Official Protocol Title:	A Phase 2a, Randomized, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of MK-1942 Added to Stable Antidepressant Therapy in Participants With Treatment-Resistant Depression
NCT number:	NCT04663321
Document Date:	28-JUL-2022

Title Page

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Protocol Title: A Phase 2a, Randomized, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of MK-1942 Added to Stable Antidepressant Therapy in Participants With Treatment-Resistant Depression

Protocol Number: 006-03

Compound Number: MK-1942

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	152126
EudraCT	Not applicable

Approval Date: 28 July 2022

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 3	28-JUL-2022	This amendment was primarily created to extend the study population by including WOCBP.
Amendment 2	27-MAY-2022	This amendment was primarily created to add safety laboratory assessments to the 14-day postdose visit (Week 6) and to change this visit to either a site visit or TC visit.
Amendment 1	07-MAR-2022	This amendment was primarily created to update the inclusion and exclusion criteria, which expands the TRD population and increases enrollment.
Original Protocol	19-OCT-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 03

Overall Rationale for the Amendments:

This amendment was primarily created to extend the study population by including WOCBP.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 2.2.2 Preclinical and Clinical Studies 2.3 Benefit/Risk Assessment 5.1 Inclusion Criteria 5.2 Exclusion Criteria 7.1 Discontinuation of Study Intervention 8.1.7.2 Concomitant Medications 8.1.12 Study Intervention Administration 8.3.6.1 Confirmation of Postmenopausal State 8.3.6.2 Pregnancy Testing	Women of childbearing potential were added to this study. Inclusion criteria, contraception requirements, and pregnancy testing were updated to reflect this additional population. Exclusion criterion excluding women with <12 months of amenorrhea receiving HRT or estrogen-based contraceptives was removed.	Study population is being extended to WOCBP as they represent a significant portion of the TRD population. Mitigation strategies have been implemented to minimize the risk of undesired pregnancies.

Section # and Name	Description of Change	Brief Rationale
8.3.8 Contraceptive Use Confirmation 8.11.1 Screening 10.2 Appendix 2: Clinical Laboratory Test 10.5 Appendix 5: Contraceptive Guidance 11 References		
2.2.2 Preclinical and Clinical Studies 2.3 Benefit/Risk Assessment	Phase 1 data were updated to reflect recently completed studies. Section 2.2.3 Ongoing Clinical Studies was removed	To align with recent IB update.
4.3.2 Maximum Dose/Exposure for This Study	Safety text previously included in Section 2.2.3 was added and data from completed studies was added. Statement on safety margins was updated to align with recent IB update.	Updated safety text for consistency across the protocol and to align with IB.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria 10.2 Appendix 2: Clinical Laboratory Tests	-eGFR exclusion criterion was revised to <30 mL/min/1.73m^2. -Liver disease exclusion criterion was updated to clarify hepatitis exclusion.	Clarification to align with other studies in the MK-1942 program. MK-1942 is not renally excreted. eGFR exclusionary threshold was updated to be consistent with severe renal impairment definition and to align with other studies in the MK-1942 program. While chronic viral hepatitis and non-viral hepatitis pose an increased risk for DILI, the evaluation of liver enzymes is not sufficient to establish clinical stability or remission. Therefore, there is a need to exclude participants with chronic viral hepatitis and non-viral hepatitis regardless of the liver enzyme stability in the previous 6 months.
5.2 Exclusion Criteria 7.1 Discontinuation of Study Intervention 8.1.7.2 Concomitant Medications 8.11.1 Screening 10.2.1 Drug Screening (Local and Central)	Intermittent cannabis use is not prohibited if abuse or substance use disorder has been ruled out by investigator.	Cannabis and its derivatives are widely used for medical purposes. This exclusion was relaxed given that intermittent use of cannabis is not expected to pose a risk to participant safety or interpretation of study results if drug abuse or substance use disorder is ruled out.
8.1.6 MGH-ATRQ	Clarified instructions to sites and focused pharmacy verification on current failed therapy. Broadened documentation options for earlier treatment(s).	To allow for more flexibility in documenting failed antidepressants taken for the current MDD episode and focus pharmacy verification on most critical time interval.

Section # and Name	Description of Change	Brief Rationale
8.1.7.2 Concomitant Medications	Moderate CYP2C19 inducers were removed from the list of prohibited medications. Sensitive CYP2C19 substrates were updated.	Results from study MK-1942-007 showed that CYP2C19 activity has a moderate impact on the PK of MK-1942. Therefore, only strong CYP2C19 inducers need to be excluded.
Throughout the document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a, Randomized, Placebo-Controlled Clinical Study to Evaluate the Efficacy and Safety of MK-1942 Added to Stable Antidepressant Therapy in Participants With Treatment-Resistant Depression

Short Title: A Phase 2a Proof-of-Concept Study of MK-1942 in Participants With TRD

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

In men and women with TRD on a stable course of antidepressant therapy:

Primary Objectives	Primary Endpoints
To compare the effect of daily MK-1942 treatment with the effect of placebo on the change from baseline in MADRS total score at Week 3. Hypothesis (H1): Daily MK-1942 treatment is superior to placebo in reducing MADRS total score at Week 3.	MADRS total score
To compare the effect of intermittent MK-1942 treatment with the effect of placebo on the change from baseline in MADRS total score at Week 1. Hypothesis (H2): Intermittent MK-1942 treatment is superior to placebo in reducing MADRS total score at Week 1.	MADRS total score
To evaluate the safety and tolerability of daily and intermittent MK-1942 treatment.	AEs Discontinuation of study intervention due to AEs

Secondary Objectives	Secondary Endpoints
To compare the effect of daily MK-1942 treatment with the effect of placebo on the change from baseline in HAM-D17 total score at Week 3. Hypothesis (H3): Daily MK-1942 treatment is superior to placebo in reducing HAM-D17 total score at Week 3.	HAM-D17 total score
To compare the effect of intermittent MK-1942 treatment with the effect of placebo on the change from baseline in HAM-D17 total score at Week 1. Hypothesis (H4): Intermittent MK-1942 treatment is superior to placebo in reducing HAM-D17 total score at Week 1.	HAM-D17 total score
To compare the effect of daily MK-1942 treatment with the effect of placebo on the change from baseline in CGI-S score at Week 3. Hypothesis (H5): Daily MK-1942 treatment is superior to placebo in reducing CGI-S score at Week 3.	CGI-S score
To compare the effect of intermittent MK-1942 treatment with the effect of placebo on the change from baseline in CGI-S score at Week 1. Hypothesis (H6): Intermittent MK-1942 treatment is superior to placebo in reducing CGI-S score at Week 1.	CGI-S score
To evaluate the PK of MK-1942 when administered daily or intermittently.	MK-1942 plasma concentration

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
To compare the effect of daily and intermittent MK-1942 treatment with the effect of placebo on the change from baseline in BAC SC score at Week 3.	BAC SC score (number of correct matches on the BAC SC cognitive test after 90 seconds)
To compare the effect of daily and intermittent MK-1942 treatment with the effect of placebo on: - the change from baseline in MADRS total score, HAM-D17 total score, HAM-D6 total score, and CGI-S score at time points through Week 4 that are not specified for the primary or secondary endpoints. - MADRS remission rate at all time points through Week 4. - the proportion of participants with a ≥50% reduction from baseline in MADRS total score at all time points through Week 4.	MADRS total score HAM-D17 total score HAM-D6 total score CGI-S score
To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	Germline genetic variation and association to clinical data collected in this study.
To investigate the relationship between the genetic polymorphisms of CYP2C19 and the pharmacokinetics of MK-1942. Variation in CYP2C19 alleles may be analyzed for association with any laboratory or clinical data collected in this study.	Germline genetic variation in CYP2C19 and association to clinical data collected in this study.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of TRD
Population	Men and women with TRD on a stable course of antidepressant therapy
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo-controlled
Study Blinding	Double-blind
Blinding Roles	Sponsor Investigator Participants or Subjects
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 36 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 140 participants will be allocated/randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin-istration	Treatment Period	Use
MK-1942 Daily Dose Group	MK-1942	5 mg, 10 mg	bid	Oral	Weeks 1, 2, 3, 4	Test Product
	Placebo	0 mg	bid	Oral	Weeks 1, 2, 3, 4	Placebo
MK-1942 Intermittent Dose Group	MK-1942	10 mg	biw	Oral	Weeks 1, 2, 3, 4	Test Product
	Placebo	0 mg	bid	Oral	Weeks 1, 2, 3, 4	Placebo
Placebo	Placebo	0 mg	bid	Oral	Weeks 1, 2, 3, 4	Placebo

Abbreviations: bid=twice-daily, biw=twice-weekly

Note 1: The dose of MK-1942 for participants in the MK-1942 daily dose group will be uptitrated as follows: 5 mg bid (Visit 4/Day 1 to Visit 5/Week 1), 10 mg bid (Visit 5/Week 1 to Visit 6/Week 2), and 20 mg bid (Visit 6/Week 2 to Visit 8/Week 4).

Note 2: Dose modification to the intended regimen of MK-1942 may occur due to intolerance or non-adherence, as described in Section 6.6.

Note 3: MK-1942 and matching placebo will be packaged in blister cards and an equal number of capsules will be administered in the morning and evening regardless of treatment assignment.

Total Number of Intervention Groups/ Arms	3
Duration of Participation	Each participant will participate in the study for approximately 9 weeks from the time the participant provides documented informed consent through the final contact. After a pretreatment screening and lead-in period of approximately 3 weeks, each participant will receive assigned intervention for approximately 4 weeks. After the end of treatment, each participant will be followed for at least 2 weeks.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

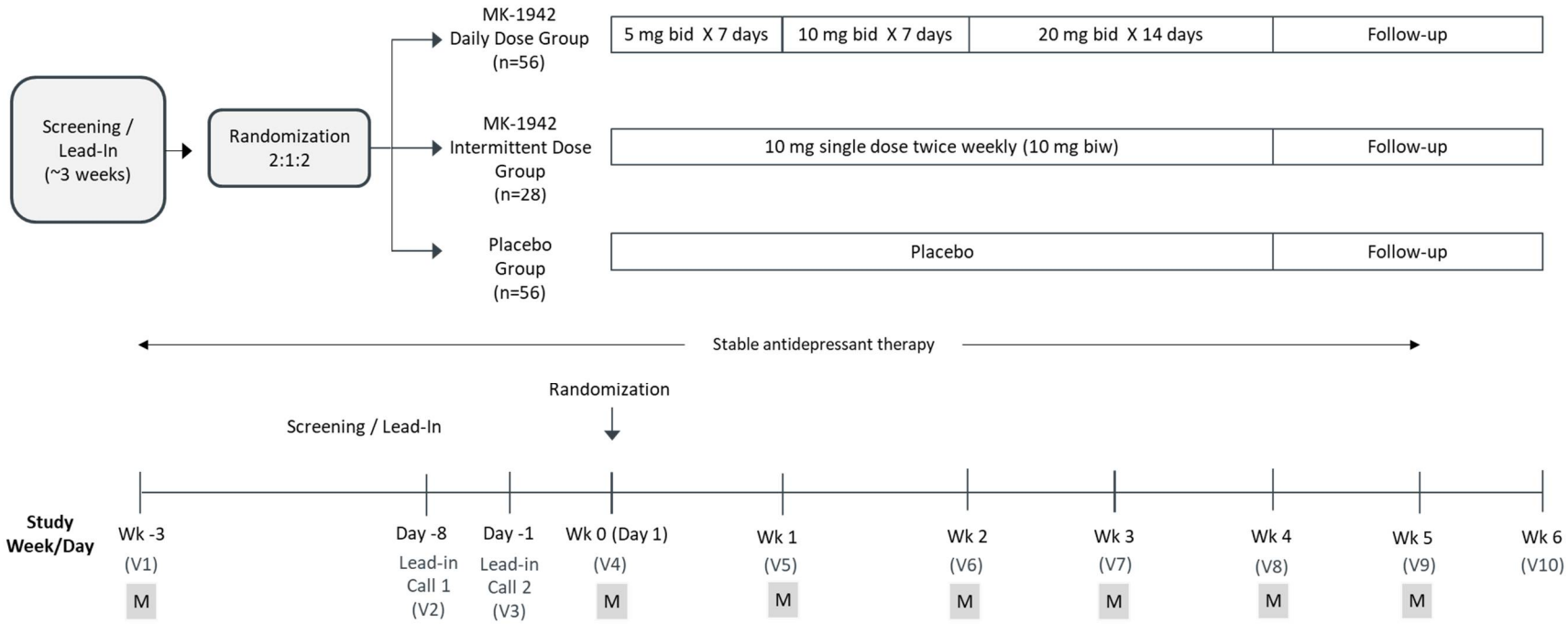
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



- M=MADRS, Wk=Week, V=Visit. At Visits 4, 5, 6, and 7, MADRS will be administered before the morning dose of study intervention.
- A phone call within the first 3 days after Visits 4, 5, 6, and 7.
- The primary diagnosis of major depressive disorder will be confirmed centrally during the pretreatment period.
- Visit 10 will occur at least 14 days after the last dose of study intervention.

1.3 Schedule of Activities

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
Administra-tive Procedures												Screening period may be less than 3 weeks (see Section 8.11.1) Clinic visits and Lead-in Calls should occur at about the same time of day in the morning.
Informed Consent	X											
Informed Consent for FBR	X											Participants remain eligible for the main study if they opt out of FBR.
Assignment of Screening Number	X											
Inclusion/ Exclusion Criteria	X	X	X	X								

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
Participant Identification Card	X			X								The randomization number will be added to the identification card at Visit 4 (Day 1).
Medical History	X											
Psychiatric History and MINI	X											MINI will also be audio recorded.
MGH-ATRQ	X											MGH-ATRQ will also be audio recorded.
Prior/ Concomitant Medication Review	X			X	X	X	X	X	X	X	X	
Contraceptive Use Confirmation	X			X	X	X	X	X	X			See Section 8.3.3
External Verification of Diagnosis	X											See Study Operations Manual (see Section 8.11.2.1) for details.

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
IRT Visit Registration	X			X	X	X	X	X			X	At Visit 8, IRT entry applies to DC visits only.
IRT Randomization				X								
Study Intervention Dispensing				X	X	X	X				X	Except for Down-titration Visit, WOCBP must have a negative urine pregnancy test immediately before study intervention is administered or dispensed.
Study Medication Guidance Dispensing and Review				X	X	X	X	X				At Visit 4, dispense guide and train participants. At Visits 5-8, review guide and retrain participants, as needed (see Section 8.1.12).

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
Witnessed Dose				X	X	X	X				X	The Day 1 AM dose must be administered on the first day of each treatment week irrespective of the time of day (see Section 8.1.12.1). A witnessed dose may not be administered at the Down-titration Visit depending on when the participant's last dose was taken (see Section 5.3.1).
Study Intervention Accountability					X	X	X	X			X	
Telephone Contacts After Visits				X	X	X	X				X	A telephone contact will be performed within the first 3 days after Visits 4, 5, 6, 7 and the Down-titration Visit, if applicable (see Section 8.1.15).

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
Efficacy Assessments												The efficacy assessments are listed in recommended order of administration (see Section 8.2).
BAC SC	X			X			X					
MADRS	X			X	X	X	X	X	X			MADRS will be audio recorded.
HAM-D17	X	X	X	X	X	X	X	X	X			Administered by the site at Visit 1 and Visits 4 to 9. Administered by the central vendor rater at Visits 2 and 3 (see Section 8.11.2). HAM-D17 will be audio recorded.
CGI-S	X			X	X	X	X	X	X			
Safety Procedures												
Full Physical Examination	X							X				
Neurological Examination	X							X				see Section 10.8

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
Vital Signs (temperature, blood pressure, pulse rate, and respiratory rate)	X			X	X	X	X	X	X			
Height	X											
Weight	X							X				
12-lead ECG (centrally read)	X			X		X		X				Measured in triplicate at each visit (see Section 8.3.4).
Alcohol Screen (breathalyzer)	X			X								
Chemistry and Hematology	X			X		X		X		X		Visit 10 laboratory assessments may be performed at a local laboratory, as needed
Urinalysis	X			X		X		X				

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
Local Urine Pregnancy Test, (WOCBP)	X			X	X	X	X	X	X			Schedule for women of child-bearing potential
Local Urine Pregnancy Test (WONCBP)	X			X				X				Schedule for women of **NON** child-bearing potential
Serum Pregnancy Test (WOCBP)*	X			X		X		X		X		*WONCBP will be tested if there is a positive urine test or ambiguous result
INR				X								
TSH	X											
FT4	X											Performed if participant has abnormal TSH value.
FSH	X											FSH may be measured to confirm postmenopausal state. (see Section 8.3.6.1 and Appendix 5).

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
Genotyping for CYP2C19				X								
Urine Drug Screen (central)	X			X	X		X					
Urine Drug Screen (local)	X			X	X		X					
C-SSRS (Baseline/ Screening Version)	X											
C-SSRS (Since Last Visit Version)				X	X	X	X	X	X	X	X	Visit 10 C-SSRS may be performed by TC, as needed.
AE Monitoring	X			X	X	X	X	X	X	X	X	Visit 10 AE monitoring may be performed by TC, as needed.

Study Period	Screening	Lead-in Call 1	Lead-in Call 2	Double-blind Treatment Period					Post-dose Follow-up Period		Down-titration	Notes
Visit Number/Title	1	2	3	4	5	6	7	8 EOT/DC	9	10 (14 days Postdose)	Down-titration Visit	
Scheduled Visit Week/Day	Wk -3/ Day -21	Day -8	Day -1	Wk 0/ Day 1	Wk 1/ Day 8	Wk 2/ Day 15	Wk 3/ Day 22	Wk 4/ Day 29	Wk 5/ Day 36	Wk 6/ Day 43	NA	
Visit Windows (Days)	-3	-3	-3	0	-1				±2	+3		
PK and Biomarkers												
MK-1942 PK Blood Sample				X	X	X	X	X				At Visit 4 (Day 1), predose and approximately 1-hour postdose PK samples will be collected. At all other visits, only predose PK samples will be collected. See Section 8.9 for FBR details.
Blood for Genetic Analysis				X								The blood sample will be collected predose in randomized participants only (see Section 8.8).

AE=adverse event, BAC SC=Brief Assessment of Cognition Symbol Coding, CGI-S=Clinical Global Impression-Severity, C-SSRS=Columbia-Suicide Severity Rating Scale, DC=discontinuation, ECG=electrocardiogram, EOT=end of treatment, FBR=future biomedical research, FSH=follicle-stimulating hormone; FT4=free T4 test, HAM-D17=17-item Hamilton Depression Rating Scale, INR=international normalized ratio, IRT=interactive response technology, MADRS=Montgomery-Asberg Depression Rating Scale, MGH-ATRQ=Massachusetts General Hospital Antidepressant Treatment Response Questionnaire, MINI=Mini International Neuropsychiatric Interview, NA=not applicable, PK=pharmacokinetic, TC=telephone call, TSH=thyroid-stimulating hormone, Wk=week, WOCBP=woman of childbearing potential, WONCBP=woman of non-childbearing potential.

2 INTRODUCTION

2.1 Study Rationale

MDD is a common mental illness that can significantly affect quality of life (Section 2.2.1). A large proportion of those with MDD either fail to respond to antidepressant therapy or initially respond to antidepressant therapy but relapse within 3 months. Ketamine and esketamine, which appear to work by increasing glutamate signaling in the brain, have been shown to rapidly improve depressive symptoms in those with TRD, but are associated with important safety concerns and abuse potential. MK-1942, which also appears to work by increasing glutamate signaling in the brain, has been generally well-tolerated in healthy adults in 4 completed Phase 1 studies and in preclinical evaluations. The purpose of this Phase 2a PoC study is to evaluate the therapeutic effect of MK-1942 in participants with TRD on stable antidepressant therapy, and to characterize the safety and tolerability of MK-1942 in this population.

While patients failing 2 or more antidepressant therapies are often considered to have TRD [Gaynes, B. N., et al 2020], this study will also enroll participants with 1 treatment failure for the current episode of moderate-to-severe MDD. This approach is considered appropriate given the high likelihood that participants with MDD who fail 1 antidepressant therapy will continue to fail additional courses of antidepressant therapy. However, the study will aim to randomize approximately 30% of participants with more than1 treatment failure (for the current episode of moderate-to-severe MDD) to ensure adequate representation of this population.

