A Phase 3b Extension Study of Adjunctive ALKS 5461 in the Treatment of Refractory Major Depressive Disorder

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CLINICAL STUDY PROTOCOL

ALK5461-218

Study title:	A Phase 3b Extension Study of Adjunctive ALKS 5461 in the Treatment of Refractory Major Depressive Disorder
Document date:	v 3.0 (incorporates Amendment 2.0): 14 Nov 2019 v 2.0 (incorporates Amendment 1.0): 01 Aug 2018 Original Protocol: 25 Jun 2018
Sponsor:	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA

PROCEDURES IN CASE OF EMERGENCY

Table 1: Study Contact Information

Role in Study	Name	Address and Telephone Number
Alkermes Medical Monitors	PPD	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA Telephone: PPD
Alkermes Global Safety Officer	PPD	Alkermes, Inc. 852 Winter Street Waltham, MA 02451 USA Telephone: PPD
CRO Medical Monitor and 24-Hour Emergency Contact	PPD	PPD PPD Raleigh, NC 27604 USA Telephone: PPD Mobile Phone: PPD
SAE and Pregnancy Reporting	PPD Safety and Pharmacovigilance	FAX Number: PPD E-mail: PPD

Abbreviations: CRO=contract research organization; SAE=serious adverse event

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 Extension Study of Adjunctive ALKS 5461 in the Treatment of Refractory Major Depressive Disorder	
Investigators: Multicenter, multicountry study to be conducted at approximately 35 sites in the US and Australia.	
Study Period: Estimated date first patient enrolled: Q3 2018 Estimated date last patient completed: Q1 2020	**Phase of development:** 3b
Objectives: The objective of this study is to evaluate the long-term safety and tolerability of adjunctive ALKS 5461 in adults who have treatment-refractory major depressive disorder (MDD).	
Methodology: This is a Phase 3b extension study to Study ALK5461-217 to evaluate the long-term safety and tolerability of adjunctive ALKS 5461 in adults who have treatment-refractory MDD.	
Number of subjects planned: All subjects who complete Study ALK5461-217 and meet eligibility criteria will be allowed to participate. It is estimated that up to 250 subjects may participate in this study. **Sample size considerations:** No formal sample size calculation has been performed for this extension study. A sample size of up to 250 subjects is based on an estimated number of subjects who may wish to continue from Study ALK5461-217.	
Main criteria for subject inclusion: Subjects who have completed scheduled participation in Study ALK5461-217 who are willing and able to follow the study procedures as outlined in the protocol, including adherence with approved antidepressant therapy and study drug regimen, are eligible for participation in the study.	
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 sublingual tablet.	
Reference therapy, dosage, duration, and mode of administration: Not applicable	
Duration of study: The study is planned to be open until approximately Q1 2020. Therefore, depending on when a subject is enrolled, the duration of participation in this study will vary. Subjects are expected to receive approximately 16 weeks to 68 weeks of ALKS 5461 within this protocol. There will be one Safety Follow-up visit, occurring 2 weeks after the last dose of ALKS 5461. The study may continue for a planned period of up to 68 weeks and/or until regulatory approval has been obtained in the United States, and the product is commercially available and reimbursed in the United States.	
Criteria for evaluation: **Safety:** The following assessments will be used to evaluate safety and tolerability throughout the study and during a 2-week post-discontinuation follow-up period:	

- Adverse events
- Serious adverse events
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical methods:

Safety: 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.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: List of Abbreviations and Definition of Terms

Abbreviation or Term	Full Form or Definition
ADT	Antidepressant therapy
AE	Adverse event
BUP	Buprenorphine
CSA	Clinical Study Agreement
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
eCRF	Electronic case report form
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious adverse event
SAM	Samidorphan
SL	Sublingual
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

5. INTRODUCTION

Major depressive disorder (MDD) is a serious, and in some cases life-threatening, condition. Current therapy is limited and insufficient for many patients. Selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors 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 comorbidity (eg, increased adiposity, insulin-resistance, cardiovascular disease, etc.) (Newcomer 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 and κ-opioid receptor antagonist, 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. 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 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 is a new molecular entity optimized for high potency and high SL bioavailability, which facilitates coformulation with BUP for SL administration.

