A Phase 1b Randomized, Placebo-controlled Study to Assess the Effect of a Single Dose of ASP8062 on the Multiple Dose Safety, Tolerability and Pharmacokinetics of Buprenorphine/Naloxone in Subjects with Opioid Use Disorder

ISN/Protocol 8062-CL-2003

Version 1.2

Incorporating Nonsubstantial Amendment 2 [See Section 13]

29 Jul 2020

NCT04447287

IND 146215

Sponsor:

Astellas Pharma Global Development Inc.
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Protocol History:
Version 1.0 Original [05 Mar 2020]
Version 1.1 Incorporating Nonsubstantial Amendment 01 [08 Jun 2020]

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SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 14 Sponsor Signature].

2. INVESTIGATOR'S SIGNATURE

A Phase 1b Randomized, Placebo-controlled Study to Assess the Effect of a Single Dose of ASP8062 on the Multiple Dose Safety, Tolerability and Pharmacokinetics of Buprenorphine/Naloxone in Subjects with Opioid Use Disorder

ISN/Protocol 8062-CL-2003

Version 1.2 Incorporating Nonsubstantial Amendment 2

29 Jul 2020

I have read all pages of this protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my personnel have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD Mmm YYYY)

Printed Name: ---------- ----------

Address: ----------

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

24-hour Contact for Serious Adverse Events See [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events]	**Please fax or email the serious adverse events/special situations worksheet to:** Astellas Pharma Global Development Inc. US Pharmacovigilance **North America fax number: +1-888-396-3750** **North America alternate fax number: +1-847-317-1241** **Email: safety-us@astellas.com**
Medical Monitor/Study Physician	PPD Development Medical Science Astellas Pharma Global Development Inc. 1 Astellas Way Northbrook, IL, 60062, US PPD
Clinical Research Contact	PPD Medical and Development Astellas Pharma Global Development Inc. 1 Astellas Way Northbrook, IL, 60062, US PPD

1 PROTOCOL SUMMARY

1.1 Synopsis

Date and Version of Protocol Synopsis:	29 Jul 2020 Version 1.2
Sponsor: Astellas Pharma Global Development Inc. (APGD)	**Protocol Number:** 8062-CL-2003
Compound Name: ASP8062	**Phase of Development:** Phase 1b
Title of Study: A Phase 1b Randomized, Placebo-controlled Study to Assess the Effect of a Single Dose of ASP8062 on the Multiple Dose Safety, Tolerability and Pharmacokinetics of Buprenorphine/Naloxone in Subjects with Opioid Use Disorder	
Planned Study Period: 1Q2020 to 3Q2020	

Study Objective(s) and Endpoint(s):

The primary, secondary and exploratory objectives and endpoints for this study are listed in the table below.

Study Objectives and Endpoints

Objective(s)	**Endpoint(s)**
Primary	
• To assess the safety and tolerability of multiple doses of buprenorphine/naloxone alone and buprenorphine/naloxone in combination with a single dose of ASP8062	• Nature, frequency and severity of AEs • Clinical laboratory tests (hematology, biochemistry and urinalysis) • Vital signs (blood pressure, pulse and respiratory rate) • 12-lead ECG • C-SSRS • SpO_2 • End tidal CO_2
Secondary	
• To assess the potential for pharmacokinetic interaction between ASP8062 and buprenorphine/naloxone	• Plasma ASP8062: AUC_{inf}, AUC_{last} and C_{max} • Plasma buprenorphine and its metabolite (norbuprenorphine): AUC_{24} and C_{max} • Plasma naloxone: AUC_{24} and C_{max}
Exploratory	
• [redacted] CCI	• [redacted] CCI
• [redacted] CCI	• [redacted] CCI

Table continued on next page

Objective(s)	Endpoint(s)
Exploratory continued	
• CCI	• CCI • CCI • CCI

AE: adverse event; C-SSRS: Columbia-Suicide Severity Rating Scale; CO_2: carbon dioxide; ECG: electrocardiogram; SpO_2: blood oxygen saturation; VAS: visual analogue scale

Planned Total Number of Study Sites and Location(s):

One study site in the US

Study Population:

Male and female subjects (18 to 60 years of age, inclusive) with moderate or severe opioid use disorder (OUD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria (DSM-5), who are willing to take buprenorphine/naloxone.