Two different dosing regimens of MK-1942 will be evaluated in this study. In the daily dose group, MK-1942 will be uptitrated as follows: 5 mg bid (Visit 4/Day 1 to Visit 5/Week 1), 10 mg bid (Visit 5/Week 1 to Visit 6/Week 2), and 20 mg bid (Visit 6/Week 2 to Visit 8/Week 4). This titration regimen was selected to help participants improve tolerance to higher doses of MK-1942 (safety data are summarized in Section 2.2.1). The primary time point to evaluate the effect of daily MK-1942 treatment on TRD is Week 3.

The intermittent dose group is included in this study to evaluate if twice-weekly dosing with 10 mg of MK-1942 can rapidly improve depressive symptoms (by Week 1) in participants with TRD, with continued evaluation of this regimen through the end of the study. Details on the scientific rationale and the dose regimens of MK-1942 in this study are in Sections 4.2 and 4.3, respectively.

2.2 Background

Refer to the IB for detailed background information on MK-1942.

2.2.1 Pharmaceutical and Therapeutic Background

MDD is a major contributor to the disease burden worldwide with lifetime prevalence ranging from 20% to 25% in women and 7% to 12% in men. MDD is a significant determinant of quality of life and survival, accounting for approximately 50% of psychiatric

consultations and 12% of all hospital admissions [Wang, J., et al 2017]. Current antidepressant therapies do not exert their full effects immediately [Zanos, P., et al 2019], and even if adequately treated, approximately 50% of patients with MDD fail to respond at all [Gaynes, B. N., et al 2020]. Moreover, even patients with TRD who respond to their current antidepressant therapy have a high rate of relapse (65% within 3 months) [Rush, A. J., et al 2006]. Healthcare costs and the risk of mortality due to suicide is elevated in patients with TRD [Reutfors, J., et al 2019].

MK-1942 is a small molecule NAM of mGluR2 that is being studied for treatment of TRD. In humans, MK-1942 suppresses the inhibitory effect of presynaptic mGluR2 on the release of glutamate in the brain, which thereby increases the synaptic levels of glutamate [Higgins, G. A., et al 2004] [Dietrich, D., et al 2002]. This increase in glutamate levels elevates postsynaptic neuron excitability and plasticity in the brain and is predicted to improve depressive symptoms. Ketamine and the S(+) enantiomer esketamine are NMDA antagonists that also appear to work by increasing glutamate signaling in the brain, and have been hypothesized to exert their effects, at least indirectly, through interactions with mGluR2 [Zanos, P., et al 2019]. They have shown clinically meaningful antidepressive effects within the first 24 to 48 hours of use [Molero, P., et al 2018]. However, due to prominent concerns about safety and abuse potential, these products are only available through a restricted program and must be taken in the office of a healthcare provider. In addition, patients must have medical supervision for at least 2 hours following their administration of ketamine or esketamine because of the substantial risk of sedation and dissociation. Thus, there remains a significant, unmet medical need for antidepressants that offer a safer and more accessible alternative for the treatment of TRD.

2.2.2 Preclinical and Clinical Studies

MK-1942 has shown to be active in the non-human primate glutamate cycling paradigm. In a preclinical study, mGluR2 knockout mice failed to demonstrate a ketamine-induced reduction of time immobile, equivalent to an antidepressant effect, in a tail suspension test compared with wild type. This result is consistent with that of another study in mice [Zanos, P., et al 2019] and supports the hypothesis that mGluR2 signaling may mediate ketamine's antidepressant effects. MK-1942 dose-dependently increases glutamate cycling as measured by MRS in rhesus monkeys. Maximal effect appears to be achieved at RO levels ≥40%. An increase in glutamate cycling, as measured by MRS, has also been observed in humans acutely after a ketamine infusion [Abdallah, C. G., et al 2018], and is postulated as a potential mechanism for the promotion of rapid antidepressant effects. Hence, for antidepressant efficacy, the target RO is at least 40%.

The preclinical safety profile of MK-1942 indicates that there are no adverse CNS or cardiovascular findings at an EM of approximately 64-times above the clinical target (~200 nM). No effects on cardiovascular parameters or vital signs were observed in rats or guinea pigs, and the changes observed at the higher doses in a cardiovascular and respiratory safety study in rhesus monkeys were reversible and/or not considered adverse. MK-1942 did not induce seizures or abnormal spike cluster activity in a 9-day electroencephalogram study in monkeys at plasma concentrations corresponding to 61-times the C_{max} corresponding to RO levels of approximately 40%.

In embryo-fetal toxicity studies in rats and rabbits, skeletal malformations were observed in rats, and increased incidences of extra gallbladder and short 13th rib occurred in rabbits. Mitigations to reduce risks for WOCBP are described in Section 2.3 Benefit /Risk.

Six Phase 1 clinical studies of MK-1942 are complete. Results from a single ascending-dose study (P001) of MK-1942 (0.1 mg to 12 mg) showed that it is absorbed rapidly and that its plasma concentrations declined in a biphasic manner, with a $t_{1/2}\alpha$ of approximately 3 hours and an apparent terminal $t_{1/2}$ of approximately 10 to 15 hours. Exposures ($AUC_{0\text{-}inf}$ and C_{max}) increase in an approximately dose-proportional fashion. Following administration of MK-1942 (4 mg) with a high-fat meal, absorption was decreased (C_{max} decreased by 52%, $AUC_{0\text{-}inf}$ decreased by 15%). Results from a PET study (P003) of MK-1942 (4 mg to 12 mg) suggest that the target RO level of approximately 41%, associated with a C_{max} of ~200 nM, may be achieved following a single dose of 10 mg of MK-1942. Results from a multiple ascending-dose study (P002) of MK-1942 showed that a twice-daily titration regimen (up to 20 mg bid) improved tolerance to MK-1942 while surpassing the target C_{max} of 200 nM. Results from a multiple ascending-dose study of MK-1942 (P004) showed that steady state C_{max}, C_{trough}, and $AUC_{0\text{-}12}$ were similar, or up to 85% higher in elderly participants compared to non-elderly participants across the 5- to 50-mg twice daily dose range, with longer apparent terminal $t_{1/2}$ in elderly participants.

P005 was a Phase 1, double-blind, placebo-controlled, DDI study of the safety, tolerability, and PK of MK-1942 and donepezil conducted in participants with AD receiving donepezil as part of their treatment for cognitive impairment associated with AD. This study is clinically complete although the CSR is not final.

P007 was a Phase 1, double-blind, placebo-controlled, single- and multiple-dose clinical study to evaluate the safety, tolerability, and PK of MK-1942 in healthy Japanese adult participants. This study is clinically complete although the CSR is not final.

In the completed Phase 1 studies, treatment with MK-1942 was generally well-tolerated. Single (4 mg to 12 mg) and repeated doses (5 mg to 50 mg) of MK-1942 were associated with episodes of dizziness (which may be associated with gait disturbance in a minority of participants), headache, and nausea. These AEs were of mild to moderate intensity and resolved without intervention. They were alleviated by titration dosing regimens. No SAEs and no clinically significant abnormalities were observed in safety measures, including those of vital signs, laboratory chemistry, hematology, urinalysis, physical examinations, or ECGs with one exception. Nonserious AEs of increased liver transaminases were observed in 2 participants after 4 weeks of study treatment during Part 2 of P007. These AEs did not meet criteria for DILI or an event of clinical interest as defined in the protocol. The liver function test abnormalities were observed only in the group exposed to MK-1942 50 mg bid and no abnormalities were observed in any of the participants exposed to lower dosages. A third subject in P005 who was on either placebo or 50 mg bid of MK-1942 had increased ALT and AST 2 weeks after completing the 4-week trial, which remains blinded (see IB for details).

There are currently no efficacy or safety data for MK-1942 in participants with TRD.

2.2.3 Information on Other Study-related Therapy

This section is not applicable to the current study.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

While no efficacy data on treatment with MK-1942 in participants with TRD are available, agents that appear to work by increasing glutamate signaling, like MK-1942, have shown clinically meaningful antidepressant effects in participants with TRD (Section 2.2.1).

Phase 1 clinical studies to date have shown that treatment with MK-1942 is generally well-tolerated. Participants may experience dizziness that is mild to moderate in intensity. In a minority of cases, the dizziness may be associated with gait disturbance. Participants may also experience headaches that are mild to moderate in intensity. Episodes of dizziness and headache may be accompanied by feelings of nausea with or without emesis. In addition, isolated cases of asymptomatic increased ALT (up to ~13x ULN) with increased AST (up to ~6x ULN) and without increased total bilirubin or ALP have been observed after 4 weeks of treatment with MK-1942 up to 50 mg bid or placebo (see IB for details). Given that the AEs observed were reversible and monitorable, there are currently no safety issues from the completed or ongoing clinical studies that preclude continued clinical investigation.

Regarding the teratogenicity risk, WOCBP make up a major portion of women with depression, including TRD [Brody, D. J., et al 2018]. Given the limited number of treatment options, and given their risk of embryo-fetal toxicity (*esketamine label*), including WOCBP in trials of potentially new medication is warranted. To reduce fetal risk, use of birth control will be required and closely monitored. Pregnancy status will be assessed weekly. Given these safeguards, the risk of pregnancy and fetal exposure to MK-1942 is extremely low.

Given the limited treatment options for participants with TRD, the serious health risks associated with inadequately treated TRD, and the available preclinical and clinical data for MK-1942 summarized above and in the IB, the benefit-to-risk assessment for conducting the current study is considered favorable.

Additional details regarding specific benefits and risks for participants participating in this clinical study are in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In men and women with TRD on a stable course of antidepressant therapy:

Objectives	Endpoints
Primary	
To compare the effect of daily MK-1942 treatment with the effect of placebo on the change from baseline in MADRS total score at Week 3. Hypothesis (H1): Daily MK-1942 treatment is superior to placebo in reducing MADRS total score at Week 3.	MADRS total score
To compare the effect of intermittent MK-1942 treatment with the effect of placebo on the change from baseline in MADRS total score at Week 1. Hypothesis (H2): Intermittent MK-1942 treatment is superior to placebo in reducing MADRS total score at Week 1.	MADRS total score
To evaluate the safety and tolerability of daily and intermittent MK-1942 treatment.	AEs Discontinuation of study intervention due to AEs
Secondary	
To compare the effect of daily MK-1942 treatment with the effect of placebo on the change from baseline in HAM-D17 total score at Week 3. Hypothesis (H3): Daily MK-1942 treatment is superior to placebo in reducing HAM-D17 total score at Week 3.	HAM-D17 total score

Objectives	Endpoints
To compare the effect of intermittent MK-1942 treatment with the effect of placebo on the change from baseline in HAM-D17 total score at Week 1. Hypothesis (H4): Intermittent MK-1942 treatment is superior to placebo in reducing HAM-D17 total score at Week 1.	HAM-D17 total score
To compare the effect of daily MK-1942 treatment with the effect of placebo on the change from baseline in CGI-S score at Week 3. Hypothesis (H5): Daily MK-1942 treatment is superior to placebo in reducing CGI-S score at Week 3.	CGI-S score
To compare the effect of intermittent MK-1942 treatment with the effect of placebo on the change from baseline in CGI-S score at Week 1. Hypothesis (H6): Intermittent MK-1942 treatment is superior to placebo in reducing CGI-S score at Week 1.	CGI-S score
To evaluate the PK of MK-1942 when administered daily or intermittently.	MK-1942 plasma concentration
Tertiary/Exploratory	
To compare the effect of daily and intermittent MK-1942 treatment with the effect of placebo on the change from baseline in BAC SC score at Week 3.	BAC SC score (number of correct matches on the BAC SC cognitive test after 90 seconds)

Objectives	Endpoints
To compare the effect of daily and intermittent MK-1942 treatment with the effect of placebo on: • the change from baseline in MADRS total score, HAM-D17 total score, HAM-D6 total score, and CGI-S score at time points through Week 4 that are not specified for the primary or secondary endpoints. • MADRS remission rate at all time points through Week 4. • the proportion of participants with a ≥50% reduction from baseline in MADRS total score at all time points through Week 4.	MADRS total score HAM-D17 total score HAM-D6 total score CGI-S score
To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	Germline genetic variation and association to clinical data collected in this study.
To investigate the relationship between the genetic polymorphisms of CYP2C19 and the pharmacokinetics of MK-1942. Variation in CYP2C19 alleles may be analyzed for association with any laboratory or clinical data collected in this study.	Germline genetic variation in CYP2C19 and association to clinical data collected in this study.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety MK-1942 in adult participants with TRD on stable antidepressant therapy. The study population will consist of male and female participants aged 18 to 65 years with a primary diagnosis of moderate-to-severe MDD (MADRS total score ≥25) who are currently experiencing a depressive episode and who have not adequately responded to 1 to 4 courses of approved antidepressant therapy (including the current course of antidepressant therapy) despite sufficient dose and duration (referred to in this document as treatment failure [for the current episode of moderate-to-severe MDD]). Prior to

randomization, participants' psychiatric history will be evaluated by the investigational site, and the primary diagnosis of moderate-to-severe MDD will be assessed centrally to confirm eligibility. Participant's depressive symptoms (based on HAM-D17) will also be assessed centrally to confirm eligibility prior to randomization. Participants will continue taking their stable background antidepressant therapy during the study.

Approximately 140 participants will be randomized in a 2:1:2 ratio to either (1) daily treatment with MK-1942 administered as 5 mg bid (Visit 4/Day 1 to Visit 5/Week 1), 10 mg bid (Visit 5/Week 1 to Visit 6/Week 2), and 20 mg bid (Visit 6/Week 2 to Visit 8/Week 4), (2) intermittent treatment with MK-1942 administered twice-weekly (10 mg biw), or (3) placebo, respectively (Section 1.2). MK-1942 or matching placebo will be administered as oral capsules. Randomization will be stratified by the number of treatment failures for the current episode of moderate-to-severe MDD to antidepressant therapy (1 vs >1) at Visit 1 (Screening). The study will aim to randomize approximately 30% of participants with more than 1 treatment failure (for the current episode of moderate-to-severe MDD) to ensure adequate representation of this population.

Details on the selection of the 2:1:2 randomization ratio are in Section 9.9.1.

For the daily dose group, the primary time point for efficacy assessments is Week 3 after participants in this group complete 3 weekly titrations with MK-1942. An additional week of treatment is included in this study to evaluate the effects of continued treatment with the 20 mg bid dose of MK-1942. For the intermittent dose group, the primary time point for efficacy assessments is Week 1. The effects of intermittent treatment with MK-1942 will also be examined through Week 4 (EOT/DC Visit). A post-dose follow-up visit (Visit 9) will occur approximately 1 week after the last dose of study intervention to evaluate the durability of MK-1942 effects on depression.

Safety will be monitored at scheduled visits and by a phone contact after each visit where study intervention is dispensed (including the Down-titration Visit, if applicable). A final post-dose follow-up visit (Visit 10) (site visit or TC) will be performed to assess laboratory safety tests, suicidality, AEs, SAEs, and other reportable safety events approximately 14 days after the last dose of study intervention or at Visit 10, whichever is later. An siDMC will evaluate the accruing unblinded safety data on a regular basis. Additionally, the siDMC will evaluate the results of an interim futility analysis performed after the first approximately 60% of randomized participants either complete Week 3 or discontinue before Week 3. The interim futility analysis will include a review of efficacy, safety, and tolerability data.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The goals of this Phase 2a PoC study are to test the hypothesis that MK-1942 reduces depressive symptoms in participants with TRD on stable antidepressant therapy, and to evaluate its safety and tolerability. The study will use a double-blind, parallel-group design in

the assessment of MK-1942 versus placebo, a standard design for studies of major depression (details on the rationale for use of placebo are in Section 4.2.2).

Two different dosing regimens of MK-1942 will be evaluated. In the daily dose group, MK-1942 will be uptitrated as follows: 5 mg bid (Visit 4/Day 1 to Visit 5/Week 1), 10 mg bid (Visit 5/Week 1 to Visit 6/Week 2), and 20 mg bid (Visit 6/Week 2 to Visit 8/Week 4). This dosing regimen was selected to achieve maximum RO levels and to reduce the incidence and severity of AEs reported in the Phase 1 program. Titrated daily dosing in the Phase 1 program enabled testing of higher doses and improved tolerability with MK-1942. The primary time point for efficacy analyses comparing the MK-1942 daily dose group with placebo is Week 3, which will allow participants in the MK-1942 daily dose group to complete 3 weekly titrations. An additional week of treatment is included in this study to evaluate the effects of continued treatment with the 20 mg bid dose of MK-1942.

The intermittent dose group will receive MK-1942 10 mg biw to evaluate whether transient exposure followed by a period of recovery promotes rapid effects (at Week 1) on depressive symptoms. This dosing regimen is similar to the administration of ketamine for treatment of depression. Although the exact mechanism remains unclear, some data suggest that the rapid antidepressant effects of medications such as ketamine may be induced by brief surges in glutamate cycling [Abdallah, C. G., et al 2018]. The 10 mg dose was selected based on available Phase 1 safety data while expected to achieve RO levels of approximately 40%. The effects of MK-1942 treatment in this group will also be examined through Week 4 (EOT/DC).

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The efficacy of MK-1942 treatment will be measured using scales that will assess changes in participants' depressive symptoms and severity of illness. Each scale will be administered by a qualified and trained rater. Participants will also complete a validated cognitive test to measure improvements in cognitive function. Details about the efficacy endpoints are provided below.

MADRS:

The MADRS (primary endpoint) is a well-established, validated scale for evaluating severity of depressive symptoms [Montgomery, S. A. and Asberg, M. 1979]. It has been widely used in pharmacotherapy studies of major depression. The 10 items comprising the MADRS evaluate the core symptoms of depression. Each item is rated on a scale from 0 to 6, with total scores ranging from 0 to 60, and higher scores corresponding to greater symptom severity [Williams, J. B. W. 2008].

HAM-D17

The HAM-D17 is a 17-item scale developed to evaluate depressive symptoms experienced by patients over the past week. Each item is rated on a scale from 0 to 2 or 0 to 4, with total

scores ranging from 0 to 52 and higher scores corresponding to greater symptom severity [Hamilton, M. 1960] [Hamilton, M. 1967] [Williams, J. B. W. 2013].

Results from 6 of the 17 items in the HAM-D17 that represent the core symptoms of MDD according to DSM-5™ criteria (depressed mood, feeling of guilt, work and activities, motor retardation, psychic anxiety, and somatic symptoms [general]) [Lin, H. S. 2019] will also be evaluated to derive the HAM-D6 scores.

CGI-S:

The CGI-S is a single-item scale for assessing global illness severity. In this study, the CGI-S is intended to measure the severity of a participant's depression. The CGI-S is rated on a 7-point scale using a range of responses from 1 (normal, not at all ill) to 7 (among the most extremely ill patients) [Guy, W. 1976].

BAC SC

In addition to antidepressant effects, preclinical data suggest that treatment with MK-1942 may enhance cognitive function by increasing glutamate signaling in the brain. There is also evidence suggesting that cognitive function in those with MDD may be improved through amelioration of depressive symptoms [Russo, M., et al 2015]. The BAC SC will be used in this study to assess potential changes in cognitive function. The BAC SC is a cognitive test that requires participants to assign numbers to non-meaningful symbols according to a key. The number of correct matches within the allowed time (90 seconds) constitutes the score [Atkins, A. S., et al 2017].

4.2.1.2 Safety Endpoints

Safety and tolerability will be assessed throughout the study by monitoring participants for AEs. Neurological and physical examinations, vital signs, 12-lead ECGs, and laboratory safety tests will be performed to detect any clinically meaningful effects. The C-SSRS will be administered to screen for the presence, and assess the severity, of possible suicidal ideation and behavior in all study participants (Section 4.2.3).

4.2.1.3 Pharmacokinetic Endpoints

Plasma samples will be drawn to evaluate the concentrations of MK-1942 at the time of the assessment of the efficacy endpoints to enable evaluation of potential PK/PD and PK/AE relationships. These data may be used in PK model development and analysis. Additional metabolites based on ongoing metabolites in safety testing analyses may also be evaluated.

