end of their dosing period: • Grade 2 or higher peripheral neuropathy Optic neuritis of any grade confirmed by an ophthalmologist	
Section 5 Trial Population	Approximately 116 healthy adult participants between 19 to55 years of age (inclusive) of both sexes who are capable of and willing to provide informed consent will be eligible for the trial.	Approximately **117** healthy adult participants between 19 to55 years of age (inclusive) of both sexes who are capable of and willing to provide informed consent will be eligible for the trial.
Section 5.1 Inclusion Criteria	16. Has clinical chemistry, hematology, coagulation, and complete urinalysis (fasted for at least 8 hours) results at Screening within the reference range for the testing laboratory unless the out-of-range results are deemed not clinically significant by the Investigator.	9. Has clinical chemistry, ~~hematology,~~ **(fasted for at least 8 hours),** coagulation, and complete urinalysis results at Screening within the reference ranges for the testing laboratory unless the out-of-range results are deemed not clinically significant by the Investigator. Added: **10. <u>For Part 2 only:</u> Has clinical hematology results for total white blood cell count, absolute neutrophil count, absolute lymphocyte count, hemoglobin, red blood cell count, and platelet count at Screening within the reference ranges for the testing laboratory.**
Section 5.3 Lifestyle Considerations	Participants with assigned male sex at birth who are not sterilized and are sexually active with a female partner of childbearing potential must agree to use condoms from Day -1 through 30 days after the last dose of study drug.	Participants with assigned male sex at birth who are not sterilized and are sexually active with a female partner of childbearing potential must agree to use condoms from Day -1 through **90 days** after the last dose of study drug.
Section 6 Study Intervention	Two study interventions will be used in this trial: participants will either receive MK-7762 or placebo by the oral route based on randomization as described in the section on trial design (Section 4).	Two study interventions will be used in this trial: participants will either receive MK-7762 or placebo by the oral route based on randomization **or treatment assignment** as described in the section on trial design (Section 4).
Section 6.1 Study Drug Administration	After completion of Part 1 of the study, an interim review of safety and PK data as well as any additional nonclinical data available will be conducted prior to a decision to commence Part 2 of the study (see Section 1.1.3.2). In Part 2 (MAD), three sequential cohorts will be administered escalating once-daily doses of MK-7762 or placebo for 28 consecutive days.	After completion of Part 1 of the study, an interim review of safety and PK data as well as any additional nonclinical data available will be conducted **and submitted for regulatory review and agreement** prior to **the Sponsor's** decision to **initiate** Part 2 of the study (see Section 1.1.3.2). In Part 2, **initiation of Cohort 7 (FE cohort) may occur approximately concurrent with initiation of MAD Cohort 8. The** three sequential **MAD** cohorts will be administered escalating once-daily doses of MK-7762 or placebo for 28 consecutive days.
Section 6.4.1 Randomization	All participants in Cohort 6 will receive open-label MK-7762.	All participants in **FE** Cohort 6 will receive open-label MK-7762 **300 mg**.

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
	In Part 2, participants in Cohorts 1-3 will be randomized 3:1 to MK-7762 or placebo. Before the trial is initiated, the telephone number and call-in directions for the Interactive Voice Response System (IVRS) and/or the log in information and instructions for the Interactive Web Response System (IWRS) will be provided to the trial site.	**In Part 2, because FE Cohort 7 and MAD Cohort 8 will enroll in parallel, eligible participants will be randomized 1:1 to these cohorts until approximately 9 participants have been enrolled to FE Cohort 7; thereafter, eligible participants will be enrolled in MAD Cohort 8 (approximately 20 participants total). All** participants in **FE Cohort 7 will receive open-label MK-7762 600 mg and be randomized 1:1:1 to the three possible sequences of standard meal, high-fat meal, and fasted state in a crossover design with washout between dosing periods; no sentinel participants will be included in Cohort 7. Participants in MAD** Cohorts **8-10 (approximately 20 participants per cohort)** will be randomized **4:4:1:1** to MK-7762 **in fasted state, MK-7762 in fed state after standard breakfast meal, placebo in fasted state, or placebo in fed state after standard breakfast meal.** ~~Before the trial is initiated, the telephone number and call-in directions for the Interactive Voice Response System (IVRS) and/or the log in information and instructions for the Interactive Web Response System (IWRS) will be provided to the trial site.~~
Section 6.4.2 Masking (Blinding)	The trial has a double-blind design in which participants and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at the trial site who will prepare oral doses of MK-7762 and placebo appropriately masked for site personnel who are authorized to administer treatment. A trial unblinding plan will be prepared before the trial begins. The Safety Review Team will review blinded aggregated safety data by cohort only (i.e., data from participants receiving MK-7762 or placebo) and may be allowed to access aggregated mean PK data by treatment group within and across cohorts to inform dose escalation decisions (see Section 4.5).	The trial has a double-blind design **for Part 1 SAD Cohorts 1-5 and Part 2 MAD Cohorts 8-10** in which participants and all site personnel will be blinded to the randomization, excepting the unblinded pharmacist(s) and pharmacy staff at the trial site who will prepare oral doses of MK-7762 and placebo appropriately masked for site personnel who are authorized to administer treatment. **There will be an unblinded review of safety and PK data following completion of Part 1 prior to initiation of Part 2.** A trial unblinding plan will be prepared before the trial begins. **In Part 1 FE Cohort 6 and Part 2 FE Cohort 7 the MK-7762 doses administered will be open-label.** The Safety Review Team will review blinded aggregated safety data by cohort only for **SAD Cohorts 1-5 and MAD Cohorts 8-10** and may be allowed to access aggregated mean PK data by treatment group within and across cohorts to inform dose escalation decisions (see Section 4.4).
Section 6.6 Concomitant and Prohibited Medications	Concomitant medications that are prohibited are listed in Appendix 2.	**Medications which associated with serotonin syndrome (listed in Appendix 2) and oxazolidinone antibiotics (e.g., linezolid and tedizolid) Concomitant medications that are prohibited are listed in Appendix 2.**

