A Phase 3b Efficacy and Safety Study of Adjunctive ALKS 5461 in Treatment Refractory Major Depressive Disorder

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CLINICAL STUDY PROTOCOL

ALK5461-217

Study title:	A Phase 3b Efficacy and Safety Study of Adjunctive ALKS 5461 in Treatment Refractory Major Depressive Disorder
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Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

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2. SYNOPSIS

Name of Sponsor/Company: Alkermes, Inc.	
Name of Investigational Product: ALKS 5461	
Name of Active Ingredient: Buprenorphine (BUP) and samidorphan (SAM)	
Title of Study: A Phase 3b Efficacy and Safety Study of Adjunctive ALKS 5461 in Treatment Refractory Major Depressive Disorder	
Investigators: Multicenter, multinational study to be conducted at approximately 35 sites	
Study Period: Estimated date of first subject's consent: Q2 2017 Estimated date of last subject's last visit: Q3 2021	**Phase of Development:** 3b

Objectives:

- To evaluate the efficacy of adjunctive ALKS 5461 for treatment refractory major depressive disorder (MDD) in adults
- To evaluate the safety and tolerability of adjunctive ALKS 5461 in adults who have treatment refractory MDD

Methodology: This is a Phase 3b multicenter study of adjunctive ALKS 5461 2/2 that will utilize a randomized, double-blind, 2-stage, placebo-controlled, sequential parallel comparison design (SPCD). The purpose of this study is to evaluate the efficacy, safety, and tolerability of adjunctive ALKS 5461 2/2 (2 mg buprenorphine [BUP]/2 mg samidorphan [SAM]) sublingually (SL) once a day in male and female subjects with treatment refractory MDD (defined as having at least 2 inadequate responses to antidepressant therapies [ADTs] in the current major depressive episode [MDE]). ALKS 5461 2/2 or placebo will be administered to subjects for 5 weeks in Stage 1 and for 6 weeks in Stage 2 (see study design schematic below).

Potential subjects will be evaluated during a Screening Period lasting up to 4 weeks. Screening will include an assessment of each subject's history of inadequate response to ADT. Based on this assessment at Screening, qualifying subjects will either participate in an 8-week Prospective Lead-in (PLI) Period (prospective inadequate responders [PIRs]) or will be eligible to bypass the PLI Period and proceed directly to Stage 1 (historic inadequate responders [HIRs]).

In Stage 1, a greater proportion of subjects will receive placebo than ALKS 5461 to ensure an adequate number of placebo nonresponders will be rerandomized in Stage 2. In Stage 1, all eligible subjects will be randomized 2:5 to receive either ALKS 5461 2/2 or placebo, respectively, for 5 weeks. Subjects receiving placebo in Stage 1 will be categorized as either placebo responders or nonresponders at the end of Stage 1.

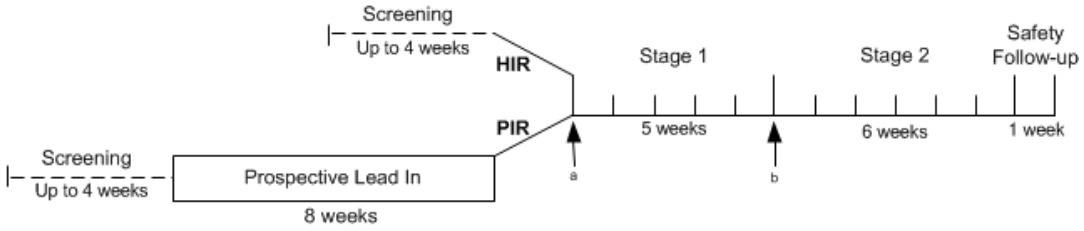
In Stage 2, subjects receiving ALKS 5461 2/2 in Stage 1 and subjects responding to placebo in Stage 1 will continue on placebo for 6 weeks (see study flow diagram). Placebo nonresponders will be rerandomized 1:1 to receive either ALKS 5461 2/2 or placebo for 6 weeks.

From the beginning of Stage 1 to the end of Stage 2, all participating subjects will take study drug (ALKS 5461 2/2 or placebo) and continue to take an approved ADT. On Day 1 (Visit 2) and for the remainder of visits during the Treatment Period, subjects will self-administer study drug in the presence of study staff. Subjects will self-administer study drug at home on days where there are not study visits.

During Stages 1 and 2, subjects will return to the clinic every week for assessments. Subjects will return to the clinic for a Safety Follow-up Visit (Visit 14) one week after Visit 13. The total study duration for a given subject will be up to approximately 24 weeks, which includes a Screening Period of up to 4 weeks,

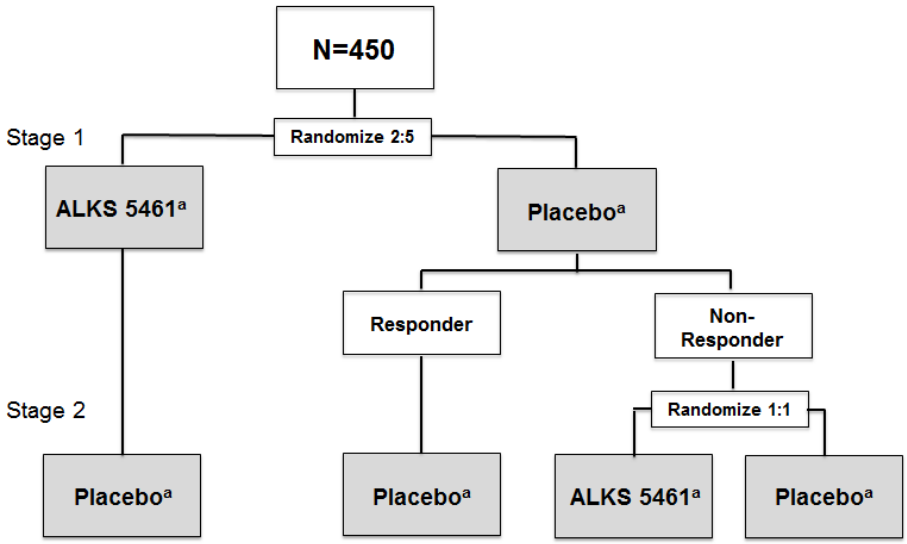
a PLI Period of up to 8 weeks (if required as determined during Screening), two treatment periods of 5- and 6-weeks duration (Stages 1 and 2 respectively), and a 1-week Follow-up Period. A schematic of the study design and a diagram depicting subject flow through the study are provided below.

Study Design Schematic



Abbreviations: HIR=historic inadequate responder; PIR=prospective inadequate responder
[a] Stage 1 treatment initiation
[b] Stage 2 treatment initiation

Study Flow Diagram



[a]Subjects will continue to take an approved antidepressant therapy

Number of Subjects Planned: Approximately 450 subjects will be randomized in Stage 1.

Main Criteria for Subject Inclusion: Male and female subjects between 18 and 70 years of age, inclusive, who meet Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition (DSM-5) criteria for primary diagnosis of MDD, in which the current major depressive episode (MDE) has lasted at least 8 weeks (if entering the PLI Period) or 12 weeks (if bypassing the PLI Period) and up to 5 years, and have had an inadequate responses to adequate courses of treatment with selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) during the current MDE may be eligible for participation in this study. Subjects must also agree to use an acceptable method of contraception for the duration of the study and at least 30 days after the last dose of study drug unless surgically sterile or postmenopausal, and be willing and able to follow study procedures as outlined in the protocol.

Investigational Product, Dosage, Duration, and Mode of Administration: ALKS 5461 consists of BUP and SAM in a 1:1 ratio. ALKS 5461 2/2 (2 mg BUP: 2 mg SAM) will be administered as a once-daily SL tablet for up to 11 weeks.

Reference Therapy, Dosage, Duration, and Mode of Administration: Placebo matched to ALKS 5461 will be administered as a once-daily SL tablet for up to 11 weeks.

Duration of Study: The total study duration will be up to approximately 24 weeks, which includes a Screening Period of up to 4 weeks, a PLI Period of up to 8 weeks (if required as determined during Screening), two treatment periods of 5- and 6-week duration (Stages 1 and 2 respectively) and a 1-week Safety Follow-up Period.

Criteria for Evaluation:

Primary Efficacy Endpoint:

1. Average change from baseline to Week 3 to the end of treatment period in Montgomery-Åsberg Depression Rating Scale-6 (MADRS-6) scores
2. Average change from baseline to Week 3 to the end of treatment period in Montgomery-Åsberg Depression Rating Scale-10 (MADRS-10) scores
3. Change from baseline to the end of treatment period in MADRS-10 scores

Secondary Efficacy Endpoints:

- MADRS response, defined as a ≥50% reduction in MADRS-10 score from baseline to the end of treatment period
- MADRS remission, defined as MADRS-10 score ≤10

Exploratory Endpoints:

- Change over time in Clinical Global Impression-Severity (CGI-S) scores
- Absolute Clinical Global Impression-Improvement (CGI-I) scores over time
- Change over time in Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) scores
- Change over time in Brief Pain Inventory-Short Form (BPI-SF) scores
- Change over time in Snaith-Hamilton Pleasure Scale (SHAPS) scores
- Change over time in Connor-Davidson Resilience Scale (CD-RISC-25) scores

Statistical Methods: Summary statistics (n, mean, standard deviation, median, minimum, and maximum values for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided for evaluated variables. All individual subject level data will be presented as data listings.

Study Populations: The Safety Population will consist of all enrolled subjects receiving at least one dose of study drug (placebo or ALKS 5461). The Full Analysis Set (FAS) population will consist of all subjects in the Safety Population who have at least one post-Baseline MADRS assessment. The Pharmacokinetic (PK) Population will consist of all subjects who have at least one measurable plasma concentration of any analyte during the Treatment Period.

Efficacy Analyses: The primary endpoint analysis will be carried out using mixed-model repeated measures (MMRM) in the context of a Sequential Parallel Comparison Design (SPCD) for each endpoint analyzed within each Stage of the trial separately. The models will include variables for Treatment Group, Visit, Treatment group-by-visit interaction term, and site as categorical fixed effects. Baseline value and baseline by visit interaction will be included as covariates in the model. The comparisons of ALKS 5461 2/2 vs placebo will be made, and the least-squares mean difference along with the corresponding 95% confidence interval and *P*-value will be reported. Adjustments for multiplicity of the primary endpoints will be made using a hierarchical testing approach with the order of testing being the rank order in which the primary endpoints are listed.

Secondary efficacy endpoints (ie, proportion of subjects achieving treatment response and proportion of

subjects achieving remission at the end of the treatment period) will be evaluated using a chi-squared test. Further details will be described in the Statistical Analysis Plan (SAP).

Pharmacokinetic Analyses: The PK data may be used in a subsequent population PK evaluation conducted outside of this study. By-subject listings of plasma concentrations will be provided.

Safety Analyses: All safety assessments including those collected during the Follow-up Period and adverse events (AEs) collected in the PLI will be summarized using descriptive statistics. Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) will be defined as AEs that occur or worsen after the first dose of study drug. The incidence of TEAEs will be summarized by system organ classes and preferred terms and by severity and relationship to study drug. Subjects with SAEs, and AEs leading to discontinuation from the study will be summarized. Results of clinical laboratory tests, vital signs, and ECG parameters will also be summarized for the absolute value and for change from baseline. The number and percentage of subjects with potentially clinically significant (PCS) values will also be summarized. The number and percentage of subjects with C-SSRS assessments at post-Baseline will be summarized. Concomitant medications will be categorized using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system. Listings will be provided for all concomitant medications.

Sample Size Considerations: Approximately 450 subjects are planned to be randomized in Stage 1 to have approximately 200 subjects rerandomized to treatment in Stage 2. This will provide at least 80% power to show superiority for ALKS 5461 2/2 compared to placebo at the one-sided alpha level 0.025, for each of the primary endpoints, assuming an effect size of at least 0.20 in Stage 1, 0.44 in Stage 2, and 0.32 overall (weighted average of Stage 1 and Stage 2); and a SD of 6.25 and 8.5 for MADRS-6 and MADRS-10 scores, respectively. Details on the clinical study simulations conducted to evaluate power and type 1 error control will be provided in the SAP.

Interim Analysis: A single interim analysis is planned when approximately 265 subjects have completed Stage 1 and approximately 120 subjects have completed Stage 2. A group sequential design with a single interim analysis for potential early efficacy conclusion stop is employed. The primary analysis will be based on the SPCD method of combination of treatment mean differences between treatments in Stages 1 and 2. The interim analysis will be conducted by an external independent statistical center and reviewed by external data monitoring committee (DMC). Alkermes will remain blinded throughout the interim analysis. The one-sided *P*-value required for efficacy conclusion at both interim and final analyses is <0.0147 (constant significance levels (Pocock 1977) in order to control overall type 1 error at 0.025 in a one-sided test. Further details will be described in the SAP for interim analysis and charter guiding the independent DMC.

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4. LIST OF ABBREVIATIONS

Table 2: List of Abbreviations and Definition of Terms

Abbreviation or Term	Full Form or Definition
ADT	Antidepressant therapy
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
BPI-SF	Brief Pain Inventory-Short Form
BUP	Buprenorphine
CD-RISC-25	Connor-Davidson Resilience Scale
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
COWS	Clinical Opiate Withdrawal Scale
C-SSRS	Columbia-Suicide Severity Rating Scale
CSA	Clinical Study Agreement
CST	Clinical Surveillance Team
CYP	Cytochrome P450
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual for Mental Disorders-Fifth Edition
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HAM-A	Hamilton Rating Scale for Anxiety
HAM-D	17-item Hamilton Rating Scale for Depression
HIR	Historic inadequate responders
HIV	Human immunodeficiency virus
ICF	Informed consent form

Table 2: List of Abbreviations and Definition of Terms (Continued)

Abbreviation or Term	Full Form or Definition
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IxRS	Interactive Voice or Web Response System
MADRS	Montgomery-Åsberg Depression Rating Scale
MADRS-6	The sum of 6 MADRS items: reported sadness (item 1); apparent sadness (item 2); inner tension (item 3); lassitude (item 7); inability to feel (item 8); and pessimistic thoughts (item 9)
MADRS-10	The sum of 10 MADRS items: reported sadness (item 1), apparent sadness (item 2), inner tension (item 3), reduced sleep (item 4), reduced appetite (item 5), concentration difficulties (item 6), lassitude (item 7), inability to feel (item 8), pessimistic thoughts (item 9), and suicidal thoughts (item 10)
MAOIs	Monoamine oxidase inhibitors
MDD	Major depressive disorder
MDE	Major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MINI v7.0.2	Mini International Neuropsychiatric Interview 7.0.2
MMRM	Mixed model repeated measures
OTC	Over-the-counter
PIR	Prospective inadequate responders
PK	Pharmacokinetics
PLI	Prospective lead-in
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form
QTcB	QT interval corrected using the Bazett formula
QTcF	QT interval corrected using the Fridericia formula
SAE	Serious adverse event
SAM	Samidorphan
SAP	Statistical Analysis Plan
SD	Standard deviation
SHAPS	Snaith-Hamilton Pleasure Scale
SIGH-D	Structured Interview Guide for the HAM-D
SIGMA	Structured Interview Guide for the MADRS

Table 2: List of Abbreviations and Definition of Terms (Continued)

Abbreviation or Term	Full Form or Definition
SL	Sublingual
SNRI	Serotonin-norepinephrine reuptake inhibitor
SPCD	Sequential parallel comparison design
SSRI	Selective serotonin reuptake inhibitor
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

5. INTRODUCTION

Major depressive disorder (MDD) is a serious, and in some cases life-threatening, condition. Current therapy is limited and insufficient. Selective serotonin reuptake inhibitors (SSRI) or serotonin-norepinephrine reuptake inhibitors (SNRI) are recommended as first-line therapy; however, the large majority of patients do not experience an adequate response (Rush et al, 2006). For patients with MDD who have an inadequate response to approved first-line antidepressant therapy (ADT) the only currently approved agents for adjunctive treatment are atypical antipsychotics. However, this class of medicines is associated with serious toxicity, including tardive dyskinesia, which may be irreversible, as well as neuroleptic malignant syndrome and agranulocytosis, both of which are potentially fatal. Further, metabolic adverse effects of some antipsychotics contribute to significant long term co-morbidity, eg, increased adiposity, insulin-resistance, cardiovascular disease etc (Newcomer and Haupt 2006). These conditions and other side effects of the atypical antipsychotics commonly lead to discontinuation of treatment (Spielmans et al, 2013).