The final decision as to which plasma samples will be assayed will be made by the Sponsor's Department of Quantitative Pharmacology and Pharmacometrics and the Clinical Monitor.

4.2.1.4 Pharmacodynamic Endpoints

Pharmacodynamic endpoints are not applicable.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

Despite the seriousness of the indication, a placebo group is necessary to evaluate the efficacy and safety of the addition of MK-1942 treatment in participants with TRD on stable antidepressant therapy. Without the use of placebo, false assumptions regarding the true efficacy of new drugs may be made. In the absence of a placebo control, it is nearly impossible to distinguish true drug effects from placebo effects in this study population. In addition, all participants will continue to take their stable background antidepressant treatment.

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

Prospective assessment of suicidal ideation and behavior will be performed in this study using the C-SSRS. This assessment is being conducted in compliance with the 2012 FDA guidance requiring prospective assessment in clinical studies conducted under IND applications and studies that are intended for submission in a NDA to the Neurology or Psychiatry Divisions of the FDA or biologics license application, as well as assessment in studies that fall within the guidance for other reasons (eg, CNS active/penetrant compounds, and known mechanisms or indications for which suicidal ideation/behavior has been previously identified as a potential concern).

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The starting dose for the MK-1942 daily dose group is 5 mg bid. The completed multiple ascending-dose study (P002) in healthy adults showed that a titration regimen with a starting dose of 5 mg bid is well-tolerated. No participants in Study P002 discontinued study intervention due to an AE and all reported AEs were either mild or moderate in intensity and resolved. The most common AEs were dizziness, headache, and nausea. The completed multiple ascending-dose study (P004) in healthy adults (non-elderly and elderly) had starting doses of either 5 mg bid or 8 mg bid, with extended dosing regimens that were generally well-tolerated. The starting and maximum dose for the MK-1942 intermittent dose group is 10 mg biw. The completed single ascending dose study (P001) in healthy adults showed that treatment with MK-1942 up to 12 mg is well-tolerated. No participants receiving MK-1942 discontinued study intervention due to an AE and all reported AEs were either mild or moderate in intensity and resolved. The most common intervention-related AEs were dizziness (associated with gait disturbance in a minority of participants), headache, and nausea. The incidence and intensity of the AEs of dizziness were strongly correlated with increasing exposure.

Based on the plasma concentration-RO relationship determined from the completed PET RO study (P003), single doses of 10 mg are anticipated to achieve a peak RO of 41%. Further, a preclinical MRS study in rhesus monkeys demonstrated that ROs ≥40% are associated with maximal increase in glutamate metabolism. Therefore, a 10-mg dose given intermittently is anticipated to precipitate a glutamate surge similar to that hypothesized to induce rapid antidepressant effects with ketamine and esketamine treatment. As a transient surge in glutamate release followed by a period of recovery may be important for promoting rapid-acting and durable antidepressant effects, intermittent administration of 10 mg biw will be evaluated in this study.

4.3.2 Maximum Dose/Exposure for This Study

In the MK-1942 daily dose group, MK-1942 will be uptitrated weekly (5 mg bid, 10 mg bid, and 20 mg bid) to assess efficacy at the primary time point (Week 3). The dose will be maintained at 20 mg bid for the last week of the study (Week 4) to obtain additional safety and tolerability data and evaluate the efficacy of longer exposure to inform the design of

future studies. The selection of this titration regimen is informed by the highest well-tolerated dosing regimens tested in both healthy adults and healthy elderly in Phase 1 studies where a gradual stepwise uptitration approach improved tolerability for AEs such as dizziness (and associated gait disturbance) and headache (but not nausea), allowing for evaluation of higher ROs. Doses up to 20 mg bid were well-tolerated in healthy adults in the completed multiple ascending-dose study (P002) (see Section 2.2.2). Safety data in healthy elderly in the Phase 1 study (P004) at doses up to 20 mg bid demonstrated similar tolerability with MK-1942 as observed in healthy adults. Doses up to 50 mg bid were also observed to be well-tolerated, but 3 out of 8 healthy non-elderly adults in the accelerated titration panel (Panel B) declined dose escalation to 30 mg bid. The most commonly reported AEs were dizziness, headache, abnormal dreams, and nystagmus (see IB for details). Studies investigating higher doses of MK-1942 reported non-serious AEs of asymptomatic increases in ALT and/or AST in 3 participants (Section 2.2.2). Laboratory values returned to normal baseline values or near normal with clear downward trends after discontinuation of study treatment in 2 participants, while 1 participant refused further testing. To ensure safety of participants, liver enzymes will be checked every 2 weeks during treatment and additional laboratory monitoring has been implemented at 2 weeks posttreatment (see SoA, Section 1.3). The dose titration for this Phase 2 PoC study will follow the gradual titration of 5 mg bid, 10 mg bid, and 20 mg bid. To minimize discontinuation of study intervention in this study, participants unable to tolerate or adhere to treatment with study intervention at or after Visit 6 (Week 2) may undergo a dose modification to the intended regimen of MK-1942 (see Section 6.6).

Because translation of RO targets to the clinical endpoint of antidepressant efficacy remains unclear and other clinical biomarkers are unavailable, doses up to 20 mg bid will be evaluated to support a well-tolerated dose approach in this study. Based on the PK-RO relationship, a mean steady state peak RO of 65% and trough RO of 49% are projected for the 20 mg bid dose of MK-1942. As the minimum RO for antidepressant efficacy is uncertain and the RO target of 40% represents the threshold for MRS and cognition activity, daily dosing with gradual titration enables exploration of maximum RO to test the mechanism and tolerability of MK-1942. The maximum dose of 20-mg bid maintains an adequate safety margin (16X) for the study population relative to the NOAEL (see IB for details).

4.3.3 Rationale for Dose Interval and Study Design

By inclusion of 2 MK-1942 treatment regimens, this study aims to investigate the therapeutic effects of higher ROs and sustained glutamate activity associated with daily treatment and the pulsatile glutamate surge potentially induced by intermittent treatment. This study will also evaluate the relationship of each regimen on the onset and time course of antidepressant effects.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

This study may be terminated early by the siDMC for safety concerns or futility based on the results of an interim analysis (see details in Section 9.7).

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data are to follow all local laws and guidelines in keeping with the needs for participant confidentiality while supporting the study of the disease, its related factors, and the IMP under investigation.

All psychiatric diagnoses specified for eligibility will be made according to DSM-5^{TM} criteria by a qualified psychiatrist (MD) or psychologist (PhD) (or equivalent qualification). All assessments of psychiatric symptoms which require an interview with the participant must be done in a language in which both the assessor and the participant are fluent. An interpreter is not permitted.

Male and female participants with TRD aged 18 to 65 years will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Meets the diagnostic criteria for moderate-to-severe MDD without psychotic features according to DSM-5^{TM} criteria (assessed via MINI) at Visit 1 (Screening).

2. Is currently experiencing an episode of moderate-to-severe MDD based on a MADRS total score ≥25 at Visit 1 (Screening).

3. Had an inadequate response, based on the investigator's or qualified delegate's clinical judgment, to 1 to 4 different courses of approved antidepressant therapy (including the current course of antidepressant therapy) of sufficient dose and duration (assessed using MGH-ATRQ) for the current episode of moderate-to-severe MDD.

4. Has HAM-D17 total scores at Visit 1 (Screening) as assessed by the site and at Visit 2 (Lead-in Call 1) and Visit 3 (Lead-in Call 2) as assessed by the central vendor rater that meet the requirements for study inclusion, as defined by the Sponsor. *Note: Site personnel and participants will be blinded to the specific HAM-D17 eligibility criteria. The central vendor rater will communicate eligibility status to the site.*

5. Has been on a stable course of antidepressant therapy for ≥4 weeks before Visit 1 (Screening).

   Note: Participants are to remain on their stable course of background antidepressant therapy through Visit 9 (Post-dose Follow-up Visit). See Section 8.1.7.2.

Note: Inclusion criteria 1 to 5 will be independently verified by the central vendor rater before randomization (see Section 8.1.8).

6. Has not initiated psychotherapy (based on participant report) for depressive symptoms in the last 3 months before Visit 1 (Screening) and agrees not to initiate a new psychotherapy for depressive symptoms or to modify their current regimen of psychotherapy for depressive symptoms from Visit 1 (Screening) to Visit 9 (Post-dose Follow-up Visit).

Demographics

7. Is male or female, from 18 years to 65 years of age inclusive, at the time of providing documented informed consent.

Male Participants

8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of study intervention:

   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

     OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

9. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 3 months postpartum, and at least one of the following conditions:

   - Not a WOCBP
     OR

   - A WOCBP and:

     – Uses a contraceptive method that is highly effective (with failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 7 days after the last dose of study intervention. Contraceptive methods with user dependency (eg, oral hormonal contraception) must be combined with a supplementary barrier method, such as male condom. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

     – Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations) both within the screening period and immediately before the first dose of study intervention. (If a urine test cannot be confirmed as negative [eg, an ambiguous result], a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.) Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.2.

     – Abstains from breastfeeding during the study intervention period and for at least 7 days after last study intervention.

– Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

10. Provides documented informed consent for the study. The participant may also provide consent for FBR. However, the participant may participate in the main study without participating in FBR.

Additional Categories

11. Is willing and considered able by the investigator to participate in protocol assessments, including recordings of interviews, adherence to treatment and visit schedules, and adherence with study procedures and restrictions.

12. Has a reliable contact person (eg, family member, social worker, case worker, case manager, or nurse) identified for emergent situations.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has an ongoing episode of MDD that started more than 2 years before Visit 1 (Screening).

2. Has a current or prior history of any personality disorder that may interfere with compliance or increase suicidal risk based on the investigator's judgment.

3. Has a current or prior history of one or more of the following:

    a) diagnosis of a psychotic disorder, bipolar and related disorders, MDD with psychosis, MDD with mixed features, posttraumatic stress disorder (if not in remission for at least 5 years before Screening), obsessive-compulsive disorder, or autism spectrum disorder.

    b) chronic convulsive disorder (eg, epilepsy or seizure disorder), except febrile seizures during childhood.

    c) neurodegenerative disorder (eg, Parkinson's, Alzheimer's, or Huntington's disease), traumatic brain injury causing ongoing cognitive difficulties, or any chronic organic disease of the central nervous system (eg, multiple sclerosis).

    d) intellectual disability of a severity that would affect the ability of the participant to participate in the study.

4. Meets criteria for substance abuse or dependence disorder (excluding caffeine and tobacco use) currently or within the 12 months before Visit 1 (Screening).

5. Has a known allergy or intolerance to the active or inert ingredients in MK-1942.

6. Has a history of malignancy ≤3 years before Visit 1 (Screening) except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

7. Has a BMI >40 kg/m^2 (BMI = weight in kg/height in meters^2); details are provided in the Study Operations Manual.

8. Has a risk factor for QTc prolongation as defined by:

   - a known history or current evidence of QTc interval >470 msec (men) or >480 msec (women), OR

   - a known history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome)

   Note: ECGs will be performed in triplicate. At Visit 1 (Screening), the average of the 3 QTcF intervals based on the central vendor overread will be used to assess eligibility. At Visit 4 (Day 1), the average of the 3 QTcF intervals based on the local ECG printout will be used to assess eligibility (additional details on ECG assessments are in Section 8.3.4).

9. Has HIV or nonstable hypothyroidism, diabetes, cardiovascular disease, or respiratory disease or has another chronic medical condition that is not considered to be adequately treated in the opinion of the investigator.

   Note: The prescribed doses and regimens of prior medications should be stable for ≥3 months before Visit 1 (Screening) and there should not be expected changes for these medications before and during the study. Treatment with a medication is considered stable if dose adjustments reflect optimizing treatment rather than reacting to significant changes in the treated conditions. Timing for substitution of prohibited medications is presented in Table 2.

10. Has a severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or administration of study intervention or may interfere with the interpretation of study results and, in the opinion of the investigator or Sponsor, would make the participant inappropriate for entry into this study.

11. Is at imminent risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in assessment of suicidal ideation on the C-SSRS) in the *past 2 months* or suicidal behavior in the *past 6 months.*

Prior/Concomitant Therapy

12. Does not meet the requirements defined in Section 8.1.7.2 (Concomitant Medications, Table 2) that specify when prohibited medications/products or prohibited doses for allowed medications must be stopped relative to Visit 1 (Screening).

13. Failed to adequately respond in the investigator's or qualified delegate's clinical judgment to treatment with ketamine or esketamine for the current or a prior episode of MDD.

14. Previously received electroconvulsive therapy (within the past 10 years), deep brain stimulation, or vagal nerve stimulation for treatment of depression. TMS is not exclusionary unless received within 6 weeks before Visit 1 (Screening).

Prior/Concurrent Clinical Study Experience

15. Is currently participating in or has previously participated in an interventional clinical study within the 2 months before Visit 1 (Screening), or has participated in >4 interventional clinical studies within the 2 years before Visit 1 (Screening).

Diagnostic Assessments

16. This exclusion criterion has been removed.

17. Has known renal disease or is experiencing renal insufficiency as defined by eGFR <30 mL/min/1.73 m^2 (MDRD) at Visit 1 (Screening).

18. Has laboratory or clinical evidence of clinically significant hepatic conditions such as one or more of the following:

    - ALT ≥1.5x ULN or AST ≥2x ULN at Visit 1 (Screening)*

      *Note: Participants may be retested 1 time at least 1 day after Visit 1 (Screening).

    - Liver disease, including but not limited to chronic viral hepatitis, non-viral hepatitis, cirrhosis, malignancies, autoimmune liver diseases (ie, autoimmune hepatitis, primary biliary cholangitis, or primary sclerosing cholangitis).

19. Has an abnormal TSH value at Visit 1 (Screening). Exception: A participant with an abnormal TSH value and a normal FT4 value may be eligible if clinically stable and without signs of hypo- or hyperthyroidism, in the investigator's judgment. Any thyroid treatment must be stable for ≥3 months before Visit 1 (Screening).

20. Routinely consumes >3 alcoholic drinks per day. One standard drink is defined as any beverage containing 14 g of pure alcohol (ie, 12 oz of beer, 8 to 9 oz of malt liquor, 5 oz of wine, 1.5 oz of distilled spirits).

21. Has a positive breath test for alcohol at Visit 1 (Screening) or Visit 4 (Day 1).

22. Has a local or central positive test result for drugs of abuse at Visit 1 (Screening) or a local positive test result for drugs of abuse at Visit 4 (Day 1). Drugs of abuse include opiates, barbiturates, amphetamine/methamphetamine, cannabis, methadone, cocaine, and phencyclidine.

    Note 1: Participants who have a positive test result at Visit 1 (Screening) due to prescribed opiates (excluding methadone), barbiturates, or amphetamines may continue in the pretreatment period if the prohibited medication is discontinued at least 1 week or 5 half-lives (whichever is longer) before the first dose of investigational intervention. The participant may be enrolled if the Visit 4 (Day 1) test for drugs of abuse is negative. A retest is not permitted for those who test positive at Visit 1 (Screening) due to non-prescription of drugs of abuse.

    Note 2: Participants who have a positive test result for cannabis at Visit 1 (Screening) must be evaluated by the investigator for substance use disorder and may be enrolled if abuse is ruled out.

Other Exclusions

23. Requires use of a language interpreter to participate in the study.

24. Had major surgery or donated or lost >1 unit of blood (approximately 500 mL) within the 4 weeks before Visit 1 (Screening).

25. Has a positive pregnancy test at Visit 1 (Screening) or Visit 4 (Day 1) (see Section 8.3.6.2) or is currently breastfeeding or plans to breastfeed during the course of the study.

26. This exclusion has been removed.

27. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants will refrain from consuming grapefruit juice, grapefruits, and grapefruit products from Visit 1 (Screening) through Visit 8 (EOT/DC Visit). Other types of fruit juice, fruits, and fruit products are permitted during the study. Sites should instruct participants to take study intervention with water.

MK-1942 should **NOT** be taken with food. Participants should fast (ie, no food or drink, except water, black coffee, black tea, or juice [except grapefruit juice]) according to the guidance below. In situations where the fasting guidance cannot be followed, the participant should fast for at least 1 hour before and 1 hour after dosing. Non-study medications can be taken with water during fasting periods.

- Evening Dosing: Participants should take their evening dose of study intervention close to bedtime, at least 1 hour after the evening meal, and should continue to fast for at least 1 hour after dosing.

- Morning Dosing (days with no clinic visit): Participants should take their morning dose of study intervention either:

    - before their morning meal with at least 1 hour fast after dosing or

    - at least 1 hour after a light breakfast with at least 1 hour fast after dosing.

- Morning Dosing (days with scheduled clinic visits): From Visit 4 (Day 1) to Visit 7 (Week 3), participants should attend clinic visits after their overnight fast. They must **NOT** take a morning dose of study intervention from the blister cards dispensed at the previous visit. Participants should **NOT** eat a meal until at least 1 hour after taking study intervention from the new blister cards dispensed in the clinic. A low fat, low caloric snack (eg, a slice of toast with jelly, a cup of skim or 1% milk, a cup of nonfat yogurt, a packet of oatmeal made with water, or a piece of fruit [except grapefruit]) can be eaten at least 1 hour before dosing at these visits to minimize hunger.

- Down-titration Visit Dosing (if applicable): The first dose of study intervention from the blister cards dispensed at the Down-titration Visit depends on when the last dose was taken from the previously dispensed blister cards. For example, if the last dose from the previously dispensed blister cards was taken in the morning on the third day after Visit 6 (Week 2), then the evening dose corresponding to the third day after Visit 6 (Week 2) will be the first dose taken from the blister cards dispensed at the Down-titration Visit. Participants should fast for 1 hour before and 1 hour after dosing. Additional information will be provided in the Study Operations Manual.

The last dose of study intervention will be taken the evening before Visit 8 (EOT/DC Visit). There are no fasting requirements for Visit 8 (EOT/DC Visit) or Visit 9 (Post-dose Follow-up Visit).

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants will be counseled to limit alcohol use to moderate amounts while participating in the study (ie, ≤3 drinks per day and not more than 21 drinks per week). One standard drink is defined as any beverage containing 14 g of pure alcohol (ie, 12 oz of beer, 8 to 9 oz of malt liquor, 5 oz of wine, 1.5 oz of distilled spirits). There are no caffeine or tobacco/nicotine restrictions.

5.3.3 Activity Restrictions

Participants will be informed about the risk of dizziness with MK-1942 treatment and will be instructed not to drive or operate heavy machinery until they determine that study intervention, taken as directed, does not affect their ability to engage in these activities.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Information on rescreening is provided in Section 8.11.1.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws consent will not be replaced.

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 study participant according to the study protocol.

Clinical supplies (study intervention provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

MK-1942 and matching placebo to be used in this study will be packaged in blister cards and an equal number of capsules will be administered in the morning and evening regardless of treatment assignment. Study interventions are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Inter-vention Type	Dose Form-ulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
MK-1942 Daily Dose Group	Experi-mental	MK-1942	Drug	Capsule	5 mg, 10mg	5 mg bid, 10 mg bid, 20 mg bid	Oral	Weeks 1, 2, 3, 4	Test Product	IMP	Central
MK-1942 Daily Dose Group	Experi-mental	Placebo	Drug	Capsule	0 mg	0 mg bid	Oral	Weeks 1, 2, 3, 4	Placebo	IMP	Central
Placebo	Placebo Comparator	Placebo	Drug	Capsule	0 mg	0 mg bid	Oral	Weeks 1, 2, 3, 4	Placebo	IMP	Central
MK-1942 Inter-mittent Dose Group	Experi-mental	MK-1942	Drug	Capsule	10 mg	10 mg biw	Oral	Weeks 1, 2, 3, 4	Test Product	IMP	Central
MK-1942 Inter-mittent Dose Group	Experi-mental	Placebo	Drug	Capsule	0 mg	0 mg bid	Oral	Weeks 1, 2, 3, 4	Placebo	IMP	Central

Abbreviations: bid=twice-daily, biw=twice-weekly, IMP=investigational medicinal product, NIMP/AxMP= noninvestigational/auxiliary medicinal product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note 1: The dose of MK-1942 for participants in the MK-1942 daily dose group will be uptitrated weekly as follows: 5 mg bid (Visit 4/Day 1 to Visit 5/Week 1), 10 mg bid (Visit 5/Week 1 to Visit 6/Week 2), and 20 mg bid (Visit 6/Week 2 to Visit 8/Week 4).