Efficacy of ALKS 5461 2/2 was demonstrated in a Phase 2 study (ALK5461-202) and a Phase 3 study (ALK5461-207). These placebo-controlled clinical studies specifically focused on patients continuing therapeutic doses of ADT who had an inadequate response to treatment. All subjects, including subjects assigned to placebo treatment, remained on background ADT throughout the Treatment period. For another Phase 3 study (ALK5461-205), post hoc analyses of multiple time points for Montgomery-Åsberg Depression Rating Scale (MADRS) score changes from baseline demonstrated that the changes for Weeks 3 through 6, and at the last visit of the Treatment period, were significantly lower among subjects in the ALKS 5461 2/2 group than with placebo. In another Phase 3 study (ALK5461-206), ALKS 5461 2/2 showed improvement vs baseline; however, the net treatment effect was obscured by a large placebo effect.

ALKS 5461 was generally well tolerated across all placebo-controlled studies. This was confirmed in a clinically complete Phase 3 long-term safety study (ALK5461-208). There has been no evidence to suggest that ALKS 5461 is associated with motor disorders or metabolic dysregulation, which are toxicities associated with atypical antipsychotics.

There is minimal evidence of abuse potential based on data from a human abuse potential study (ALK5461-212) and data from the ALKS 5461 clinical development program to-date.

Taken together, these findings indicate that ALKS 5461 has the potential to address an unmet medical need in this serious condition.

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

5.1. Study Rationale and Selection of Study Design

Safety and tolerability data from clinical studies to date show that ALKS 5461 was 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. This is an open-label, Phase 3b, multicenter extension study of Study ALK5461-217 designed to assess safety and tolerability for up to an additional 68 weeks of treatment.

5.2. Study Dose Selection

This is an extension study for subjects who have completed Study ALK5461-217 (11 weeks of treatment plus the 1-week Follow-up period). Thus, the dose level selected for this study (ALKS 5461 2/2) is the same as the dose administered in Study ALK5461-217.

6. STUDY OBJECTIVES

The objective of this study is to assess the long-term safety and tolerability of ALKS 5461 as an adjunctive treatment for refractory MDD.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Subject Inclusion Criteria

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 informed consent
2. Be 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)
3. Be willing and able to follow the study procedures and visits as outlined in the protocol
4. Have the potential to benefit from the administration of ALKS 5461, in the opinion of the Investigator
5. Have completed treatment in Study ALK5461-217. The following criteria are to be met based on the time between completing Study ALK5461-217 and enrolling in this study:
   - **<30 days:** Investigator attestation that no changes have occurred with the subject that would compromise safety
   - **≥30 days:** Investigator should review key criteria to ensure subject still meets eligibility requirements[1]. Discussion with the Medical Monitor will occur as necessary

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 his or her ability to adhere to the protocol visit schedule or fulfill visit requirements
2. Is pregnant, planning to become pregnant, or is breastfeeding during the study
3. 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 Screening Columbia-Suicide Severity Rating Scale (C-SSRS)
   c. The subject has attempted suicide at any time after enrollment in Study ALK5461-217

[1] Investigators will be provided with a checklist to ensure review of key criteria. A sample checklist is provided in Section 20 (Appendix A).

4. 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 Visit 1
5. Has a positive test for drugs of abuse at Visit 1

7.3. Subject Withdrawal

Subjects who are screen failures may be eligible for rescreening only if rescreening is approved by the Medical Monitor.

A subject may be discontinued from the study at any time if the subject, Investigator, or Sponsor determines that it is not in the best interest of the subject to continue participation. Reasons for discontinuation include:

- Adverse event
- Lost to follow-up
- Withdrawal by subject
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Other

If a subject withdraws from the study for any reason, any ongoing adverse events (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 visit and a 2-week postdiscontinuation Safety Follow-up visit. The Early Termination visit should be scheduled as close as possible to the subject's last dose of study drug. If the subject fails or refuses to return to the study site, an attempt must be made to contact the subject by telephone in order to assess as many safety 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. The reason for study discontinuation will be documented and made on the appropriate electronic case

report form (eCRF). If a subject is lost to follow-up, a reasonable attempt to contact the subject must be made and documented.