The development of an adjunctive treatment that avoids the toxicity associated with atypical antipsychotics is an important step toward addressing the suboptimal treatment of MDD and the related public health consequences. The Sponsor is developing ALKS 5461, a fixed-dose, combination tablet consisting of buprenorphine (BUP) and samidorphan (SAM) in a 1:1 (weight/weight) ratio for once-daily, sublingual (SL) administration as an adjunctive therapy to antidepressants for the treatment of MDD.

ALKS 5461 consists of a combination of BUP, a μ-opioid receptor partial agonist that also blocks κ-opioid activation and SAM, a potent, μ-opioid receptor antagonist. ALKS 5461 offers a unique mechanism of action for the treatment of MDD: modulation of the opioid system. ALKS 5461 is intended to support opioid tone in brain regions with impaired endogenous activity and dampen opioid tone in upregulated region. From 1982 to the present, there have been several published studies of BUP in depressed patients (Bodkin et al, 1995; Emrich et al, 1982; Karp et al, 2014; Nyhuis et al, 2008). These studies demonstrated striking antidepressant effects with BUP treatment, particularly in patients with MDD who have had multiple prior inadequate responses to therapy. Despite this evidence of efficacy with BUP, the risk of diversion, abuse and dependence have precluded routine clinical use of BUP, and opioids in general, in the treatment of depression. ALKS 5461 was specifically designed to confer therapeutic benefits in the treatment of depression through the opioid system, while addressing the risk of abuse or addiction and dependence potential normally associated with opioids. SAM (a μ-opioid receptor antagonist) is a new molecular entity optimized for high potency and high SL bioavailability, which facilitates coformulation with BUP (a μ-opioid receptor partial agonist) for SL administration.

Efficacy has been observed with ALKS 5461 in subjects with MDD in a Phase 2 study (Study ALK5461-202), and several Phase 3 studies have recently completed. Although the primary endpoint was not met for one Phase 3 study (Study ALK5461-205), supportive evidence of the efficacy of ALKS 5461 in the treatment of MDD was observed. In a differently designed Phase 3 study (Study ALK5461-206) ALKS 5461 2/2 showed improvement vs Baseline; however, the net treatment effect was obscured by a large placebo effect. The third Phase 3 study

(Study ALK5461-207) of ALKS 5461 in MDD met the pre-specified primary endpoints of significantly reducing depression scores compared to placebo, as measured by MADRS-6 and MADRS-10. The Phase 3 long-term safety study (Study ALK5461-208) for ALKS 5461 is ongoing. In the completed studies with ALKS 5461, ALKS 5461 was generally well-tolerated. Altogether these findings support continued investigation of ALKS 5461 and indicate that it has the potential to address an unmet medical need for treatment of the serious condition of MDD.

Results from nonclinical and clinical investigations available to date on the pharmacokinetics (PK), safety, and efficacy of ALKS 5461, as well as of SAM and BUP as individual and coadministered therapeutic agents, are summarized in the ALKS 5461 Investigator's Brochure.

5.1. Study Dose Selection

In the completed studies with ALKS 5461, ALKS 5461 was generally well-tolerated. In Phase 2 and Phase 3 studies, data on the short-term and long-term safety and tolerability of ALKS 5461 have been and are being collected. The selected dose of ALKS 5461 2/2 in the current study is supported by clinical safety, tolerability and efficacy data from prior studies of ALKS 5461.

5.2. Study Rationale and Selection of Study Design

The purpose of this study is to evaluate the efficacy, safety, and tolerability of adjunctive ALKS 5461 2/2 (2 mg BUP/ 2 mg SAM) SL once a day in male and female subjects with treatment refractory MDD (defined as having at least 2 inadequate responses to antidepressant therapies [ADTs] in the current major depressive episode [MDE]). This study will utilize a sequential parallel comparison design (SPCD) that is intended to address high placebo response common to clinical trials in MDD. The study will employ two treatment stages, with the majority of subjects in the first treatment stage randomized to placebo. Subjects randomized to placebo in Stage 1 who do not exhibit a response (ie, placebo nonresponders) will be rerandomized in Stage 2. All other subjects will receive placebo. The efficacy analysis will be performed on the full analysis set (FAS) and include (a) subjects in Stage 1 and (b) subjects in Stage 2 who were placebo nonresponders in Stage 1. Efficacy will be evaluated as the weighted average of the efficacy estimates from individual stages. The duration of Stage 1 and Stage 2 will be 5 and 6 weeks, respectively.

6. OBJECTIVES

The objectives of this study are:

- To evaluate the efficacy of adjunctive ALKS 5461 for treatment refractory MDD in adults
- To evaluate the safety and tolerability of adjunctive ALKS 5461 in adults who have treatment refractory MDD

7. SELECTION AND WITHDRAWAL OF SUBJECTS

Note that an inadequate response to ADT is defined as <50% reduction in symptom severity to a course of treatment at an adequate dose at least 8 weeks in duration, inclusive of up to 3 weeks of titration into the adequate dose range, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ). Even if this antidepressant is taken concomitantly with a second antidepressant, for the purposes of this study, only one ADT inadequate response will be considered.

An adequate dose of an ADT is defined as a dose that is greater than or equal to the minimum dose on the ATRQ (see Section 20). Note that ADTs taken during the study may not exceed the maximum daily dose listed in Section 21.

7.1. Subject Inclusion Criteria

7.1.1. At Screening (Visit 1)

7.1.1.1. All Subjects

Each subject must meet all of the following inclusion criteria to be qualified to participate in this study.

1. Be willing and able to provide government issued identification. If government issued identification does not contain a photograph, a second form of photographic identification will be required
2. Is between 18 and 70 years of age, inclusive
3. Be willing and able to provide informed consent
4. Be willing and able to provide informed consent for assessment of participation in multiple clinical studies via a clinical study subject registry
5. Have a body mass index (BMI) of 18.0 to ≤40.0 kg/m^2
6. Is willing to abide by the contraception requirements for the duration of the study (please refer to Section 8.4.1 for additional details regarding contraception)
7. Have a Diagnostic and Statistical Manual for Mental Disorders-Fifth Edition (DSM-5) primary diagnosis of MDD as assessed and confirmed by the Mini International Neuropsychiatric Interview 7.0.2 ([MINI v7.0.2] administered by qualified site staff); primary diagnosis is defined as the primary source of current distress and functional impairment, in the opinion of the Investigator
8. Be willing and able to follow the study procedures and visits as outlined in the protocol (including agreeing not to enroll in any other clinical studies)

7.1.1.2. Subjects Entering the Prospective Lead-in Period

In addition to the general inclusion criteria listed in Section 7.1.1.1, in order to qualify for participation in this study, each subject entering the PLI Period must meet all of the following criteria:

9. Have a current MDE with duration of at least 8 weeks and up to 5 years at Screening
10. One of the following:
    a. Not be currently taking any ADT
    b. SSRI or SNRI being taken for the current MDE is not at an adequate dose and/or duration is ≤4 weeks
    c. Is experiencing an inadequate response to their current ADT and switching ADT is in in the best interest of the subject per investigator judgment and ADT will be discontinued 2 weeks prior to Visit 1a
11. Have 1 to 3 prior inadequate responses to ADT in the current MDE at Screening/Visit 1. Prior inadequate response within the current MDE must be to an ADT medication listed on the ATRQ (see Section 8.3.9.1.1)
12. Have a 17-item Hamilton Rating Scale for Depression (HAM-D) total score ≥22 at Screening/Visit 1 and at PLI Visit 1a

7.1.1.3. Subjects Bypassing the Prospective Lead-in Period (Historical Inadequate Responders)

In addition to the general inclusion criteria listed in Section 7.1.1.1, in order to qualify for participation in this study, each subject bypassing the PLI Period must meet all of the following criteria:

13. Have a current MDE duration of at least 12 weeks and up to 5 years at Screening
14. Currently treated with an SSRI or SNRI (ie, paroxetine, fluoxetine, sertraline, citalopram, escitalopram, vilazodone, vortioxetine, venlafaxine, duloxetine, desvenlafaxine, or levomilnacipran) for at least 8 weeks at Visit 2. The 8 weeks of ADT is inclusive of up to 3 weeks for titration into the adequate dose range, with the same, adequate dose over the last 4 weeks that is expected to remain stable throughout the study and which does not exceed the labeled maximum daily dose. The 8 weeks of ADT may include up to 28 days of the Screening Period
15. Have an inadequate response to current ADT treatment[1]
16. Have 2 to 4 inadequate responses to ADT (inclusive of current inadequate response) in the current MDE by Visit 2[2]. Prior inadequate response within the current MDE must be to an ADT medication listed on the ATRQ (see Section 8.3.9.1.1)
17. Have a HAM-D total score ≥18 at Screening

[1] HIR subjects can enter the study as a PIR if the subject is experiencing an inadequate response to their current ADT and switching ADT is in the best interest of the subject per investigator judgment. ADT will then be discontinued 2 weeks prior to Visit 1a of the PLI.

[2] At Screening, HIR subjects who are on an adequate dose of ADT, but whose ADT duration is >4 and <8 weeks, may complete the remaining duration requirement (<4 weeks) in the Screening Period (ie, before Visit 2).

Note for inclusion criteria 11, 14, *and* 16: *If a subject experienced an adequate response to an ADT for at least 4 weeks and subsequently relapsed (tachyphylaxis), but remained on the same ADT* ***at the same or lower dose****, this would not represent an inadequate response to the ADT.*

7.1.2. Visit 2

7.1.2.1. All Subjects

In addition to the general inclusion criteria listed in Section 7.1.1.1, in order to qualify for participation in this study, each subject must meet all of the following criteria:

18. Have 2 to 4 inadequate responses to ADT within the current MDE
19. Have confirmation of ADT medication history
20. Have detectable concentrations of approved ADT during Screening or PLI Period as assessed by PK sampling
21. Have a site-administered HAM-D total score ≥18 at Visit 2
22. Have a Clinical Global Impression-Severity (CGI-S) score of ≥4 at Visit 2
23. Have met criteria for HIR/PIR as determined by an interactive voice or web response system (IxRS) at Visit 2

7.1.2.2. Subjects Participating in the Prospective Lead-in Period (Prospective Inadequate Responders)

In addition to the general inclusion criteria listed in Section 7.1.1.1 and Section 7.1.2.1, in order to qualify for participation in this study, each subject participating in the PLI Period must meet all of the following criteria:

24. Have been treated during the PLI Period with escitalopram, sertraline, duloxetine, venlafaxine, or fluoxetine for at least 8 weeks, inclusive of up to 3 weeks of titration into the adequate dose range, with the same adequate dose over the last 4 weeks that does not exceed the labeled maximum daily dose. Note that if the subject cannot tolerate the selected ADT upon treatment initiation, it is acceptable to switch to another one of the 5 available ADTs within the first week of treatment, as deemed appropriate by the Investigator. The second ADT must then be taken for at least 7 weeks and in the adequate dose range for at least 5 weeks, with the same dose over the last 4 weeks that does not exceed the maximum daily dose
25. Have met additional masked criteria for PIR as determined by an IxRS at Visit 1f

7.2. Subject Exclusion Criteria

Each subject must not have any of the following conditions to be qualified to participate in this study.

1. Has any finding that in the view of the Investigator or Medical Monitor would compromise the safety of the subject or affect their ability to adhere to the protocol visit schedule or fulfill visit requirements

2. Has any other significant medical condition (eg, neurological, psychiatric, or metabolic) or clinical symptom that could unduly risk the subject or affect the interpretation of study data (eg, unstable hypothyroidism or active cancer or treatment for cancer within the last 5 years [with the exception of non-melanomatous skin cancers], poorly controlled diabetes [HbA1c > 9.0], or gastric bypass)
3. Has any current primary DSM-5 diagnosis other than MDD, where primary diagnosis is defined as the primary source of current distress and functional impairment, in the opinion of the Investigator
4. Have any of the following psychiatric conditions per DSM-5 criteria, as assessed by the MINI v7.0.2. Conditions not assessable by the MINI v7.0.2 should be assessed by clinical judgment:
    a. Lifetime history of a diagnosis of delirium, dementia, schizophrenia, or other psychotic disorder (including psychotic depression), or bipolar I or II disorder
    b. History within the past 12 months of a DSM-5 diagnosis of eating disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, or acute stress disorder
    c. Clinically significant current DSM-5 diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder
    d. Current diagnosis or clinical evidence of any cognitive disorder at Screening
5. Has experienced hallucinations, delusions, or any psychotic symptoms in the current MDE
6. Has been hospitalized for MDD within 3 months before Screening
7. Has initiated any psychosocial intervention (eg, psychotherapy, support group, or social counseling) within 6 weeks of Screening or have an anticipated need for initiating any psychosocial intervention during the study in the judgment of the Investigator and/or Medical Monitor. A stable course of any psychosocial intervention initiated >6 weeks prior to Screening is permitted to continue throughout the study
8. Has used:
    a. Antipsychotics other than quetiapine or quetiapine XR, oral aripiprazole, olanzapine/fluoxetine, or brexpiprazole with 1 year of screening or within the current MDE, whichever is longer[3]
    b. Any long-acting antipsychotic (lifetime)
    c. Ketamine (lifetime)
    d. A course of pharmacotherapy (including prescription or over the counter medications) or natural supplements for insomnia, if initiated within 30 days of screening

[3] Number of subjects treated with antipsychotics within the current MDE prior to enrollment will be monitored throughout the study. The Sponsor reserves the right to restrict subjects entering the study with the goal of achieving fewer than 30% of subjects with previous exposure to antipsychotics within the current MDE. This threshold of 30% is approximate and it is recognized that that the final proportion might be lower or higher.