Note 2: Dose modification to the intended regimen of MK-1942 may occur due to intolerance or non-adherence, as described in Section 6.6.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number.

Refer to Section 8.1.12 for details regarding administration of the study intervention.

6.1.1 Medical Devices

No medical devices are used in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an IRT system. There are 3 study intervention arms. Participants will be assigned randomly in a 2:1:2 ratio to either (1) daily treatment with MK-1942 administered as 5 mg bid (Visit 4/Day 1 to Visit 5/Week 1), 10 mg bid (Visit 5/Week 1 to Visit 6/Week 2), and 20 mg bid (Visit 6/Week 2 to Visit 8/Week 4), (2) intermittent treatment with MK-1942 administered twice-weekly (10 mg biw), or (3) placebo, respectively.

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factor(s):

1. Number of treatment failures (1 vs >1) for the current episode of moderate-to-severe MDD

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. MK-1942 and placebo will be packaged identically so that the blind is maintained. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for ≥2 days within a weekly treatment interval will lead to the participant being retrained on compliance by site personnel. Any additional interruptions from the protocol-specified treatment plan for ≥2 days within a weekly treatment interval will require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Participants in the daily dose and intermittent dose groups who have substantial non-adherence with study intervention may undergo a dose modification to the intended regimen of MK-1942 (in a blinded manner), as described in Section 6.6. Dose modification for non-adherence is not applicable to the placebo group.

Compliance with study intervention will be analyzed to assess the percentage of days when participants take the prescribed capsules of study intervention (Section 9.11). Adherence with study intervention will be assessed to facilitate clinical decision making on appropriate dosing (additional details on adherence are provided in the Study Operations Manual).

Participants will be directed to bring all dispensed blister cards to each visit. Participants' compliance with study intervention will be monitored using technology that collects data on when capsules are removed from blister cards and through participant interview by site personnel. If a participant's report is inconsistent with electronically captured compliance data, then site personnel will reconcile the differences and determine the most accurate

representation of study intervention administration. The electronically captured dispensing data can be annotated after reconciliation occurs.

6.5 Concomitant Therapy

Medications, therapies, or products specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or treatments specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Prohibited medications, therapies, and products and prohibited dose strengths for allowed medications are listed in Table 2. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant receives concomitantly during the study (from Visit 1 [Screening] through Visit 10 [14-day Post-dose Follow-up Visit]) should be recorded in the study database.

Any licensed COVID-19 vaccine (including for emergency use) in a particular country is permitted in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (ie, those not licensed or approved for emergency use) are not permitted.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

As described in Section 4.1 (Overall Design) and shown in Section 1.2 (Schema), the dose of MK-1942 for participants in the daily dose group will be uptitrated as follows: 5 mg bid (Visit 4/Day 1 to Visit 5/Week 1), 10 mg bid (Visit 5/Week 1 to Visit 6/Week 2), and 20 mg bid (Visit 6/Week 2 to Visit 8/Week 4). The dose of MK-1942 (10 mg biw) for participants in the intermittent dose group will remain stable throughout the study (unless down-titration for intolerance or non-adherence occurs). Participants in the placebo group will not receive treatment with MK-1942.

To minimize discontinuation of study intervention, participants unable to tolerate treatment with study intervention at or after Visit 6 (Week 2) may undergo a dose modification to the intended regimen of MK-1942 in a blinded manner. Participants who are intolerant to treatment in the MK-1942 daily dose group will maintain the 10 mg bid dose at Visit 6 (Week 2) or will down-titrate from 20 mg bid to 10 mg bid after Visit 6 (Week 2). Participants who are intolerant to treatment in the MK-1942 intermittent dose group will maintain the 10 mg biw dose at Visit 6 (Week 2) or will down-titrate from 10 mg biw to

5 mg biw after Visit 6 (Week 2). Participants in the placebo group will undergo mock dose modification reflecting changes in doses relative to the 2 other groups.

Additionally, participants in the daily dose group who have substantial non-adherence with study intervention may also undergo a dose modification to the intended regimen of MK-1942 (in a blinded manner), as described below. This is because substantial non-adherence could diminish the improved tolerance developed through uptitration to AEs (Section 2.2.2) associated with MK-1942 treatment. Guidance on how to assess substantial non-adherence and additional details on the management of MK-1942 dosing are provided in the Study Operations Manual.

Participants in the daily dose group with substantial non-adherence during the prior week of treatment may have their dose of MK-1942 managed as follows:

- Non-adherence prior to Visit 5 (Week 1): The dose of MK-1942 will be uptitrated from 5 mg bid to 10 mg bid according to the prespecified dosing schedule (Section 1.2).

- Non-adherence prior to Visit 6 (Week 2): The 10 mg bid dose of MK-1942 will be maintained for the remainder of the study (ie, the participant will not uptitrate to the intended maximum study dose of 20 mg bid).

- Non-adherence prior to Visit 7 (Week 3): The dose of MK-1942 will be down-titrated from 20 mg bid to 10 mg bid; the 10 mg bid dose will be maintained for the remainder of the study.

Participants in the intermittent dose group with substantial non-adherence during the prior week of treatment may have their intended dose regimen managed as follows:

- Non-adherence prior to Visit 5 (Week 1) or Visit 6 (Week 2): The 10 mg biw dose of MK-1942 will be maintained according to the prespecified dosing schedule (Section 1.2)

- Non-adherence prior to Visit 7 (Week 3): The dose of MK-1942 will be down-titrated from 10 mg biw to 5 mg biw; the 5 mg biw dose will be maintained for the remainder of the study.

Participants in the placebo group with substantial non-adherence will undergo mock dose modifications reflecting changes in doses relative to the 2 other groups.

Because it is not possible to comprehensively account for all scenarios of non-adherence, the Sponsor should be consulted when management of a participant's study intervention is in question.

Participants who undergo a dose modification to the intended regimen for intolerance or non-adherence with study intervention will not undergo any further dose modifications for the remainder of the study.

All study intervention assignments/modifications will be completed using the IRT system.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.17). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.6.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 1.3 and Section 8.11.5.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, place the participant at unnecessary risk from continued administration of study intervention.

- The participant has a positive urine or serum pregnancy test. See Section 8.3.6.2 for pregnancy testing requirements.

- The participant has an ALT ≥3x ULN

- The participant has an AST ≥3x ULN with total bilirubin ≥2x ULN and ALP <2x ULN

- The participant has an AST ≥3x ULN with ALT value >100 IU/L

  Note 1: Liver function tests are to be confirmed by repeat testing within 48 hours of initial test results. If test results are unable to be confirmed within this timeframe, the study intervention should be withheld until test results are available. Study intervention should be discontinued if unable to repeat testing.

  Note 2: If the investigator identifies a clear cause for the liver enzyme elevations unrelated to study intervention, then study intervention may be continued with approval by the Sponsor.

- The participant meets either of the following criteria for QTcF interval at a visit (**Note**: ECGs will be performed in triplicate [Section 8.3.4]):

  - The average of the 3 QTcF intervals based on either the local ECG printout or subsequent central vendor overread is >500 msec.

  - The average of the 3 QTcF intervals based on either the local ECG printout or subsequent central vendor overread increased by >60 msec, relative to the central vendor overread average at Visit 4 (Day 1).

- The participant reports suicidal ideation with intent, with or without a plan or method through an AE or C-SSRS (ie, a positive response to Items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior. If the reported suicidal ideation is passive, and participant expressly denies any intent to act, and who, after evaluation, is not judged to be at serious risk for self-harm during the study, the participant may continue on study intervention. Refer to Sections 8.3.7.1 on Clinical Assessments for Suicidal Ideation and Behavior Monitoring (for requirements pertaining to the evaluation of such events), and Section 8.4.7 for Events of Clinical Interest.

- The participant is unable to tolerate treatment with study intervention before Visit 6 (Week 2).

  Note: Participants who are unable to tolerate study intervention after a dose modification to the intended regimen should be discontinued from study intervention.

- The participant begins to use a prohibited medication/therapy/product or a prohibited dose of an allowed medication listed in Section 8.1.7.2 (Concomitant Medications, Table 2). This criterion includes participants who test positive (local or central) for a drug of abuse (except cannabis, which is not prohibited if abuse or substance use disorder is ruled out).

  Note: Participants who are willing and able to safely (per the investigator) stop using the prohibited medication/therapy/product (including drugs of abuse) or reduce from a prohibited to an acceptable dose for an allowed medication through Visit 9 (Post-dose Follow-up Visit) may continue study intervention at the investigator's discretion.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Sections 8.1.16 and 8.1.16.1. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

See Section 8.1.15 for guidance on contacting participants who miss a scheduled visit or TC.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

All study-related medical decisions must be made by an investigator who is a qualified physician.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study is approximately 80 mL (see the central laboratory manual).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant or their legally acceptable representative prior to participating in this clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician (or a qualified designee), to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

Medical history will be obtained by the investigator (or qualified designee).

Clinically significant findings in physical and neurological examinations, laboratory tests, ECGs, or other evaluations during the pretreatment period are to be noted in the participant's medical history.

All available history of psychiatric conditions and symptoms that are not core symptoms of depression (eg, agitation, anxiety, insomnia), including those captured in the MINI evaluation (Section 8.1.5), are to be recorded in the medical history. Other medical history conditions that occurred within the last 5 years are also to be recorded.

8.1.5 Psychiatric History and MINI

A psychiatric history will be obtained by the investigator (or qualified designee). The investigator may review and use multiple information sources (eg, medical charts, pharmacy verification of medication treatment, participant self-report, and healthcare professional or paraprofessional report) to obtain relevant historical information. All psychiatric diagnoses specified in the inclusion/exclusion criteria will be made according to the relevant DSM-5™ criteria.

The MINI will be administered by a qualified site rater and used to confirm the diagnosis of MDD (without psychotic features). It will also be used to evaluate other psychiatric comorbidities, and to assess elements of the psychiatric history.

The investigator (or qualified designee) will use their best estimate based on available information sources (as noted above) to determine the onset of a participant's current episode of MDD and the total number of prior episodes in a participant's lifetime.

8.1.6 MGH-ATRQ

The MGH-ATRQ will be administered by a qualified site rater at Visit 1 (Screening) to determine the number of prior antidepressant treatment failures participants experienced for the current episode of MDD. The instrument collects drug class and drug name, assesses adequacy of dose and duration of treatment, and collects degree of symptomatic improvement with each treatment. Participants are required to have had an inadequate response based on the rater's clinical judgment to at least 1, but no greater than 4, different courses of approved antidepressant therapy (including the current course of antidepressant therapy) of sufficient dose and duration for the current episode of moderate-to-severe MDD to be eligible for the study (Section 5.1).

Sites should verify with a pharmacy (verbal or written records) that participant meets inclusion criteria for current antidepressant therapy taken for at least 4 weeks before Visit 1. Earlier treatment(s) taken for the current episode may be confirmed based on participant or provider reporting or other medical records. The Sponsor should be consulted if pharmacy verification of antidepressant medications is unable to be obtained during the pretreatment period.

8.1.7 Prior and Concomitant Medications Review

8.1.7.1 Prior Medications

The investigator (or qualified designee) will review and record prior antidepressant medications and other prior psychiatric medications taken by the participant within 2 years before Visit 1 (Screening). Other prior medications taken by the participant within 3 months before Visit 1 (Screening) will also be recorded.

8.1.7.2 Concomitant Medications

The investigator (or qualified designee) will review and record medications/products taken by the participant during the study. Participants are to remain on their stable course of background antidepressant therapy and permitted psychotropic medications from Visit 1 (Screening) to Visit 9 (Post-dose Follow-up Visit).

WOCBP who are taking oral contraceptive medications should remain on them during the intervention period and for at least 7 days after the last dose of study intervention. Based on the unbound concentrations observed in vivo, induction of CYP enzymes by MK-1942 is not anticipated to be clinically relevant or to impact the exposure of common oral contraceptives via CYP3A induction.

Prohibited medications/therapies/products and prohibited doses for allowed medications listed in Table 2 should not be administered from Visit 1 (Screening) to Visit 9 (Post-dose Follow-up Visit). These include strong inducers of CYP2C19 because they could affect the oxidative metabolism of MK-1942. Sensitive substrates of CYP2C19 are prohibited because MK-1942 has the potential to inhibit CYP2C19 metabolism. Additionally, other agents with glutamatergic activity could influence the effects of MK-1942 and are also prohibited.

Treatment with other medications/therapies/products listed in Table 2 or with doses above the thresholds listed in Table 2 is prohibited to minimize their potential effects on depressive symptoms.

Table 2 categorizes prohibited medications/therapies/products and prohibited doses of medications by those that participants must discontinue at Visit 1 (Screening) to wash-off during the Lead-in Period and those that participants must be off for ≥4 weeks before Visit 1 (Screening). For the latter category, participants' medications/products should not be discontinued or adjusted before the study for the sole purpose of eligibility. Participants on a medication/product or a prohibited dose of a medication in this latter category within the 4

weeks before Visit 1 (Screening) should be screen-failed and can be rescreened after the ≥4 week requirement is met (see Section 8.11.1).

The investigator (or qualified designee) must consider if discontinuation or adjustment of a medication/product in Table 2 can be done safely without significant destabilization or increased suicidality.

The list of prohibited medications/therapies/products in Table 2 is not comprehensive. Investigators should contact the sponsor for clarification regarding questions about a treatment that may be in a prohibited category but is not on the list.

Table 2 Prohibited Medications/Therapies/Products and Prohibited Dose Strengths for Allowed Medications

Prohibited Medications/Therapies/Products and Prohibited Dose Strengths for Allowed Medications	**Eligibility Relative to Visit 1 (Screening)**
CYP2C19 Inducers and Substrates	
Strong CYP2C19 inducers, such as: artemisinin, carbamazepine (strong inducer), norethisterone, rifampin, primidone.	• Participants must be off these medications for ≥4 weeks before Visit 1 (Screening).
Sensitive CYP2C19 substrates, such as: clopidogrel, fluoxetine (doses >40 mg/day are prohibited), moclobemide, tolbutamide, voriconazole, warfarin	• Participants must not be on doses of fluoxetine >40 mg/day or any treatment with moclobemide within the 4 weeks before Visit 1 (Screening). • Other medications in this category must be discontinued at Visit 1 (Screening).
Agents With Glutamatergic Activity	
ketamine, esketamine, N-acetylcysteine, lamotrigine, topiramate, riluzole	• Participants must be off these medications for ≥4 weeks before Visit 1 (Screening). Note: Participants who have been off ketamine or esketamine for ≥4 weeks, but who had an inadequate response to either of these treatments, are not eligible for the study (Section 5.2).
Other Medications and Therapies	
Atypical antipsychotics (use of low dose atypical antipsychotics [eg, quetiapine ≤100 mg/day, or equivalent] for sleep is permitted)	• Except when taken at low doses for sleep, participants must be off these medications for ≥4 weeks before Visit 1 (Screening).
Electroconvulsive therapy, deep brain stimulation, vagal nerve stimulation, TMS	• Any prior treatment with one or more of these therapies is exclusionary (Section 5.2). Electroconvulsive therapy is exclusionary if received within the past 10 years. TMS is exclusionary if received within 6 weeks before Visit 1 (Screening).

Prohibited Medications/Therapies/Products and Prohibited Dose Strengths for Allowed Medications	Eligibility Relative to Visit 1 (Screening)
Herbal drugs/dietary supplements that may affect mood, including but not limited to, St. John's wort, artemisinin, ginseng, valerian, cassia, licorice (glycyrrhizin), ginkgo	• Participants must be off St. John's wort for ≥4 weeks before Visit 1 (Screening). • Other products in this category must be discontinued at Visit 1 (Screening).
Drugs of abuse, including opiates, barbiturates, amphetamine/methamphetamine, cannabis, methadone, cocaine, and phencyclidine	• Participants on prescribed opiates (except methadone, see below), barbiturates, or amphetamines must discontinue these treatments at Visit 1 (Screening). Note: Participants who have a positive test result at Visit 1 (Screening) due to prescribed opiates (excluding methadone), barbiturates, or amphetamines may continue in the pretreatment period if the prohibited medication is discontinued at least 1 week or 5 half-lives (whichever is longer) before the first dose of investigational intervention (See Section 5.2). • Participants on methadone or drugs of abuse are not eligible. • Intermittent cannabis is not prohibited if abuse or substance use disorder has been ruled out.
Prohibited Dose Strengths for Allowed Medications	
Doses of lorazepam >3 mg/day or the equivalent dose of other benzodiazepines	• Participants must not be on prohibited doses of benzodiazepines or partial benzodiazepines within the 4 weeks before Visit 1 (Screening). • For participants on an allowed dose of a benzodiazepine or partial benzodiazepine, the dose should be stable for ≥4 weeks before Visit 1 (Screening).
Doses of the following partial benzodiazepine agonists: zolpidem >10 mg/day, zaleplon >20 mg/day, zopiclone >15 mg/day	
High-dose biotin (>5 mg/day) is prohibited 1 day before and on the day of pregnancy testing.	

8.1.8 External Verification of Diagnosis

A central vendor rater will be used to confirm that each participant randomized to study intervention meets entry criteria for currently having an ongoing and stable episode of treatment-resistant moderate-to-severe MDD. To support confirmation of eligibility, the site will submit information for each participant to the central vendor rater during the pretreatment period (Section 8.11.2.1). The required materials are specified in the Study Operations Manual.

A participant is not eligible for randomization until confirmation of eligibility is provided by the central vendor rater.

8.1.9 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization OR intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on rescreening are provided in the Study Operations Manual.

8.1.10 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.11 IRT Visit Registration, IRT Randomization, and Study Intervention Dispensing

The investigator (or designee) will register the participant in IRT at the visits specified in the SoA. Participants who satisfy all entry criteria will be assigned a randomization number via IRT at Visit 4 (Day 1). Participants who do not meet eligibility criteria will be entered into IRT as screen failures. IRT will also be used to identify the study intervention supplies that will be dispensed to participants at the visits specified in the SoA. Refer to the IRT user manual for details about the IRT system.

8.1.12 Study Intervention Administration

Blinded study intervention will be administered as oral capsules and packaged in blister cards. At Visit 4 (Day 1), participants will be educated by a trained member of the site staff on appropriate dosing and fasting instructions (see Section 5.3.1), package opening, and the requirement to return all blister cards at each visit. At Visit 4 (Day 1), sites will provide participants with a copy of the Study Medication Guidance and train participants on how to use the guide. Sites will be expected to review this guide during each treatment visit (V5 to V8) and provide retraining, as needed. Documentation of participant training will be filed with the participant's source documents.

If the participant's pregnancy test is positive, study intervention must not be dispensed. Sites must hold or discontinue study intervention as described in Section 8.3.6.2 and Section 7.1.

Details on appropriate handling, storage, and accountability of study intervention are provided in Section 6.2.2.

8.1.12.1 Timing of Dose Administration

The first dose of blinded study intervention is preferred to occur in the morning and will be witnessed (see Section 8.1.13) in the clinic at Visit 4 (Day 1) after all assessments and procedures (except collection of the post-dose PK sample) specified in the SoA are complete. The next dose of blinded study intervention will be taken unsupervised at home in the evening after Visit 4 (Day 1).

Evening clinic visits are not preferred but may be done if morning visits are not feasible for participants. Participants should NOT skip the first dose of study intervention from each week's supply (Day 1 AM), even if they conduct a visit in the evening. The PM dose should not be the first dose taken on Day 1. See the Study Operations Manual for more information.