The study may continue for a planned period of up to 68 weeks and/or until regulatory approval has been obtained, and the product is commercially available and reimbursed.

7.4. Replacement of Subjects

Subjects who withdraw after receiving the first dose of study drug in this study will not be replaced.

8. STUDY DESIGN

8.1. Overall Study Design and Plan

This is an open-label, Phase 3b, multicenter extension study to evaluate the long-term safety and tolerability of ALKS 5461 administration for use as an adjunctive therapy to antidepressants for the treatment of refractory MDD. Subjects who completed treatment in Study ALK5461-217 will be eligible for enrollment into the study.

At Visit 1, all eligible, consenting subjects will begin the Treatment period. Dosing is described in detail in Section 9.1.2. From Day 1 onward, all participating subjects will take ALKS 5461 2/2 and an approved ADT.

Study staff will administer the first dose of ALKS 5461 on Day 1. From that point on during the Treatment period, the staff will dispense ALKS 5461 for subjects' self-administration. Subjects will be advised to take the study drug at bedtime.

During the Treatment period, subjects will return to the clinic for periodic scheduled visits, at which safety and tolerability will be assessed, as well as a 2-week postdiscontinuation Follow-up visit.

8.2. Schedule of Visits and Assessments

Eligibility criteria and assessments described in Section 8.3 will occur on Day 1 of the study.

For a missed visit, the study site should attempt to contact the subject to reschedule.

Subjects who discontinue from the study prematurely will be encouraged to return for an Early Termination visit and a 2-week postdiscontinuation Follow-up visit. See Section 7.3 for additional details.

See Table 3 for a full schedule of assessments.

Table 3: Schedule of Assessments

	Screening Visit Transition from Previous Study[a, b, c]	**Week 1**	**Week 2**	**Week 6**	**Week 12**	**Visits every 8 Weeks (Weeks 20, 28, 36, 44, 52, 60)**	**Week 68 EOT/ET Visit**[d]	**Safety Follow-Up Visit**
Day	SCN/1	8 (±4)	15 (±4)	43 (±4)	85 (±4)	Every 56 (±4) days	477 (±4)	14 (±4) days after the final dose of study drug
Visit	1	2	3	4	5	6, 7, 8, 9, 10, 11	12	13
Informed Consent	X							
Qualification/ Diagnostic Assessments								
Eligibility Review	X							
Medical and Psychiatric History Updates	X							
Qualification/ Safety Assessments								
Symptom-driven Physical Examination	X							
Urine Pregnancy Test (all women)	X	X	X	X	X	X	X	X
Urine Drug Screen[e]	X							
C-SSRS (since last visit)	X	X	X	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X
Additional Study Procedures								
Dispensation of Study Drug[f]	X	X	X	X	X	X		
Study Drug Adherence Review[g]		X	X	X	X	X	X	

Abbreviations: AE=adverse event; C-SSRS=Columbia-Suicide Severity Rating Scale; EOT=end of treatment; ET=early termination; SCN=Screening

[a] Screening (Visit 1) may occur on the same day as the Safety Follow-up Visit of the preceding Study ALK5461-217, in which case the procedures of these two visits may be combined.
[b] Procedures already performed in ALK5461-217 do not need to be repeated in ALK5461-218. Information from the antecedent study will be re-entered into the electronic data capture system for Study ALK5461-218.
[c] If the subject is screened ≥30 days after completing ALK5461-217, Investigators will review key eligibility criteria in order to ensure subject still meets requirements (Sample checklist is provided in Section 20, Appendix A).
[d] ET visit should occur as close as possible to subject's last dose.
[e] Urine drug screen testing will be performed at Visit 1 and at subsequent visits as needed based on the Investigator's judgment.
[f] At each specified dispensing visit, subjects will receive a supply of ALKS 5461 to last until the following visit.
[g] Adherence for study drug based on subject query.

8.3. Study Procedures Descriptions

Details of the study procedures are described below.