9. Started on a prohibited medication between Screening and Visit 2 other than those being washed out as indicated in the prohibited medications requiring washout (see Section 8.4.2.1)
10. Has used opioid agonists (eg, codeine, oxycodone, tramadol, morphine) or opioid antagonists (eg, naloxone, naltrexone) within 14 days prior to Screening, has an anticipated need for opioid use at any point during the study (eg, planned surgery), or has used an extended-release formulation of an opioid antagonist within 2 months prior to Screening
11. Subject is unwilling to discontinue the use of prohibited medications or the Investigator recommends against discontinuation of prohibited medications
12. Has received electroconvulsive therapy treatment within the last 2 years or within the current MDE or failed a course of electroconvulsive treatment at any time
13. Poses a current suicide risk, as evidenced by any of the following:
    a. In the opinion of the Investigator, the subject may be at risk for suicide
    b. The subject responds "Yes" to Question 4 ("Active Suicidal Ideation with Some Intent to Act, Without Specific Plan") or Question 5 ("Active Suicidal Ideation with Specific Plan and Intent") on the Baseline/Screening Columbia-Suicide Severity Rating Scale (C-SSRS), within the past 12 months
    c. The subject has attempted suicide within the past 2 years
14. Has a QT interval >450 msec for males and >470 msec for females, assessed in a relaxed state, as corrected by the Fridericia formula (QTcF) observed at Visit 1 or 2
15. Has an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) measurement of >2 × the upper limit of normal (ULN) at Visit 1
16. Has current evidence of or history of any of the following:
    a. Compromised respiratory function (eg, chronic obstructive pulmonary disease, respiratory depression, signs or symptoms of hypoxia at Screening)
    b. Thyroid pathology (unless stabilized and euthyroid for >3 months at the time of Screening)
    c. Seizure disorder (excluding febrile seizures)
    d. Hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection
    e. Myasthenia gravis
    f. Any contraindicated medical condition as per the approved labeling for BUP
17. Has current evidence of or a history (in the past 12 months) of alcohol or substance use disorder (excluding tobacco) per DSM-5 criteria as assessed by the MINI v7.0.2
18. Has a positive breath alcohol test at Screening or Visit 2
19. Has a positive test for drugs of abuse at Screening or Visit 2 (excluding drugs that are permitted as per protocol; see Section 8.4.2.2)
20. Is pregnant, planning to become pregnant, or is breastfeeding during the study
21. Has a history of either of the following:
    a. Severe gastrointestinal intolerance, allergy, or hypersensitivity to opioid agonists (eg, BUP, oxycodone) or opioid antagonists (eg, naltrexone, naloxone)

b. Nausea and/or vomiting when taking an opioid agonist or opioid antagonist that interfered with the ability to continue on the drug

22. Has had a significant blood loss (>500 mL) or blood donation (including platelets or plasma) within 60 days of Screening or between Screening and Randomization or anticipated blood donation at any time during the study
23. Has participated or is currently participating in any of the following:
    a. An interventional clinical study for any indication (except for MDD) within the last 2 years
    b. An interventional clinical study for MDD within the past 6 months
24. Has participated or is currently participating in the double-blind portion or open-label extension phase of a prior clinical study of ALKS 5461
25. Is an employee of the Investigator or study center, or immediate family[4] of such employees or the Investigator
26. Is an employee or immediate family[4] of an employee (permanent, temporary contract worker, or designee responsible for the conduct of the study) of Alkermes or designated clinical research organization

7.3. Subject Withdrawal

Subjects who do not qualify at Visit 2, including subjects who complete the PLI Period but who are not randomized into Stage 1, will be considered screen failures. Subjects who are screen failures may be eligible for rescreening only if rescreening is approved by the Medical Monitor. Subjects who withdraw after entering treatment (Stage 1 or 2) will not be replaced. Subjects are considered to have completed the study if they completed visits spanning the duration of the Treatment Period and the Safety Follow-up Visit.

A subject may be withdrawn from the study at any time if the subject, Investigator, or Sponsor or designee determines that it is not in the best interest of the subject to continue.

Examples of reasons for withdrawal may include, but are not limited to, the following:

- Adverse Event (AE)
- Lack of efficacy
- Physician's decision
- Pregnancy
- Protocol deviation (including noncompliance with study drug or study procedures)
- Withdrawal by subject
- Lost to follow-up
- Study terminated by Sponsor
- Other

[4] Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

Subjects may not enter another clinical study while participating in this study. If entry in another clinical study is confirmed by subject report or through confirmation using a clinical study subject registry, the subject will be withdrawn from the study.

If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up. If, in the opinion of the Investigator, it is necessary to monitor a subject beyond the Safety Follow-up Visit, the Follow-up Period may be extended as necessary. In such instances, the Sponsor and the Investigator will agree to an acceptable follow-up schedule.

In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable effort to ascertain the reason(s) for withdrawal, while fully respecting the subject's rights. Subjects are to be asked to return to the clinic for an Early Termination (ET) Visit. The ET visit should be scheduled as close as possible to the subject's last dose and will mimic the assessments scheduled to be conducted at Visit 13. Additionally, an attempt will be made to schedule a Follow-up Visit 1 week after the subject's last dose equivalent to Visit 14. If the subject fails or refuses to return to the study center, an attempt must be made to contact the subject by telephone in order to assess as many safety and efficacy parameters as possible. All data collected over the telephone must be documented and kept in the subject's record.

The Investigator must maintain a record of all subjects who fail to complete the study. A full explanation of the reason for study discontinuation will be made on the appropriate electronic case report form (eCRF). The reason for discontinuation will be documented. If a subject is lost to follow-up, reasonable attempts to contact the subject must be made and documented.

7.4. Replacement of Subjects

Subjects who withdraw after entering treatment (Stages 1 or 2) will not be replaced.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

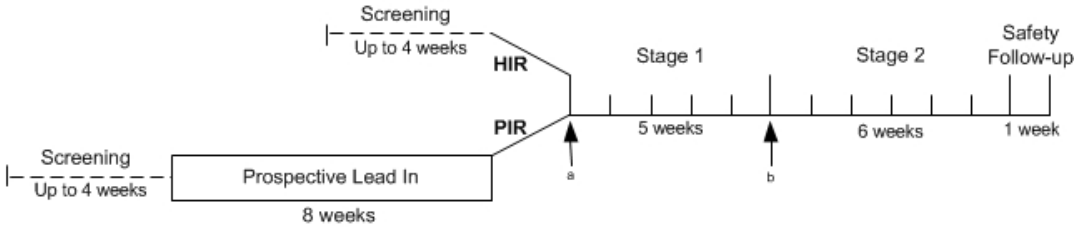
The purpose of this study is to evaluate the efficacy, safety, and tolerability of adjunctive ALKS 5461 2/2 (2 mg BUP/2 mg SAM) SL once a day in male and female subjects with treatment refractory MDD. This is a Phase 3b multicenter study of adjunctive ALKS 5461 2/2 that will utilize a SPCD, which is intended to address high placebo response common to clinical trials in MDD. The study will employ two treatment stages, with the majority of subjects in the first treatment stage randomized to placebo (ie, Stage 1 randomization ratio 2:5 for ALKS 5461 2/2:placebo, respectively). Subjects randomized to placebo in Stage 1 who do not exhibit a response (ie, placebo nonresponders) will be rerandomized in Stage 2 to ALKS 5461 2/2 or placebo in a 1:1 ratio. All other subjects will receive placebo. The efficacy analysis will be performed on the FAS population and include (a) subjects in Stage 1 and (b) subjects in Stage 2 who were placebo nonresponders in Stage 1. Efficacy will be evaluated as the weighted average of the efficacy estimates from individual stages. The duration of Stage 1 and Stage 2 will be 5 and 6 weeks, respectively.

ALKS 5461 2/2 (plus current, approved ADT) or placebo (plus current, approved ADT) will be administered to subjects for 5 weeks in Stage 1 and for 6 weeks in Stage 2 (see Figure 1). For the purpose of ensuring the integrity of the study and minimizing expectancy effects, certain study design details (eg, criteria used to define Stage 1 nonresponders) are not fully described in this protocol; such details are further described within a separate restricted-access unmasked protocol addendum.

During Stages 1 and 2, subjects will return to the clinic every week for assessments. Subjects will return to the clinic for a Safety Follow-up Visit (Visit 14), 1 week after Visit 13. The total study duration for a given subject will be up to approximately 24 weeks, which includes a Screening Period of up to 4 weeks, an 8-week PLI Period (if required as determined during Screening), two treatment periods of 5- and 6-weeks duration (Stages 1 and 2 respectively) and a 1-week Follow-up Period.

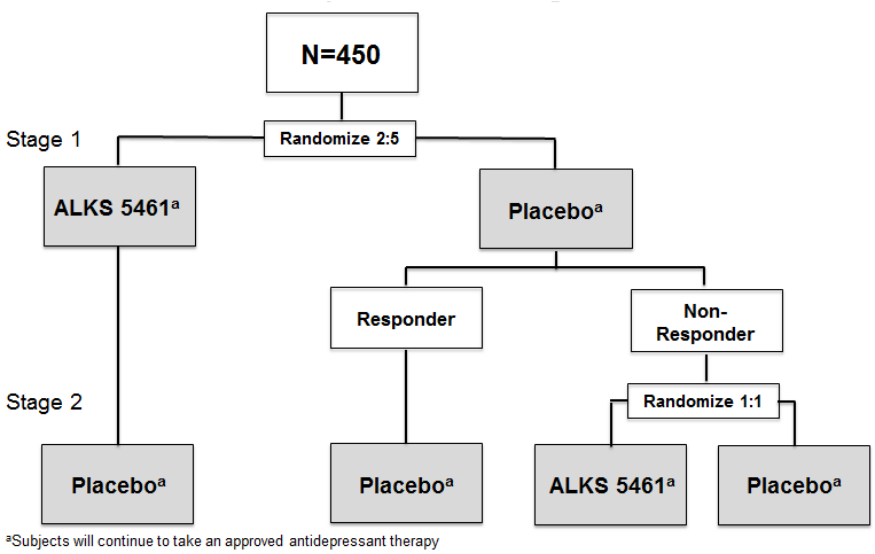
A schematic of the study design is provided below in Figure 1. A diagram depicting subject flow through the study is provided in Figure 2.

Figure 1: Study Design Schematic



Abbreviations: HIR=historic inadequate responder; PIR=prospective inadequate responder
[a] Stage 1 treatment initiation
[b] Stage 2 treatment initiation

Figure 2: Study Flow Diagram



Details regarding assessments in Stages 1 and 2 and the Follow-up Period are provided in Section 8.1.3, Section 8.1.4, and Section 8.1.5, respectively. Details regarding visit-specific study procedures are provided in Section 8.3.

8.1.1. Screening Period (Visit 1)

Potential subjects will be evaluated during a Screening Period lasting up to 4 weeks. Screening will include an assessment of each subject's history of inadequate response to ADT. Based on this assessment at Screening, qualifying subjects will either participate in an 8-week PLI Period (prospective inadequate responders [PIRs]) or will be eligible to bypass the PLI Period and proceed directly to Stage 1 (historic inadequate responders [HIRs]). Throughout the PLI Period, subjects will return to the clinic for brief assessments.

All HIR subjects who are on an adequate dose of ADT at the Screening Visit, but whose ADT duration is more than 4 weeks and less than 8 weeks, may complete the remaining dosing duration requirement in the Screening Period.

Subjects will be eligible to bypass the PLI Period if at Screening they meet all of the following criteria:

- Have a current MDE duration of at least 12 weeks and up to 5 years at Screening
- Currently treated with an SSRI or SNRI for at least 8 weeks at Visit 2. The 8 weeks of ADT is inclusive of up to 3 weeks for titration into the adequate dose range, with the same, adequate dose over the last 4 weeks that is expected to remain stable throughout the study and which does not exceed the labeled maximum daily dose
- Have an inadequate response to current ADT treatment
- Have 2 or 3 inadequate responses to ADT (inclusive of current inadequate response) in the current MDE. Prior inadequate response within the current MDE must be to an ADT medication listed on the ATRQ
- Have a HAM-D total score ≥18 at Screening

- Have met criteria for HIR as determined by an interactive voice or web response system (IxRS) at Visit 2

The prior inadequate response during the current MDE (if any) must have been to an ADT listed on the ATRQ and may be at any dose that exceeds the minimum dose listed on the ATRQ.

8.1.2. Prospective Lead-in Period (Visits 1a-1f)

Subjects will participate in the 8-week prospective lead-in if, at Screening/Visit 1, they meet all of the following criteria:

- Have a current MDE with duration of at least 8 weeks and up to 5 years at Screening/Visit 1;
- Are not currently taking an ADT *OR* whose SSRI or SNRI taken for the current MDE is not at an adequate dose (see Section 21) or if the duration is ≤ 4 weeks *OR* subject is experiencing an inadequate response to their current ADT and switching ADT is in the best interest of the subject per investigator judgment and ADT will be discontinued 2 weeks prior to Visit 1a;
- Have had 1 to 3 prior inadequate responses to an ADT (as listed in Section 21) in the current MDE at Screening/Visit 1 (prior inadequate response within the current MDE must be to an ADT listed in Section 21); and
- Have a HAM-D total score of ≥22 at Screening/Visit 1 and at PLI Visit 1a

Note: If a subject experienced an adequate response to an ADT for at least 4 weeks and subsequently relapsed (tachyphylaxis), but remained on the same ADT ***at the same or lower dose****, this would not represent an inadequate response to the ADT.*

Subjects who participate in the PLI Period will receive open-label administration of one of the following approved ADTs after meeting entry criteria at Visit 1a (HAM-D total score ≥22): escitalopram, sertraline, duloxetine, venlafaxine, or fluoxetine for at least 8 weeks, inclusive of up to 3 weeks of titration into the adequate dose range, with the same adequate dose over the last 4 weeks that does not exceed the labeled maximum daily dose. Note that if the subject cannot tolerate the selected ADT upon treatment initiation, it is acceptable to switch to another one of the 5 available ADTs within the first week of treatment, as deemed appropriate by the Investigator. The second ADT must then be taken for at least 7 weeks and in the adequate dose range for at least 5 weeks, with the same dose over the last 4 weeks that does not exceed the maximum daily dose.

Throughout the PLI Period, subjects will return to the clinic for brief assessments (Visits 1a-1f) that will occur weekly for the first 4 weeks and biweekly for the remainder of the PLI Period. At Visit 1f, subjects will be assessed for eligibility in an automated interactive response system (IxRS) using masked criteria. Based on this assessment, subjects will be classified as either one of the following:

- Eligible to continue in the study: These subjects will be scheduled for Visit 2. If at Visit 2, all entry criteria are met, subjects will be designated as PIR subjects, and may enter the double-blind Treatment Period

- Screen failures: Screen failures may be eligible for rescreening with Medical Monitor approval

8.1.3. Stage 1 (Visits 2-7)

Regardless of method of entry, all subjects will have been taking an SSRI or SNRI for at least 8 weeks at the beginning of Stage 1 (Visit 2) and at an adequate dose for at least 5 weeks, and at the same dose for at least 4 weeks. At Visit 2, PIR and HIR subjects who meet all entry criteria will be eligible to enter the 5-week Treatment Period and will be randomized 2:5 to receive either ALKS 5461 2/2 or placebo for 5 weeks.

From Visits 2 to 7, all participating subjects will take study drug (ALKS 5461 2/2 or placebo) and continue to take an approved ADT.

On Day 1 (Visit 2) and for the reminder of visits during the Treatment Period, subjects will self-administer study drug in the presence of study staff. Subjects will self-administer study drug when at home on days when there are not study visits.

8.1.4. Stage 2 (Visits 8-13)

In Stage 2, subjects receiving ALKS 5461 2/2 in Stage 1 and subjects responding to placebo in Stage 1 will continue on placebo for 6 weeks (see Figure 2). Placebo nonresponders will be rerandomized 1:1 to receive either ALKS 5461 2/2 or placebo for 6 weeks. All participating subjects will continue to take an approved ADT.

Staff will dispense study drug (ALKS 5461 or placebo) during on-site visits for subjects to self-administer study drug at home on days where there are not study visits. At those scheduled on-site study visit days, subjects will self-administer one dose of study drug in the presence of study staff. Subjects will return to the clinic every week for assessments.

8.1.5. Safety Follow-up Period (Visit 14)

Subjects who complete Stage 2 (Visit 13) or who prematurely discontinue during either Stage 1 or 2 should return to the clinic 1 week later for a Safety Follow-up Visit (Visit 14).

8.2. Schedule of Visits and Assessments

The schedule of assessments for all study subjects is shown in Table 3. The schedule of assessments during the PLI Period is shown in Table 4.

Premature discontinuation procedures are provided in Section 7.3. All ET Visit procedures are listed in Table 3.