Except for days with scheduled clinic visits during the double-blind treatment period, administration of study intervention will continue to occur unsupervised at home at approximately the same time in the morning and approximately the same time in evening. On days with scheduled clinic visits during the double-blind treatment period, participants must not take a morning dose of study intervention from the blister cards dispensed at the previous visit. Participants will take their morning dose of study intervention in the clinic from the newly dispensed blister cards. For participants who undergo a dose modification after Visit 6 (Week 2) (Section 6.6), the timing for administration of study intervention on the day of the Down-titration Visit will be determined by when the participant took their previous dose (Section 5.3.1).

MK-1942 should **NOT** be taken with food. Dosing guidelines relative to meals are provided in Section 5.3.1.

If a participant misses a dose of study intervention in the morning or evening, the missed dose should be taken as soon as possible. If more than 6 hours have passed since the participant's normal morning or evening dosing time, then the missed dose should be skipped, and the next dose should be taken as normal.

8.1.13 Witnessed Dose

Administration of study intervention will be witnessed by a trained member of the site staff at visits specified in the SoA. Each witnessed dose will be taken after assessments and procedures for the visit are complete (except for collection of the post-dose PK sample at Visit 4 [Day 1]). The time of dosing will be recorded.

8.1.14 Study Intervention Accountability

Accounting for compliance and adherence with study intervention is described in Section 6.4.

8.1.15 Telephone Contacts (Site to Participant)

A telephone contact will be performed within the first 3 days after Visit 4 (Day 1), Visit 5 (Week 1), Visit 6 (Week 2), Visit 7 (Week 3), and the Down-titration Visit (if applicable) by

trained site personnel to monitor for AEs and compliance with study intervention and to encourage adherence with the fasting guidelines (Section 5.3.1). Visit 10 (Week 6) may be completed as a telephone contact, as needed (ie, if a site visit is not feasible). Additional telephone contacts/visits may be performed at the investigator's discretion.

The investigator is responsible for ensuring that all telephone contacts are performed by a staff member who is a health care professional qualified to elicit a discussion with the participant that will lead to a clinically meaningful disclosure on the participant's well-being. Telephone contacts are to be documented in the source documents and the investigator must review the entry within 2 days. However, if the participant reports any clinically concerning events (eg, SAEs, ECIs) during a TC, then the investigator must be promptly notified. The investigator will contact the participant to determine if a clinic visit is warranted.

If the participant cannot be reached by telephone at the regularly scheduled time or misses a visit, the site should make at least 3 attempts (in addition to the initial phone call) to contact the participant within 48 hours of the missed scheduled time. The participant's reliable contact person should be called if attempts to contact the participant are not successful. All phone contacts and attempts should be recorded in source documents.

8.1.16 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 7.1.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the EOT/DC Visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.16.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between

the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.17 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

8.1.18 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

Rating scale assessments at clinic visits will be performed by site raters who meet the qualification and training requirements per scale. Rater qualifications, training and applicable certification processes are established in the Study Operations Manual. Each assessment scale may require different raters, but it is strongly encouraged that the same rater evaluates the same participant for the duration of the study. As a best practice, back-up raters should be identified for each participant to improve continuity and reliability of the ratings.

To avoid the influence of participant fatigue at in-clinic visits, it is recommended that sites administer the BAC SC first, followed by the MADRS (primary endpoint) and the HAM-D17. The CGI-S is recommended as the last clinical assessment so that all relevant information can be reviewed when completing the CGI-S.

While concerns have been raised that recording assessments could theoretically compromise participant privacy, this issue must be balanced with the need to conduct methodologically adequate and scientifically rigorous studies that are capable of testing key hypotheses. Given that the key endpoints in this study involve subjective clinical judgments, monitoring the adequacy of participant interviews and ratings is essential and part of strong research methodology. Prior studies suggest that the failure to adequately monitor such ratings can substantially increase the risk of failed studies [Khan, A., et al 2013].

To ensure the highest level of data quality, both the data and audio recordings (MINI and MGH-ATRQ, MADRS, HAM-D17) of some study assessments will be collected using a tablet and the audio recordings will be reviewed by the central rater vendor. The vendor will use the audio recordings to provide feedback and suggestions to raters regarding scale administration and scoring, as needed, to ensure consistency across all raters and sites. Vendor feedback may be used to refine scores entered by the site for an individual rating, at the discretion of the site rater. Data for both the audio recordings and the tablet are encrypted in order to protect the participant's privacy and are automatically uploaded to a secure cloud-based server. Additional details are provided in the Study Operations Manual.

8.2.1 MADRS, HAM-D17, CGI-S, BAC SC

This study will use 3 rating scales to assess depressive symptoms (MADRS, HAM-D17, CGI-S) and a test to assess cognitive function (BAC SC). The MADRS and HAM-D17 will be administered in accordance with a structured interview guide [Williams, J. B. W. 2008] [Williams, J. B. W. 2013]. A subset of 6 items (HAM-D6) derived from the HAM-D17 will also be evaluated. The scales and the cognitive test are described in Section 4.2.1.1 and will be administered at the visits specified in the SoA. During the double-blind treatment period, the scales and the cognitive test will be administered before the witnessed dose of study intervention (Section 8.1.13).

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood to be drawn over the course of the study (from

pre-study to post-study visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in the central laboratory manual.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical and Neurological Examinations

A complete physical examination, including a neurological examination, will be conducted at the visits specified in the SoA, per institutional standard. The investigator (or qualified designee, consistent with local requirements) will perform the examinations of the following organ systems:

- Head, eyes, ears, nose, and throat
- Neck
- Respiratory system
- Cardiovascular system
- Abdomen
- Skin and extremities
- General appearance
- Neurological system (see Appendix 8)

Height and weight will also be measured and recorded (Section 8.3.3).

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any medical conditions found during the physical and neurological examinations will be recorded in the Sponsor database.

8.3.2 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes of rest and will include temperature, blood pressure, pulse rate, and respiratory rate.

It is recommended that individual sites use the same method for measuring temperature (eg, oral, tympanic) in all participants throughout the study.

For blood pressure readings, the correct size of the blood pressure cuff and correct positioning on the participant's arm is essential for accurate measurements. It is recommended that individual sites use the same method (manual or automated) for measuring blood pressure and pulse throughout the study.

8.3.3 Height/Weight

Height (inches/centimeter) will be measured and recorded at the visits specified in the SoA. Measurements should be rounded to the nearest inch/centimeter (without shoes).

Body weight will be measured using a standardized scale (provided by the Sponsor if requested) and should be rounded to the nearest pound/kilogram. Participants' weight should be measured after voiding and while wearing light clothing (eg, no coats or heavy sweatshirts). The site should follow their local procedures to ensure the body weight scale is working properly.

8.3.4 ECGs

Twelve-lead ECGs will be performed when the participant is in the supine position after 5 to 10 minutes of rest using a central ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTcF intervals according to the instructions in a separate ECG instruction manual. Cardiologist overread will be provided by the central ECG vendor.

All scheduled ECGs will be performed in triplicate. ECG measurements should be obtained in close succession; ie, less than 2 minutes apart with all 3 measurements completed in less than 4 minutes.

At Visit 1 (Screening), the average of the 3 QTcF intervals based on the central vendor overread will be used to assess eligibility. At Visit 4 (Day 1), the average of the 3 QTcF intervals based on the local ECG printout will be used to assess eligibility (Section 5.2).

During the double-blind treatment period, participants will discontinue study intervention if the average of the 3 QTcF intervals at a visit is either >500 msec or increases by >60 msec relative to Visit 4 (Day 1). Details on discontinuation of study intervention due to QTcF results are in Section 7.1.

If ECG assessments were missed entirely at the scheduled visit during treatment or if all ECGs at a visit were invalid due to technical issues, the ECG should be obtained at the next scheduled visit.

8.3.5 Alcohol Screen (Breathalyzer)

An alcohol breath test will be performed at Visit 1 (Screening) and Visit 4 (Day 1). Participants must have a negative alcohol breath test at both visits to be eligible for the study (Section 5.2). A breathalyzer will be provided to each site by the Sponsor.

8.3.6 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant

changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention or through completion of Visit 10, whichever is later, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.6.1 Confirmation of Postmenopausal State

Female participants whose postmenopausal status is in question are required to have 2 pretreatment FSH measurements (approximately 2 weeks apart with a minimum interval of 10 days) in the postmenopausal range (Appendix 5). The first FSH measurement will be obtained at Visit 1 (Screening). Participants whose first FSH measurement is in the postmenopausal range, but who cannot have a second measurement within approximately 2 weeks of Visit 1 (Screening), should be excluded. These participants may be rescreened after consulting with the Sponsor.

8.3.6.2 Pregnancy Testing

General Guidance

Pregnancy testing will be performed as specified in the SoA and is not required during a Down-titration Visit.

During the screening period (pre-randomization):

- If urine test is positive, a serum pregnancy test is required to confirm or dismiss the initial result. The participant should be excluded unless a negative status is confirmed by 2 negative serum pregnancy tests performed approximately 24 hours apart.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required and must be negative to proceed to randomization. The participant must be excluded from participation if the serum pregnancy result is positive.

During the treatment and follow-up period:

- If urine test is positive, a serum pregnancy test is required. Study intervention should be held until a negative status is confirmed by 2 negative serum pregnancy tests performed approximately 24 hours apart.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. Study intervention should be held until a negative serum pregnancy test is obtained.
- Participants with a positive serum pregnancy test (or positive urine test and participant refuses the required follow-up serum test) must be discontinued from study intervention and followed as specified in Section 7.1.

Local serum tests may be performed in the event that the central laboratory results would not be available in time for prompt decision making.

Participants should not take products containing high-dose biotin (>5 mg/day) 1 day before and on the day of pregnancy testing as this might interfere with the results of the test.

WOCBP

All WOCBP (see Section 10.5.1 for definition) participating in the study will have a highly sensitive local urine pregnancy test AND serum pregnancy test at the visits indicated in the SoA and when pregnancy is suspected. A negative pregnancy test is required immediately (ie, on the same day) before dosing at each scheduled visit.

WONCBP

All WONCBP (see Section 10.5.1 for definition) participating in the study will have a highly sensitive urine pregnancy test at Visits 1, 4, and 8.

8.3.7 Suicidal Ideation and Behavior Monitoring

8.3.7.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

Suicidal ideation and behavior will be prospectively assessed during this study using the C-SSRS. The C-SSRS should be administered by trained raters at specified time points, as specified in the SoA, as well as at unscheduled visits as clinically indicated. Site staff should review the contents of the C-SSRS for completeness.

If the C-SSRS is administered by someone other than the investigator, consider providing the completed C-SSRS to the investigator for review, prior to their assessment of the participant and to further inform their evaluation.

The C-SSRS is not explicit about whether the participant specifically has ideation at the time of screening. If a participant reports a prior history of ideation/behavior, the assessor should also inquire and document if this is also present at the time of the screening visit.

Participants who at any time during this study report suicidal ideation or behavior that is considered to be an AE, either between visits or during visit interviews, must be assessed by the investigator. Participants who report suicidal ideation with intent, with or without a plan or method (ie, a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker, or mental health nurse practitioner (or comparable professional qualification in countries outside the United States). After that evaluation, only those participants whose suicidal ideation is considered by the evaluator to be passive, and who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the study may continue in the study; other participants must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety. In addition, all AEs of suicidal ideation or behavior must be recorded as an ECI (Section 8.4.7). Sites are to designate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

8.3.8 Contraceptive Use Confirmation

Male (where appropriate) and WOCBP participants are required to use contraception to prevent pregnancy during the study as defined by Section 5.1 Inclusion Criteria, No 8 and No 9, respectively. WOCBP must have continual contraception use for at least 3 months before screening. Participants who do not meet the 3-month requirement may be rescreened. Participants will be asked at study visits per the SoA to verbally confirm their use of contraception since the prior visit, according to the Contraceptive Guidance in Appendix 5. Confirmation should be noted in the source documents for each visit. In addition, for WOCBP, sites should complete the applicable CRF according to the data entry guidelines.

In cases of contraception non-compliance, that in the investigator’s judgment increases the risk for pregnancy, the investigator should hold study intervention until the case is discussed with the Sponsor and a final determination made.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention allocation/randomization through 14 days following cessation of study intervention or through the completion of Visit 10, whichever is later, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in). Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - hepatic-related events listed in Section 8.4.7 - require regulatory reporting	Not required	Within 24 hours of learning of event

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-hepatic-related events as listed in Section 8.4.7 (unless serious) - do not require regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event
ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event				

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of “ectopic” pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. Elevated AST ≥3x ULN

2. Elevated ALT ≥2x ULN or twice the baseline value

3. Elevated total bilirubin ≥2x ULN with ALP <2x ULN

4. AEs of dizziness that are rated by the investigator as being moderate or severe in intensity.

5. AEs related to gait disturbance, independent of feelings of dizziness.

6. Suicidal ideation and/or behavior or any self-injurious behavior reported as an AE.

7. QTcF interval meeting either of the criteria specified for study intervention discontinuation (Section 7.1).

Note that the above AEs and QTcF criteria are classified as ECIs only after the first dose of study intervention is administered. Sites should refer to the study ECI guidance document for details on assessment and follow-up, including follow-up on elevated liver function tests that met ECI criteria as assessed at Visit 10.

8.5 Treatment of Overdose

In this study, an overdose is defined as any dose that exceeds the morning or evening dose prescribed in this protocol (Section 6.1).

No specific information is available on the treatment of overdose of MK-1942. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

8.6.1 Blood Collection for Plasma MK-1942

Sample collection, storage, and shipment instructions for plasma samples will be provided in the central laboratory manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for Genetic Analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for CYP2C19 genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation

and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to CYP2C19. Leftover extracted DNA will be stored for FBR.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the Operations/Laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

– Leftover DNA for future research

– Leftover main study PK plasma samples stored for future research

8.10 Health Economics Medical Resource Utilization and Health Economics

This section is not applicable.

8.11 Visit Requirements

Visit requirements are outlined in the SoA. Specific procedure-related details are provided in Section 8.

Scheduling Visits

The interval between visits during the double-blind treatment is short (7 days), and the visits at which study intervention is dispensed are followed by a TC within the first 3 days after the visit (Section 8.1.15). The site should carefully schedule visits and phone calls to minimize participant burden.

It is preferable for visits (in-clinic and Lead-in calls) to be scheduled at about the same time of day in the mornings for consistency, and for in-clinic visits, to minimize prolonged fasting durations (fasting guidance is provided in Section 5.3.1). Evening clinic visits are not preferred but may be done if morning visits are not feasible for participants. Participants with evening clinic visits should be scheduled at about the same time of day in the evening for consistency. See the Study Operations Manual for more information on evening clinic visits.

A visit should occur within the scheduling window shown in the SoA. Visits during the double-blind treatment period should be scheduled relative to Visit 4 (Day 1), regardless of the actual day the previous visit occurred on. If any visits deviate from the schedule, an attempt should be made to follow the original visit schedule for subsequent visits.

Visit Reminders

During the double-blind treatment period, it is recommended that site personnel contact participants on the day before each clinic visit to remind them to (1) fast according to Section 5.3.1, (2) hold their morning doses of study intervention from the blister cards dispensed at

the previous visit (not applicable at Visit 4 [Day 1]), (3) bring their opened and unopened blister cards to the visit (not applicable at Visit 4 [Day 1]), and (4) bring their Study Medication Guidance (not applicable at Visit 4 [Day 1]).

8.11.1 Screening

Participants must provide documented informed consent before any study-specific procedures are performed. Screening period may be less than 3 weeks if all assessments are completed.

At Visit 1 (Screening), participants will be evaluated to determine if they fulfill the eligibility requirements in Sections 5.1 and 5.2. A psychiatric diagnostic assessment will be performed using the MINI to confirm the diagnosis MDD (without psychotic features), and the MADRS will be administered to assess participants' depressive symptom severity. The HAM-D17 will be administered by the site at Visit 1 (Screening) and by the central vendor rater at Visits 2 and 3 (Lead-in Calls 1 and 2, respectively) (see Section 8.11.2). Additional assessments of psychiatric symptoms and safety evaluations will be performed as specified in the SoA. The participant's medical history, prior and concomitant medications, and demographic information will be obtained. If available results support eligibility, then participants will discontinue taking any prohibited medications/products listed in Table 2 that must be stopped at Visit 1 (Screening). There are other prohibited medications/products and prohibited doses of allowed medications in Table 2 that participants must be off for ≥4 weeks before Visit 1 (Screening). Participants who do not meet the ≥4 week requirement for one or more of these prohibited medications/products will be screen-failed, but can rescreen once the ≥4 week requirement is met (additional information on rescreening is provided below and in the Study Operations Manual).

Results from the scales assessing MDD and documentation of prior treatment failures for the current episode of MDD will be submitted to the central vendor rater (required information is provided in the Study Operations Manual). These data, and those from the HAM-D17 at Visits 2 and 3 (Lead-in Calls 1 and 2, respectively) (see Section 8.11.2), will be used by the central vendor rater to determine eligibility. A participant may not be randomized until confirmation from the central vendor rater is received.

A participant's central laboratory results, final central ECG interpretation, and confirmation of having treatment-resistant moderate-to-severe MDD by the central vendor rater will be pending at Visit 1 (Screening). If the participant is later deemed ineligible based on review of these data, the participant will be screen-failed before randomization.

Split Screening Visit Option

To reduce participant burden, Visit 1 (Screening) may be split into more than 1 day. If this screening option is chosen, it is required that documented informed consent for the main study is obtained (Section 8.1.1.1) and a screening number is assigned (Section 8.1.9) on the first day of screening. Additionally, it is recommended that the MINI, MADRS, and HAM-D17 are each administered on the same screening day. Otherwise, the distribution of Visit 1 (Screening) procedures across more than 1 day is at the site's discretion.

Rescreening

In some circumstances, participants who are excluded may be rescreened. Such circumstances may include, but are not limited to, rescreening due to FSH testing requirements (Section 8.3.6.1), after laboratory abnormalities resolve, after the required off drug period for a prohibited medication/product is attained (Section 8.1.7.2), or if needed to meet contraceptive requirements (Section 8.3.8). Sites should consult the Sponsor before rescreening participants due to FSH testing requirements (Section 8.3.6.1). Additional details on rescreening procedures and other reasons for rescreening are described in the Study Operations Manual. Sponsor consultation is required if a participant is to be rescreened for reasons not described in the protocol or Study Operations Manual OR if a participant is to be rescreened more than 1 time due to screen failure.

8.11.2 Lead-in Calls

At Lead-in Calls 1 and 2 (Visits 2 and 3, respectively), the central vendor rater will administer the HAM-D17. Site personnel and participants will be blinded to the eligibility criterion associated with the HAM-D17 (Section 5.1). The central vendor rater will inform the site if a participant is eligible for randomization based on the results from the HAM-D17 and other materials provided to assess MDD (Section 8.11.2.1). The participant may not be randomized until confirmation from the central vendor rater is available.

Lead-in Calls 1 and 2 should occur when the participant is in a private and comfortable location. If preferred, the participant may go to the site to take the Lead-in Calls from the central vendor rater. In this case, the participant should be in a room without site personnel. The site will be contacted by the central vendor rater if there is any indication of suicidality based on responses to the HAM-D17.

8.11.2.1 Central Vendor Rater Review of Participant Eligibility

A participant may not be randomized until confirmation of eligibility is received from the central vendor rater. The following information will be reviewed by the central vendor rater to assess eligibility:

- Documentation assessing MDD (diagnostic interviews, symptom severity scales, and supporting records)
- Documentation of prior treatment failures for the current episode of MDD
- HAM-D17 total scores at Visit 1 (Screening) and Visits 2 and 3 (Lead-in Calls 1 and 2, respectively)

The information listed above is not comprehensive; additional details are provided in the Study Operations Manual.

The central vendor rater will inform the site if a participant is eligible before Visit 4 (Day 1). Participants who do not meet eligibility criteria will be screen-failed.

8.11.3 Treatment Period

Each visit should be performed as specified in the SoA

Participants who satisfy all entry criteria will be randomized (via IRT) to double-blind study intervention at Visit 4 (Day 1). Participants will be educated by a trained member of the site staff on appropriate dosing instructions (including missed doses, Section 8.1.12.1) and fasting guidance (Section 5.3.1). The first dose of study intervention will be witnessed by a member of the site staff in the clinic. Witnessed dosing will continue at all visits where study intervention is dispensed, including the Down-titration Visit (if applicable, and depending on when the participant took their last dose of study intervention; see Section 5.3.1).