Number of Subjects to be Enrolled/Randomized:

Approximately 30 subjects to complete at least 18 subjects (i.e., 12 subjects on ASP8062 and 6 subjects on placebo ASP8062). Approximately 8 female subjects will be enrolled so that at least 25% of the enrolled subjects are female.

Study Design Overview:

This is a randomized, subject- and investigator-blinded, placebo-controlled, single sequence study comprising of male and female subjects with OUD.

Subjects will be screened for up to 28 days prior to first investigational product (IP) administration. Eligible subjects will be admitted to the clinical unit on day -1 and will be residential for a single period of 27 days/26 nights. Subjects will receive multiple sublingual doses of buprenorphine/naloxone on days 1 through 26. Buprenorphine/naloxone dosing will begin once a clinical opiate withdrawal scale ≥ 5 is achieved. Titration may be extended based on subject tolerability; however, subjects must be on a stable dose of 16/4 mg buprenorphine/naloxone by day 5. Subjects will be on a stable, total daily dose of 16/4 mg buprenorphine/naloxone on days 5 through 18. After randomization on day 12, subjects will receive a single oral dose of 60 mg ASP8062 or placebo ASP8062 (2:1 ratio) concomitantly with buprenorphine/naloxone and undergo repeat intensive safety assessment on day 12 with continued safety and pharmacokinetic assessments up to day 23 (264 hours postdose of ASP8062 or placebo ASP8062). The stable dose of buprenorphine/naloxone (16/4 mg) will be down-titrated from days 19 through 26. Subjects are to remain awake, seated or semirecumbent and avoid lying on either the left or right side for at least 4 hours postdose on days 11 and 12.

Subjects will be discharged from the clinical unit after completion of down-titration on the condition that all required assessments have been performed and that there are no medical reasons for a longer stay in the clinical unit; which is the end-of-study visit (ESV). Prior to discharge, subjects will be provided with local buprenorphine and methadone providers for their reference.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

Subject is eligible for participation in the study if all of the following apply:

1. Institutional Review Board/Independent Ethics Committee-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization for US study sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is a male or female subject between 18 to 60 years of age, inclusive at screening.
3. Subject has a body mass index range of 18 to 36 kg/m^2, inclusive and weighs at least 50 kg at screening.
4. Subject has a diagnosis of moderate or severe OUD according to the DSM-5 at screening.
5. Subject tests positive for opioids at screening and/or on day -1 or subject shows signs of opioid withdrawal on day -1.
6. Subject is willing to take buprenorphine/naloxone and is not taking buprenorphine or buprenorphine/naloxone at screening.
7. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
    a. Not a woman of childbearing potential (WOCBP) (see [Appendix 12.3 Contraception Requirements])
    b. WOCBP who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent through at least 30 days after final IP administration.
8. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 30 days after final IP administration.
9. Female subject must not donate ova starting at first dose of IP and throughout the study period and for 30 days after final IP administration.
10. Male subject with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception (see [Appendix 12.3 Contraception Requirements]) throughout the study period and for 90 days after final IP administration.
11. Male subject must not donate sperm during the treatment period and for 90 days after final IP administration.
12. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom and spermicide for the duration of the pregnancy throughout the study period and for 90 days after final IP administration.
13. Subject agrees not to participate in another interventional study while participating in the present study.
14. Participant must be willing to abstain from smoking (including use of tobacco-containing products and nicotine or nicotine-containing products [e.g., electronic vapes] from at least 1 hour predose through at least 8 hours postdose on days 11 and 12.

Exclusion Criteria:

Subject will be excluded from participation in the study if any of the following apply:

1. Subject has received any investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to screening.
2. Subject has any condition which, in an investigator's opinion, makes the subject unsuitable for study participation.
3. Female subject who has been pregnant within 6 months prior to screening or breastfeeding within 3 months prior to screening.
4. Subject has a known or suspected hypersensitivity to ASP8062, buprenorphine, naloxone or any components of the formulations used.