Table 3: Schedule of Assessments

			Stage 1						Stage 2						Safety Follow-up
Day	**SCN[a]**	**PLI (see Table 4)**	**1**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**36 (±2)**	**43 (±2)**	**50 (±2)**	**57 (±2)**	**64 (±2)**	**71 (±2)**	**ET/78[b] (±2)**	**85 (±3)**
Visit	**1**	**1a-1f**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Informed Consent	X														
Qualification/ Diagnostic Assessments															
Eligibility Review[c]	X		X												
Demographics	X														
Medical and Psychiatric History	X														
On-site ATRQ	X		X												
MINI v7.0.2	X														
Height	X														
Complete Physical Examination	X														
17-item HAM-D	X		X[e]												
Serology Testing	X														
Breath Alcohol Test[d]	X		X												
Eligibility Assessment by IxRS			X												
Qualification/ Safety Assessments															
Urine Drug Screen[d,f]	X		X[e]					X	X					X	X
Pregnancy Testing (all women)[g]	X		X[e]					X	X						

Table 3: Schedule of Assessments (Continued)

			Stage 1						Stage 2						Safety Follow-up
Day	**SCN[a]**	**PLI (see Table 4)**	**1**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**36 (±2)**	**43 (±2)**	**50 (±2)**	**57 (±2)**	**64 (±2)**	**71 (±2)**	**ET/78[b] (±2)**	**85 (±3)**
Visit	**1**	**1a-1f**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Symptom-driven Physical Examination			X[e]	X				X	X					X	X
Weight/Vital Signs[h]	X		X[e]	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[i]	X		X[e]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X[e]	X				X	X					X	X
Blood and Urine Safety Samples	X		X[e]	X				X	X					X	X
COWS[j]			X[e]						X[e]					X	X
Adverse Event Monitoring	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review[k]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Substance Use[l]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments															
MADRS[m]	X		X[e]	X	X	X	X	X[e]	X	X	X	X	X	X	
CGI-S	X		X[e]	X	X	X	X	X[e]	X	X	X	X	X	X	
CGI-I				X	X	X	X	X[e]	X	X	X	X	X	X	
Q-LES-Q-SF			X[e]	X	X	X	X	X[e]	X	X	X	X	X	X	

Table 3: Schedule of Assessments (Continued)

			Stage 1						Stage 2						Safety Follow-up
Day	**SCN[a]**	**PLI (see Table 4)**	**1**	**8 (±2)**	**15 (±2)**	**22 (±2)**	**29 (±2)**	**36 (±2)**	**43 (±2)**	**50 (±2)**	**57 (±2)**	**64 (±2)**	**71 (±2)**	**ET/78[b] (±2)**	**85 (±3)**
Visit	**1**	**1a-1f**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Additional Study Procedures															
HAM-A			X[e]												
BPI-SF			X					X						X	
SHAPS			X					X						X	
CD-RISC-25			X					X						X	
Patient Questionnaire	X														
Plasma Sample for ADT Concentration[n]	X[o]		X	X				X	X					X	X
Plasma Samples for Study Drug Concentration[n]				X				X	X					X	X
Witness Study Drug Dose[p]			X	X	X	X	X	X	X	X	X	X	X		
Dispense Study Drug[q]			X	X	X	X	X	X	X	X	X	X	X		
Study Drug Adherence Review[r]				X	X	X	X	X	X	X	X	X	X	X	
ADT Adherence Review[r]			X[s]	X	X	X	X	X	X	X	X	X	X	X	X
Review of Text Message Adherence Reminder Use[t]			X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: ADT=antidepressant therapy; ATRQ=Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; BPI-SF=Brief Pain Inventory-Short Form; CD-RISC-25=Connor-Davidson Resilience Scale; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression-Severity; COWS=Clinical Opiate Withdrawal Scale; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=Early Termination; HAM-A=Hamilton Rating Scale for Anxiety; HAM-D=17-item Hamilton Rating Scale for Depression; HIR=historic inadequate responder; IxRS=Interactive voice or web response system; MADRS=Montgomery-Åsberg Depression Rating Scale; MINI v7.0.2=Mini International Neuropsychiatric

Interview 7.0.2; PIR=prospective inadequate responder; PLI=Prospective Lead-in; Q-LES-Q-SF=Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SCN=Screening; SHAPS=Snaith-Hamilton Pleasure Scale

[a] For HIR subjects, Screening Period will occur within 28 days prior to Visit 2. For PIR subjects, Screening Period will occur within 28 days prior to Visit 1a. For PIR subjects, an 8-week PLI Period including Visits 1a through 1f will occur between Screening and Visit 2. See Table 4 for Schedule of Assessments during the PLI Period.

[b] If a subject terminates early, then an Early Termination (ET) Visit will be arranged, at which time all Visit 13 assessments will be performed. Additionally, an attempt will be made to schedule a Follow-up Visit 1 week after the subject's last dose equivalent to Visit 14.

[c] Sites will complete the CST Pre-Baseline Packet at Screening (Visit 1) and submit the data to the CST so that review may be completed as soon as possible after Screening (Visit 1) and before the next study visit.

[d] Breath alcohol test and urine drug screen may be repeated at any point during the study based on Investigator's judgment.

[e] Assessment must be completed predose.

[f] Centralized drug screen testing at Screening, local drug screen testing (via dipstick) at other timepoints.

[g] Serum pregnancy at Screening, urine pregnancy for all other timepoints.

[h] Vital sign measurements at all visits include oral temperature, blood pressure, heart rate, and respiratory rate. Blood pressure, heart rate, and respiratory rate will be measured after the subject is in a supine position for at least 5 minutes.

[i] At Screening the "Baseline/Screening" version of the C-SSRS will be administered and at all other visits the "Since Last Visit" version will be administered.

[j] The COWS will be administered by a medical professional.

[k] All medications (prescription and nonprescription, including vitamins, and herbal supplements) taken 2 months prior to Screening, including psychiatric medication taken 5 years prior to Screening, and all ADTs will be recorded at Screening. Any changes will be recorded at subsequent visits.

[l] Subject will be queried at Screening on substances (including illicit drugs, alcohol, and tobacco) used within 30 days, with updates made at each subsequent visit.

[m] The MADRS should be administered prior to the HAM-D, CGI-I, CGI-S, HAM-A, C-SSRS, Q-LES-Q-SF, BPI-SF, SHAPS, and CD-RISC-25 on visits when multiple assessments are scheduled.

[n] The PK samples will evaluate concentrations of BUP, SAM, and ADT at specified visits. One pre-dose PK should be drawn at each indicated visit. When PK and safety blood samples are scheduled to be collected on the same day, efforts will be made to collect during the same draw.

[o] Applies only to HIR subjects.

[p] Study drug will be self-administered at all on-site visits in the presence of study site personnel.

[q] Study drug will be dispensed for self-administration at Visits 2 through12. Subjects will be advised to take the study drug at bedtime on days where there are not study visits, starting on Day 2. Time of dosage administration may be subsequently adjusted by the Investigator based on tolerability.

[r] Adherence for study drug and ADT based on subject query and pill count.

[s] For PIR subjects only.

[t] Text adherence reminders on subjects' personal mobile devices will occur daily throughout the Treatment Period.

Table 4: Schedule of Assessments: Prospective Lead-in Period

Week (± 2 days)	SCN[a]	1	2	3	4	6	8
PLI Visit		1a	1b	1c	1d	1e	1f
17-item HAM-D	Procedures for Visit 1 are displayed in Table 3.	X[b]		X		X	X
Initiate/Prescribe ADT		X[c]					
ADT Dose Adjustment, as needed		X	X	X	X		
Plasma Sample for ADT Concentration					X		
ADT Adherence Review[d]			X	X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X
Concomitant Medication Review[e]		X	X	X	X	X	X
Substance Use		X	X	X	X	X	X
C-SSRS[f]		X	X	X	X	X	X
Urine Pregnancy Testing		X					
Eligibility Assessment by IxRS							X[g]

Abbreviations: ADT=antidepressant therapy; C-SSRS=Columbia-Suicide Severity Rating Scale; HAM-D=17-item Hamilton Rating Scale for Depression; IxRS=Interactive voice or web response system; PLI=Prospective Lead-in; SCN=Screening

[a] Screening to occur within 28 days of Visit 1a.

[b] At Visit 1a, HAM-D to be completed prior to any other procedures. A subject with a HAM-D <22 will be considered ineligible per inclusion criterion 12, will be considered a screen failure, and will not participate in any further procedures.

[c] After confirming a HAM-D score of ≥ 22 at Visit 1a, ADT will be initiated at the discretion of the Investigator and as locally available.

[d] Adherence based on subject query and pill count.

[e] Any changes to concomitant medications since prior visit should be recorded, including changes to ADT, prescription and nonprescription medications, vitamins, and herbal supplements.

[f] "Since Last Visit" version will be administered at all timepoints.

[g] Eligibility for continuation to be assessed by IxRS. Based on this assessment, subjects will be deemed either eligible to continue into Visit 2 or ineligible to continue into the double-blind Treatment Period of this study. Subjects deemed eligible will continue into the double-blind Treatment Period.

8.3. Study Procedures Descriptions

Details of the study procedures are described below. The schedule of assessments for all study subjects is shown in Table 3. The schedule of assessments during the PLI Period is shown in Table 4.

8.3.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the Principal Investigator or designated study personnel as outlined in Section 17.3.

Prior to the administration of any study-specific procedures, authorized study personnel will obtain written informed consent from each potential subject.

8.3.2. Eligibility Review

An eligibility review will be conducted by the Investigator at the visits specified in Table 3 using the subject inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2.

For those subjects that participate in the PLI Period, eligibility will be confirmed based on HAM-D scores at Visit 1 and PLI Visit 1a. A subject who does not meet the HAM-D criteria at entry to Visit 1a (HAM-D total score ≥22) will be considered a screen failure and will not participate in further procedures.

For subjects participating in the PLI Period, an additional eligibility review will be conducted by an IxRS at Visit 1f and Visit 2 using masked criteria. Based on this assessment, subjects will be classified as one of the following:

- Eligible to continue in the study: These subjects will be scheduled for Visit 2. If at Visit 2, all entry criteria are met, subjects will be designated as PIR subjects, and will be randomized into the double-blind Treatment Period (Stage 1)
- Screen failures: Screen failures may be eligible for rescreening with Medical Monitor approval

For all subjects at Visit 2, the Investigator will conduct an eligibility review using the subject inclusion criteria in Section 7.1.2.1, exclusion criteria in Section 7.2, and filling out the ATRQ. Subjects meeting eligibility criteria at Visit 2 will be randomized into Stage 1.

8.3.3. Demographics and Medical History

Subject's demographic data and medical history will be reviewed and documented at the timepoints specified in Table 3. The psychiatric history should include start date of first episode of MDD, duration of current MDE, number of lifetime MDEs, number of prior lifetime ADT failures, and number of ADT failures within the current MDE.

8.3.4. Concomitant Medication Review

At Screening, all subjects will be asked about psychiatric medications they have taken within the last 5 years (including all ADTs as specified in Table 3), and any other medications they have taken in the last 2 months, including prescription and nonprescription medications, vitamins, and

supplements. At each subsequent visit, review of concomitant medications will be repeated as specified in Table 3 and Table 4.

The Investigator will record the following data on all medications used by the subject, as applicable: name, dose, regimen, route of administration, start and stop dates, and the indication for use.

8.3.5. Substance Use

Substances (including illicit drugs, alcohol, and tobacco) consumed/used within 30 days will be reviewed and recorded at the timepoints specified in Table 3 and Table 4, including name, amount, frequency, and start and stop dates. Changes at each subsequent visit as specified in Table 3 and Table 4 will be recorded for all participating subjects.

8.3.6. Vital Signs and Weight

Vital signs (ie, oral temperature, blood pressure, heart rate, and respiratory rate) will be assessed at the timepoints specified in Table 3. Blood pressure, heart rate, and respiratory rate will be measured after the subject has been resting in a supine position for at least 5 minutes.

Effort will be made to measure all blood pressure and pulse rate from the same arm, preferably the subject's dominant arm, throughout the study.

The blood pressure cuff will be calibrated per study site standard procedures. Automated measurement is preferred, but if performed manually, pulse rate will be measured in the brachial artery for at least 30 seconds.

All subjects will be weighed at the timepoints shown in Table 3.

Subjects should be weighed on the same scale for each measurement under the same conditions, with a consistent amount of clothing for each measurement. Subjects should remove shoes and all personal items prior to body weight measurement.

8.3.7. Physical Examination and Height

A complete physical examination will be performed at the Screening Visit only as specified in Table 3. A symptom-driven physical examination will be performed at the timepoints specified in Table 3. Height will be measured at the Screening Visit only as specified in Table 3.

8.3.8. 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be conducted at the timepoints specified in Table 3. All scheduled ECGs must be performed after the subject has rested quietly for at least 5 minutes in the supine position.

Electrocardiograms will be conducted using calibrated equipment and assessed by a qualified clinician. The following ECG parameters will be collected: heart rate, RR, PR, QRS, and QT. QTcB (QT interval corrected using the Bazett formula) and QTcF (QT interval corrected using the Fridericia formula) will be automatically calculated by the ECG machine.

8.3.9. Structured Interviews and Questionnaires

Brief descriptions of each of the structured interviews and questionnaires to be administered are provided below.

Table 3 and Table 4 show the timepoints at which each measure should be administered.

Clinician-administered scales, structured interviews, and questionnaires will be administered by trained and qualified study personnel.

The Montgomery-Åsberg Depression Rating Scale (MADRS) will be administered prior to the other structured interview scales (ie, HAM-D, CGI-S, Clinical Global Impression-Improvement [CGI-I], Hamilton Rating Scale for Anxiety [HAM-A], C-SSRS, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form [Q-LES-Q-SF], Brief Pain Inventory-Short Form [BPI-SF], Snaith-Hamilton Pleasure Scale [SHAPS], and Connor-Davidson Resilience Scale [CD-RISC-25]) on visits when multiple assessments are scheduled.

8.3.9.1. Assessments for Study Eligibility

8.3.9.1.1. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire

The ATRQ is a questionnaire used to document history of ADT and to determine treatment resistance in MDD (Chandler et al, 2010). The ATRQ will be administered at the timepoints indicated in Table 3. The ATRQ executed at the site will be administered by a trained-rater. A sample of the ATRQ can be found in Section 20.

8.3.9.1.2. Mini International Neuropsychiatric Interview

Known as the MINI v7.0.2, this is a short, clinician-administered diagnostic interview, with an administration time of approximately 15 minutes. The MINI v7.0.2 has been validated against the much longer Structured Clinical Interview for DSM diagnoses. The MINI v7.0.2 will be administered at the Screening Visit as specified in Table 3.

8.3.9.1.3. Seventeen-item Hamilton Rating Scale for Depression

The HAM-D is a clinician-administered 17-item depression scale designed to be sensitive to treatment effects (Hamilton 1960). The Structured Interview Guide for the HAM-D (SIGH-D) will be used for administration during visits, at the timepoints specified in Table 3 and Table 4.

8.3.9.1.4. Clinical Surveillance Team Eligibility Review

The Clinical Surveillance Team (CST) is a division of PPD CNS Clinical Development. The CST eligibility review is an independent evaluation of the eligibility of the subject. Sites will complete the CST Pre-Baseline Packet at Screening and submit the data to the CST so that review may be completed as soon as possible after Screening and before the next study visit as indicated in Table 3. The Investigator may use the results of this tool at his or her discretion.

8.3.9.2. Safety Assessments

8.3.9.2.1. Columbia-Suicide Severity Rating Scale

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior (Posner et al, 2011). The "Baseline/Screening" version of the instrument will be administered at the Screening visit only and the "Since-Last-Visit" version will be administered at all other timepoints as specified in Table 3 and Table 4.

8.3.9.2.2. Clinical Opiate Withdrawal Scale

The COWS is an 11-item questionnaire designed to measure a patient's level of opiate withdrawal (Wesson and Ling 2003). The COWS should be administered by a medical professional at the timepoints specified in Table 3.