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
Section 7.1.1 Pausing Rules	Pausing rules (reasons for pausing the study) are in effect during the active enrollment and dosing period. Section 4.5.1 outlines pausing rules. If any of the pausing criteria are met, enrollment/patient accrual as well as dosing of enrolled participants will be suspended pending IDMC's review of all available safety data and the U.S FDA will be notified in an expedited manner.	Pausing rules (reasons for pausing the study) are in effect during the active enrollment and dosing period. Section 4.4.1 outlines **trial** pausing rules. If any of the pausing criteria are met, enrollment/**participant** accrual as well as dosing of enrolled participants will be suspended pending IDMC's review of all available safety data, and the U.S FDA will be notified in an expedited manner. **In contrast to trial pausing rules, discontinuation of treatment for individual MAD participants (per rules outlined in Section 1.1.5 do not require cessation of participant enrollment or of dosing of all enrolled participants in MAD cohorts.**
Section 7.3 Lost to Follow-Up	A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits (3 failed visits) and is unable to be contacted by the study site (3 failed attempts per failed visit).	Deleted: ~~A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits (3 failed visits) and is unable to be contacted by the study site (3 failed attempts per failed visit).~~
Section 8.4.1 Vital Signs and Body Mass Index (BMI)	Weight will be assessed weekly in the MAD cohorts in Part 2.	**In the MAD cohorts in Part 2, weight** will be assessed weekly **and then on Day 31, 33, and 36.**
Section 8.4.3 Visual Assessment	A visual assessment will be conducted at Screening to assess eligibility for all trial participants and repeated during the treatment period for Part 2 participants per the SoA to assess for possible signs of optic neuropathy toxicity from repeat dosing. During Screening, the Investigator or their delegate will conduct assessments of visual acuity and color vision. At subsequent visits in Part 2**,** trial staff will conduct tests of visual acuity and color vision.	A visual assessment will be conducted at Screening to assess eligibility for all trial participants and repeated during the treatment period for Part 2 **MAD** participants per the SoA to assess for possible signs of optic neuropathy toxicity from repeat dosing. During Screening, the Investigator or their delegate will conduct assessments of visual acuity and color vision. At subsequent visits in Part 2 **MAD Cohorts 8-10,** trial staff will conduct tests of visual acuity and color vision.
Section 8.4.4. Peripheral Sensory Neuropathy Screening	Peripheral sensory neuropathy screening will be conducted using the BPNS test at Screening to assess eligibility and repeated during the treatment period for Part 2 participants per the SoA to assess for signs of peripheral neuropathy toxicity from repeat dosing.	Peripheral sensory neuropathy screening will be conducted using the BPNS test at Screening to assess eligibility and repeated during the treatment period for Part 2 **MAD Cohort 8-10** participants per the SoA to assess for signs of peripheral neuropathy toxicity from repeat dosing.
Section 8.4.5. Electrocardiogram and Holter Monitoring	At the **Screening visit**, triplicate standard 12-lead ECGs will be performed for eligibility determination. The triplicate ECGs should be separated by at least 1 minute. At all **subsequent trial visits** where an ECG is scheduled, ECGs will be performed as triplicate readings with a minimum of 1 minute between ECGs.	At the **Screening visit,** triplicate standard 12-lead ECGs will be performed for eligibility determination. The triplicate ECGs should be separated by **approximately** 1 minute. At all **subsequent trial visits** where an ECG is scheduled, ECGs will be performed as triplicate readings with **approximately** 1 minute between ECGs.