5. Subject has had previous exposure with ASP8062.
6. Subject has any of the liver function tests (alkaline phosphatase, alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase and total bilirubin [TBL]) > 2 × upper limit of normal (ULN) on day -1. In such a case, the assessment may be repeated once.
7. Subject has any clinically significant history of allergic conditions (including drug allergies, asthma or anaphylactic reactions, but excluding untreated, asymptomatic, seasonal allergies) prior to first IP administration, as judged by an investigator.
8. Subject has any history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal and/or other major disease or malignancy, as judged by the investigator, with exception of history of cholecystectomy.
9. Subject has current or recent diagnosis (within the last 12 months) of moderate or severe alcohol, sedative, hypnotic, anxiolytic, cocaine or any other substance use disorder (except for opioids, caffeine, tobacco or nicotine) according to the DSM-5 at screening.
10. Subject has a history or presence of any clinically significant psychiatric disorders such as, bipolar 1, schizophrenia, schizoaffective disorder or major depressive disorders, as judged by an investigator.
11. Subject tests positive for alcohol, benzodiazepine or methadone on day -1. Subject tests positive for buprenorphine on day -1.
12. Subject has had recent suicidal ideation within the last 12 months or subject who is at significant risk to commit suicide, as judged by the investigator, using the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or since the last visit on day -1.
13. Subject has/had febrile illness or symptomatic, viral, bacterial (including upper respiratory infection) or fungal (noncutaneous) infection within 1 week prior to day -1.
14. Subject has any clinically significant abnormality following the investigator's review of the physical examination, electrocardiogram (ECG) and protocol-defined clinical laboratory tests at screening or on day -1.
15. Subject has a mean pulse < 45 or > 110 beats per minute (unless out of range [> 110 beats per minute] pulse is deemed to be secondary to opioid withdrawal, as judged by the investigator); mean systolic blood pressure > 150 mmHg; mean diastolic blood pressure > 95 mmHg (unless out of range blood pressure is deemed to be secondary to opioid withdrawal, as judged by the investigator) (measurements taken in duplicate after subject has been resting in the supine position for at least 5 minutes; pulse will be measured automatically) on day -1. If the mean blood pressure exceeds the limits above, 1 additional duplicate may be taken.
16. Subject has a mean corrected QT interval using Fridericia's formula (QTcF) of > 450 msec (for male subjects) and > 470 msec (for female subjects) on day -1. If the mean QTcF exceeds the limits above, 1 additional duplicate ECG may be taken.
17. Subject has used any prescribed drugs, vitamins and natural or herbal remedies (including, St. John's Wort) in the 2 weeks prior to first IP administration, except for rescue medications, milk of magnesia, acetaminophen, topical dermatological products, including corticosteroid products, hormonal contraceptives and hormone replacement therapy (HRT).
18. Subject has used any inducer of CYP2C8, 2C9 or 3A4-related metabolism (e.g., barbiturates, rifampin, aprepitant, ritonavir, apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, phenobarbital, primidone, armodafinil, modafinil, and rufinamide) in the 3 months prior to day -1.
19. Subject has had significant blood loss or donated approximately 500 mL of whole blood (excluding plasma donation) within 56 days prior to screening or donated plasma within 7 days prior to day -1.

20. Subject has a positive serology test for antibodies to human immunodeficiency virus type 1 and/or type 2, acute hepatitis B virus infection or acute hepatitis C virus infection, excluding asymptomatic hepatitis C virus infection at screening.
21. Subject has loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.
22. Criterion removed.
23. Subject is an employee of Astellas, the study-related contract research organizations or the clinical unit.

Investigational Product(s):

Name/Use:

ASP8062 (test product)

Placebo ASP8062 (placebo)

Suboxone® (buprenorphine/naloxone) (test product)

Dose(s):

ASP8062: single dose of 60 mg ASP8062 (2 × 30 mg tablets)

Placebo ASP8062: single dose of placebo ASP8062 (2 × tablets)

There will be no modification for the single planned ASP8062 dose of 60 mg.

Buprenorphine/naloxone: multiple doses of buprenorphine/naloxone (sublingual film)
On day 1, subjects will receive a 4/1 mg buprenorphine/naloxone dose in the morning and a 4/1 mg buprenorphine/naloxone dose in the afternoon. On day 2, subjects will receive an 8/2 mg buprenorphine/naloxone dose in the morning and a 4/1 mg buprenorphine/naloxone dose in the afternoon. On day 3, subjects will receive a 12/3 mg buprenorphine/naloxone dose in the morning. On day 4, subjects will receive a 16/4 mg buprenorphine/naloxone dose in the morning. Titration may be extended based on subject tolerability; however, subjects must be on a stable dose of 16/4 mg buprenorphine/naloxone by day 5. Subjects not on a stable dose of 16/4 mg buprenorphine/naloxone by day 5 will be discontinued from the study. Subjects will be on a stable, total daily dose of 16/4 mg buprenorphine/naloxone on days 5 through 18. The stable dose of buprenorphine/naloxone (16/4 mg) will be down-titrated from days 19 through 26, according to the table below.