8.3.9.3. Efficacy Assessments

8.3.9.3.1. Montgomery-Åsberg Depression Rating Scale

The MADRS is a clinician-administered, 10-item depression scale designed to be sensitive to the effects of antidepressant treatment (Montgomery and Asberg 1979). The Structured Interview Guide for the MADRS (SIGMA) will be used for administration during visits, at the timepoints specified in Table 3.

8.3.9.3.2. Clinical Global Impression–Severity

The CGI-S is a clinician-administered scale that measures severity of mental illness (Guy 2000). The CGI-S asks that the clinician rates the subject relative to their past experience with patients with MDD. The CGI-S will be administered during visits, at the timepoints specified in Table 3.

8.3.9.3.3. Clinical Global Impression–Improvement

The CGI-I is a clinician-administered scale that measures intensity of mental illness (Guy 2000). The CGI-I asks that the clinician rates the subject relative to their past experience with patients with MDD. The CGI-I will be administered during visits, at the timepoints specified in Table 3.

8.3.9.4. Exploratory Assessments

8.3.9.4.1. Hamilton Rating Scale for Anxiety

The HAM-A is a clinician-administered 14-item scale developed to measure the severity of anxiety symptoms (Hamilton 1959). The Structured Interview Guide for the HAM-A (SIGH-A) will be used for administration of the scale at the timepoint specified in Table 3.

8.3.9.4.2. Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form

The Q-LES-Q-SF is a self-report measure designed to measure the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning (Endicott et al, 1993). Summary scores have been found to be reliable and valid measures of these dimensions in a group of depressed outpatients. The Q-LES-Q will be administered during visits, at the timepoints specified in Table 3.

8.3.9.4.3. Brief Pain Inventory-Short Form

The BPI-SF is a self-report measure that takes approximately 5 minutes to administer and is designed to assess the severity of pain as well as its impact on functioning. The BPI-SF will be administered at the timepoints specified in Table 3.

8.3.9.4.4. Snaith-Hamilton Pleasure Scale

Anhedonia is defined as the loss of capacity to experience pleasure from routine life activities. It is a core deficit identified in major depression (DSM-5) (Hasler et al, 2004). The SHAPS is a patient-rated questionnaire that evaluates anhedonia and contains 14 items (Snaith et al, 1995). These items assess the individual's ability to enjoy and draw pleasure from routine life activities. The questionnaire covers enjoyment within the domains of social interaction, interests/pastimes, sensory experience, and food/drink. The scale has been validated and has shown excellent psychometric properties in clinical samples (Nakonezny et al, 2010; Snaith et al, 1995). The SHAPS will be administered at the timepoints specified in Table 3.

8.3.9.4.5. Connor-Davidson Resilience Scale

Resilience can be defined as a measure of stress coping ability (Luthar et al, 2000). The CD-RISC-25 is a brief, self-rated measure of resilience that has sound psychometric properties (Connor and Davidson 2003). The CD-RISC-25 will be utilized to quantify the change in resilience with treatment in the study. It will be administered at the timepoints specified in Table 3.

8.3.9.4.6. Patient Questionnaire

A questionnaire will be administered at the Screening visit as specified in Table 3 in order to determine items of importance to patients with depression interested in research participation (see Section 22). The questionnaire will request that subjects rate the importance of symptoms of depression that appear on the MADRS.

8.3.10. Laboratory Assessments

8.3.10.1. Serology Testing

Tests for HIV, hepatitis B surface antigen, and hepatitis C antibody will be performed at Screening and must be negative to qualify for study participation, as indicated in Table 3.

8.3.10.2. Breath Alcohol Test

A breath alcohol test will be conducted at the timepoints indicated in Table 3. A negative breath alcohol test will be required for a subject to enter into the study. However, the test may be repeated at any time during the study based on Investigator judgment.

8.3.10.3. Urine Drug Screen

All subjects will undergo a urine drug screening for drugs of abuse at Visit 1. Laboratory analysis of the urine drug screen at Visit 1 will be centralized. At all other timepoints specified in Table 3, subjects will have a urine drug screen via dipstick; results will be analyzed by the local laboratory. Samples will be collected in accordance with the site's usual procedures.

Urine drug screening will be performed for amphetamines, barbiturates, benzodiazepines, cocaine (metabolite), tetrahydrocannabinol, opioids, and phencyclidine. The opioid panel to be administered at Visit 1 (analyzed centrally) will include BUP, codeine, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

Drug screens administered after Visit 1 (analyzed locally) will include all aforementioned opioids except for BUP because appearance of BUP in these samples could lead to unblinding of treatment assignment.

A negative urine drug screen at Visit 1 and Visit 2 will be required for a subject to continue in the study. However, an exception may be made for a benzodiazepine, when such medication is medically indicated for insomnia. The Visit 1 and/or Visit 2 urine drug screen may be repeated based on Investigator judgment.

The urine drug screen may also be performed at any time during the study, should the Investigator feel it is warranted. Action taken in response to a positive urine drug screen after Visit 2 should be based on a medical evaluation in consultation with the Medical Monitor.

8.3.10.4. Pregnancy Testing

A serum pregnancy test will be administered to all participating female subjects at Screening as specified in Table 3. At the Screening visit, results must be negative for the subject to be eligible for the study.

At all other timepoints specified in Table 3, all female subjects will have urine pregnancy testing; results must be negative for a subject to continue in the study.

A positive pregnancy test result at any time will necessitate the subject's immediate withdrawal from the study and reporting to Alkermes within 24 hours as detailed in Section 13.5. Additional follow-up will be required as detailed in Section 8.4.1.

8.3.10.5. Hematology, Biochemistry, and Urinalysis

Blood and urine samples for laboratory assessments will be collected at the timepoints specified in Table 3. Specific hematology, biochemistry, and urinalysis assessments are listed in Table 5. Samples will be collected in accordance with the site's usual procedures and analyzed by a central laboratory.

Table 5: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit Hemoglobin Glycosylated Hemoglobin (HbA1C)[a] Platelets Red blood cell count Total and differential [(absolute)] white blood cell count	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatine phosphokinase Creatinine C-Reactive Protein Gamma-glutamyl transferase Glucose[b] High-density lipoprotein Lactic dehydrogenase Low-density lipoprotein Magnesium Phosphorus Potassium Prolactin[a] Sodium Thyroid-stimulating hormone[c] Total bilirubin Total cholesterol Total protein Triglycerides Uric acid	Bilirubin Color and appearance Glucose Ketones Leukocytes Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal* Nitrite Occult blood pH Protein Specific gravity Urobilinogen

Abbreviation: ET=Early Termination Visit
[a] Only at Visit 1, Visit 2, Visit 7, and Visit 13/ET
[b] Nonfasting
[c] Only at Visit 1

Reference ranges for evaluated laboratory tests will be supplied by the assigned laboratory before the study starts. Procedures for sampling and processing laboratory assessments will be described in a separate laboratory manual.

In the event of a difficult blood draw or where there is a limited quantity of blood available for testing, blood collection for biochemistry should be prioritized over hematology.

If unexplained abnormal laboratory test values are observed, follow-up samples may be obtained for repeat testing as clinically indicated.

Results of clinical laboratory testing will appear on electronically produced laboratory reports submitted directly to the site from the central laboratory, if applicable.

8.3.11. Pharmacokinetic Sampling for Study Drug and Antidepressant Therapy Concentrations

Plasma samples for PK will be collected at the timepoints indicated in Table 3 and Table 4.

The date and time of last dose of study drug as well as ADT, and the date and time of the PK blood draw will be recorded. Blood samples for these analyses will be stored at -20°C±10°C.

Samples will be assayed by a central laboratory for determination of BUP and SAM concentrations, as well as relevant metabolites. Concentrations of background ADTs that subjects report taking during the study will also be quantified.

8.3.12. Drug Dispensation and Reconciliation

On Day 1 (Visit 2), subjects will self-administer the first dose of study drug in the presence of study staff. For the remainder of Stages 1 and 2, staff will dispense study drug during visits (see Table 3) to observe self-administration of first dose and for subjects to self-administer study drug when at home. The study drug use and storage information will be explained to/reviewed with subjects. Subjects will be advised to take the study drug at bedtime (see Section 9.1.2). See Section 9.2, and Section 10.4 for additional information regarding treatment adherence and accountability.

8.3.12.1. Review of Text Message Adherence Reminder Use

Remote adherence reminders will be sent to subjects via text messages to their personal mobile devices. Text message adherence reminders will occur daily during the Treatment Period (see Table 3). Reviews of the use of these reminders will occur at each on-site visit during the Treatment Period (see Table 3).

8.3.13. Adverse Event Monitoring

The monitoring of AEs will begin once informed consent is obtained and will be performed at each visit (see Section 13). All AEs will be monitored continuously until the completion of the final study visit (see Table 3 and Table 4).

Section 13.1 and 13.2, respectively define AEs and serious adverse events (SAEs).

Section 13.4 provides guidance on the monitoring and recording requirements for AEs. Section 13.5 provides guidance on the reporting requirements for SAEs.

8.4. Study Requirements and Restrictions

8.4.1. Contraception and Pregnancy

All male and female subjects must agree to use an acceptable method of contraception for the duration of the study and 30 days after the final dose of study drug unless they are surgically sterile or postmenopausal (see below). The following are considered acceptable methods of contraception:

1. Double-barrier protection (eg, a condom with spermicide or a diaphragm with spermicide)
2. Intrauterine device
3. Oral contraceptive pills and other hormonal methods (eg, a vaginal ring, contraceptive patch, contraceptive implant); oral contraceptives are required to be initiated at least 30 days prior to Screening

Subjects who are abstinent are eligible, provided they agree to use an acceptable contraceptive method should they become sexually active.

Subjects who are surgically sterile are exempt from the requirement to use contraception. Women who have undergone a hysterectomy, bilateral tubal ligation, or bilateral salpingo-oophorectomy are considered surgically sterile. Men who have undergone a vasectomy are considered surgically sterile. Surgical sterility in a partner is not considered an approved acceptable method of contraception for subjects.

Women who are postmenopausal are also exempt from the requirement to use contraception. For the purpose of this study, postmenopausal is defined as the permanent cessation of menstruation for at least 12 months prior to Screening in women who are 45 years of age or older.

If a subject becomes pregnant while participating in the study, she will be discontinued from study drug immediately. The ET and Safety Follow-up Visits will be scheduled and the pregnancy will be reported to Alkermes. Pregnancies will be followed until completion or termination. Pregnancies in female partners of male subjects should also be reported and will be followed in the same manner.

A Pregnancy Report Form must be submitted to Alkermes (fax number in Section 13.5) within 24 hours of awareness of the pregnancy, irrespective of whether an AE has occurred. The pregnancy will be followed until delivery or termination. If the outcome of the pregnancy meets the criteria for classification as a SAE, it should be reported following the SAE procedure (see Section 13.5).

8.4.2. Concomitant Medications

All medications taken by a given subject 2 months prior to Visit 1 through follow-up and all ADTs taken in the current MDE will be recorded as detailed in Section 8.3.4. The concomitant medication review on each visit will include all prescription medications including ADT, over-the-counter medications, and vitamins and dietary supplements.

Subjects are permitted to continue taking concomitant medications during the study provided that these medications are clinically appropriate and are not prohibited by the exclusion criteria or study restrictions (see Section 8.4.2.1 for details on medications requiring washout and Section 8.4.2.3 for details on prohibited medications). The Investigator may discontinue or adjust the dose of any of these concomitant medications to ensure subject safety. At the Investigator's discretion, new concomitant medications may be administered during the course of the study for the treatment of an AE or a change in disease state. If a prohibited medication is needed, the Investigator should notify the Medical Monitor as soon as possible to discuss the continued participation of the subject in the study.

Dose adjustment of approved ADT during the PLI Period is permitted for optimal therapeutic effect within the recommended approved dose range (see Section 8.4.2.2.1). Dosing of ADT must remain within the recommended dose range and may not exceed the maximum labeled dose, per US Food and Drug Administration (FDA) approved labeling. At Visit 2, no changes in ADT (medication or dose level) can be made for the duration of the treatment periods (ie, during Stages 1 and 2, and the Safety Follow-up; see Section 8.4.2.2.1).

8.4.2.1. Medications Requiring Washout

In order to be enrolled at Visit 2 and at the Investigator's discretion, subjects must wash out from prohibited medications. Durations for some specific medications are listed in Table 6. For other prohibited medications, the minimum duration of washout should be at least 2 weeks, and should be discussed with the Medical Monitor. Washouts must be completed (ie, the subject must be off the prohibited medication) by Visit 1a (for PIR) or Visit 2 (for HIR). Subjects for whom washout is determined not to be clinically appropriate must be excluded from study participation.

Table 6: Medications Requiring Washout Prior to Visit 2

Medication Name	Washout Duration
Lithium	4 weeks
Monoamine oxidase inhibitors (MAOIs)	4 weeks
Bupropion	4 weeks
Anti-epileptic and antipsychotic[a] drugs	2 weeks
Others (psychostimulants, T3)	At least 2 weeks[b]

[a] Previous use of aripiprazole, quetiapine, brexpiprazole, or fluoxetine/olanzapine permitted up to a maximally approved dose for MDD, outlined in Section 23 (see Exclusion Criterion 8.a).
[b] Should be discussed with Medical Monitor.

8.4.2.2. Permitted Medications

At the Investigator's discretion, new concomitant medications may be administered during the course of the study for the treatment of an AE or a change in disease state. Details regarding ADTs and pain management therapies that are permitted in the study are provided below.

8.4.2.2.1. Antidepressant Therapy

In this protocol, ADT refers to the following medications, defined for each of the following 3 circumstances:

- Historical ADT, completed in current MDE prior to Screening may include any antidepressant medication listed on the ATRQ
- For HIR subjects, current ADT at Screening is limited to citalopram, escitalopram, fluoxetine, paroxetine, sertraline, vilazodone, vortioxetine, desvenlafaxine, duloxetine, levomilnacipran, or venlafaxine
- For PIR subjects, ADT during the PLI Period is limited to escitalopram, fluoxetine, sertraline, duloxetine, or venlafaxine. For PIR subjects, they should not be assigned to an ADT or a different formulation of the same ADT that they have failed during the

current MDE. Further, if a PIR subject had a prior failure to citalopram, he/she should not be assigned to receive escitalopram

At Visit 2, all subjects must have been on an SSRI or SNRI regimen for ≥8 weeks, inclusive of up to 3 weeks for titration into the adequate dose range, with the same, adequate dose over the last 4 weeks, and must agree to continue with and make no changes to this regimen (medication or dose level) for the duration of the study.

For PIR subjects, if the subject cannot tolerate the chosen ADT upon treatment initiation at Visit 1a, it is acceptable to switch to another one of the 5 ADTs within the first week of treatment (by Visit 1b), as judged appropriate by the Investigator. The second ADT must then be taken for at least 7 weeks prior to Visit 2 and in the adequate dose range for at least 5 weeks, with the same adequate dose over the last 4 weeks.

An adequate dose is defined as a dose that is greater than or equal to the minimum dose on the ATRQ (see Section 21). For ADT taken during the course of the study (ie, not historical ADT), doses may not exceed the maximum labeled dose.

The approved ADT regimen may not be changed or modified after the first 4 weeks of the PLI Period and throughout the remainder of the study for PIR subjects and must be unchanged from 4 weeks prior to Visit 2 throughout the remainder of the study for HIR subjects.

It is noted that ADT usage patterns will be monitored throughout the study to ensure approximately representative ADT utilization. The Sponsor reserves the right to restrict specific ADT usage. Additionally, no more than 4 of every 6 subjects at a site should be assigned to any one ADT without permission from the Medical Monitor.