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
	Continuous 12-lead ECGs (Holters) will be recorded on Day 1 in Part 1 and on Day 1 and 28 in Part 2.	Continuous 12-lead ECGs (Holters) will be recorded on Day 1 in Part 1 **Cohorts 1-5** and on Day 1 and **Day 28** in Part 2 **Cohorts 8-10**.
Section 8.4.6. Clinical Laboratory Assessments	In the event one or more abnormal laboratory value is obtained prior to randomization that is judged to be clinically significant by the Investigator, the participant will be excluded from study enrollment, as described in Section 5.2.	In the event **that** one or more abnormal laboratory **values is are** obtained prior to randomization that is judged to be clinically significant by the Investigator, the participant will be excluded from study enrollment. **However, for Part 2 of the trial, the following hematology parameters with screening results outside the respective normal range will require exclusion from enrollment (Section 5.1): total white blood cell count, absolute neutrophil count, absolute lymphocyte count, hemoglobin, red blood cell count, and platelet count.**
Section 8.4.9. Pharmacokinetic Assessment	Additional blood will be collected from participants in Part 1, Cohort 4 and Part 2, Cohort 3 at the same PK sampling timepoints for storage for possible future qualitative and/or quantitative analysis of any significant metabolites identified. Urine collection for PK will only be conducted for Part 1, Cohort 4 and Part 2, Cohort 2.	Additional blood will be collected from participants in Part 1, **SAD** Cohort 4 and Part 2, **MAD Cohort 10** at the same PK sampling timepoints for storage for possible future qualitative and/or quantitative analysis of any significant metabolites identified. Urine collection for PK will only be conducted for Part 1, **SAD** Cohort 4 and Part 2, **MAD Cohort 9.**
Table 16, Table 17, Table 18	**Table 12 Plasma PK Sampling Timepoints for Part 1 (SAD)** Timepoint (day): Day 1 – Cohorts 1 – 6 Day 8[a] – Cohort 6 | Day 2 – Cohorts 1 – 6 Day 9[a] – Cohort 6 | Day 3 – Cohorts 1 – 6 Day 10[a] – Cohort 6 | Day 4 – Cohorts 1 – 6 Day 11[a] – Cohort 6 | Day 7 – Cohorts 1 – 6 Day 14[a] – Cohort 6 | ET Timepoint (hours): 0 1 2 3 4 5 6 8 12 | 24 | 36 | 48 | 72 | 144 | NA PK sample: X X X X X X X X X | X | X | X | X | X | X a: Start of second dosing period for Cohort 6 (FE Cohort) to be determined by PK results from previous SAD cohorts to ensure washout period of at least 5 half-lives between ET = Early Termination **Table 13 Plasma PK Sampling Timepoints for Part 2 (MAD)** Timepoint (Day): D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8-13 | D14 | D15-20 | D21 | D22-27 Timepoint (Hour): 0 1 2 3 4 5 6 8 12 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 2 | 0 | 0 2 | 0 PK sample: X X X X X X X X | X | X | X | X | X | X | X | X X | X X | X | X | X X | X Timepoint (Day): D28 | D29 | D33 Timepoint (Hour): 0 1 2 3 4 5 6 8 12 | -- | -- PK sample: X X X X X X X X | X | X | X[b] Timepoint 0 is within 30 minutes before dosing D = Day; C = Cohort; ET = Early Termination a: To be collected 24 hours after last dose (i.e., last dose administered on Day 28 for Cohorts 1-3) b: Day 33 PK sample for Cohorts 1-3 can be collected at random time as well as Early Termination visit PK sample	**Table 16 Plasma PK Sampling Timepoints for Part 1, Cohorts 1-5** Timepoint (day): Day 1 – Cohorts 1 – 6 Day 8[a] – Cohort 6 | Day 2 – Cohorts 1 – 6 Day 9[a] – Cohort 6 | Day 3 – Cohorts 1 – 6 Day 10[a] – Cohort 6 | Day 4 – Cohorts 1 – 6 Day 11[a] – Cohort 6 | Day 7 – Cohorts 1 – 6 Day 14[a] – Cohort 6 | ET Timepoint (hours): 0 1 2 3 4 5 6 8 12 | 24 | 36 | 48 | 72 | 144 | NA PK sample: X X X X X X X X X | X | X | X | X | X | X a: Start of second dosing period for Cohort 6 (FE Cohort) to be determined by PK results from previous SAD cohorts to ensure washout period of at least 5 half-lives between ET = Early Termination **Table 17 Plasma PK Sampling Timepoints for Part 2, FE Cohort 7** Timepoint (day): Periods 1, 2[a], and 3[a] (Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8) | ET Timepoint (hours): 0 1 2 4 6 8 12 | 24 | 36 | 48 | 72 | 96 | 120 | 144 | 168 | NA PK sample: X X X X X X X | X | X | X | X | X | X | X | X a: Start of second and third dosing period for Part 2 Cohort 7 (FE Cohort) is after a washout period of at least 8 days to ensure washout period of at least 5 half-lives between doses. ET = Early Termination **Table 18 Plasma PK Sampling Timepoints for Part 2, MAD Cohorts 8-10** Timepoint (Day): D1 | D2 | D3 | D4 | D5 | D6 | D7 | D8-13 | D14 | D15-20 | D21 | D22-27 Timepoint (Hour): 0 1 2 4 6 8 12 | 0 | 0 | 0 | 0 | 0 | 0 8 | 0 | 0 8 | 0 | 0 8 | 0 PK sample: X X X X X X X | X | X | X | X | X | X | X | X | X | X | X Timepoint (Day): D28 | D29 | D30-36 Timepoint (Hour): 0 1 2 4 6 8 12 | -- | -- PK sample: X X X X X X X | X[a] | X[b] Timepoint 0 is within 60 minutes before dosing (120 minutes for Day 1) D = Day; C = Cohort; ET = Early Termination a: To be collected 24 hours after last dose (i.e., last dose administered on Day 28 for Cohorts 8-10) b: Days 30-36 PK sample for Cohorts 8-10 should be collected within ±3-hour time window of time of last study drug administration on Day 28

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
Section 9 Statistical Considerations	• For Part 1 Cohort 1-5, participants will be counted once according to the dose level (or placebo) received. Pre-dose observations on Day 1 or Day -1 are used as the baseline. • For Part 1 Cohort 6 (FE Cohort), participants will be counted in each period according to the dosing condition (fed or fasted) in that period. Pre-dose observations on Day 1 or Day -1 will be used as the baseline for both dosing periods. • For Part 2 Cohorts 1-3, participants will be counted once according to the dose level (or placebo) received. Observations on Day -1 or Day 1 before the first administration of study drug will be used as the baseline.	• For Part 1, **SAD** Cohort 1-5, participants will be counted once according to the dose level (or placebo) received. Pre-dose observations on Day 1 or Day -1 are used as the baseline. • For **Part 1, FE Cohort 6**, participants will be counted in each period according to the dosing condition (fed or fasted) in that period. Pre-dose observations on Day 1 or Day -1 will be used as the baseline for both dosing periods. • **For Part 2, FE Cohort 7, participants will be counted in each period according to the dosing condition (fasted or fed) in that period. Pre-dose observations on Day 1 or Day -1 will be used as the baseline for each of the three dosing periods.** • **For Part 2, MAD Cohorts 8-10,** participants will be counted once according to the dose level (or placebo) received. Observations on Day -1 or Day 1 before the first administration of study drug will be used as the baseline.
Section 9.3 Statistical Methods		Added: Pooling of MK-7762 safety data will also be described in the SAP.
Section 9.3.1 Primary Analyses of Safety	For Part 1, the primary analysis will cover the time period from pre-dose on Day 1 to Day 7 for Cohort 1-5, and Day 7 of each dosing period (fed or fasted) for Cohort 6 (Food Effect Cohort). For Part 2, the primary analysis will cover the time period from pre-dose on Day 1 to Day 33 for Cohort 1. Safety summaries will be inclusive of all participants in the safety population, unless stated otherwise.	For Part 1, the primary analysis will cover the time period from pre-dose on Day 1 to Day 7 for **SAD Cohorts 1-5**, and Day 7 of each dosing period (fed or fasted) for **FE** Cohort 6 (Food Effect Cohort). For **Part 2, FE Cohort 7**, the primary analysis will cover the time period from pre-dose on Day 1 to **Day 8** for **each dosing period (fed or fasted). For Part 2, MAD Cohorts 8-10, the primary analysis will cover the time period from pre-dose on Day 1 to Day 36.** Safety summaries will be inclusive of all participants in the safety population, unless stated otherwise.
Section 9.3.1.1. Treatment-emergent AEs, SAEs and AESI	All AEs, inclusive of SAEs and AESI will be recorded from Screening through Day 7 for Cohorts 1-5, through Day 7 of the second dosing period for Cohort 6 (FE Cohort) for Part 1 and through Day 33 for Cohorts 1-3 in Part 2. Treatment-emergent AEs (TEAEs) are defined as AEs with onset after receipt of one or more doses of study drug through the end of study period for that participant (see Section 10.2.2). The following will be summarized by dose level, across all MK-7762 dose levels, and across all placebo cohorts:	All AEs, inclusive of SAEs and AESI will be recorded from Screening through Day 7 for **Part 1, SAD** Cohorts 1-5, through Day 7 of the second dosing period for **Part 1, FE Cohort 6, through Day 8 of the third dosing period for Part 2, FE Cohort 7**, and through **Day 36 for Part 2, MAD Cohorts 8-10.** Treatment-emergent AEs (TEAEs) are defined as AEs with onset after receipt of one or more doses of study drug through the end of study period for that participant (see Section 10.2.2). The following will be summarized by dose level, ~~across all MK-7762 dose levels~~, and across all placebo cohorts:

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
Section 9.3.1.3. Adverse Events of Special Interest	• Hepatotoxicity, as defined by all the following: o Elevated ALT or AST >3x upper limit of normal (ULN), o Elevated total bilirubin >2x ULN, o No evidence of cholestasis, and o No alternative explanation than drug-induced liver injury for the elevation in ALT/AST and total bilirubin, such as viral hepatitis	• Hepatotoxicity, as defined by **presence of all of** the following: o Elevated ALT or AST >3× upper limit of normal (ULN), o Elevated total bilirubin >2× ULN, and o No evidence of cholestasis **(normal or minimally elevated ALP)** ~~o No alternative explanation than drug-induced liver injury for the elevation in ALT/AST and total bilirubin, such as viral hepatitis~~
Section 9.3.1.4 ECG Analyses	ECGs will be performed as per the SoAs in Section 1.3. Cardiodynamic ECG evaluation may be performed on ECG and PK data from all participants dosed under fasted conditions, based on observed PK and other project considerations. If this evaluation is performed, the primary analysis will be based on concentration-QTc (C-QTc) modeling of the relationship between the plasma concentrations of MK-7762 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) >10 msec at clinically relevant plasma concentrations. The effect of MK-7762 on the placebo-corrected ΔQTcF, ΔHR (heart rate), ΔRR, ΔPR, and ΔQRS (ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS) will also be evaluated at each post-dosing time point ('by-time point' analysis) using the Intersection Union Test. In addition, an analysis of categorical outliers will be performed for changes in HR, RR, PR, QRS, QTcF, T-wave morphology and U-wave presence. Cardiodynamic ECG evaluation will be described in a separate ECG statistical analysis plan (ECG SAP).	**ECG data will be performed collected based on 12-lead recording in triplicate and based on continuous Holter monitoring, as per the SoAs in Section 1.3. The primary analysis of ECG will be based on the 12-lead recording. Data from the continuous Holter monitoring will be analyzed if deemed necessary based on PK, safety, or other development considerations and will be considered exploratory (see Section 9.4.2).** ~~Cardiodynamic ECG evaluation may be performed on ECG and PK data from all participants dosed under fasted conditions, based on observed PK and other project considerations. If this evaluation is performed, the primary analysis will be based on concentration-QTc (C-QTc) modeling of the relationship between the plasma concentrations of MK-7762 and change-from-baseline QTcF (ΔQTcF) with the intent to exclude an effect of placebo-corrected ΔQTcF (ΔΔQTcF) >10 msec at clinically relevant plasma concentrations. The effect of MK-7762 on the placebo-corrected ΔQTcF, ΔHR (heart rate), ΔRR, ΔPR, and ΔQRS (ΔΔQTcF, ΔΔHR, ΔΔPR, and ΔΔQRS) will also be evaluated at each post-dosing time point ('by-time point' analysis) using the Intersection Union Test. In addition, an analysis of categorical outliers will be performed for changes in HR, RR, PR, QRS, QTcF, T-wave morphology and U-wave presence. Cardiodynamic ECG evaluation will be described in a separate ECG statistical analysis plan (ECG SAP).~~
Section 9.4.2 ECG Exposure-Response Analysis	The relationship between QTcF and MK-7762 plasma concentrations will be explored graphically and through the development of a pharmacodynamic model to characterize these relationships. This analysis will be described in an independent analysis plan and reported separately.	**If deemed necessary based on PK, safety, or other development considerations, the relationship between QTcF based on continuous Holter monitoring and MK-7762 plasma concentrations may be explored** graphically and through the development of a pharmacodynamic model to characterize these relationships.