Schedule of Down-titration of Buprenorphine/Naloxone Dose

Day(s)	Subjects with Stabilized Buprenorphine/Naloxone Dose of 16/4 mg
18	16/4 mg
19	8/2 mg
20	8/2 mg
21	8/2 mg
22	4/1 mg
23	4/1 mg
24	4/1 mg
25	2/0.5 mg
26	2/0.5 mg
27	(Discharge/ESV)

ESV: end-of-study visit

Mode(s) of Administration:

On all dosing days (excluding days 11 and 12), buprenorphine/naloxone will be administered sublingually under standardized fed conditions (i.e., meals will be served up to 1 hour predose or at least 2 hours postdose). Water will be allowed ad libitum. On days 11 and 12, buprenorphine/naloxone will be administered sublingually under fasting conditions (i.e., no food or

beverage will be allowed from at least 10 hours predose through at least 4 hours postdose). Water intake will be prohibited from at least 1 hour predose through at least 2 hours postdose.

On day 12, ASP8062 or placebo ASP8062 will be administered orally under fasting conditions (i.e., no food or beverage will be allowed from at least 10 hours predose through at least 4 hours postdose) with approximately 240 mL water. Water intake will be prohibited from at least 1 hour predose through at least 2 hours postdose except for the approximately 240 mL water to swallow the IP.

Concomitant Treatment (Medication and Nonmedication Therapy) Restrictions or Requirements:

All medicinal products other than the IPs, including prescribed or nonprescribed drugs (including vitamins and natural and herbal remedies, e.g., St. John's Wort), used from first IP administration until the ESV will be considered concomitant medication.

Subjects will only be allowed to use the following concomitant medication(s), if needed, from first IP administration until the ESV:

- Rescue medications:
  - Hydroxyzine pamoate: 50 mg (1 or 2 × tablets) every 6 hours, as needed
  - Mylanta/Maalox: 10 to 20 mL, per product instruction, as needed
  - Loperamide: 2 mg, per product instruction, as needed
  - Methocarbamol: 750 mg (1 or 2 × tablets) every 6 hours, as needed
  - Ibuprofen: 200 mg (2 × tablets) every 6 hours, as needed
  - Promethazine: 25 mg oral or intramuscular, every 6 hours, as needed
  - Clonidine: 0.1 mg, every 12 hours, as needed
- Milk of magnesia (except for days 11 and 12)
- Acetaminophen (up to 2 g/day)
- Topical dermatological products, including corticosteroid products
- Hormonal contraceptives
- HRT

If a subject's health condition necessitates the use of any medication other than the permitted medications during the study, the investigator and medical monitor, or designee(s), will discuss the case and determine if the subject should be withdrawn from the study and/or excluded from analysis sets, depending on if, and how, the medication(s) used influence(s) the study outcome. The nonpermitted concomitant medication will be recorded as a protocol deviation.

All concomitant treatments (medication and nonmedication therapy) will be documented.

Duration of Treatment:

Single dose of 60 mg ASP8062 or placebo ASP8062 on day 12 with concomitant administration of buprenorphine/naloxone (16/4 mg).

Multiple doses of buprenorphine/naloxone for up to 26 days.

Formal Stopping Rules:

Discontinuation of Individual Subject(s) From Study Treatment:

A subject must discontinue study treatment for any of the following reasons:

- Subject requests to stop treatment
- Any clinical adverse events (AEs), laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject
- Participation in another interventional study while participating in the present study
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Female subject becomes pregnant

Discontinuation of the Study:

The sponsor will terminate this study if 1 of the following criteria are met. The sponsor will unblind the affected subject(s) to an investigator/delegate, before a final decision is made.

1. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12, ≥ 5 ASP8062-treated subjects experience ASP8062-related AEs of severe intensity that are considered by an investigator to be of clinical concern
2. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12, ≥ 3 ASP8062-treated subjects experience an ASP8062-related serious adverse event and there is no plausible alternate explanation for these events
3. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12, ≥ 5 ASP8062-treated subjects show at least 1 of the following findings in 2 consecutive measurements within 24 hours postdose:
   - ALT or AST ≥ 3 × ULN and ALT or AST is ≥ 3 × day 11 (day prior to concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062) values
   - ALT or AST ≥ 2 × ULN and ALT or AST ≥ 5 × day 11 (day prior to concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062) values
   - TBL ≥ 2 × ULN and subject does not have Gilbert Syndrome
4. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12, ≥ 3 ASP8062-treated subjects have QTcF interval ≥ 500 msec in 2 consecutive measurements within 24 hours postdose
5. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12:
   - ≥ 4 ASP8062-treated subjects experience ASP8062-related symptomatic decrease in blood oxygen saturation (SpO_2) requiring more than 2 liters of supplemental oxygen via nasal cannula or,
   - ≥ 1 ASP8062-treated subjects experience ASP8062-related symptomatic decrease in SpO_2 requiring intubation, for medically significant respiratory depression

Statistical Methods:

Sample Size Justification:

Approximately 30 subjects will be enrolled to complete at least 18 subjects (i.e., 12 subjects on ASP8062 and 6 subjects on placebo ASP8062). Approximagely 8 female subjects will be enrolled so that at least 25% of the enrolled subjects are female. Subjects who discontinue early from the study may be replaced at the discretion of the sponsor. No formal sample size calculation is performed as this is not a statistically powered study. The number of subjects is based on the precedent set by other studies in similar nature. The number of subjects planned is considered sufficient to achieve the study objectives.

Based on the literature, the intrasubject coefficient of variation for pharmacokinetic parameters AUC_{inf} and C_{max} of buprenorphine and naloxone are estimated to be 26%. Assuming the underlying variability is similar to 26% and the true underlying ratio is 100%, the 90% CI will lie within (77.0, 129.0) with > 80% probability.

Efficacy:

CCI

Safety:

To characterize the safety profile, descriptive statistics will be provided for AEs, clinical laboratory tests (hematology and biochemistry), vital signs (blood pressure, pulse and respiratory rate), 12-lead ECGs and SpO_2.

Pharmacokinetics:

Descriptive statistics will be presented for plasma concentrations buprenorphine and its metabolite (norbuprenorphine) and naloxone by treatment group (B/N + ASP and buprenorphine/naloxone alone [B/N alone]) and scheduled sample time. Plasma concentrations of ASP8062 will be listed and summarized using descriptive statistics by scheduled sample time.

To assess the effect of ASP8062 on the pharmacokinetics of buprenorphine and its metabolite (norbuprenorphine) and naloxone, an analysis of variance (ANOVA) model with treatment (B/N + ASP and B/N alone) as a fixed effect and subject as a random effect will be fitted on natural logarithm-transformed AUC_{24} and C_{max}. Within the ANOVA, the least square (LS) mean differences between buprenorphine/naloxone in combination with ASP8062 and buprenorphine/ naloxone alone, along with 90% CIs for the differences will be estimated. The LS means for AUC_{24} and C_{max} will be back-transformed to produce the geometric LS means and presented with the number of subjects for each treatment. The geometric LS mean ratios and their corresponding 90% CIs for each pharmacokinetic parameter will be presented by back-transforming and expressed as percentages.