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 on Screening/Day 1 using the subject inclusion criteria in Section 7.1 and exclusion criteria in Section 7.2.

8.3.3. Demographics and Medical History

Subject's demographic data and medical history will be carried over from the antecedent study. If ≥30 days have elapsed since end-of-treatment in ALK5461-217, medical history for the interval period will be queried and updated as necessary.

8.3.4. Concomitant Medication Review

At each visit, subjects will be asked about the medications they have taken since the last visit, including prescription and nonprescription medications, vitamins, and supplements. In particular, use of opioid agonists (eg, codeine, oxycodone, tramadol, or morphine) should be queried.

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

8.3.5. Study Drug Adherence Review

At each specified dispensing visit, subjects will receive a supply of ALKS 5461 to last until the following visit. Subjects will be instructed to bring the blister pack (see Section 10.4) with them to each subsequent visit. Drug adherence for ALKS 5461 will be reviewed with subjects at each visit.

8.3.6. Safety Assessments

8.3.6.1. Adverse Event Monitoring

Adverse events will be monitored continuously from the time a subject signs the informed consent document until the completion of the final study visit. Adverse events and serious adverse events (SAEs) are defined in Sections 13.1 and 13.2, respectively. Section 13.4 provides guidance on the monitoring and recording requirements for AEs. Section 13.5 provides guidance on the reporting requirements for SAEs.

8.3.6.2. Columbia-Suicide Severity Rating Scale

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior (Posner et al, 2011). The C-SSRS will be administered at each visit as specified in Table 3 and will be assessed for the period since the last visit.

8.3.7. Pregnancy Testing

A urine pregnancy test will be administered to all participating female subjects predosing and at all subsequent visits during the Study period. Results must be negative prior to administration of study drug.

A positive pregnancy test result at any time will necessitate the subject's immediate withdrawal from the study. Additional follow-up may be required as detailed in Section 8.4.1.

8.3.8. Drug testing

Urine drug screen testing will be performed (via dipstick) at Visit 1. Following that, screening will be performed based on the Investigator's judgment.

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, and contraceptive implant); oral contraceptives should have been 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. Partner vasectomy is not considered an approved acceptable method of contraception for a female subject.

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 Early Termination and Safety Follow-up visits will be scheduled

and the pregnancy will be reported to Alkermes. Additional follow-up may be required. 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 (per Section 13.5) immediately, 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 any AE that occurred during pregnancy and/or the outcome of the pregnancy meets the criteria for classification as an 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 between the completion of ALK5461-217 and the first dose of ALKS 5461 in this study will be recorded, as detailed in Section 8.3.4.

Subjects are permitted to continue taking concomitant medications during the study provided that these medications are clinically appropriate and are not prohibited. 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 Treatment period is permitted for optimal therapeutic effect within the recommended dose range. Further, subjects are not permitted to change ADTs during the course of the study period.

8.4.2.1. Antidepressant Therapy

Subjects 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.

8.4.3. 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 21 [Appendix B] for a list of prohibited inducers and moderate-to-strong inhibitors of CYP3A4). **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:
  - Monoamine oxidase inhibitors (eg, phenelzine, tranylcypromine, selegiline)

  - Lithium
  - Tricyclic antidepressants (eg, amitriptyline, nortriptyline, desipramine)
  - Psychostimulants (eg, methylphenidate, dextroamphetamine/amphetamine)
  - Bupropion
  - Additional agents (prescription or over-the-counter) 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)
- Use of systemic corticosteroids
- Antipsychotics

Hypnotic agents will be permitted within the dose range approved by the Food and Drug Administration for insomnia.

8.4.4. Pain Management

Because the ALKS 5461 coformulation 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 the 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.

9. TREATMENT OF SUBJECTS

9.1. Study Drug Dose and Administration

9.1.1. Description of ALKS 5461

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.

9.1.2. Study Drug Dose and Dosing Regimen

Dosing begins on Day 1. One tablet will be taken SL on each dosing day. The tablet should be placed under the tongue and kept under the tongue until completely dissolved. **The tablet must not be swallowed.** Eating and drinking should be avoided for 15 minutes after dosing. At the first visit, study site personnel will administer the tablet and visually confirm that the tablet has dissolved completely. Subjects will then self-administer the daily SL dose; it is recommended that subjects take ALKS 5461 at bedtime.