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
		In this case, the details of the analyses will be described **in independent a separate ECG analysis plan and will be considered exploratory.**
Section 9.5 Interim Analyses	No interim analyses are planned for the study, but blinded safety data will be monitored by the trial SRT at the conclusion of each dosing level to inform dose escalation decisions within the SAD and MAD components (see Section 1.1.4.1). An unblinded review of safety and PK data will be conducted after Part 1 to inform progression to Part 2 (28-day MAD; see Section 1.1.3.2).	No **formal** interim analyses are planned for the study, but blinded safety data will be monitored by the trial SRT at the conclusion of each dosing level to inform dose escalation decisions within the SAD and MAD components (see Section 1.1.4.1). An unblinded review of safety and PK data will be conducted after **completion of Part 1 to inform progression be submitted for regulatory review and agreement to proceed to Part 2** (28-day MAD; see Section 1.1.3.2).
Section 9.6 Sample Size and Power	Assuming all cohorts receive MK-7762 treatment, 74 participants will be exposed to MK-7762 (38 from Part 1 and 36 from Part 2). With 74 participants across all doses of MK-7762 in Parts 1 and 2, there is 80% (90%) power to observe at least one AE in the study if the true AE rate due to MK-7762 is 2.2 % (3.1%).	Assuming all cohorts receive MK-7762 treatment **as planned, 95 participants will be exposed to MK-7762 (30 from SAD cohorts, 8 from** ~~With 74 participants across all doses of MK-7762 in Parts 1 and 2, there is 80% (90%) power to observe at least one AE in the study if the true AE rate due to MK-7762 is 2.2 % (3.1%).~~**FE Cohort 6, 9 from FE Cohort 7, and 48 from MAD cohorts).**
Section 10.2.1. Definition of Adverse Event	Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).	Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator ~~(i.e., not related to progression of underlying disease).~~
Section 10.2.4 Definition of SAE	If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).	If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met ~~(e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).~~
Section 10.2.6 Definition of AESI	• Hepatotoxicity, as defined by all the following: o Elevated ALT or AST >3x ULN, o Elevated total bilirubin >2x ULN, o No evidence of cholestasis, and o No alternative explanation than drug-induced liver injury for the elevation in ALT/AST and total bilirubin, such as viral hepatitis	• Hepatotoxicity, as defined by **the presence of all of the** following: o Elevated ALT or AST >3× ULN, o Elevated total bilirubin >2× ULN, and o No evidence of cholestasis **(normal or minimally elevated ALP)** ~~o No alternative explanation than drug-induced liver injury for the elevation in ALT/AST and total bilirubin, such as viral hepatitis~~

Section Number	Text in Version 3	Text in Version 4 (Amendment 3)
Section 10.2.7 Recording and Follow-up of AEs (including SAEs and AESIs)	Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences	Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences **that are not detected by laboratory tests.**
Section 10.2.7.1 Assessment of AE Intensity (Severity)	An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (see Section 10.2.4), not when it is rated as severe.	An event is defined as 'serious' when it meets at least 1 of the predefined **criteria** as described in the definition of an SAE (see Section 10.2.4), not when it is rated as severe.
Section 10.3 Contraceptive Guidance and Collection of Pregnancy Information	Male participants who are not sterilized and are sexually active with a female partner of childbearing potential must agree to use condoms from Day -1 through 30 days after the last dose of study drug. Investigators must make an effort to collect outcomes of pregnancies discovered during the trial and communicate them to the Sponsor and PPD	Male participants who are not sterilized and are sexually active with a female partner of childbearing potential must agree to use condoms from Day -1 through **90 days** after the last dose of study drug. Investigators must make an effort to collect outcomes of pregnancies discovered during the trial and communicate **any known outcome to** PPD
Section 11 References		Added: **Ernest JP, Jia Ni Goh J, Strydom N, et al. Translational predictions of phase 2a first-in-patient efficacy studies for antituberculosis drugs. Eur Respir J. 2023 Jan, 2300165.**

Changes in Version 5.0:

The protocol has been modified to include the following:

- Additional cardiac monitoring and safety ECGs.
- Effort to enroll female participants and stratify by sex in Part 2.
- The principal investigator's responsibility for monitoring safety.
- Follow up for participants who discontinue study drug due to a safety event.
- Inclusion of administrative changes and minor clarifications throughout

Section Number	Text in Version 4 (Amendment 3)	Text in Version 5 (Amendment 4)
Title Page		**Amendment 4 (Version 5.0)** added to title page.
Section 1.1.3.1 SAD and Food Effect (SAD/FE)	Amendment 3 (Version 4.0) If recommended by the SRT and approved by the Sponsor, the two sentinel participants will be dosed with MK-7762 in the fed state after the washout period previously determined, and the remaining 6 participants in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.	Amendment **4** (Version **5.0**) If recommended by the SRT and approved by the Sponsor, the two sentinel participants will be dosed with MK-7762 in the fasted state after the washout period previously determined, and the remaining 6 participants in Cohort 6 will subsequently be dosed with MK-7762 in fed and fasted states in a crossover manner employing the washout period previously determined.
Section 1.1.3.3 Part 2 – Food Effect and MAD (FE/MAD)		Moved sentence: In Part 2, effort will be made to enroll as many females as possible.
Section 1.1.4.1 Safety Review and Dose Escalation Decisions	See Section 4.4 for further details, including the pausing rules for which the SRT will monitor. See Section 4.4.2. for further details on the trial IDMC.	Deleted: ~~See Section 4.4 for further details, including the pausing rules for which the SRT will monitor.~~ Added: The Principal Investigator will be responsible for the identification of any event(s) which meet one or more of the pausing rules and the notification of the SRT, as outlined in Section 4.5.1. See **Section 4.5.2.** for further details on the trial IDMC.
Section 1.1.4.2 IDMC	The charter will be approved prior to Screening of the first trial participant. See ~~Section 4.4.2.~~ for further details on the trial IDMC.	The charter will be approved prior to Screening of the first trial participant **in either Part 1 or Part 2.** See **Section 4.5.2.** for further details on the trial IDMC.
Section 1.1.5 Rules for Discontinuation of Study Drug for Individual Participants in Part 2, MAD Cohorts 8-10	Study treatment discontinuation in one or more MAD Cohorts 8-10 participants does not require a pause in trial enrollment or in dosing for all currently enrolled participants (see Section 4.4.1).	Added: **The Principal Investigator will be responsible for the identification of safety laboratory abnormalities and/or clinical AEs which meet the rules of discontinuation of study drug for individual participants, as outlined above. The Principal Investigator will ensure discontinuation of study drug and thereafter inform the SRT.** Study treatment discontinuation in one or more **participants** in MAD Cohorts 8-10 does not require a pause in trial enrollment or in dosing for all currently enrolled participants.
Table 4	Amendment 3 (Version 4.0)	Amendment **4** (Version **5.0**)