Telephone contacts will be performed within the first 3 days after Visit 4 (Day 1), Visit 5 (Week 1), Visit 6 (Week 2), and Visit 7 (Week 3), and the Down-titration Visit (if applicable) by trained site personnel (Section 8.1.15) to monitor for AEs and compliance with study intervention and to encourage adherence with the fasting guidance (Section 5.3.1).

Compliance with study intervention and adherence with the fasting guidance will also be reinforced at each clinic visit during the double-blind treatment period.

If there are extenuating circumstances that do not enable the participant to attend a scheduled clinic visit (ie, incapacitating health conditions or local or national emergency situations), a telephone, video, or home visit using site staff or a nursing service may be used, if allowed by local regulations, in accordance with Sponsor guidelines.

8.11.4 Down-titration Visit

To minimize discontinuation of study intervention, participants who are unable to tolerate or who have substantial non-adherence with study intervention **after** Visit 6 (Week 2) may down-titrate MK-1942/matching placebo to a lower dose (Section 6.6). If this occurs between scheduled visits, the participant will return to the clinic (with the previously dispensed blister cards) for the Down-titration Visit and undergo the procedures specified in the SoA.

The timing of the first dose of study intervention from the blister cards dispensed at the Down-titration Visit will be determined by when the participant took their previous dose. Details are provided in Section 5.3.1.

8.11.5 EOT/DC Visit

EOT/DC Visit procedures specified in the SoA will be performed at the end of the treatment period (Visit 8 [Week 4]). Additionally, participants who discontinue study intervention prematurely should have an EOT/DC Visit as soon as possible after the decision to discontinue study intervention is made. For participants who discontinue study intervention prematurely, prohibited medications/products/therapies (Table 2) can be started after the EOT/DC Visit.

8.11.6 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Any participant who prematurely discontinues study intervention will be encouraged to continue their participation in the study off study intervention and be followed for all remaining study visits (Section 7.1) as outlined in the SoA. Note that PK samples will not be collected if a participant discontinues study intervention.

8.11.7 Post-dose Follow-up Period

Visit procedures specified in the SoA will be performed at the Post-dose Follow-up visits (Visit 9 [Week 5] and Visit 10 [Week 6]). Since participants will be off study intervention, there are no fasting requirements associated with these visits.

Because there are efficacy assessments at the Post-dose Follow-up Visit 9, participants who completed the double-blind treatment period on study intervention should not start prohibited medications/products/therapies (Table 2) until after the completion of this visit.

Safety assessments will be performed 14 days after the last dose of study intervention or at Visit 10, whichever is later, to collect laboratory test specimens, AEs, SAEs, C-SSRS, and other reportable safety events. As needed, instead of a site visit, Visit 10 laboratory assessments may be performed at a local laboratory and Visit 10 non-laboratory assessments may be performed by TC.

8.11.8 Poststudy

Participants will not be followed after completion of the study follow-up period.

Medical Management Poststudy Sessions (Optional)

At the discretion of the investigator based on medical need as a result of being in the trial and the transition off of the trial to standard of care, a participant may be offered up to 4 additional, optional sessions (reimbursed per the site study budget) with site medical staff to support the participant's transition off of the trial to standard of care. Additional medication or other medical procedures/treatments recommended or provided by site staff as after-study care will not be part of the additional sessions and will be the responsibility of the site or participant. These sessions may be conducted by phone or in person. These sessions may occur only up until six (6) months after the participant's last study visit. No additional data collection is required from these sessions beyond that already specified in the protocol (eg, safety reporting per Protocol Section 8.4).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes

to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Other planned analyses (eg, those specific to the analysis of PK data, patient-reported outcomes, and future biomedical research) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Phase 2a, randomized, placebo-controlled clinical study to evaluate the efficacy and safety of the addition of MK-1942 in participants with TRD on stable antidepressant therapy.
Treatment Assignment	The study will be conducted as a double-blind study under in-house blinding procedures. Treatment allocation/randomization will occur centrally using IRT. Participants will be randomized in a 2:1:2 ratio to (1) daily treatment with MK-1942 administered as 5 mg bid (Visit 4/Day 1 to Visit 5/Week 1), 10 mg bid (Visit 5/Week 1 to Visit 6/Week 2), and 20 mg bid (Visit 6/Week 2 to Visit 8/Week 4), (2) intermittent treatment with MK-1942 administered twice-weekly (10 mg biw), or (3) placebo. MK-1942 or matching placebo will be administered as oral capsules. Randomization will be stratified by the number of treatment failures (1; >1) for the current episode of moderate-to-severe MDD.
Analysis Populations	Efficacy: FAS Safety: APaT PK: PP
Primary Efficacy Estimand	The primary objective is to assess the efficacy of MK-1942 added to stable antidepressant therapy in participants with TRD. • **Treatment**: For the MK-1942 daily dose group, this will include dose modification allowed for intolerability or non-adherence at or after 2 weeks of treatment with primary evaluation after 3 weeks of therapy. For the MK-1942 intermittent dose group, the primary evaluation will be after 1 week of therapy. • **Population**: The population targeted by the scientific question: individuals aged 18 to 65 years diagnosed with TRD. • **Variable**: Week 3 change from baseline in MADRS total score for the MK-1942 daily dose group and Week 1 change from baseline in MADRS total score for the MK-1942 intermittent dose group. • **Intercurrent events:** The intercurrent events are IE1) discontinuation of study medication, IE2) discontinuation of stable antidepressant therapy, IE3) initiation of a non-study antidepressant therapy, and IE4) premature unblinding of either the investigator or participant. • **Population level-summary**: difference (MK-1942 daily dose versus placebo) in mean change from baseline at Week 3 and difference (MK-1942 intermittent dose versus placebo) in mean change from baseline at Week 1.

Primary Endpoint(s)	• Change from baseline in MADRS total score at Week 3 (MK-1942 daily dose versus placebo) • Change from baseline in MADRS total score at Week 1 (MK-1942 intermittent dose versus placebo)
Key Secondary Endpoints	• Change from baseline in HAM-D17 total score at Week 3 (MK-1942 daily dose versus placebo) • Change from baseline in HAM-D17 total score at Week 1 (MK-1942 intermittent dose versus placebo) • Change from baseline in CGI-S score at Week 3 (MK-1942 daily dose versus placebo) • Change from baseline in CGI-S score at Week 1 (MK-1942 intermittent dose versus placebo)
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by comparing MK-1942 to placebo with respect to mean change from baseline in MADRS total score at Week 3 (MK-1942 daily dose versus placebo) and Week 1 (MK-1942 intermittent dose versus placebo) using a longitudinal ANCOVA model.
Statistical Methods for Key Safety Analyses	95% CIs (Tier 2 endpoints) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method.
Interim Analyses	A non-binding interim futility analysis will be performed when the first ~60% of the randomized participants either complete Week 3 or discontinue before Week 3. Results will be reviewed by an siDMC. Futility may be declared if the conditional power based on the change from baseline at Week 3 (MK-1942 daily dose versus placebo) and change from baseline at Week 1 (MK-1942 intermittent dose versus placebo) is less than 10% for both treatment comparisons. Details are provided in Section 9.7.
Multiplicity	The Type-1 error will be strongly controlled across the primary and key secondary hypotheses using a Bonferroni procedure to control for the 2 different MK-1942 dose comparisons to placebo in conjunction with sequential testing to control for the primary and 2 key secondary endpoints (see Section 9.8).
Sample Size and Power	The planned sample size is 140 (56 in the MK-1942 daily dose group, 28 in the MK-1942 intermittent dose group, and 56 in the placebo group). There is ~92% probability that at least 1 of the 2 MK-1942 groups will be superior to placebo as measured by change in MADRS total score at Week 3 (MK-1942 daily dose versus placebo) or Week 1 (MK-1942 intermittent dose versus placebo) under the primary assumptions as provided in Table 10.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. The official, final database will not be unblinded until the participant completes the last study-related TC or visit, withdraws from the study, or is lost to follow-up.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study intervention assignment.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.3.1 Estimands

In the language of ICH E9(R1) [Food and Drug Administration 2021], there are 4 'intercurrent events' of interest: IE1) discontinuation of study intervention, IE2) discontinuation of stable antidepressant therapy, IE3) initiation of a non-study antidepressant therapy, and IE4) premature unblinding of either the investigator or participant.

Primary Objective

Primary Estimand [based on 'hypothetical strategy' in ICH E9(R1)]

To address the primary objective, an estimand based on HS will be used. This 'HS estimand' is intended to contrast the effect of MK-1942 (daily and intermittent dosing), relative to placebo, when initiated with stable antidepressant therapy under a ***hypothetical*** scenario in which there is no discontinuation of study intervention nor stable antidepressant therapy, no initiation of a non-study antidepressant therapy, and no premature unblinding of either the investigator or participant during an envisioned follow-up period of up to 4 weeks (with primary assessment at Week 3 for the MK-1942 daily dose group and at Week 1 for the MK-1942 intermittent dose group).

The HS estimand consists of the following attributes:

- Target population: individuals aged 18 to 65 with TRD
- Endpoint: Week 3 change from baseline in MADRS total score for the MK-1942 daily dose group and Week 1 change from baseline in MADRS total score for the MK-1942 intermittent dose group
- Treatment regimen: MK-1942 or placebo initiated with stable antidepressant therapy without discontinuation of study intervention or stable antidepressant therapy, without initiation of a non-study antidepressant therapy, and without premature unblinding of either the investigator or participant during an envisioned follow-up period of up to 4 weeks (with primary assessment at Week 3 for the MK-1942 daily dose group

[and dose modification allowed for intolerability or non-adherence at or after 2 weeks of treatment] and at Week 1 for the MK-1942 intermittent dose group)

- Population-level summary: mean of the endpoint noted above, compared between treatment regimens (MK-1942 daily dose versus placebo and MK-1942 intermittent dose versus placebo)

(Note: for estimating the HS estimand, data collected after the occurrence of IE1, IE2, IE3 or IE4 will be discarded in the main analysis.)

Supplemental Estimand [based on 'treatment policy strategy' in ICH E9(R1)]

A supplemental estimand based on TPS will be used. This 'TPS estimand' is intended to contrast the effect of MK-1942 (daily and intermittent dosing), relative to placebo, when initiated with stable antidepressant therapy, regardless of how long study medication, stable antidepressant therapy or non-study antidepressant therapy are used or if premature unblinding of either the investigator or participant occurs during an envisioned follow-up period of up to 4 weeks (with primary assessment at Week 3 for the MK-1942 daily dose group and at Week 1 for the MK-1942 intermittent dose group).

The TPS estimand has the same target population, endpoint, and population level-summary as the HS estimand of the primary objective, but differs in the treatment regimen attribute.

The TPS estimand consists of the following attributes:

- Target population: individuals aged 18 to 65 with TRD

- Endpoint: Week 3 change from baseline in MADRS total score for the MK-1942 daily dose group and Week 1 change from baseline in MADRS total score for the MK-1942 intermittent dose group

- Treatment regimen: MK-1942 or placebo initiated with stable antidepressant therapy without discontinuation of study intervention or stable antidepressant therapy, without initiation of a non-study antidepressant therapy, and without premature unblinding of either the investigator or participant during an envisioned follow-up period of up to 4 weeks (with primary assessment at Week 3 for the MK-1942 daily dose group [and dose modification allowed for intolerability or non-adherence at or after 2 weeks of treatment] and at Week 1 for the MK-1942 intermittent dose group).

- Population-level summary: mean of the endpoint noted above, compared between treatment regimens (MK-1942 daily dose versus placebo and MK-1942 intermittent dose versus placebo)

(Note: for estimating the TPS estimand, data collected after occurrence of IE1, IE2, IE3 or IE4 will be included in the main analysis)

Secondary Objectives

Both HS and TPS estimands, as described for the primary efficacy endpoint will be applied to the key secondary efficacy endpoints. For all other efficacy endpoints, only the HS estimand, as described for the primary efficacy endpoint, will be applied.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

9.4.1 Efficacy Endpoints

A summary of the primary, secondary, and tertiary/exploratory efficacy endpoints by MK-1942 dosing regimen is provided in Table 4.

Primary Endpoint

The MADRS is a 10-item clinician-rated instrument for assessing severity of depressive symptoms; these 10 items are summed to obtain the MADRS total score. Change from baseline in MADRS total score at Week 3 (MK-1942 daily dose versus placebo) and Week 1 (MK-1942 intermittent dose versus placebo) are primary endpoints.

Key Secondary Endpoints

The HAM-D17 is a 17-item clinician-rated instrument for assessing the effects of antidepressant treatments on depressive symptoms; these 17 items are summed to obtain the HAM-D17 total score. Change from baseline in HAM-D17 total score at Week 3 (MK-1942 daily dose versus placebo) and Week 1 (MK-1942 intermittent dose versus placebo) are key secondary endpoints.

The CGI-S is a single-item clinician-rated scale for assessing global illness severity. Change from baseline in CGI-S at Week 3 (MK-1942 daily dose versus placebo) and Week 1 (MK-1942 intermittent dose versus placebo) are key secondary endpoints.

Tertiary/Exploratory Endpoints

The BAC SC consists of digit symbol pairs followed by a list of digits for assessing cognitive performance. The number of correct matches within the allowed time (90 seconds) constitutes the score and will be evaluated as an exploratory endpoint for both treatment comparisons at Week 3.

The 6-item HAM-D6 is a subset of the HAM-D17. It consists of 6 items (depressed mood, work and activities, somatic symptoms general, feelings of guilt, anxiety psychic, and retardation); these items are summed to obtain the HAM-D6 total score. Change from baseline in HAM-D6 total score at Weeks 1, 2, 3, and 4 (for the 2 treatment comparisons) are exploratory endpoints.

Change from baseline in MADRS total score, HAM-D17 total score, and CGI-S score at time points not specified as primary or secondary (for the 2 treatment comparison) are exploratory endpoints.

MADRS remission, defined as a MADRS total score ≤12, will be used to assess improvement in depressive symptoms. The percentage of participants in remission will be evaluated as an exploratory endpoint for both treatment comparisons at each time point. MADRS response defined as a ≥50% reduction from baseline in MADRS total score will be used to assess improvement in depressive symptoms. The percentage of participants with a ≥50% reduction from baseline in MADRS total score will be evaluated as an exploratory endpoint for both treatment comparisons at each time point.

Table 4 Efficacy Measures by Dosing Regimen and Timepoint

MK-1942 Daily Dose	**MK-1942 Intermittent Dose**
Primary Efficacy Measure	
Change from baseline in MADRS total score at Week 3	Change from baseline in MADRS total score at Week 1
Key Secondary Efficacy Measures	
Change from baseline in HAM-D17 total score at Week 3	Change from baseline in HAM-D17 total score at Week 1
Change from baseline in CGI-S at Week 3	Change from baseline in CGI-S at Week 1
Tertiary/Exploratory Efficacy Measures	
Change from baseline in BAC SC at Week 3	Change from baseline in BAC SC at Week 3
Change from baseline in MADRS total score at Weeks 1, 2 and 4	Change from baseline in MADRS total score at Weeks 2, 3, and 4
Change from baseline in HAM-D17 total score at Weeks 1, 2, and 4	Change from baseline in HAM-D17 total score at Weeks 2, 3, and 4
Change from baseline in HAM-D6 total score at Weeks 1, 2, 3, and 4	Change from baseline in HAM-D6 total score at Weeks 1, 2, 3, and 4
Change from baseline in CGI-S score at Weeks 1, 2, and 4	Change from baseline in CGI-S score at Weeks 2, 3, and 4
The percentage of participants in remission defined as a MADRS total score ≤12 at Weeks 1, 2, 3, and 4	The percentage of participants in remission defined as a MADRS total score ≤12 at Weeks 1, 2, 3, and 4
The percentage of participants with a response defined as a ≥50% reduction from baseline in MADRS total score at Weeks 1, 2, 3, and 4	The percentage of participants with a response defined as a ≥50% reduction from baseline in MADRS total score at Weeks 1, 2, 3, and 4
BAC SC=Brief Assessment of Cognition Symbol Coding, CGI-S=Clinical Global Impression–Severity, HAM-D6=6-item Hamilton Depression Rating Scale, HAM-D17=17-item Hamilton Depression Rating Scale, MADRS=Montgomery-Asberg Depression Rating Scale	

Table 5 describes the directionality of improvement in efficacy measures.

Table 5 Directionality of Improvement in Efficacy Measures

Measurement	Direction of Improvement	Direction of Treatment Differences (Versus Placebo) Including Favorable Efficacy
MADRS total score	Decrease	Negative
HAM-D17 total score	Decrease	Negative
HAM-D6 total score	Decrease	Negative
CGI-S score	Decrease	Negative
BAC SC # correct	Increase	Positive
BAC SC=Brief Assessment of Cognition Symbol Coding, CGI-S=Clinical Global Impression–Severity, HAM-D6=6-item Hamilton Depression Rating Scale, HAM-D17=17-item Hamilton Depression Rating Scale, MADRS=Montgomery-Asberg Depression Rating Scale		

Details pertaining to the imputation and calculation of MADRS total score and HAM-D17 total score when 1 or more of the items is missing is discussed in Section 9.4.4. The number and percent of participants with a ≥50% response in MADRS total score will be summarized by treatment group and timepoint according to the following equation.

%-response in MADRS total score = (postdose – baseline)/baseline)

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values, ECGs, and vital signs.

Responses on the C-SSRS are classified according to 11 prespecified categories (Ideation: Passive, Active-nonspecific, Active-method, Active-method and intent, and Active-method, intent and plan; Behavior: Preparatory actions or behaviors, Aborted attempt, Interrupted attempt, Suicide attempt, and Completed suicide; Non-suicidal Self-Injurious Behavior). The most severe treatment-emergent event within each of 3 broad categories (suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior) reported at a visit will be used for analysis and reporting. An event is considered treatment-emergent during the assessment phase if it is either newly emerged or is more severe than the most severe event reported to have occurred in the study-defined pretreatment reference period.

9.4.3 Pharmacokinetic Endpoints

The PK endpoint is MK-1942 plasma concentrations.

9.4.4 Derivation of Efficacy Endpoints

Because it is possible to have missing items within the MADRS (primary endpoint), the following rules will be implemented to derive the total score. If ≤20% of the items are missing (eg, at most 2 of the 10 items are missing), then the missing items will be replaced

with the average (rounded to the nearest unit) of the remaining items for that participant at that visit; otherwise, the total score will be missing at that visit. The sum of the 10 items is the total score.

The HAM-D17 consists of 17 items. Eight of the items are rated from 0 to 2 and 9 of the items are rated from 0 to 4. Because it is possible to have missing items within the HAM-D17, the following rules will be implemented to derive the total score. If ≤20% (or at most 3 items) are missing, then the missing items will be imputed as follows for that participant at that visit. Since items 1, 2, 10, 11, 12, 13, 14, 16 and 17 are rated on a unit scale from 0 to 4, and items 3, 4, 5, 6, 7, 8, 9 and 15 are rated on a unit scale from 0 to 2, if any of the items rated from 0 to 2 are missing, then it will be imputed by dividing items rated from 0 to 4 by 2 and averaged with the existing items (and rounded to the nearest unit); otherwise, for imputation of other missing items, items rated from 0 to 2 score will be multiplied by 2 and averaged with the existing items (and rounded to the nearest unit). If more than 3 items are missing from the HAM-D17, the total score will be missing at that visit. The sum of the 17 items is the total score.