9.2. Treatment Adherence

As indicated in Table 3, subjects will receive at each specified dispensing visit a supply of study drug (ALKS 5461) that will last until the following visit. Study drug adherence will be reviewed with the subject 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. Full site-level accountability will be carried out as described in Section 10.4.

9.3. Method of Assigning Subjects to Treatment

All participating subjects will receive ALKS 5461.

9.4. Blinding

Not applicable.

9.5. Study Drug Dose Adjustment and Stopping Rules

Beginning on Day 1, all participating subjects will receive open-label ALKS 5461 2/2. No dose titration will be allowed.

Section 7.3 outlines procedure for when a subject discontinues from the study.

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 κ-opioid receptor antagonist, 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.

Buprenorphine is a Schedule III narcotic in the United States, and SAM is a Schedule II controlled substance in the United States. Therefore, ALKS 5461 must be handled in accordance with restrictions related to Schedule II controlled substances in the United States. In Australia, ALKS 5461 should be handled according to local regulations. See Section 10.3 and Section 10.5 for information on storage and handling of controlled substances, respectively.

Study drug is white-to-off-white in color, non-debossed, triangle-shaped tablet. The SL tablet formulation contains excipients commonly used in products approved by the United States Food and Drug Administration, 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 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

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

The Investigator will take adequate precautions, including storage of the investigational product 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 product is returned or destroyed.

Subject-level study drug accountability will be documented in the subjects' source documents. If study 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 study 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.

10.5. Handling and Disposal

In both the US and Australia, 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 drug must be accounted for in a drug accountability record.

11. ASSESSMENT OF EFFICACY

No formal efficacy assessments will be conducted in the study. Based on the Investigator's judgment, efficacy assessments consistent with the local clinical practice will be documented.

12. ASSESSMENT OF PHARMACOKINETICS

No pharmacokinetic sampling is planned in this study.

13. ASSESSMENT OF SAFETY

Safety and tolerability will be assessed on the basis of:

- Adverse events
- Serious adverse events
- C-SSRS results

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 preexisting conditions and are documented on the medical history eCRF. Preexisting conditions that worsen during the study are entered on the AE eCRF.

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 Alkermes, and additional follow-up may be required.

13.2. Definition of Serious Adverse Events

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 a 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, 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 as 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 or her best clinical judgment. The criteria listed in Table 4 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 4: 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.

13.4. Monitoring and Recording of Adverse Events

Adverse event data collection will begin after a subject signs the ICF and will continue until completion of the Safety Follow-up visit or 2 weeks after the final dose of study drug. 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 sending an email or facsimile of 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

This extension study is not designed to formally assess ALKS 5461. Data collection will be limited to information needed to determine eligibility, describe patient demographics and exposure, collect safety information, and meet regulatory reporting requirements.

14.1. Sample Size Considerations

No formal sample size calculation has been performed for this extension study. A sample size of up to 250 subjects is based on an estimated number of subjects who may wish to continue from Study ALK5461-217.

14.2. General Statistical Methodology

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.

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 (ALKS 5461).

14.3. Demographics and Baseline Characteristic Data

Demographics and baseline characteristics such as gender, age, race, and weight will be summarized with descriptive statistics to assess the comparability of the study groups.

14.4. Efficacy Analyses

No formal efficacy analysis will be performed for this study.

14.5. Pharmacokinetic Analyses

No pharmacokinetic analysis will be performed for this study.

14.6. Patient Questionnaire

Not applicable for this study.

14.7. Safety and Tolerability Analyses

All safety assessments 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. 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.

Further details will be described in the Statistical Analysis Plan.

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 (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. 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 study 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 the drug will be released to the Investigator. The protocol must be reapproved 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 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 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 or 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, 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 in the United States 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 system maintains a full audit trail.

Adverse events will be coded using MedDRA. Concomitant medications will be categorized using the WHO-Anatomical Therapeutic Chemical 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 until 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.