Subjects in the United States must use the ADT pharmacy card provided during the study and may not seek reimbursement from their private insurance and/or local, state or federally funded healthcare programs for ADT utilized in the study.

8.4.2.2.2. Pain Management

Because the ALKS 5461 co-formulation contains SAM, a μ-opioid receptor antagonist, subjects may experience reduced or ineffective analgesia when taking an opioid analgesic agent concurrently with ALKS 5461, including several days after last dosing of ALKS 5461.

In the event of an emergency, pain management of the subject should include the following:

- Regional analgesia or use of non-opioid analgesics
- If opiate anesthesia or analgesia is required, the subject should be continuously monitored, in an anesthesia care setting, by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and the maintenance of a patent airway and assisted ventilation
- Close monitoring by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation

For subjects requiring emergency opioid analgesics prior to dosing, study drug should not be administered. If opioid analgesics are required after study drug has been administered, it may

take several days for opiate sensitivity to be restored, since SAM is an opioid antagonist and could interfere with opioid-mediated pain management.

8.4.2.3. Prohibited Medications

If a prohibited medication is needed, the Investigator should notify the Medical Monitor as soon as possible to discuss the continued participation of the subject in the study.

Prohibited medications include: antipsychotics, additional antidepressants other than the assigned background antidepressant, mood stabilizers, varenicline, anxiolytics, and CYP3A4 inhibitors and inducers (see Section 24 for a list of prohibited inducers and moderate-to-strong inhibitors of CYP3A4). All prohibited medications will be discontinued during Screening with a washout period of 2 to 4 weeks, unless specified otherwise. **This is not an exhaustive list of prohibited medications. The Investigator should consult with the Medical Monitor regarding other potentially prohibited medications.**

Prohibited medication or treatment categories include, but are not restricted to, the following:

- Agents that might have antidepressant or related pharmacodynamics effects. This includes but is not restricted to:
  - MAOIs (eg, phenelzine, tranylcypromine, selegiline)
  - Lithium
  - Tricyclic antidepressants (eg, amitriptyline, nortriptyline, desipramine)
  - Psychostimulants (eg, methylphenidate, dextroamphetamine/amphetamine)
  - Bupropion
  - Additional agents (prescription or over-the-counter [OTC]) for purpose of treating MDD or augmenting the effects of the ADT
- Anti-epileptic medications (eg, topiramate, gabapentin, lamotrigine, or oxcarbazepine) at any dose or duration for any indication
- Opioid agonists (eg, codeine, oxycodone, tramadol, or morphine) or opioid antagonists (eg, naloxone or naltrexone)
- The initiation or dose adjustment of hormone replacement therapy (including testosterone) or a hormonal contraceptive. Such therapy is permissible if a stable dose of hormone replacement therapy or hormonal contraceptive is taken for at least 30 days before Visit 1a (PIR) or Visit 2 (HIR) and the same stable dose is expected to be taken throughout the study (please refer to Section 8.4.1 for additional details regarding contraception)
- Use of systemic corticosteroids within 30 days before Visit 1a (PIR) or Visit 2 (HIR) and throughout the study
- Antipsychotics
- The receipt of new onset psychotherapy within 6 weeks of Screening or new onset psychotherapy at any time during the study (including any significant change in

psychotherapy) is prohibited; a stable psychotherapy regimen that has been initiated >6 weeks prior to Screening is permitted. For subjects who are receiving a stable psychotherapy regimen upon entry into the study, efforts should be made to maintain a psychotherapy regimen and schedule consistent with that existing at the beginning of the study

- Use of moderate-to-strong inhibitors or inducers of CYP3A4 (prescription medications, over-the-counter medications, or dietary supplements) within 30 days before Screening through follow-up is prohibited (refer to Section 24 for a list of CYP3A4 inhibitors and inducers)

Initiation of a course of pharmacotherapy (including prescription or over-the-counter medications) or natural supplements for insomnia (eg, benzodiazepines, zolpidem, trazodone, antihistamines, melatonin) is not permitted if started within 30 days of screening or if started at any time during the study. Prescriptions, over-the-counter medications, and natural supplements are permitted to be used for insomnia if they have been used stably for at least 30 days before screening not more than 3×/week, and are expected to be used stably ≤3 times per week throughout the study. Note that although antihistamines are restricted per these criteria when used for insomnia, they are permitted as needed throughout the study for indications other than insomnia (eg, environmental allergies).

Permitted dose levels for hypnotics when used for insomnia are limited to ≤2 mg/day of lorazepam (or equivalent benzodiazepine dose), ≤100 mg/day of trazodone, ≤10 mg/day of zolpidem or zaleplon, and ≤12.5 mg/day of zolpidem extended-release.

Hypnotic agents for psychiatric indications other than insomnia are prohibited from 30 days prior to screening through the follow-up visit.

Pharmacotherapy (including prescription or over the counter medications) or natural supplements for anxiety are prohibited from 30 days prior to screening through the follow-up visit.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

9.1.1. Description of ALKS 5461 and Placebo

ALKS 5461 consists of BUP, a US Schedule III narcotic, and SAM, a US Schedule II controlled substance. Thus, ALKS 5461 should be treated as a Schedule II controlled substance within the US. Outside the US, ALKS 5461 should be handled according to local regulations. See Section 10 for information on storage and handling of controlled substances.

The ALKS 5461 drug product will be formulated as tablets for SL administration and will contain a ratio of 1:1 BUP: SAM as free base equivalents by weight.

Placebo will be prepared using a similar formulation composition without BUP and SAM to create blinded study drug.

9.1.2. Study Drug Dose and Dosing Regimen

Subjects will take one SL tablet per day of study drug (ie, ALKS 5461 2/2 or placebo) for 5 weeks in Stage 1 and 6 weeks in Stage 2.

At Visit 2 (Day 1) and at scheduled on-site study visit days, subjects will take study drug in the presence of study site personnel who will visually confirm that the tablet has dissolved completely. **The tablet must not be swallowed.** Eating and drinking should be avoided for 15 minutes after dosing. From Day 2 on, subjects will self-administer study drug; it is recommended that subjects take study drug at bedtime. Timing of self-administration may be subsequently adjusted by the Investigator based on tolerability.

If, in the opinion of the Investigator, the ADT should be taken at approximately the same time of day as the study drug, then the ADT should be taken first followed by study drug.

9.2. Treatment Adherence of Study Drug and ADT

As indicated in Table 3, subjects will receive at each specified dispensing visit a supply of study drug (ALKS 5461 or placebo) that will last until the following visit. Study drug and ADT adherence reviews will include pill counts at each visit as specified in Table 3. Subjects will be instructed to bring each dispensed blister pack with them to each subsequent visit to return any remaining study drug, and drug adherence will be reviewed. Remote adherence reminders will be sent to subjects daily during the Treatment Period via text message to their personal mobile devices. Subjects will be instructed to bring in containers of their approved ADT for verification of dosing adherence. Study drug adherence will be determined at each on-site visit by counting tablets returned and comparing counts with the calculated expected number. ADT adherence will also be reviewed with subjects at each on-site visit via pill count. Physical check of medication including prescription fill date is required and must be documented in source. The concentrations of BUP and SAM, and background ADTs will be quantified as described in Section 8.3.11.

Samples will be assayed by a central laboratory for determination of BUP and SAM concentrations, as well as relevant metabolites. Concentrations of background ADTs that subjects report taking during the study will also be quantified.

9.3. Method of Assigning Subjects to Treatment

Based on an assessment of history of inadequate response to ADT, eligible subjects will be assigned at Screening to begin either an 8-week PLI Period (PIR subjects) or to bypass the PLI Period and proceed to Stage 1 (HIR subjects).

At the beginning of Stage 1, all eligible subjects will be randomized to receive either ALKS 5461 or placebo for 5 weeks. Once a randomization number has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study.

At the beginning of Stage 2, subjects receiving ALKS 5461 2/2 in Stage 1 and subjects who responded to placebo in Stage 1 (placebo responders) will continue on placebo for 6 weeks (see Figure 2). Placebo nonresponders will be rerandomized to receive either ALKS 5461 2/2 or placebo for 6 weeks.

For both stages, codes will be prepared by an independent biostatistician who is not otherwise involved in this study. Study drug randomization will remain blinded to the subjects, Investigator, and Sponsor during the course of the study.

9.4. Blinding and Unblinding

9.4.1. Blinding

The PLI Period will include open-label assignment to escitalopram, sertraline, duloxetine, venlafaxine, or fluoxetine, chosen at the Investigator's discretion.

All attempts will be made to conceal the treatment assignment of blinded study drug from the subjects, investigators, study personnel, and Sponsor personnel throughout the study.

9.4.2. Unblinding

Unblinding will occur after the database lock.

If the Investigator deems it necessary to break the study blind in the interest of a subject's medical safety, he or she must make every effort to contact the PPD Medical Monitor before the blind is broken. If the site is unable to contact the PPD Medical Monitor, every effort must be made to contact the Sponsor's Medical Monitor. If the site is unable to contact the Medical Monitor prior to breaking the blind, the Medical Monitor must be contacted within 24 hours following disclosure of study drug assignment.

The Investigator is responsible for all study-related medical decisions. When the Investigator deems it necessary, emergency unblinding may be done without contacting a Medical Monitor. Any premature unblinding should be promptly documented and explained to the Medical Monitor.

If the blinded code is broken by any party, the reason must be fully documented. Breaking the blind for a single subject will not affect the blind for the remaining subjects.

9.5. Study Drug and Antidepressant Therapy Dose Adjustment and Stopping Rules

Elective dose reduction is not permitted during the study. If a subject develops tolerability issues, the Investigator should discuss management options with the Medical Monitor. If the subject is unable to tolerate the study drug dose level despite attempted management options, or refuses to continue taking study drug, study drug should be discontinued.

Dose adjustment of approved ADT during the PLI Period is permitted for optimal therapeutic effect within the recommended approved dose range for the first 4 weeks (see Section 8.4.2.2.1). Dosing of ADT must remain within the recommended dose range and may not exceed the maximum labeled dose, per US Food and Drug Administration (FDA) approved labeling. At Visit 2, no changes in ADT (medication or dose level) can be made for the duration of the treatment periods ([ie, during Stages 1 and 2] see Section 8.4.2.2.1).

The study may be stopped at any time or study sites may be closed at the Sponsor's discretion.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

The investigational product for this study is ALKS 5461, a fixed-dose combination of BUP, a μ-opioid receptor partial agonist, and SAM, a μ-opioid receptor antagonist.

The ALKS 5461 drug product is formulated as tablets for SL administration and will contain a ratio of 1:1 BUP:SAM (2 mg BUP/ 2 mg SAM) as free base equivalents by weight.

Placebo will be prepared using a similar formulation composition without SAM and BUP.

Buprenorphine is a Schedule III narcotic in the US, and SAM is a Schedule II controlled substance in the US. Therefore, within the US, ALKS 5461 must be handled in accordance with restrictions related to Schedule II controlled substances. Outside the US, ALKS 5461 should be handled according to local regulations.

All study drug is white to off-white in color nondebossed triangle-shaped tablet. The SL tablet formulation contains excipients commonly used in products approved by the FDA, and accepted for use as food additives in Europe, including lactose monohydrate, microcrystalline cellulose, crospovidone, sucralose, citric acid, sodium citrate, and magnesium stearate.

10.2. Packaging and Labeling

Study drug will be packaged in child-resistant blister packs. All packaging will be labeled in a manner that meets applicable local and regulatory requirements.

Subjects will receive child-resistant blister packs containing 9 tablets at each dispensing visit as specified in Table 3 to supply a sufficient number of tablets to last until the next scheduled visit.

Subjects should follow the dosing instructions as printed on the packaging.

10.3. Storage

ALKS 5461 must be stored in accordance with local controlled substance requirements, and in the US, restrictions related to Schedule II controlled substances.

The Investigator will take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

Complete details on storage condition requirements can be found in the Investigator's Brochure.

10.4. Accountability

The Investigator will be responsible for the oversight of recording the receipt and administration of study drug, and for insuring the supervision of the storage and allocation of these supplies. The Investigator is required to maintain current drug dispensing and accountability logs throughout the study. The Investigator may delegate accountability duties to an appropriate and qualified pharmacist or staff member who is under the supervision of the Investigator.

The Investigator or designee must allow the Clinical Research Associate or equivalent to perform drug reconciliation during each study monitoring visit. All unused supplies will be checked against the study drug movement records before investigational drug is returned or destroyed.

Subject-level study drug accountability will be documented in the subjects' source documents and eCRFs. If drug cannot be accounted for, actions will be taken that are appropriate for a drug containing controlled substances. These actions may include but are not limited to re-training subject on adherence or discontinuation of subject from the study.

The clinical site is required to maintain current drug dispensation and accountability logs throughout the study. All unused supplies will be checked against the drug movement records during the study and/or at the end of the study. Any broken or chipped tablets should be stored at the sites until drug accountability is completed.

Refer to Section 9 for additional study drug reconciliation procedures.

10.5. Handling and Disposal

All unused study drug must be handled and disposed of in accordance with Good Clinical Practice (GCP), Good Manufacturing Practice and Schedule II controlled substance requirements, as applicable. At the end of the study the Sponsor will provide additional instruction as to the disposition of unused study drug. Until instructions have been provided, each study site must store unused materials on site in the manner described in Section 10.3. All study medication must be accounted for in a drug accountability record.

11. ASSESSMENT OF EFFICACY

11.1. Primary Efficacy Endpoint

The primary efficacy endpoints are:

1. Average change from baseline to Week 3 to the end of treatment period in MADRS-6 scores
2. Average change from baseline to Week 3 to the end of treatment period in MADRS-10 scores
3. Change from baseline to the end of treatment period in MADRS-10 scores

The MADRS-10 is the sum of all 10 items and ranges from 0 to 60. The MADRS-6 represents the core symptoms of depression and is defined as the sum of the following 6 items: item 1 reported sadness; item 2 apparent sadness; item 3 inner tension; item 7 lassitude; item 8 inability to feel; and item 9 pessimistic thoughts. MADRS-6 scores range from 0 to 36.

11.2. Secondary Efficacy Endpoints

In addition, secondary endpoints are:

- MADRS response, defined as a ≥50% reduction in MADRS-10 score from Baseline to the end of treatment period
- MADRS remission, defined as MADRS-10 score ≤10

11.3. Exploratory Endpoints

Exploratory endpoints are:

- Change over time in CGI-S scores
- Absolute CGI-I scores over time
- Change over time in Q-LES-Q-SF scores
- Change over time in BPI-SF scores
- Change over time in SHAPS scores
- Change over time in CD-RISC-25 scores

12. ASSESSMENT OF PHARMACOKINETICS

Concentrations of BUP, SAM, their relevant metabolites, and reported background ADTs will be quantified in plasma samples collected for PK evaluation. Plasma samples will be collected at timepoints shown in Table 3 and Table 4. By-subject listings and summary tables of plasma concentrations will be provided.

Pharmacokinetic data may be used in a subsequent population PK evaluation conducted outside of this study.

13. ASSESSMENT OF SAFETY

Safety and tolerability will be assessed on the basis of:

- Treatment-emergent AEs (TEAEs)
- Clinical laboratory parameters (hematology, chemistry, and urinalysis)
- Vital signs
- Weight
- ECG parameters
- C-SSRS results
- COWS scores

13.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject who has been administered a pharmaceutical product. The occurrence, which may or may not have a causal relationship with the investigational treatment, may include any clinical or laboratory change that does not commonly occur in that subject and is considered clinically significant.

Illnesses present prior to the subject signing the informed consent form (ICF) are considered to be pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. Clinically significant values will be considered AEs and will be recorded as such on the eCRFs.