Section Number	Text in Version 4 (Amendment 3)	Text in Version 5 (Amendment 4)
Schedule of Activities for Part 1, FE Cohort 6	ii: Participants will receive a single dose in 2 treatment periods: one after a high fat, high calorie breakfast (fed) and the second treatment period under fasted conditions (or the opposite order). The fed and fasted treatment periods will be separated by a washout period of at least five half-lives. See Section 4.1.4.	**i:** Participants will receive a single dose in 2 treatment periods: one after a high fat, high calorie breakfast (fed) and the second treatment period under fasted conditions (or the opposite order). The fed and fasted treatment periods will be separated by a washout period of at least five half-lives. See **Section 4.1**.
Table 5 Schedule of Activities for Part 2, FE Cohort 7	Day 2 Trial Timepoint: 24 c: 12-lead safety ECG for on-site evaluation will be recorded at Screening, on Days -1, 1, 2, 3 and 7 for each Period and at the end of the trial (Day 7 of Period 3). The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with approximately 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 Period 1, on Day 1 Period 2 and Day 1 Period 3 should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Day 2, and Day 7 should be taken at approximately the same time as the study drug was administered. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator. When safety ECGs coincide with vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs.	Day 2 Trial Timepoint: 24-36 c: 12-lead safety ECG for on-site evaluation will be recorded at Screening, on Days -1, 1, 2, 3 and **8** for each Period and at the end of the trial (**Day 8** of Period 3). The ECGs should be obtained after the participant has been allowed to rest in a supine position for at least 5 minutes before the 1st ECG. All ECGs will be recorded in triplicate with approximately 1 minute between the 1st and 2nd and 2nd and 3rd ECGs. Day -1 ECG should be done during admission to the Clinical Trials Unit. ECGs on Day 1 Period 1, on Day 1 Period 2 and Day 1 Period 3 should be collected within 120 minutes prior to dosing and at approximately 2, 6, 12 and 24-hours post-dose. ECGs on Day 2**, Day 3**, and **Day 8** should be taken at approximately the same time **of day** as the study drug was **previously** administered. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator. When safety ECGs coincide with vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by ECGs then vital signs. Added: Continuous ECG Recording on Day 1, Day 2, and Day3 Added new footnote **d**: **In each of the dosing periods a continuous ECG recording will be performed for 50 hours, starting two-hour pre-dose on Day 1. 12-lead ECGs will be extracted from the continuous ECG recording at the following time points, paired with PK sampling: at 3 time points within two hours prior to dosing (e.g., -45, -30 and -15 minutes) and at one time point each at approximately 1, 2, 4, 6, 8, 12, 24, 36, and 48-hours post-dose. Participants will rest in a supine position for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first**

Section Number	Text in Version 4 (Amendment 3)	Text in Version 5 (Amendment 4)
		followed by safety ECGs then vital signs, except ECG extractions may occur before blood sample collection. Footnote lettering was adjusted to accommodate new footnote d.
Table 6 Schedule of Activities for Part 2, MAD Cohorts 8-10	 Footnote f: 12-lead safety ECG for on-site evaluation will be recorded at Screening, Day -1, Days 1-3, 7, 14, 21, 28, 29, and 36. Day 29 and Day 36 ECGs should be taken at approximately the same time as the study drug was administered on Day 28. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator or designee g: Continuous ECG recordings will be performed for ~~25~~ hours, ~~starting one hour pre-dose on Day 1 and Day 28~~. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: At 3 time points within ~~one~~ hour prior to dosing (eg, -75, -60 and -45 minutes) and at one time point each at approximately 1, 2, 4, 6-, 8-, 12-, and 24-hours post-dose. k: ~~Days 30~~ (±1 day) within ±3-hour time window of time of last study drug administration on Day 28 l: Urine will be collected for PK analysis at the following times only from MAD ~~Cohort 9~~	Added: **Day 30 and added "X" for Safety ECG recording, continuous ECG recording, blood sample collection for PK analysis** Day 31: Added "X" to **Safety ECG recording and continuous ECG recording** Footnote f: 12-lead safety ECG for on-site evaluation will be recorded at Screening, Day -1, Days 1-3, 7, 14, 21, 28, 29, **30, 31**, and 36. **ECGs on Day 29, Day 30, Day 31 and Day 36 should be taken at** approximately the same time as the study drug was administered on Day 28. Safety ECGs will be reviewed and interpreted on-site by the Principal Investigator or designee g: Continuous ECG recordings will be performed for **26** hours **beginning on Day 1, and 50 hours beginning on Day 28**, starting two pre-dose on Day 1 and Day 28. 12-lead ECGs will be extracted at the following time points, paired with PK sampling: At 3 time points within two hours prior to dosing (eg, -75, -60 and -45 minutes) and at one time point each at approximately 1, 2, 4, 6-, 8-, 12-, and 24-hours post-dose on **Day 1 and Day 28), and at approximately 36- and 48-hours post-dose on(Day 28 only**. Participants will rest in a supine position for at least 10 minutes before a 5-minute extraction at each time point. When ECG extractions coincide with safety ECGs, vital signs, PK sample collection, and/or safety sample (blood or urine) collection, PK and safety blood sample collection should be done first followed by safety ECGs then vital signs, except ECG extractions may occur before blood sample collection. k: Added: **Day 30: 48 hours (±30 hours) after the Day 28 dose** **Days 31-36** (±1 day) within ±3-hour time window of time of last study drug administration on Day 28 l: Urine will be collected for PK analysis at the following times only from MAD **Cohort 10**
Section 2.6.2.2 MAD Cohorts 8-10	Enrollment of the MAD cohorts will be sequential and safety and PK data from each cohort will be reviewed prior to enrollment of higher doses (Section 4.4).	Enrollment of the MAD cohorts will be sequential and safety and PK data from each cohort will be reviewed prior to enrollment of **participants to receive** higher doses (Section 4.4).