19. REFERENCES

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20. APPENDIX A: CHECKLIST USED TO REVIEW KEY ELIGIBILITY CRITERIA WITH SUBJECTS ENTERING ≥30 DAYS AFTER COMPLETING ALK5461-217

Alkermes
Patient inspired

CHECKLIST & INVESTIGATOR ATTESTATION

Subject Number:	Protocol No.:	Anticipated Screening/Visit 1 Date:	Site Investigator/Site Number
	ALK5461-218		

NOTES:

- This form must be completed for all ALK5461-217 Completers whose treatment completion date (VISIT 13) is ≥30 days from ALK5461-218 Screening Visit (VISIT 1)
- Submit this form completed to PPD for any ALK5461-217 subject who completed Visit 13 (End of Treatment) ≥ 30 days from planned screening date
- Investigator is encouraged to call the Medical Monitor to discuss each case in advance of dosing in ALK5461-218 as needed
- Ensure the fully executed form is obtained prior to scheduling Visit 1

Key Criteria	Is item applicable to this subject?	Comments
GENERAL INFORMATION:		
Subject participated or is participating in another clinical trial since completion of ALK5461-217	☐ Yes ☐ No	If yes, provide details:
Changes in contraceptive method since completion of ALK5461-217	☐ Yes ☐ No	If yes, provide details of new/planned contraceptive method:
For females, is the subject pregnant or planning to become pregnant	☐ Yes ☐ No	

ANTIDEPRESSANT THERAPY (ADT) ASSESSMENT:		
Confirm ADT details for the subject	Current ADT: Dose: Frequency: Start Date:	
Please detail any changes and/or interruptions of the subject's ADT since completion of ALK5461-217 including root causes or confirm there have been no changes. If the subject has changed his or her ADT, please provide detail on his or her level of improvement and clinical judgment regarding initiating augmentation therapy:		
MEDICAL AND PSYCHIATRIC HISTORY ASSESSMENT:		
Has the subject attempted suicide or has the perceived risk of suicide increased since completion of the ALK5461-217 study?	☐ Yes ☐ No	If yes, provide details:
Have there been any significant changes to Medical History, Psychiatric History or Concomitant Medications, e.g. - Newly identified or emergent allergies - Substance abuse (disclosed or suspected by PI) - New psychiatric diagnoses - Hospitalization for psychiatric reasons - Initiation of ECT therapy - New medication(s) initiated - Medications discontinued	☐ Yes ☐ No	

If yes, please complete the table below to detail all changes:

Medical/Psychiatric History Term (please use DSM-5 terminology for psychiatric diagnoses)	Onset Date	End Date/ Ongoing	Associated Medications	Concomitant Treatment Include non-pharmacological therapies	Dose/ Freq	Start Date	Stop Date / Ongoing	Requires Washout?	Washout completion date (if applicable)
			☐ Y ☐ N					☐ Y ☐ N	
			☐ Y ☐ N					☐ Y ☐ N	
			☐ Y ☐ N					☐ Y ☐ N	
			☐ Y ☐ N					☐ Y ☐ N	
			☐ Y ☐ N					☐ Y ☐ N	
			☐ Y ☐ N					☐ Y ☐ N	
			☐ Y ☐ N					☐ Y ☐ N	
			☐ Y ☐ N					☐ Y ☐ N	

OTHER OBSERVATIONS:	
Other concerns/information?	☐ Yes ☐ No
Please provide detail:	

Principal Investigator

Note: If the third option below is selected, you will not receive an acknowledgment (i.e. full execution of this form from PPD

- ☐ I attest that no changes have occurred with the subject
- ☐ I attest that there are new findings, however in my view these changes would NOT compromise safety when dosed in ALK5461-218
- ☐ I attest there are new findings that in my view would compromise the safety of the subject if dosed in ALK5461-218

PI Name _____ Signature _____ Date _____

PPD **Medical Director**

I acknowledge the Principal Investigators' attestation based on information provided by the site on this form.

Reviewer's Name _____ Signature _____ Date _____

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

A list of CYP3A4 inhibitors and inducers that subjects are to avoid is presented in Table 5 below. This list is not comprehensive.

Table 5: 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).