Pregnancy is not considered an AE, although a subject will be withdrawn from the study if a pregnancy occurs. As described in Section 8.4.1, the pregnancy, including a partner's pregnancy, must be reported to the Sponsor, and additional follow-up will be required.

13.2. Definition of a Serious Adverse Event

An SAE is any AE, occurring at any dose and regardless of causality, that:

- Results in death
- Is life-threatening. The subject is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

- Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require intervention to prevent one of the other outcomes listed above.

Admission to a hospital or an inpatient unit for a nonmedical reason (ie, social stay admission) during the study, in the absence of untoward medical occurrence, will not be considered an SAE, but will be captured as an AE.

Hospitalization due to worsening of behavioral health-related issues should be reported as an SAE.

13.3. Relationship to Study Drug

The assessment of study drug relationship to each AE will be reported on the appropriate source document (and SAE form, in the event of an SAE) by the Investigator (or designated Subinvestigator) according to his/her best clinical judgment. The criteria listed in Table 7 should be used to guide this assessment. Please note that not all criteria must be present to be indicative of a particular drug relationship. All study drugs are considered "test drugs" for the purposes of the definitions listed in the table.

Table 7: Adverse Event Causality Guidelines

Relationship	Criteria for assessment
Definitely related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
Probably related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
Possibly related	There is evidence of exposure to the test drug. AND The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
Probably not related	There is evidence of exposure to the test drug. AND There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
Definitely not related	The subject did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

Abbreviation: AE=adverse event

13.4. Monitoring and Recording of Adverse Events

All AE data collection will begin after a subject signs the ICF and will continue until completion of the Safety Follow-up Visit. Any AE or SAE having an onset after the Safety Follow-up Visit will not be collected or reported unless the Investigator feels that the event may be related to the study drug.

Subjects will be instructed by the Investigator or designee to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded on the AE eCRFs.

The Investigator will assess all AEs regarding any causal relationship to the study drug (see Section 13.3), the intensity (severity) of the event, action taken, and subject outcome.

The following criteria should be used to guide the assessment of intensity (severity):

- **Mild:** Causes awareness of sign or symptom, but is easily tolerated; does not interfere with usual activities
- **Moderate:** Causes discomfort enough to interfere with usual activities
- **Severe:** Is incapacitating; results in inability to work or perform usual activities

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

For clinical study safety reporting purposes, the most recent version of the Investigator's Brochure will be used as the reference document to designate event expectedness.

Withdrawal from the study as a result of an AE, and any therapeutic measures that are taken, shall be at the discretion of the Investigator. If a subject withdraws from the study for any reason, any ongoing AEs will be followed until resolution, until deemed stable by the Investigator, or until the subject is deemed by the Investigator to be lost to follow-up.

13.5. Reporting of Serious Adverse Events and Pregnancy

All SAEs and pregnancies must be reported to PPD within 24 hours of discovery, by faxing the report to the following:

Attention: PPD Safety and Pharmacovigilance
FAX Number: PPD
In case of fax issues, e-mail: PPD

The written report for SAEs should be submitted on the SAE form provided for this purpose. The SAE report must include the Investigator's opinion as to whether the event is study drug-related. If this relationship is determined to be possibly, probably, or definitely related to study drug, evidence to support this assessment must also be provided.

The written report for pregnancies in female subjects and in female partners of male subjects should be submitted on the Pregnancy Report Form provided for this purpose.

14. STATISTICS

14.1. Sample Size Considerations

Approximately 450 subjects are planned to be randomized in Stage 1 to have approximately 200 subjects rerandomized to treatments in Stage 2. This will provide at least 80% power to show superiority for ALKS 5461 2/2 compared to placebo at the one-sided alpha level 0.025, for each of the three primary endpoints, assuming an effect size of at least 0.20 in Stage 1, 0.44 in Stage 2, and 0.32 overall (average of Stage 1 and Stage 2); and a SD of 6.25 and 8.5 for MADRS-6 and MADRS-10 scores, respectively. Details on the clinical study simulations conducted to evaluate power and type 1 error control will be provided in the Statistical Analysis Plan.

14.2. General Statistical Methodology

The statistical analysis methods are briefly described below. A comprehensive description of the statistical analysis will be included in the Statistical Analysis Plan (SAP) to be finalized before database lock and unblinding.

Summary statistics (n, mean, standard deviation, median, minimum, and maximum values for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided for evaluated variables. All individual subject level data will be presented as data listings.

Unless stated otherwise, statistical tests will be one-sided with alpha=0.025 and confidence intervals will be two-sided and will be set at an alpha of 0.05.

14.2.1. Study Populations

14.2.1.1. Safety Population

The Safety Population will consist of all enrolled subjects who received at least one dose of study drug (placebo or ALKS 5461).

14.2.1.2. Full Analysis Set

The Full Analysis Set (FAS) Population will consist of all subjects in the Safety Population who have at least one post-Baseline MADRS assessment.

14.2.1.3. Pharmacokinetic Population

The PK Population is defined as all subjects who have at least one measurable plasma concentration of any analyte during the Treatment Period.

14.3. Demographics and Baseline Characteristic Data

Demographics and baseline characteristics such as gender, age, race, weight, BMI, vital signs, and clinical laboratory data will be summarized with descriptive statistics to assess the comparability of the study groups. If there are heterogeneities between study groups in any of the subject characteristics that are of clinical importance or could affect the treatment outcome, the

impact of the imbalances will be investigated and, if necessary, appropriate adjustments made in the efficacy and safety analyses.

Psychiatric history including duration of current MDE, number of lifetime MDEs, number of prior lifetime ADT failures and number of ADT failures within the current MDE will be summarized by Treatment Group and overall for the safety populations using the number of observations and percentage of subjects reporting each category.

14.4. Efficacy Analyses

The primary efficacy endpoints will be:

1. Average change from baseline to Week 3 to the end of treatment period in MADRS-6 scores
2. Average change from baseline to Week 3 to the end of treatment period in MADRS-10 scores
3. Change from baseline to the end of treatment period in MADRS-10 scores

The primary endpoint analysis will be carried out on the full analysis set using mixed model repeated measures (MMRM) in the context of a Sequential Parallel Comparison Design (SPCD) for each endpoint analyzed separately, in Stage 1 and in Stage 2. The models will include variables for treatment group, visit, treatment group-by-visit interaction term, and site as categorical fixed effects. Baseline value and baseline value-by-visit interaction will be included as covariates in the model. The comparisons of ALKS 5461 2/2 vs placebo will be made, and the least-squares mean difference along with the corresponding 95% confidence interval and *P*-value will be reported. Adjustments for multiplicity of the primary endpoints will be made using a hierarchical testing approach with the order of testing being the rank order in which the primary endpoints are listed. The study will be considered positive in the final analysis if the efficacy endpoint MADRS-6 from baseline to Week 3 through the end of the treatment period is statistically significant.

Secondary efficacy endpoints (ie, proportion of subjects achieving treatment response and proportion of subjects achieving remission at the end of the treatment period) will be evaluated using a chi-squared test.

Further details will be described in the SAP.

14.5. Pharmacokinetic Analyses

No formal PK analysis will be performed for this study. Descriptive summaries of concentration data will be provided and by-subject listings of plasma concentrations will be provided.

14.6. Patient Questionnaire

By-subject listings of data from the patient questionnaire will be provided.

14.7. Safety and Tolerability Analyses

All safety assessments including those collected during the Follow-up Period and AEs collected in the PLI will be summarized using descriptive statistics. Reported AE terms will be coded

using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) will be defined as AEs that occur or worsen after the first dose of study drug. The incidence of TEAEs will be summarized by system organ classes and preferred terms and by severity and relationship to study drug. Subjects with SAEs and AEs leading to discontinuation from the study will be summarized. Results of clinical laboratory tests, vital signs, and ECG parameters will also be summarized for the absolute value and for change from Baseline. The number and percentage of subjects with potentially clinically significant (PCS) values will also be summarized. The number and percentage of subjects with C-SSRS assessments at post-Baseline will be summarized. Concomitant medications will be categorized using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system. Listings will be provided for all concomitant medications.

14.8. Interim Analysis

A single interim analysis is planned when approximately 265 subjects have completed Stage 1 and approximately 120 subjects have completed Stage 2. A group sequential design with a single interim analysis for potential early efficacy conclusion stop is employed. The primary analysis will be based on the SPCD method of combination of treatment mean differences between treatments in Stages 1 and 2. The interim analysis will be conducted by an external independent statistical center and reviewed by external data monitoring committee (DMC). Alkermes will remain blinded throughout the interim analysis. The one-sided *P*-value required for efficacy conclusion at both the interim and final analyses is <0.0147 (constant significance levels (Pocock 1977)) in order to control overall type 1 error at 0.025 in a one-sided test.

The external and independent DMC will consist of three voting members (including one chairperson) and one nonvoting member, chosen by Alkermes based on their qualifications, expertise, and experience. The activities of the DMC will be coordinated by the chairperson of the DMC. The DMC will be supported by an independent statistical team, consisting of an independent statistician (a nonvoting member of the DMC) and an independent programming team, who are part of an independent statistical center. Dissemination of interim study results and deliberations of the DMC prior to "end of study" will be carefully controlled by the DMC and others with knowledge of the data in order to ensure study integrity and to avoid any introduction of bias.

The primary charge of the DMC will be to evaluate efficacy outcomes according to details included in the prespecified SAP for interim analysis. In the event the study is not stopped early for efficacy, Alkermes intends to continue enrollment to yield approximately 450 randomized subjects in Stage 1 and approximately 200 randomized subjects in Stage 2. The study will not be stopped early for futility.

The DMC will not make decisions about the study, but will rather make recommendations. Within 2 business days following the DMC meeting to discuss the interim analysis results, the DMC Chairperson will send DMC recommendations to the Alkermes Steering Committee. Should the DMC recommend stopping the study, the DMC will also recommend to Alkermes that all subject enrollment activity should stop until the decision to terminate or to continue the study is finalized by Alkermes.

Further details will be described in the SAP for interim analysis and in the charter guiding the activities associated with the interim analysis and of the DMC.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Monitoring of the study site (including, but not limited to, reviewing eCRFs for accuracy and completeness) will be performed by an Alkermes Monitor or designee.

15.2. Audits and Inspections

By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of Alkermes, a regulatory authority, and/or an institutional review board (IRB)/independent ethics committee (IEC) may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, subject charts and source documents, and other records relative to study conduct. The purpose of an Alkermes audit or inspection is to systematically and independently examine all study-related activities and documents (eg, laboratory reports, x-rays, workbooks, subjects' medical records) to determine whether these activities were conducted, and data recorded, analyzed and accurately reported, according to the protocol, GCP guidelines of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and any applicable regulatory requirements.

The Investigator should contact Alkermes immediately if contacted by a regulatory agency regarding an inspection.

15.3. Institutional Review Board/Independent Ethics Committee

The Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, as well as all materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

This study will be conducted under GCP and all applicable regulatory requirements. To ensure data accuracy, completeness and compliance, the study site should have processes in place for data review and quality control. Alkermes may also conduct a quality assurance audit. Please see Section 15.2 for details regarding the audit process.

16.1. Case Report Forms

This study will use eCRFs (using computer and tablet-based applications). All eCRF data must be based on source documents or approved to be the original data (ie, data directly reported on the eCRF). All eCRFs will be completed by the clinic staff prior to review by the Alkermes Monitor or designated representative.

The Alkermes Monitor or designated representative will review all source records on-site and compare them to the data collected on the eCRF.

16.2. Confidentiality of Data

By signing this protocol, the Investigator affirms to Alkermes that he or she will maintain in confidence information furnished to him or her by Alkermes and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of Alkermes. Please refer to the Clinical Study Agreement (CSA) for details.

17. ETHICAL CONSIDERATIONS

17.1. Ethics Review

The clinical site's IRB/IEC must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB/IEC prior to enrolling subjects into the study; written approval from the committee must be received by Alkermes before drug will be released to the Investigator. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulatory requirements require.

The Investigator is responsible for submitting all protocol changes and SAE reports to the IRB/IEC according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

All relevant correspondence from the IRB/IEC will be forwarded by the respective study site to the Sponsor in a timely fashion.

17.2. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the ICH Guideline E6, and all applicable local regulatory requirements. Good Clinical Practice (GCP) is an international ethical and scientific quality standard used for designing, conducting, recording, and reporting studies involving the participation of human subjects. Alkermes is committed to complying with this standard to provide assurance that the rights, safety, and well-being of study subjects will be protected, consistent with the principles having their origin in the Declaration of Helsinki.

17.3. Written Informed Consent

The Investigator (or authorized designee) at each center will ensure that the subject (or the subject's legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved informed consent form (ICF) that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided in a language understandable to the subject and must not include any language that waives the subject's legal rights. Prospective subjects must also be informed of their right to withdraw consent without prejudice at any time during the study. If the subject chooses to participate, he/she must sign the ICF before any study-specific procedures are conducted.

All subjects will be informed of their rights to privacy and will be made aware that the study data will be submitted to Alkermes, the IRB, the contract research organization (CRO), if applicable, and to regulatory authorities for review and evaluation for the duration of the study and until the project has been approved for marketing, or is withdrawn from investigation. They will also be informed that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and approved by the IRB, and then signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain the original, signed ICF in the subject's source documents. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

An overview of study data handling and recordkeeping procedures and restrictions is provided in the subsequent sections; please refer to the CSA for further details.

18.1. Data Capture

As stated in Section 16.1, this study will use eCRFs for capturing data. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture systems maintain full audit trails.

The assessments described in Section 8.3.9 will be captured via an electronic data capture method, with the exception of the MINI v7.0.2 which will be captured on paper. A paper copy of all laboratory reports will remain with the source documents at the study site. All electronic source data collected outside of the eCRF, such as assessments captured by electronic data capture, central laboratory, central ECG or central MRI data, will be transferred directly to EDC or directly to Alkermes for incorporation into the final datasets. All out-of-range laboratory values will be deemed as clinically significant or not clinically significant by the Investigator. Clinically significant values will be considered AEs and will be recorded as such on the eCRFs.

All AEs will be coded using MedDRA. Concomitant medications will be categorized using the WHO-ATC classification system.

18.2. Inspection of Records

Alkermes or its representative will be allowed to conduct site visits to the investigational facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts, and source documents and other records relative to study conduct.

18.3. Retention of Records

Retention and storage of all essential clinical study documents shall be governed by the terms and conditions of the site's CSA and in accordance with ICH guidelines/local regulatory requirements as follows:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by the terms of the CSA. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with the applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

18.4. Use of Information and Publication Policy

Data generated in this study are proprietary information that are the sole property of Alkermes. Results of the study are to be held in confidence by both the investigators and the Sponsor.

Please refer to the CSA for details on the procedures for publishing and presenting data.

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20. APPENDIX A: MASSACHUSETTS GENERAL HOSPITAL ANTIDEPRESSANT TREATMENT RESPONSE QUESTIONNAIRE (ATRQ)–SAMPLE

Adapted for ALK5461-217 Visit 1:

Please use an interview format to record the responses to this questionnaire. Begin by saying, *"I'd like to summarize your use of antidepressant medication during this current episode of depression which began on [date episode began]. Do you agree that [date episode began] is when the current period of depression started?"* Please circle the subject's answer, and record the date of onset of the most recent depressive episode below.

YES NO

Date: _____

1. "*Have you received any treatment for depression with medications since the beginning of* ***THIS CURRENT*** *episode or period of depression, from [date episode began] until today?"* Please circle the subject's answer.