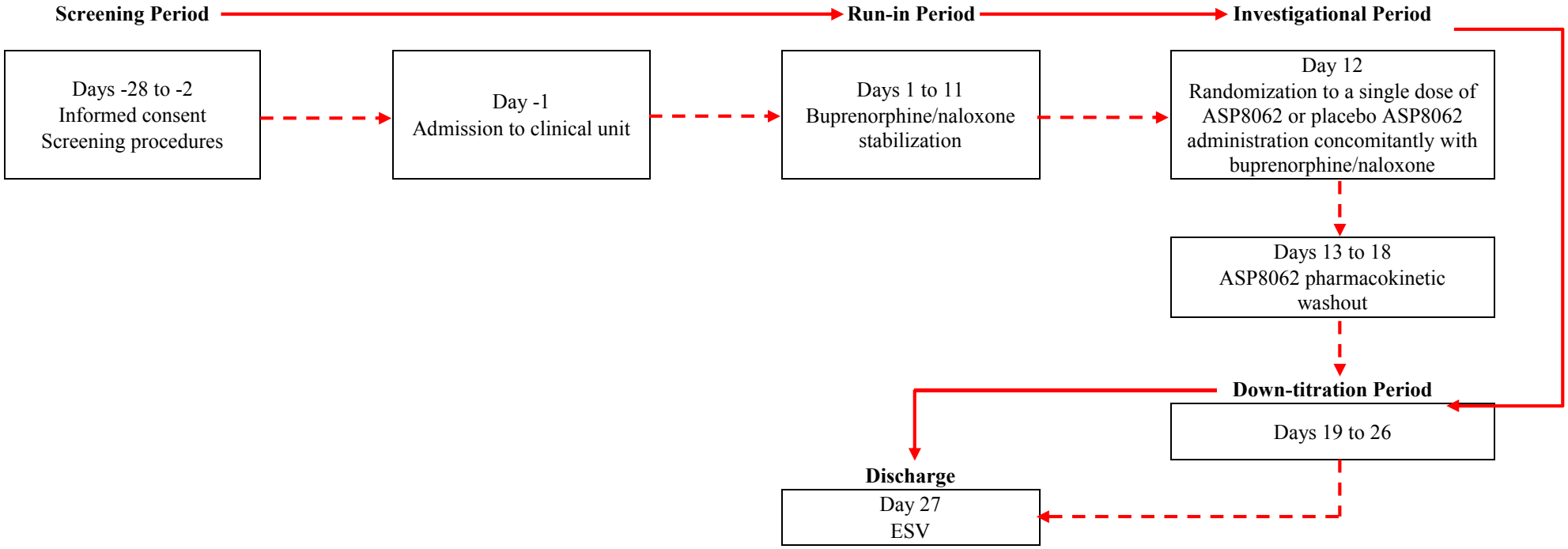
If all subjects did not complete treatment, then the above analyses will be repeated using an ANOVA with fixed effects for treatment and subject; this analysis will only include subjects with complete data in all treatments.

Interim Analyses:

Not applicable.

1.2 Study Schema

Figure 1 Flow Chart



ESV: end-of-study visit

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

Study Phase	**Screening Period[1]**		**Run-in Period**			**Investigational Period**				**Down-titration Period**	**Discharge/ ET[2]**
			Buprenorphine/Naloxone alone			**ASP8062/ Buprenorphine/ Naloxone**	**Buprenorphine/Naloxone alone**			**Buprenorphine/ Naloxone alone**	
Day(s)	**-28 to -2**	**-1**	**1**	**2 to 10**	**11**	**12**	**13**	**14 to 17**	**18**	**19 to 26[3]**	**27 ESV[2]**
Residential Period		X	X	X	X	X	X	X	X	X	
Informed Consent	X										
Inclusion and Exclusion Criteria	X	X									
Randomization						X					
Demographics	X										
Medical History	X	X									
Drug Use History/TLFB[4]	X	X									
Body Weight and Height[5]	X	X									X
Clinical Laboratory Tests[6]	X	X	X		X	X	X	X	X	X	
Drugs of Abuse/Alcohol Tests	X	X									
Pregnancy Test (Female Subjects Only)[7]	X	X								X	
FSH Test (Postmenopausal Female Subjects Only)	X										
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X
Continuous Pulse Oximetry[9]					X	X					
12-lead ECG[10]	X	X			X	X					X
Physical Examination	X	X									X
C-SSRS[11]	X	X									X
Spot SpO_2[12]		X			X	X					X
Continuous and Spot End Tidal CO_2[13]					X	X					
COWS		X	X								
Opioid Craving VAS Training[14]		X									

Table continued on next page

Study Phase	**Screening Period[1]**		**Run-in Period**			**Investigational Period**				**Down-titration Period**	**Discharge/ ET[2]**
			Buprenorphine/Naloxone alone			**ASP8062/ Buprenorphine/ Naloxone**	**Buprenorphine/Naloxone alone**			**Buprenorphine/ Naloxone alone**	
Day(s)	**-28 to -2**	**-1**	**1**	**2 to 10**	**11**	**12**	**13**	**14 to 17**	**18**	**19 to 26[3]**	**27 ESV[2]**
Opioid Craving VAS[15]		X			X	X					
ASP8062 or Placebo ASP8062 Administration[16]						X					
Buprenorphine/naloxone Administration[17]			X	X	X	X	X	X	X	X	
Buprenorphine/naloxone down-titration period										X	
Blood Sampling for ASP8062 Pharmacokinetics[18]						X	X	X	X	X	
Blood Sampling for Buprenorphine/naloxone and Metabolite (Norbuprenorphine) Pharmacokinetics[19]					X	X	X			X	
Blood Sample for Biomarker[20]		X	(X)								
Blood Sample for PGx Analysis[20]		X	(X)								
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X
Previous/Concomitant Treatment (Medication and Nonmedication Therapy)	X	X	X	X	X	X	X	X	X	X	X