Section Number	Text in Version 4 (Amendment 3)	Text in Version 5 (Amendment 4)
Section 4.1 Part 1 – SAD and Food Effect (SAD/FE)	Amendment 3 (Version 4.0) Figure 2 Title: Schema of Part 1, Cohorts 1-5 **Table 11 Title: Single Ascending Dose (Part 1) – Planned Dose Cohort 6** ~~(Food Effect Cohort)~~	Amendment **4** (Version **5.0**) Figure 2 Title: Schema of Part 1, **SAD** Cohorts 1-5 **Table 11 Title: Food Effect (Part 1) – Planned Dose Cohort 6**
Section 4.2 Part 2 –Food Effect and MAD (FE/MAD)	FE Cohort 7 will be an open-label, three-period evaluation of 600 mg of MK-7762 in at least 9 participants who will complete each of the three dosing periods. See Figure 4 and Table 12. Part 2 of the trial will consist of a ~~food effect~~ cohort and three sequential cohorts to evaluate escalating once daily doses of MK-7762 or placebo for 28 days. FE Cohort 7 will be an open-label, three-period evaluation of 600 mg of MK-7762 in at least 9 participants who ~~will~~ complete each of the three dosing periods. See Figure 4 and Table 12. Within each MAD cohort, half of the participants will be dosed in the fasted state and half of the participants will be dosed after a standard breakfast meal. Each of the three MAD cohorts will have approximately 20 participants randomized 4:4:1:1 to receive MK-7762 in fasted state, MK-7762 after standard breakfast meal, placebo in fasted state, or placebo after standard breakfast meal.	FE Cohort 7 will be an open-label, three-period evaluation of 600 mg of MK-7762 in at least 9 participants who will complete each of the three dosing periods, **separated by a washout period of at least 8 days** (See Figure 4 and Table 12). Part 2 of the trial will consist of a **FE** cohort and three sequential **MAD** cohorts to evaluate escalating once daily doses of MK-7762 or placebo for 28 days. FE Cohort 7 will be an open-label, three-period evaluation of 600 mg of MK-7762 in at least 9 participants who **should** complete each of the three dosing periods, separated by a washout period of at least 8 days (See Figure 4 and Table 12). **If a participant from Cohort 7 withdraws from the trial after receiving no more than a single dose of MK-7762, the participant will be replaced. Participants who withdraw from the trial after receiving at least 2 doses of MK-7762 will not be replaced.** Within each MAD cohort, half of the participants will be dosed in the fasted state and half of the participants will be dosed after a standard breakfast meal. Each of the three MAD cohorts will have approximately 20 participants randomized 4:4:1:1 to receive MK-7762 in fasted state, MK-7762 after standard breakfast meal, placebo in fasted state, or placebo after standard breakfast meal.
	Table 12 title: Single Ascending Dose (~~Part 1~~) – Planned Dose ~~Cohort 6~~ (Food Effect Cohort) Figure 5 title: Schema of MAD Cohorts 8-10, ~~Part 2~~ Table 13 title: Multiple Ascending Dose (Part 2) – ~~Planned Cohorts~~	Table 12 title: Food Effect (Part 2) – Cohort 7 Figure 5 title: Schema of **Part 2**, MAD Cohorts 8-10 Table 13 title: Multiple Ascending Dose (Part 2) –**Cohorts 8-10** Added: **In Part 2, effort will be made to enroll as many females as possible.**

Section Number	Text in Version 4 (Amendment 3)	Text in Version 5 (Amendment 4)
Section 4.5 Dose Escalation Decisions and Safety Review Team	~~After regulatory authority agreement and Sponsor approval to proceed to Part 2 of the trial, there will be approximately concurrent initiation of FE Cohort 7 and MAD Cohort 8.~~	**After regulatory authority agreement and Sponsor approval to proceed, Part 2 will initiate.**
Section 4.5.1 Trial Pausing Rules	~~If a pausing rule is met~~, the SRT will ask the IDMC to conduct a review of unblinded safety data. The IDMC will make a recommendation to the Sponsor regarding the further conduct of the trial.	**The Principal Investigator will monitor individual participant safety and be responsible for the identification of any event(s) which meet one or more of the pausing rules listed above and notifying the SRT. If pausing rule is confirmed,** the SRT will ask the IDMC to conduct a review of unblinded safety data. The IDMC will make a recommendation to the Sponsor regarding the further conduct of the trial.
Section 4.5.2 IDMC	The charter will be approved prior to Screening of the first trial participant.	The charter will be approved prior to Screening of the first trial participant **enrolled in Part 1 or Part 2.**
Section 4.6 End of Trial Definition, Participant Completion of Trial, and Follow up of Adverse Events	Any participant withdrawn from the trial before their last scheduled trial visit will be asked to return for an early termination visit. ~~Participants for whom study drug is permanently stopped or changed by the Investigator will be asked to undergo this early termination visit within 2 weeks of discontinuing study drug regardless of the reason for study drug discontinuation.~~ Assessments to be conducted at the early termination visit are specified in Section 1.3. An individual participant is considered to have completed the trial if he/she completes the final scheduled visit for their assigned cohort. If a participant has an AE that has not resolved or is not otherwise explained at the final trial visit, the AE will be documented as either "Not Resolved/Not Recovered" or "Resolving/Recovering". ~~However, follow up of a SAE or AESI must continue until the event is resolved or the condition has stabilized.~~	Any participant withdrawn from the trial before their last scheduled trial visit **for reasons not related to a safety event** will be asked to return for an early termination visit within 2 weeks. Assessments to be conducted at the early termination visit are specified in Section 1.3. An individual participant is considered to have completed the trial if he/she completes the final scheduled visit for their assigned cohort. If a participant has an AE that has not resolved or is not otherwise explained at the final trial visit, the AE will be documented as either "Not Resolved/Not Recovered" or "Resolving/Recovering". **Follow up of safety events associated with withdrawal of study drug is described in Section 7.2.**
Section 5 TRIAL POPULATION	~~Effort will be made to enroll as many females as possible.~~	Added: **In Part 2, effort will be made to enroll as many females as possible.** Deleted. Effort will be made to enroll as many females as possible.
Section 6.1 Study Drug Administration	~~In Part 2, initiation of Cohort 7 (FE cohort) may occur approximately concurrent with initiation of MAD Cohort 8. The three sequential MAD cohorts will be administered~~	**In Part 2, initiation of Cohort 7 (FE cohort) will occur following enrollment of MAD Cohort 8.**