The single imputation approach described above allows the total score to be calculated using the strength of the other items collected at that time, for that participant. The Sponsor believes this approach to be more accurate than either setting the entire score to missing or to imputing the worst possible score. More complicated missing data approaches are not thought to be warranted, since the amount of missing data within an assessment is expected to be extremely low.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who:

- receive at least 1 dose of study intervention
- have at least 1 post-randomization observation for the analysis endpoint subsequent to at least one dose of study intervention
- have baseline data for those analyses that require baseline data

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS population.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which

they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

At least 1 laboratory, vital sign or ECG measurement obtained subsequent to at least 1 dose of study intervention is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 Pharmacokinetic Analysis Populations

The PP Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data will be included in the PP dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type-1 error control strategy are described in Section 9.8. Nominal p-values and 90% CIs will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

9.6.1 Statistical Methods for Efficacy Analysis

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

The treatment regimen intended for evaluation of the primary efficacy objectives is the randomized treatment administered as add-on therapy to stable antidepressant therapy as directed. For the MK-1942 daily dose group, this will include dose modification allowed for intolerability or non-adherence at or after 2 weeks of treatment with primary evaluation after 3 weeks of therapy. For the MK-1942 intermittent dose group, the primary evaluation will be after 1 week of therapy. The primary analysis strategy (HS) will exclude data collected after discontinuation of study intervention or stable antidepressant therapy, initiation of a non-study antidepressant therapy or premature unblinding of either the investigator or participant. A supplemental analysis strategy (TPS) will also be evaluated in which data collected after these intercurrent events will be included.

A single statistical model including data from all 3 treatment groups through Week 4 will be used to contrast the treatment comparisons/timepoints of interest for each of the primary and secondary efficacy endpoints. The primary analysis is based on a longitudinal ANCOVA

model including calculated change from baseline at Week 1, Week 2, Week 3, and Week 4. The model will handle missing data (both intermittent missing and monotone missing due to dropout) using the missing at random assumption. This model will be used to generate confidence intervals and p-values (compared with placebo). This model assumes a different mean for each treatment at each of the repeated time points in the analysis. In this model, time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will include categorical terms for treatment, number of treatment failures (1; >1) for the current episode of moderate-to-severe MDD, and week, as well as a continuous term for baseline response. In addition, the model will also include the interaction terms of week-by-treatment and week-by-baseline response. The treatment difference in terms of the mean change from baseline at a given time point will be estimated, and as appropriate, tested from the model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger approximation will be used to compute the degrees of freedom [Kenward, M. G. and Roger, J. H. 1997]. A sensitivity analysis will be performed for the primary and key secondary hypotheses to assess the robustness of the primary findings with respect to the handling of missing data. Specifically, a control-based mean imputation approach, with a tipping-point component, will be applied [Mehrotra, D. V., et al 2017]. Details related to this sensitivity analysis will be provided in the sSAP.

As outlined in Table 6, supportive analyses will be performed for the primary and the key secondary hypotheses to assess the robustness of the primary findings with respect to (1) the impact of intercurrent events; and (2) the handling of missing data. Details related to supportive analyses will be provided in the sSAP.

Basic summary statistics will be computed for all efficacy endpoints over time. This minimally includes means and standard deviations for continuous-type endpoints and counts and percentages for categorical endpoints.

Table 6 summarizes the key efficacy analyses.

Table 6 Analysis of Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method[b]	Analysis Population	Missing Data Approach
Primary Hypotheses				
Change from baseline at Week 3 in MADRS total score (MK-1942 daily dose versus placebo)	P	Longitudinal ANCOVA[c] with HS estimand	FAS	Model-based[d]
	S	Longitudinal ANCOVA with HS estimand and Control-Based Mean Imputation[c]	FAS	Control-based mean imputation
	S	Longitudinal ANCOVA[c] with TPS estimand	FAS	Model-based[d]
Change from baseline at Week 1 in MADRS total score (MK-1942 intermittent dose versus placebo)	P	Longitudinal ANCOVA[c] with HS estimand	FAS	Model-based[d]
	S	Longitudinal ANCOVA with HS estimand and Control-Based Mean Imputation[c]	FAS	Control-based mean imputation
	S	Longitudinal ANCOVA[c] with TPS estimand	FAS	Model-based[d]
Secondary Hypotheses				
Change from baseline at Week 3 in HAM-D17 total score (MK-1942 daily dose versus placebo)	P	Longitudinal ANCOVA[c] with HS estimand	FAS	Model-based[d]
	S	Longitudinal ANCOVA with HS estimand and Control-Based Mean Imputation[c]	FAS	Control-based mean imputation
	S	Longitudinal ANCOVA[c] with TPS estimand	FAS	Model-based[d]
Change from baseline at Week 1 in HAM-D17 total score (MK-1942 intermittent dose versus placebo)	P	Longitudinal ANCOVA[c] with HS estimand	FAS	Model-based[d]
	S	Longitudinal ANCOVA with HS estimand and Control-Based Mean Imputation[c]	FAS	Control-based mean imputation
	S	Longitudinal ANCOVA[c] with TPS estimand	FAS	Model-based[d]

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method[b]	Analysis Population	Missing Data Approach
Change from baseline at Week 3 in CGI-S (MK-1942 daily dose versus placebo)	P	Longitudinal ANCOVA[c] with HS estimand	FAS	Model-based[d]
	S	Longitudinal ANCOVA with HS estimand and Control-Based Mean Imputation[c]	FAS	Control-based mean imputation
	S	Longitudinal ANCOVA[c] with TPS estimand	FAS	Model-based[d]
Change from baseline at Week 1 in CGI-S (MK-1942 intermittent dose versus placebo)	P	Longitudinal ANCOVA[c] with HS estimand	FAS	Model-based[d]
	S	Longitudinal ANCOVA with HS estimand and Control-Based Mean Imputation[c]	FAS	Control-based mean imputation
	S	Longitudinal ANCOVA[c] with TPS estimand	FAS	Model-based[d]

ANCOVA=Analysis of covariance, CGI-S=Clinical Global Impression-Severity; FAS=full analysis set, HAM-D17=17-item Hamilton Depression Rating Scale; HS=hypothetical strategy; MADRS=Montgomery-Asberg Depression Rating Scale; MDD= major depressive disorder; TPS=treatment policy strategy

[a] P=Primary approach, S=Supportive approach

[b] Statistical models are described in further detail below.

[c] Longitudinal data analysis model with terms for treatment, number of treatment failures (1 treatment failure; >1 treatment failure [for the current episode of moderate-to-severe MDD]), week, and baseline response. In addition, the model will also include the interaction terms of week-by-treatment and week-by-baseline response.

[d] Imputation for missing items as noted in Section 9.4.4 will be conducted prior to using this model-based approach.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and an interim analysis is described in Section 9.7 (Interim Analyses) and in Section 9.8 (Multiplicity), respectively.

9.6.2 Statistical Methods for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet PDLC criteria in laboratory, vital signs, and ECG parameters are either prespecified as “Tier 1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol as the evaluation of safety and tolerability is focused on estimating rather than testing treatment differences and the incidence of AEs of special interest is anticipated to be rare.

Tier 2 Events

Membership in Tier 2 requires that at least 7% of participants (corresponding to at least 4 participants in the MK-1942 daily dose group, 2 participants in the MK-1942 intermittent dose group, and 4 participants in the placebo group) in any treatment group exhibit the event. The threshold of at least 7% was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events (and when a treatment group of half-allocation has less than 2 events) and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 7% or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will also be considered Tier 2 endpoints.

Dizziness AEs of moderate or severe intensity and gait disturbance independent of feelings of dizziness AEs are Tier 2 AEs.

Tier 3 Events

Safety endpoints that are not Tier 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Categorical Safety Measures

C-SSRS

The percentage of participants with any treatment-emergent suicidal ideation or with any treatment-emergent suicidal behavior will be analyzed per the tiered analysis strategy outlined above, and will be considered as either Tier 2 or Tier 3 events, depending on the number of participants with an event observed within each treatment group. Additionally, the 11 prespecified categories of suicidal ideation and behavior will be summarized. Participant counts (and cumulative counts) for each category will be based upon the most severe treatment-emergent event observed during the assessment period.

In constructing the treatment-emergent C-SSRS analyses, a pretreatment reference period is required, from which a baseline score for each of the 3 categories (ideation, behavior, nonsuicidal self-injury) is derived. For this study, the baseline score for each of the 3 categories will be taken as the maximum score arising from the 3 predose C-SSRS administrations. The first predose administration references lifetime history. Each subsequent predose administration references the timeframe since the last predose administration.

It is noted that the first predose administration actually consists of 2 separate administrations; 1 using lifetime as the reference period and another using fixed-time intervals (6 months for behavior and 2 months for ideation). The fixed-time administration is solely included for inclusion/exclusion purposes (noting that the contemporaneous maximum lifetime baseline score may not be less than the maximum fixed-time baseline score by definition).

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 7 summarizes the safety analysis.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-related AE		X	X
	Any Serious and Drug-related AE		X	X
	Discontinuation due to an AE		X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥7%) of participants in 1 of the treatment groups)		X	X
	Dizziness AEs of moderate or severe intensity		X	X
	Gait disturbance independent of feelings of dizziness AEs		X	X
Tier 3	Specific AEs, SOCs or PDLCs[a] (incidence <7% of participants in all treatment groups)			X
	Change from baseline results (Labs, ECGs, Vital Signs)			X

AE=adverse event, CI=confidence interval, ECG=electrocardiogram, PDLC=Pre-Defined Limit of Change, SOC=System Organ Class, X=results will be provided

[a]Includes only those endpoints not prespecified as Tier 2 endpoints.

9.6.3 Statistical Methods for Pharmacokinetic Analysis

Plasma concentrations will be summarized by nominal timepoint using the following (non-model-based) descriptive statistics: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 × standard deviation/arithmetic mean), median, minimum, maximum, GM, and geometric percent CV (calculated as 100 × sqrt (exp(s^2) -1), where s^2 is the observed variance on the natural log-scale). The effect of genetic polymorphism of CYP2C19 on MK-1942 PK may be assessed and described in a separate document.

9.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics.

The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

One non-binding interim futility analysis will be performed in this study. The interim analysis will be performed when the first ~60% of randomized participants either complete Week 3 or discontinue before Week 3. The interim analysis calculation assumes the same SDs used for the study power and sample size estimates, and assumes that the remaining data (after interim analysis) will be distributed similarly to that observed at the interim. The endpoints, timing, and purpose of the interim analysis are summarized in Table 8 below.

Table 8 Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
Change from baseline at Week 3 in MADRS total score (MK-1942 daily dose versus placebo) Change from baseline at Week 1 in MADRS total score (MK-1942 intermittent dose versus placebo)	First ~60% of randomized participants either complete Week 3 or discontinue prior to Week 3	Assess futility
MADRS=Montgomery-Asberg Depression Rating Scale		

Study enrollment is likely to be ongoing at the time of the interim analysis. Blinding to treatment assignment will be maintained at all investigational sites. The results of the interim analysis will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an internal unblinded statistician and

statistical programmer performing the interim analysis, who will have no other responsibilities associated with the study.

Treatment-level results and/or participant-level data from the interim analysis will be provided by the unblinded statistician to the siDMC which consists of Sponsor personnel (and external experts, as appropriate). Limited additional Sponsor personnel may be unblinded to the treatment level results of the interim analysis, if required, in order to act on the recommendations of the siDMC. The extent to which individuals are unblinded with respect to results of the interim analysis will be documented by the unblinded statistician.

The processes by which recommendations and decisions are reached and communicated are documented in the siDMC charter for the Sponsor. The protocol-specific siDMC charter will be referenced in the CSR. Prior to final study unblinding, individuals who have been unblinded at any level will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

If the study is stopped early, the CSR will include all available data up to and including the close-out visits. This approach to include all available information is in line with the ICH-E9 guideline, the ITT principle and the CHMP guideline on adaptive designs.

The decision of whether to terminate the study for futility will be based on CP, ie, the likelihood of correctly detecting a (standardized) treatment difference at the end of the study given the results at the interim, corresponding to the primary hypotheses (ie, MADRS change from baseline at Week 3 (MK-1942 daily dose versus placebo) and at Week 1 (MK-1942 intermittent dose versus placebo). If the CP is <10% for both primary hypotheses, the study may be stopped for futility. If the truth is a SES of 0.230 for MK-1942 daily dose versus placebo and 0.277 for MK-1942 intermittent dose versus placebo (ie, not only do we observe it at the interim, but the remaining data also have that distribution), this equates to a CP of 10% for each contrast. The interim analysis will include data for participants who completed the study or dropped out as well as the partial data of ongoing participants. Additional details regarding the calculation of the CP will be described in the sSAP.

The operating characteristics of the interim futility analysis are in Table 9. Based on this information and assuming a correlation of 0.5 between treatment comparisons, the probability the study may be deemed futile if both alternative hypotheses are true is 2.5% based on the marginal probabilities (7.6% and 8.6%). The probability the study may be deemed futile if both null hypotheses are true is 70.7% based on the marginal probabilities (81.3% and 81.4%).

Table 9 Operating Characteristics of the Interim Futility Analysis

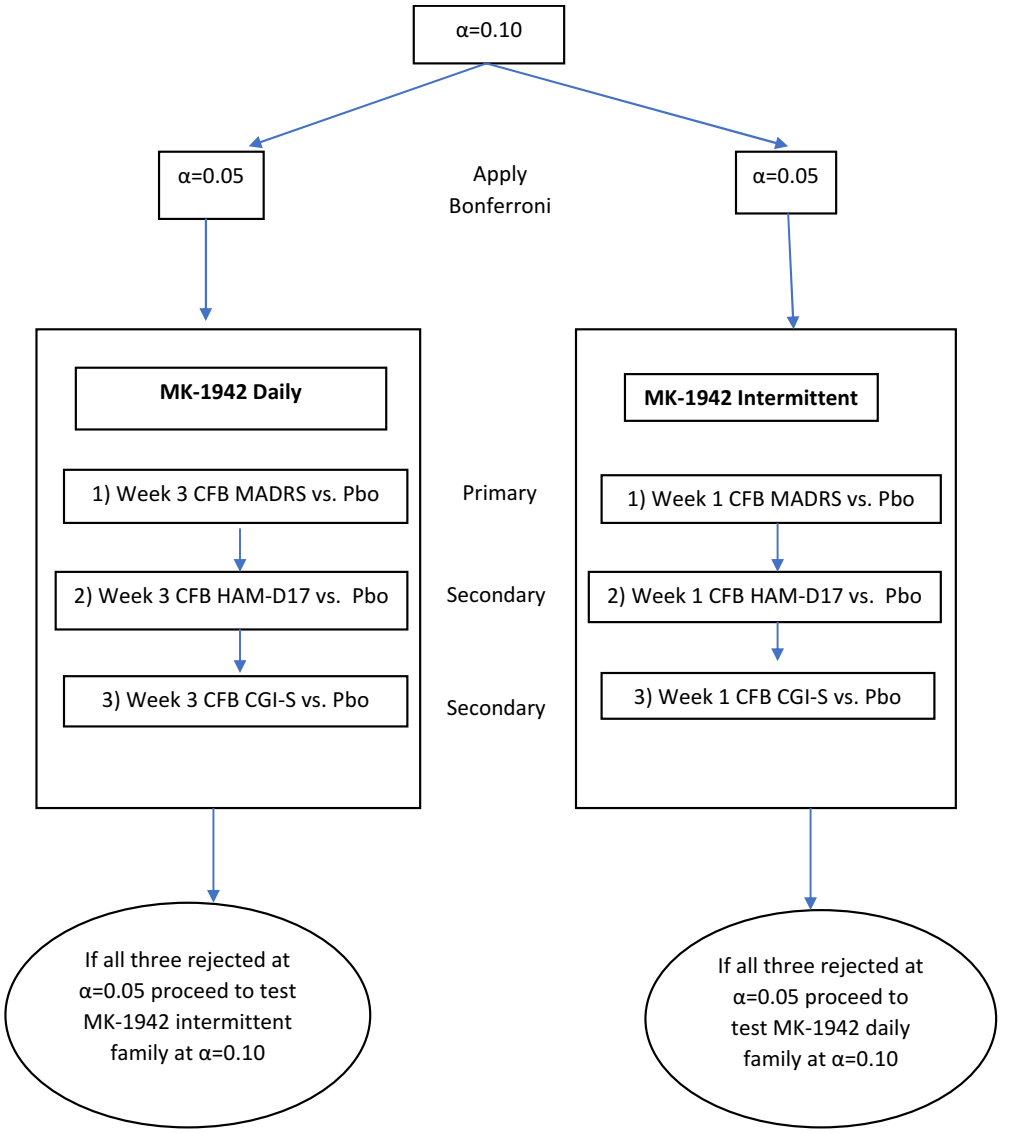
		Daily Dose Group			Intermittent Dose Group			Probability Study Futile	
Timing of Futility Interim Analysis	Futility CP Criterion	Futility SES Boundary	Probability Futile Based on SES=0	Probability Futile Based on SES=0.6	Futility SES Boundary	Probability Futile Based on SES=0	Probability Futile Based on SES=0.7	Both Null Hypotheses True	Both Alternative Hypotheses True
First ~60% randomized who complete or discontinue before Week 3	<10%	0.230	81.3%	7.6%	0.277	81.4%	8.6%	70.7%	2.5%
CP=conditional power, SES=standardized effect size									

9.8 Multiplicity

The study has 2 MK-1942 treatment dose comparison "families" of interest (MK-1942 daily dose versus placebo and MK-1942 intermittent dose versus placebo). Each family has 3 hypotheses that correspond to the primary endpoint and two key secondary endpoints and will be tested and controlled at the 2-sided α=0.05 level using a closed testing sequential approach. Specifically, within each of the two dose families, the primary hypothesis will be tested at the 2-sided α=0.05 level. If the primary null hypothesis is rejected, then testing will proceed to the first secondary hypothesis (still at 2-sided α=0.05 level). Testing will continue to the remaining key secondary hypothesis (ie, with formal significance declared for a given hypothesis only if that hypothesis is significant and all hypotheses preceding it within that family are significant).

Since the study will be considered positive if either treatment comparison is positive (at the 5% level), the family-wise error at the study level is 10%. It is noted that if all 3 hypotheses within a dose family are rejected at the 2-sided α=0.05 level, then the other dose family may proceed to be tested using the full 2-sided α=0.10 level (again following the sequential ordering within the family). Figure 2 outlines the testing strategy used to address the multiplicity issues.

Figure 2 Testing Strategy to Address Multiplicity



CFB=change from baseline; CGI-S=Clinical Global Impressions-Severity; HAM-D17= 17-item Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

Sample size was determined based on change from baseline in MADRS total score at Week 3 (for MK-1942 daily dose versus placebo) and Week 1 (for MK-1942 intermittent dose versus placebo). This study will randomize 56 participants into the MK-1942 daily dose group, 28 into the MK-1942 intermittent dose group, and 56 into the placebo group. With these sample

sizes and assuming an 8% dropout rate after 1 week and 10% dropout rate after 3 weeks, each treatment comparison has at least 80% (marginal) power to demonstrate superiority compared to placebo at the 2-sided 5% α-level; the probability that at least 1 MK-1942 dosing regimen demonstrates superiority compared with placebo is 92%. These calculations assume the underlying SES for change from baseline in MADRS total score at Week 3 (MK-1942 daily dose versus placebo) is -0.6 (eg, corresponds to a mean treatment difference of -6 points and a standard deviation of 10.0 points) and the underlying SES for change from baseline in MADRS total score at Week 1 (MK-1942 intermittent dose versus placebo) is -0.7 (eg, corresponds to a mean treatment difference of -6.5 points and a standard deviation of 9.3 points) and use a normal test. The intermittent dose group has a smaller sample size due to the anticipation that rapid effect will be seen. Therefore, the primary timepoint of interest is Week 1. Because of the shorter time frame, the sample size has been adjusted to account for lower variance, larger treatment difference, and smaller dropout rate versus the daily dose group, where given the 2 week titration, the primary timepoint of interest is Week 3.The underlying treatment SESs are regarded as a clinically relevant for the difference between the 2 treatments. The sample size calculation also accounts for the interim futility analysis. The SESs for this study were based on results of prior publications for MDD and TRD [Sanacora, G., et al 2014] [Canuso, C. M., et al 2018].

Table 10 provides the assumptions for mean differences, standard deviations, and SESs as well as the marginal power for each treatment comparison, and the probability that at least 1 MK-1942 dosing regimen is successful.