YES NO

2. If **YES**, review the list on pages 2 and 3 and put a check next to any medication(s) that the subject has taken for **at least 8 weeks** during THIS episode or period of depression. *"Let's review each medication you have taken, and let me know which ones you have taken for at least 8 weeks during this episode of depression."*

3. Of those medication(s) that the subject has taken for at least 8 weeks (checked from the list on pages 2 and 3), put a second check next to those that the subject has taken at a dosage **equal to or greater than** the minimum dosage listed for that medication **for at least 5 weeks**. *"Now, let's go through each, and let me know which of these you have taken at a dosage* ***equal to or greater than*** *the dose I mention, for* ***at least 5 weeks."***

4. For all medication(s) that have at least 1 check mark on the list on pages 2 and 3, please put a third check next to those that the subject has taken with another drug [e.g., buspirone (Buspar), lithium, psychostimulants such as methylphenidate (Ritalin), atypical antipsychotics such as olanzapine (Zyprexa)] added to augment or boost the antidepressant effect. *"Were any of the medications you mentioned taken with another drug to augment or boost the antidepressant effect of another antidepressant? If so, which ones?"*

5. Of the medications checked on pages 2 and 3, please write below the name of the one that the subject reports helped them the most with their depression: "*Of the medications that you have taken during this episode of depression, which one do you feel helped you the most with your depression*?

_____

6. *"If a rating of 100 is "completely improved" and 0 is "not improved at all", how close to 100 did you get on this medication?"* Read the four options below, and put a check next to the answer provided.

a) less than 25% improved
b) between 25% and 49% improved
c) between 50% and 75% improved
d) more than 75% improved

List of Antidepressant Medications.

Drug Class Brand Name	Generic Name	At least 8 weeks	Minimum Dose	At least 5 weeks at ≥ minimum dose	Agent added to augment or boost effect?
Tricyclic Antidepressants					
Adapin	doxepin	_____	150mg/d	_____	_____
Anafranil	clomipramine	_____	150mg/d	_____	_____
Asendin	amoxapine	_____	150mg/d	_____	_____
Endep/Elavil	amitriptyline	_____	150mg/d	_____	_____
Ludiomil	maprotiline	_____	150mg/d	_____	_____
Norpramin	desipramine	_____	150mg/d	_____	_____
Pamelor	nortriptyline	_____	75mg/d	_____	_____
Sinequan	doxepin	_____	150mg/d	_____	_____
Surmontil	trimipramine	_____	150mg/d	_____	_____
Tofranil	imipramine	_____	150mg/d	_____	_____
Vivacti	protriptyline	_____	30mg/d	_____	_____
Azafen	pipofezine*	_____	150mg/d	_____	_____
Agedal/Elronon	noxiptiline*	_____	100mg/d	_____	_____
Monoamine Oxidase Inhibitors (MAOIs)					
Marplan	isocarboxazid	_____	30mg/d	_____	_____
Nardil	phenelzine	_____	45mg/d	_____	_____
Parnat	tranylcypromine	_____	30mg/d	_____	_____
Emsam	selegiline patch	_____	6mg/24 hrs	_____	_____
Aurorix	moclobemide*	_____	300mg/d	_____	_____
Pirazidol	pirlindole*	_____	200mg/d	_____	_____
Selective Serotonin Reuptake Inhibitors (SSRIs)					
Luvox	fluvoxamine*	_____	50mg/d	_____	_____
Paxil	paroxetine	_____	20/25/mg/d	_____	_____
Prozac	fluoxetine	_____	20mg/d	_____	_____
Zoloft	sertraline	_____	50mg/d	_____	_____
Celexa	citalopram	_____	20mg/d	_____	_____
Lexapro	escitalopram	_____	10mg/d	_____	_____
Viibryd	vilazodone	_____	40mg/d	_____	_____
Brintellix	vortioxetine	_____	10mg/d	_____	_____

* Note: This medication is not FDA approved for major depressive disorder in the United States. Subjects should not be enrolled while taking this medication, although they may have a previous failure of an adequate trial of this medication within this major depressive episode.

Drug Class **Brand Name**	**Generic Name**	**At least 8 weeks**	**Minimum Dose**	**At least 5 weeks at ≥ minimum dose**	**Agent added to augment or boost effect?**
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)					
Effexor	venlafaxine	_____	150mg/d	_____	_____
Cymbalta	duloxetine	_____	60mg/d	_____	_____
Pristiq	desvenlafaxine	_____	50mg/d	_____	_____
Savella	milnacipran*	_____	100mg/d	_____	_____
Fetzima	levomilnacipran	_____	40mg/d	_____	_____
Other Antidepressants					
Desyrel	trazodone	_____	300mg/d	_____	_____
Serzone	nefazodone	_____	300mg/d	_____	_____
Wellbutrin	bupropion	_____	300mg/d	_____	_____
Remeron	mirtazapine	_____	15mg/d	_____	_____
Valdoxan	agomelatine*	_____	25mg/d	_____	_____
Stablon	tianeptine*	_____	37.5mg/d	_____	_____
Edronax	reboxetine*	_____	4mg/d	_____	_____
Bolvidon/Depnon, Norval/Tolvon	mianserin*	_____	30mg/d	_____	_____
Insidon	opipramol*	_____	150mg/d	_____	_____

*Note: This medication is not FDA approved for major depressive disorder in the United States. Subjects should not be enrolled while taking this medication, although they may have a previous failure of an adequate trial of this medication within this major depressive episode.

Did you receive electro-convulsive treatment (ECT) during **this current** episode (please circle one):

YES NO

Did you **ever** receive vagal nerve stimulation (VNS) or deep brain stimulation (DBS) (please circle one):

YES NO

Adapted for ALK5461-217 Visit 2:

Please use an interview format to record the responses to this questionnaire. Begin by saying, *"I'd like to summarize your use of antidepressant medication between Visit 1 on [date patient completed Visit 1] and today."*

1. "*Are you currently taking any antidepressant medication(s)?"* Please circle the subject's answer.

YES NO

2. If YES, review the list on pages 2 and 3 and put a check next to any medication(s) that the subject has been taking for at least 8 weeks, (or at least 7 weeks if the subject switched to a second ADT during the PLI). *"Let's review each medication you have taken since the last visit (including ones you may have started before the last visit) or are currently taking, and let me know which one you have taken for at least 8 weeks."* Adjust language appropriately as noted above if the subjected switched to a new ADT during the PLI and the 7-week duration is relevant).

3. Of those medication(s) that the subject has taken for at least 8 weeks (or 7 weeks as described in item 2) and checked from the list on pages 2 and 3, put a second check next to those that the subject has been taking at a dosage equal to or greater than the minimum dosage listed for that medication for at least 5 weeks. *"Now, let's go through each, and let me know which of these you have taken at a dosage equal to or greater than the dose I mention, for at least 5 weeks."*

4. For the new medication(s) that have at least 1 check mark on the list on pages 2 and 3, please put a third check next to those that the subject has taken with another drug [e.g., buspirone (Buspar), lithium, psychostimulants such as methylphenidate (Ritalin), atypical antipsychotics such as olanzapine (Zyprexa)] added to augment or boost the antidepressant effect. "Where any of the medications you mentioned taken with another drug to augment or boost the antidepressant effect of another antidepressant? If so, which ones?"

5. Record the degree to which the subject thinks they have improved with the current antidepressant treatment. *"Now I'd like to talk about how much you think your depression has improved with your current antidepressant. If a rating of 100 is "completely improved" and 0 is "not improved at all", how close to 100 did you get on this medication?"* Read the four options below, and put a check next to the answer provided.

a) less than 25% improved
b) between 25% and 49% improved
c) between 50% and 75% improved
d) more than 75% improved

List of Antidepressant Medications.

Drug Class **Brand Name**	**Generic Name**	**At least 8 weeks****	**Minimum Dose**	**At least 5 weeks at ≥ minimum dose**	**Agent added to augment or boost effect?**
Tricyclic Antidepressants					
Adapin	doxepin	_____	150mg/d	_____	_____
Anafranil	clomipramine	_____	150mg/d	_____	_____
Asendin	amoxapine	_____	150mg/d	_____	_____
Endep/Elavil	amitriptyline	_____	150mg/d	_____	_____
Ludiomil	maprotiline	_____	150mg/d	_____	_____
Norpramin	desipramine	_____	150mg/d	_____	_____
Pamelor	nortriptyline	_____	75mg/d	_____	_____
Sinequan	doxepin	_____	150mg/d	_____	_____
Surmontil	trimipramine	_____	150mg/d	_____	_____
Tofranil	imipramine	_____	150mg/d	_____	_____
Vivacti	protriptyline	_____	30mg/d	_____	_____
Azafen	pipofezine*	_____	150mg/d	_____	_____
Agedal/Elronon	noxiptiline*	_____	100mg/d	_____	_____
Monoamine Oxidase Inhibitors (MAOIs)					
Marplan	isocarboxazid	_____	30mg/d	_____	_____
Nardil	phenelzine	_____	45mg/d	_____	_____
Parnat	tranylcypromine	_____	30mg/d	_____	_____
Emsam	selegiline patch	_____	6mg/24 hrs	_____	_____
Aurorix	moclobemide*	_____	300mg/d	_____	_____
Pirazidol	pirlindole*	_____	200mg/d	_____	_____
Selective Serotonin Reuptake Inhibitors (SSRIs)					
Luvox	fluvoxamine*	_____	50mg/d	_____	_____
Paxil	paroxetine	_____	20/25/mg/d	_____	_____
Prozac	fluoxetine	_____	20mg/d	_____	_____
Zoloft	sertraline	_____	50mg/d	_____	_____
Celexa	citalopram	_____	20mg/d	_____	_____
Lexapro	escitalopram	_____	10mg/d	_____	_____
Viibryd	vilazodone	_____	40mg/d	_____	_____
Brintellix	vortioxetine	_____	10mg/d	_____	_____

* Note: This medication is not FDA approved for major depressive disorder in the United States. Subjects should not be enrolled while taking this medication, although they may have a previous failure of an adequate trial of this medication within this major depressive episode.

** Or at least 7 weeks if the subject switched to a second ADT during the PLI Period.

Drug Class **Brand Name**	**Generic Name**	**At least 8 weeks****	**Minimum Dose**	**At least 5 weeks at ≥ minimum dose**	**Agent added to augment or boost effect?**
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)					
Effexor	venlafaxine	_____	150mg/d	_____	_____
Cymbalta	duloxetine	_____	60mg/d	_____	_____
Pristiq	desvenlafaxine	_____	50mg/d	_____	_____
Savella	milnacipran*	_____	100mg/d	_____	_____
Fetzima	levomilnacipran	_____	40mg/d	_____	_____
Other Antidepressants					
Desyrel	trazodone	_____	300mg/d	_____	_____
Serzone	nefazodone	_____	300mg/d	_____	_____
Wellbutrin	bupropion	_____	300mg/d	_____	_____
Remeron	mirtazapine	_____	15mg/d	_____	_____
Valdoxan	agomelatine*	_____	25mg/d	_____	_____
Stablon	tianeptine*	_____	37.5mg/d	_____	_____
Edronax	reboxetine*	_____	4mg/d	_____	_____
Bolvidon/Depnon, Norval/Tolvon	mianserin*	_____	30mg/d	_____	_____
Insidon	opipramol*	_____	150mg/d	_____	_____

*Note: This medication is not FDA approved for major depressive disorder in the United States. Subjects should not be enrolled while taking this medication, although they may have a previous failure of an adequate trial of this medication within this major depressive episode.

** Or at least 7 weeks if the subject switched to a second ADT during the PLI Period.

Did you receive electro-convulsive treatment (ECT) during **this current** episode (please circle one):

YES NO

Did you **ever** receive vagal nerve stimulation (VNS) or deep brain stimulation (DBS) (please circle one):

YES NO

21. APPENDIX B: DAILY DOSING TABLE FOR ANTIDEPRESSANT THERAPY TAKEN DURING THE STUDY

Table 8: Daily Dosing Allowed for Antidepressant Therapy Taken During the Study

Brand Name	Generic Name	Minimum Adequate Daily Dose (mg)	Maximum Daily Dose (mg)	Permitted for PIR Subjects?
SSRIs				
Paxil	paroxetine	20/25	50	No
Paxil CR	paroxetine	20/25	62.5	No
Prozac	fluoxetine	20	80	Yes
Zoloft	sertraline	50	200	Yes
Celexa	citalopram	20	40	No
Lexapro	escitalopram	10	20	Yes
Viibryd	vilazodone	40	40	No
Brintellix	vortioxetine	10	20	No
SNRIs				
Effexor	venlafaxine	150	375	Yes
Effexor XR	venlafaxine	150	225	Yes
Cymbalta	duloxetine	60	120	Yes
Pristiq	desvenlafaxine	50	400	No
Fetzima	levomilnacipran	40	120	No

Abbreviations: CR=controlled-release; PIR=prospective inadequate responder; SNRIs=serotonin-norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors; XR=extended-release

22. APPENDIX C: PATIENT QUESTIONNAIRE

Question 1: Below is a list of symptoms associated with depression. We are interested in knowing how important each one is to you. Please rate each item on how important it is to you from 0 (Not important) to 4 (Extremely important / Essential). Please rate each item independently of the others.

Item #	*Description*	*Importance to you (0 to 4)*				
		0 - Not important	1 - Somewhat important	2 - Important	3 - Very important	4 -Extremely important / Essential
1	Feeling sad or unhappy	☐	☐	☐	☐	☐
2	Looking sad or depressed to other people	☐	☐	☐	☐	☐
3	Feeling anxious or nervous or agitated	☐	☐	☐	☐	☐
4	Ability to fall and stay asleep	☐	☐	☐	☐	☐
5	Interest in food (lack of interest or increased appetite)	☐	☐	☐	☐	☐
6	Ability to concentrate or collect thoughts	☐	☐	☐	☐	☐
7	Ability to get things started, how quickly you are able to get everyday things done	☐	☐	☐	☐	☐
8	Interest in things you typically enjoy, ability to experience joy, zest for life	☐	☐	☐	☐	☐
9	Feelings of guilt, putting yourself down	☐	☐	☐	☐	☐
10	Feeling that life isn't worth living, better off dead	☐	☐	☐	☐	☐

23. APPENDIX D: MAXIMUM DOSES OF ANTIPSYCHOTICS APPROVED FOR MDD

Table 9 lists the antipsychotics for which prior use is allowed in this study. It gives the maximum approved doses for MDD of these antipsychotics.

Table 9: Maximum antipsychotic approved doses for MDD

Antipsychotic	Maximum approved dose
Aripiprazole	30 mg/day
Quetiapine	300 mg/day
Brexpiprazole	3 mg/day
Olanzapine/fluoxetine	12 mg/50 mg/day

24. APPENDIX E: PARTIAL LIST OF PROHIBITED CYTOCHROME P450 (CYP) 3A4 INHIBITORS AND INDUCERS

The following is a list of CYP3A4 inhibitors and inducers that subjects are to avoid within 30 days before Screening through follow-up. This list is not comprehensive.

Table 10: Partial List of Cytochrome P450 (CYP) 3A4 Inhibitors and Inducers

Moderate-to-Strong Inhibitors		Moderate-to-Strong Inducers
Aprepitant	Imatinib	Bosentan
Boceprevir	Ketoconazole	Carbamazepine
Ciprofloxacin	Lopinavir/Ritonavir	Efavirenz
Clarithromycin	Nefazodone	Enzalutamide
Conivaptan	Nelfinavir	Etravirine
Crizotinib	Posaconazole	Modafinil
Danoprevir/Ritonavir	Ritonavir	Phenobarbital
Diltiazem	Saquinavir/Ritonavir	Phenytoin
Erythromycin	Telaprevir	Rifampin
Fluconazole	Troleandomycin	Rifabutin
Indinavir/Ritonavir	Verapamil	St. John's Wort
Itraconazole	Voriconazole	–

Source: (Food and Drug Administration 2016)