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	~~escalating once-daily doses of MK-7762 or placebo for 28 consecutive days.~~	
Section 6.4.1 Randomization	~~In Part 2, because FE Cohort 7 and MAD Cohort 8 will enroll in parallel, eligible participants will be randomized 1:1 to these cohorts until approximately 9 participants have been enrolled to FE Cohort 7; thereafter, eligible participants will be enrolled in MAD Cohort 8 (approximately 20 participants total).~~ Randomization and treatment of each participant will take place on Day 1.	**In Part 2, effort will be made to enroll as many females as possible in FE Cohort 7 and in MAD Cohorts 8-10. Randomization to treatment group within a cohort will be stratified by sex. Cohort 8 will be enrolled first, and following its enrollment completion, at least 9 participants will be enrolled in FE Cohort 7. After FE Cohort 7 enrollment is complete, MAD Cohorts 9 and 10 will be enrolled sequentially with dose escalation recommendations made by the SRT (see Section 4.5).** Randomization and treatment of each participant **in a MAD cohort** will take place on Day 1.
Section 7.1.1. Pausing Rules	Pausing rules (reasons for pausing the study) are in effect during the active enrollment and dosing period. ~~Section 4.4.1 outlines trial pausing rules~~. Refer to ~~Section 4.4~~ for the role of SRT and ~~Section 4.4.2~~ for the role of the IDMC.	Pausing rules (reasons for pausing the study) are in effect during the active enrollment and dosing period. **The Principal Investigator will be responsible for the identification of any event(s) which meet one or more of the pausing rules and notification of the SRT, as outlined in Section 4.5.1.** Refer to **Section 4.5** for the role of SRT and **Section 4.5.2** for the role of the IDMC.
Section 7.2 Participant Discontinuation or Withdrawal from the Study	• non-serious AE Participants who are withdrawn because of occurrence of AE should be clearly distinguished from participants who are withdrawn for other reasons. Participants who are withdrawn because of a ~~SAE or an AESI will be followed until the event resolves or stabilizes. Refer to Section 10.1.4 regarding the informed consent process.~~	• non-serious AE **(including AESI and/or safety laboratory abnormality)** Participants who are withdrawn **from study drug** because of **the** occurrence of **a safety event** should be clearly distinguished from participants who are withdrawn for other reasons. Participants who are withdrawn because of a **safety event, including a SAE, an AESI, a non-serious AE, or a safety laboratory abnormality, will be followed until the planned end-of-study visit for that participant, and the required safety assessments will be performed at each visit. Ongoing SAEs at the time of the end-of-study visit will be followed until resolution or stabilization.**
Section 8.4.5. Electrocardiogram	Continuous 12-lead ECGs (Holters) will be recorded on Day 1 in Part 1 Cohorts 1-5 and on Day 1 and Day 28 in Part	Continuous 12-lead ECGs (Holters) will be recorded on Day 1 in Part 1 Cohorts 1-5, **on Day 1 in Part 2 Cohort 7,** and on Day 1 and Day 28 in

Section Number	Text in Version 4 (Amendment 3)	Text in Version 5 (Amendment 4)
and Holter Monitoring	2 Cohorts 8-10. ECGs to be used in the ECG exposure-response analysis will be selected by pre-determined time points as defined in the separate analysis plan (see Section 9.4.2).	Part 2 Cohorts 8-10. ECGs to be used in the ECG exposure-response analysis will be selected by pre-determined time points as defined in the separate analysis plan (see Section 9.4.2).
Section 10.1.2. Trial Oversight		Added: • **The Principal Investigator will be responsible for the identification of safety laboratory abnormalities and/or clinical AEs which meet the rules of discontinuation of study drug for individual participants. In such instance, the Principal Investigator will ensure discontinuation of study drug and thereafter inform the SRT.** • **The Principal Investigator will monitor individual participant safety and be responsible for the identification of any event(s) which meet one or more of the pausing rules listed above and notifying the SRT.**
	• The operational details of the SRT, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to the time that the first participant is enrolled. • The SRT will review the blinded safety and tolerability data accumulated from SAD and MAD cohorts (see ~~Section 1.1.3.2 and Section 4.4~~).	• The operational details of the SRT, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to the time that the first participant is enrolled **in either Part 1 or Part 2.** • The SRT will review the blinded safety and tolerability data accumulated from SAD and MAD cohorts (see **Section 1.1.4.1. and Section 4.5).**
	• The operational details of the IDMC, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to the time that the first participant is enrolled. • The IDMC will then review all relevant unblinded safety data and recommend the next course of action(s) to the Sponsor (see ~~Section 1.1 and Section 4~~).	• The operational details of the IDMC, including their composition, roles, and responsibilities, will be defined in its charter, which will be available prior to the time that the first participant is enrolled **either Part 1 or Part 2.** • The IDMC will then review all relevant unblinded safety data and recommend the next course of action(s) to the Sponsor (see **Section 4.5**).
Section 10.2.6. Definition of AESI	• ~~Peripheral~~ neuropathy ~~of severity grade 3 or above~~ • Optic neuritis confirmed by an ophthalmologist • ~~Grade 3 or above anemia, leukopenia, or thrombocytopenia~~	• **Grade ≥2 peripheral neuropathy** • **Grade ≥3 anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia** • Optic neuritis **of any grade** confirmed by an ophthalmologist

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