Table 10 Primary Assumptions, Marginal Power, and Probabilities for MADRS Total Score

Assumed Week 3/Week 1 Mean Treatment Difference in CFB (Daily Dose, Intermittent Dose)	Assumed Week 3/Week 1 CFB SD (Daily Dose, Intermittent Dose)	Assumed Week 3/Week 1 SES (Daily Dose, Intermittent Dose)	Marginal Power for Daily Dose Versus Placebo	Marginal Power for Intermittent Dose Versus Placebo	P (At Least One Hypothesis is Positive, corr.=.5)
(6.0, 6.5)	(10.0, 9.3)	(0.60, 0.70)	83.0%	80.8%	92.0%

CFB=change from baseline; corr=correlation; MADRS=Montgomery-Asberg Depression Rating Scale; SD=standard deviation; SES=standardized effect size

Sample sizes are 56 participants in the MK-1942 daily dose group, 56 participants in the placebo group, and 28 participants in the MK-1942 intermittent dose group.

Assumes dropout rate is 8% at Week 1 and 10% at Week 3.

9.9.2 Sample Size and Power for Safety Analyses

Table 11 and Table 12 summarize the percentage point differences between 2 treatment groups for a variety of hypothetical underlying incidences of AEs. These calculations assume (1) 56 participants in the MK-1942 daily dose group and 56 participants in the placebo group (Table 11) and (2) 28 participants in the MK-1942 intermittent dose group and 56 participants in the placebo group (Table 12). The calculations are based on a 2-sided 5%

α-level and the method proposed by Miettinen and Nurminen [Miettinen, O. and Nurminen, M. 1985]; no multiplicity adjustments are considered.

Table 11 Differences (95% CIs) in Incidence in AEs Between MK-1942 Daily Dose and Placebo

Incidence of Adverse Event		Risk Difference	
MK-1942 Daily Dose (%)	Placebo (%)	Percentage Points	95% CI[a]
10.7	5.4	5.4	(-5.5, 17.0)
14.3	5.4	8.9	(-2.4, 21.3)
19.6	5.4	14.3	(2.2, 27.4)
14.3	10.7	3.6	(-9.3, 16.7)
19.6	10.7	8.9	(-4.7, 22.8)
25.0	10.7	14.3	(0.0, 28.7)
19.6	14.3	5.4	(-8.9, 19.7)
25.0	14.3	10.7	(-4.2, 25.6)
30.4	14.3	16.1	(0.6, 31.3)

AE=adverse event, CI=confidence interval

Incidences presented here are hypothetical and do not represent actual AEs in either group.

[a] Based on Miettinen and Nurminen method with 56 participants per treatment group using a 2-sided 5% α level.

Table 12 Differences (95% CIs) in Incidence in AEs Between MK-1942 Intermittent Dose and Placebo

Incidence of AE		Risk Difference	
MK-1942 Intermittent Dose (%)	Placebo (%)	Percentage Points	95% CI[a]
10.7	5.4	5.4	(-6.3, 22.6)
14.3	5.4	8.9	(-3.6, 26.9)
21.4	5.4	16.1	(1.9, 35.0)
14.3	10.7	3.6	(-10.5, 22.1)
21.4	10.7	10.7	(-4.9, 30.2)
25.0	10.7	14.3	(-2.1, 34.0)
21.4	14.3	7.1	(-9.2, 27.0)
25.0	14.3	10.7	(-6.3, 30.9)
28.6	14.3	14.3	(-3.4, 34.6)

AE=adverse event, CI=confidence interval

Incidences presented here are hypothetical and do not represent actual AEs in either group.

[a] Based on Miettinen and Nurminen method with 28 participants in the MK-1942 intermittent dose group and 56 in the placebo group using a 2-sided 5% α level.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 90% CI) for the primary and key secondary endpoints will be estimated and plotted within each category of each subgroup. Confidence intervals will only be produced if both treatment groups (MK-1942 dose group and placebo) have at least 25% of their sample within each subgroup. Summary statistics for subgroups will be provided regardless of sample size. The following are examples of classification variables:

- Gender (female; male)
- Age group (<median; ≥ median years)
- Race (white; other)
- Prior Antipsychotics Use
- Baseline MADRS total score (<median; ≥median score)
- Baseline duration of current depressive episode (<median; ≥median duration)
- Number of prior depressive episodes (<median; ≥median number)
- Baseline BMI (<median; ≥median value)
- Number of treatment failures (1 treatment failure; >1 treatment failure) for the current episode of moderate-to-severe MDD

HAM-D17 anxiety/somatization factor score (<7: ≥7)

- 7 (somatic symptoms gastrointestinal)
- 9 (somatic symptoms general)
- 12 (anxiety psychic)
- 13 (anxiety somatic)
- 14 (hypochondriasis)
- 15 (insight)

In addition, a forest plot will be produced, which provides the estimated treatment differences and confidence intervals for the treatment effect across the categories of subgroups listed above.

9.11 Compliance (Medication Adherence)

In this study, as part of the routine recording of the amount of study intervention taken by each participant, the number of capsules remaining in study packaging will be counted, reviewed, and recorded at regular intervals. Study intervention records will be used to calculate participant compliance.

A day within the study will be considered an "On-Therapy" day if the participant takes all of the prescribed capsules for that day.

For a participant who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from randomization to the date of the last dose of study intervention.

For each participant, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

9.12 Extent of Exposure

The extent of exposure to study intervention will be evaluated by summary statistics (N, mean, median, standard deviation). Additionally, the total number of days each participant took a particular total daily dose of study intervention will be identified and summarized (as participant counts and percentages) within duration categories (eg, for the Treatment period: <1 week, ≥1 week but <2 weeks, ≥2 weeks but <3 weeks, ≥3 weeks but <4 weeks, and ≥4 weeks, where 1 week is defined as 7 days).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

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

The participant must be informed that his/her 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.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate siDMC will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency (details are provided in the siDMC charter) for evidence of adverse effects of study intervention. The siDMC will also evaluate the results of an interim futility analysis performed after the first approximately 60% of randomized participants either complete Week 3 or discontinue before Week 3. The interim futility analysis will include a review of efficacy, safety, and tolerability data (see Section 9.7). The siDMC will determine whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

10.1.4.2 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study 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.

If publication activity is not directed by the Sponsor, 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.

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov,

www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator

or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

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

Study monitors will perform ongoing source data review and 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 study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study 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 documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

Laboratory tests performed in this study are shown in Table 13.

Notes on Laboratory Testing:

- The investigator (or qualified designee) must document their review of each laboratory safety report.
- Additional laboratory tests may be performed at any time during the study as determined by the investigator or required by local regulations.
- Local laboratory tests may be performed in the event that the central laboratory results would not be available in time for timely decision making on either study intervention administration and/or response evaluation. If a local test is performed, it is important that a sample for central analysis is obtained at the same time. For Visit 10, if a participant cannot attend the in-person site visit, scheduled safety laboratory assessments may be performed at a local laboratory and other non-laboratory assessments will be performed by TC. Results from the local laboratory should be entered into the appropriate CRF.
- Screening laboratory tests may **NOT** to be repeated if the initial results are exclusionary, except where repeat tests are allowed in the eligibility criteria (Section 5.2). Rescreening may be performed after a participant's laboratory abnormality initially leading to exclusion resolves (information on rescreening is provided in Section 8.11.1). Laboratory criteria for study intervention discontinuation are in Section 7.1.
- If laboratory tests were not performed at a scheduled visit or results are invalid, then they must be obtained at the next scheduled visit. If a pregnancy test was missed at a scheduled visit, the test should be obtained as soon as possible (eg, at an unscheduled visit, if necessary).

Guidance on Pregnancy Testing:

- Pregnancy testing:
  - Pregnancy testing should be conducted at the visits specified in the SoA. Highly-sensitive, local urine tests are required immediately (ie, on the same day) before dosing for WOCBP, with central serum tests performed every 2 weeks during treatment and in case of positive or ambiguous urine results.
  - A positive pregnancy test during the double-blind treatment period requires discontinuation of study intervention as described in Section 8.3.6.2 and Section 7.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	WBC	WBC count with differential (absolute, percentage): • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils	
	Platelets		
	RBC	Morphology, MCV, RDW	
	Hemoglobin	MCH, MCHC	
	Hematocrit		
Chemistry	Creatinine (includes eGFR calculation) Phosphorus Calcium CK Sodium Potassium Chloride CO_2 or bicarbonate	AST (SGOT) ALT (SGPT) Albumin Total protein Alkaline phosphatase Lactate Dehydrogenase Gamma-Glutamyl Transpeptidase Globulin Urea Nitrogen Uric Acid Total bilirubin Indirect bilirubin and Direct bilirubin	Glucose
Urinalysis	Color & clarity Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase Microscopic examination (reported if detected), includes bacteria, casts, crystals, epithelial cells, RBC, WBC, yeast, oval fat bodies, fat, mucous, sperm, trichomonas		

Laboratory Assessments	Parameters
Other Tests	Central serum hCG pregnancy test Local urine pregnancy test INR at Visit 4 (Day 1) only TSH with reflex FT4 FSH – female only, if applicable Urine drug screen includes: • Amphetamines/MDMA • Barbiturates • Benzodiazepines • Cannabinoids • Cocaine • Methadone • Opiates • Phencyclidine Breathalyzer for alcohol use Genotyping for CYP2C19 Serology (HIV antibody, HbsAg, and hepatitis C virus antibody) • Serologies are at the discretion of the investigator
ALT=alanine amino transferase, AST=aspartate aminotransferase, CK=creatine kinase, eGFR=estimated glomerular filtration rate, FSH=follicle-stimulating hormone, FT4=free thyroxine T4, HbsAg=hepatitis B surface antigen, INR = international normalized ratio, RBC=red blood cell, SGOT=serum glutamic-oxaloacetic transaminase, SGPT=serum glutamate-pyruvate transaminase, TSH=thyroid-stimulating hormone, WBC=white blood cell	

10.2.1 Drug Screening (Local and Central)

The investigator (or qualified designee) should instruct the participant to refrain from using drugs of abuse (including opiates, barbiturates, amphetamine/methamphetamine, methadone, cocaine, and phencyclidine) and should limit alcohol use to moderate amounts during the study (Section 5.3.2). Drug screens (local and central) will be performed at visits specified in the SoA. Participants with a positive test result for these drugs of abuse based on either the local or central assessment at Visit 1 (Screening) or the local assessment at Visit 4 (Day 1) are not eligible for the study. However, participants who have a positive test result at Visit 1 (Screening) for **prescribed** opiates (excluding methadone), barbiturates, or amphetamines may continue in the pretreatment period if the prohibited medication is discontinued at least 1 week or 5 half-lives (whichever is longer) before the first dose of investigational intervention. The participant may be enrolled if the Visit 4 (Day 1) local assessment for drugs of abuse is negative. Retesting is not permitted for positive test results for non-prescription drugs of abuse.

Participants who have a positive test result for cannabis at Visit 1 (Screening) must be evaluated by the investigator and may be enrolled if abuse or substance use disorder are ruled out.

Participants who test positive for a drug of abuse (except cannabis, which is not prohibited if abuse or substance use disorder is ruled out) during the double-blind treatment period (Table 2) will be counseled to abstain from future use during the study, and may continue on study intervention at the discretion of the investigator. Participants who are unwilling to abstain from future use with a drug of abuse will be discontinued from study intervention. Urine drug screens can be performed at the discretion of the investigator if a participant is thought to be under the influence of a drug of abuse.

Local urine drug screens are employed in this study for early detection, with central urine drug screens performed at the same visits for confirmation of results.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a 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 a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

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.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

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 disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 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.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **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.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant 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 (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

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 1 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.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

Is a cancer

Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- 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 CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

    - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

    - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

    - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    ◦ If yes, did the AE resolve or improve?

    ◦ If yes, this is a positive dechallenge.

    ◦ If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    ◦ If yes, did the AE recur or worsen?

◦ If yes, this is a positive rechallenge.

◦ If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    ◦ There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    ◦ Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor 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.

- 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.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool 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 CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b,e] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[d] (confirmed to be in place within the last year by treating healthcare provider) • Non-hormonal IUD (confirmed to be in place within the last year by treating healthcare provider) • Bilateral tubal occlusion • Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records or medical examination.
Highly Effective Contraceptive Methods That Are User Dependent[b,e] *Failure rate of <1% per year when used consistently and correctly.*
Note: Barrier method (eg, condoms) must be used in addition to these user-dependent contraceptive methods. • Combined (estrogen- and progestogen- containing) hormonal contraception[c] o Oral o Intravaginal o Transdermal • Progestogen-only hormonal contraception[c] o Oral
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b. Investigator must confirm that the contraceptive method will not expire during the study. c. If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. d. IUS is a progestin releasing IUD. e. Must have continual use for at least 3 months before screening. Note: The following are not acceptable methods of contraception: – Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. – Male condom with cap, diaphragm, or sponge with spermicide. – Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3,4]

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3,4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3,4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally

identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3,4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3,4]

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3,4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3,4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3,4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3,4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3,4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions[3,4]

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: General Neurological Examination

The general neurological examination will be performed at the time points specified in the SoA.

Note to the investigator: If at any time abnormalities are observed in the general neurological examination, the investigator should do additional examinations as needed based on his or her medical judgment.

The general neurological examination includes all of the modules listed below, with the exception of Module 1, and is intended to be a general screening examination and is sufficient for this study and participant population.

MODULE 2 – CRANIAL NERVE ASSESSMENT

A. II – Visual Fields and Acuity

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus)

Note: Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

D. V – Facial Sensation, Jaw Strength

E. VII – Muscles of Facial Expression (wrinkle brow, squeeze eyes shut, smile)

F. VIII – Auditory Acuity (assessed using a bed-side screening test, eg, by rubbing fingers on each side of participant's head or by whispering numbers)

G. XI – Shoulder Shrug

H. XII – Tongue Protrusion (midline)

Score: left and right (except for H)

Grade: **NORMAL or ABNORMAL**

MODULE 3 – MOTOR SYSTEM

A. Muscle Tone

1. Ask the participant to relax.

2. Flex and extend the participant's elbows and knees (bilaterally).

3. There is a small, continuous resistance to passive movement.

4. Observe for involuntary movements (eg, tremor, tics, fasciculations). Observe for resistance to passive movement; observe for decreased (flaccid) or increased (rigid/spastic) tone.

Score: *left and right*

Grade: **NORMAL, INCREASED, or DECREASED**

B. Muscle Strength

1. Ask the participant to stand up from sitting without using hands

Grade: **NORMAL or ABNORMAL**

2. Test proximal limb strength by having the participant flex and extend the knees and elbows against your resistance (test bilaterally, and compare 1 side to the other).

Score: left and right

Grade: 5/5: normal; 4/5: movement against resistance impaired; 3/5: movement against gravity but not against resistance; 2/5: visible movement but not against gravity; 1/5: visible contraction; 0/5: no visible activity

3. Test distal limb strength by having the participant conduct dorsiflexion and plantar flexion of the participant's feet; finger abduction and handgrip strength against your resistance (test bilaterally, and compare 1 side to the other).

Score: left and right

Grade: 5/5: normal; 4/5: movement against resistance impaired; 3/5: movement against gravity but not against resistance; 2/5: visible movement but not against gravity; 1/5: visible contraction; 0/5: no visible activity

C. Pronator Drift

1. Ask the participant to hold both arms straight forward with, palms up and eyes closed for ~10-15 seconds as tolerated; watch for how well the arm position is maintained.

Score: left and right

Grade: **NORMAL or ABNORMAL**

MODULE 4 – REFLEXES

A. Biceps

B. Knee

Note: Other deep tendon reflexes may be tested at investigator's discretion (eg, elbow, wrist or Achilles tendon)

Score: left and right

Grade: **NORMAL, INCREASED, DECREASED or ABSENT**

C. Babinski

Score: left and right

Grade: **NORMAL or ABNORMAL**

MODULE 5 – COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

1. Testing each hand separately, ask the participant to tap the distal thumb with the tip of each finger, in sequence, as fast as possible.

Score: left and right

Grade: **NORMAL or ABNORMAL**

Reminder: If the rapid alternate movements are disturbed, the participant will be asked to strike his/her hand on the thigh, raise the hand, turn it over and then strike the back of the hand down on the same place.

B. Point-to-Point Movements

1. Ask the participant to touch your index finger and their nose alternately several times. Move your finger about as the participant performs this task.

Score: left and right

Grade: **NORMAL or ABNORMAL**

2. Ask the participant to place 1 heel on the opposite knee and then run it down the shin to the big toe. Repeat this for both sides.

Score: left and right

Grade: **NORMAL or ABNORMAL**

C. Romberg

1. Ask the participant to stand with both feet together and eyes closed for 20 to 30 seconds without support.

2. Be prepared to catch the participant if they are unstable.

Grade: **NORMAL or ABNORMAL**

D. Gait

1. Ask the participant to walk across the room, turn and come back (assess posture, balance, swinging of arms and movement of the legs).

Grade: **NORMAL or ABNORMAL**

2. Ask the participant to walk heel-to-toe in a straight line (tandem gait).

Grade: **NORMAL or ABNORMAL**

MODULE 6 – SENSORY

A. Pin prick: safety pin touched lightly to skin of forearms and legs, bilaterally.

B. Temperature: warm or cool object touched to skin of forearms and legs, bilaterally.

C. Vibration: tuning fork vibration detection in finger (thumb or distal finger), toe bilaterally.

D. Position sense: perception of thumb and toe movement, bilaterally.

Score: left and right

Grade: **NORMAL OR ABNORMAL (for each A to D)**

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
AD	Alzheimer's disease
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APaT	all-participants-as-treated
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
AxMP	auxiliary medicinal product
BAC SC	Brief Assessment of Cognition Symbol Coding
bid	twice-daily
biw	twice-weekly
BMI	body mass index
CFB	change from baseline
CGI-S	Clinical Global Impression-Severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CK	creatinine kinase
C_{max}	maximum plasma concentration
CNS	central nervous system
CO_2	carbon dioxide
corr	correlation
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CP	conditional probability
CRF	case report form
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	plasma concentration at last timepoint before next dose
CYP	cytochrome P450
CYP2C19	cytochrome P450 2C19
CYP3A	cytochrome P450 3A
DC	discontinuation
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EM	exposure margins
EMA	European Medicines Agency
EOT	end of treatment
EU CTR	European Union Clinical Trial Regulation
FAS	full analysis set

Abbreviation	Expanded Term
FBR	future biomedical research
FDA	US Food and Drug Administration
FSH	Follicle-stimulating hormone
FT4	free T4 test
GCP	Good Clinical Practice
GM	geometric mean
HAM-D6	6-item Hamilton Depression Rating Scale
HAM-D17	17-item Hamilton Depression Rating Scale
HBsAg	hepatitis B surface antigen
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HS	hypothetical strategy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intention-to-treat
IU/L	international units per liter
IVRS	interactive voice response system
LDL	low density lipoprotein
MADRS	Montgomery-Asberg Depression Rating Scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	doctor of medicine
MDD	major depressive disorder
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MGH-ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
mGluR2	metabotropic glutamate receptor 2
MINI	Mini International Neuropsychiatric Interview
mRNA	messenger RNA
NA	not applicable
NAM	negative allosteric modulator
NDA	new drug application
NIMP	non-investigational medicinal product
NMDA	N-methyl-D-aspartate
NOAEL	no observed adverse effect level
NSAE	nonserious adverse event
PD	pharmacodynamics
PDLC	predefined limit of change
PET	positron emission technology
PK	pharmacokinetic
PoC	proof-of-concept
PP	per-protocol
QD	once daily

Abbreviation	Expanded Term
QTcF	QTc using the Fridericia formula
RBC	red blood cell
RDW	red cell distribution width
RNA	ribonucleic acid
RO	receptor occupancy
SAC	scientific advisory committee
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SES	standardized effect size
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamate-pyruvate transaminase
siDMC	standing internal data monitoring committee
SLAB	supplemental laboratory
SoA	schedule of activities
SOC	system organ class
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TC	telephone call
T_{max}	time to maximum concentration
TMS	transcranial magnetic stimulation
TPS	treatment policy strategy
TRD	treatment-resistant depression
TSH	thyroid-stimulating hormone
ULN	upper-limit of normal
WBC	white blood cell
WOCBP	woman of childbearing potential
WONCBP	woman of nonchildbearing potential

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