COWS: clinical opiate withdrawal scale; C-SSRS: Columbia-Suicide Severity Rating Scale; CO_2: carbon dioxide; ECG: electrocardiogram; ESV: end-of-study visit; ET: early termination; FSH: follicle-stimulating hormone; PGx: pharmacogenomics; SpO_2: blood oxygen saturation; TLFB: timeline follow-back; VAS: visual analogue scale

1. Screening period is days -28 to -1. Eligibility will be confirmed at screening and on day -1. Subjects who do not meet eligibility criteria on day -1 are considered screen failures.
2. Subjects will be discharged from the clinical unit after completion of down-titration on the condition that all required assessments have been performed and that there are no medical reasons for a longer stay in the clinical unit; which is the ESV. Upon early termination or if a subject discontinues early from the study, discharge/ESV procedures will be performed upon early termination/discontinuation.
3. The stable dose of buprenorphine/naloxone (16/4 mg) will be down-titrated from days 19 through 26.
4. TLFB will be collected for 2 weeks prior to screening or on day -1 (prior to any assessments).

Footnotes continued on next page

5. Height to be collected at screening only.
6. Clinical laboratory tests include blood collection for serology tests (at screening only), hematology and biochemistry and urine collection for urinalysis. Blood samples will be collected at screening, on day -1 and predose on day 1. Blood samples will be collected predose on day 11, at the following postdose time point on day 11: 2 hours, predose on day 12 and at the following postdose time point on day 12: 2 hours. Blood samples will also be collected once daily on days 13 through 18 and day 26. Urine samples will be collected at screening, on day -1 and predose on day 1. Urine samples will be collected predose on day 11, at the following postdose time point on day 11: 2 hours, predose on day 12 and at the following postdose time point on day 12: 2 hours.
7. Blood pregnancy test at screening and urine pregnancy test on days -1 and 26.
8. Vital signs include measurements of blood pressure, pulse, respiratory rate and oral temperature. Measurements will be taken after the subject has been resting in the supine position for at least 5 minutes. Measurements will be taken in duplicate at screening and on day -1 and at all other time points as single measurements. Oral temperature will be taken as a single measurement at all time points. Measurements will be taken at screening, on day -1 and predose on days 1, 4 and 8. Measurements will be taken predose on day 11, at the following postdose time points on day 11: 1, 2, 4, 8 and 12 hour(s), predose on day 12 and at the following postdose time points on day 12: 1, 2, 4, 8 and 12 hour(s). Measurements will also be taken once daily on days 13 through 18. During the down-titration period, vital signs will be taken once daily at approximately the same time each day through the ESV.
9. Continuous pulse oximetry will begin predose on days 11 and 12 until at least 8 hours postdose.
10. 12-lead ECGs will be taken after the subject has been resting in the supine position for at least 5 minutes. 12-lead ECGs will be taken in duplicate. 12-lead ECGs will be taken at screening, on day -1, predose on day 11 and at the following postdose time points on day 11: 2, 4 and 12 hours, predose on day 12 and at the following postdose time points on day 12: 2, 4 and 12 hours and at the ESV.
11. The version of the C-SSRS to be used at screening is the “Baseline/Screening” version and the version to be used on day -1 and at the ESV is the “Since Last Visit”.
12. Spot SpO_2 measurements will be taken on day -1, predose on day 11, at the following postdose time points on day 11: 1, 2, 4, 8 and 12 hour(s), predose on day 12, at the following postdose time points on day 12: 1, 2, 4, 8 and 12 hour(s) and at the ESV.
13. Continuous end tidal CO_2 to be collected starting predose on days 11 and 12 until 8 hours postdose. Timepoints will be recorded predose and 1, 2, 4 and 8 hours postdose. The cannula may be removed while subjects dose or eat.
14. Opioid craving VAS training will occur on day -1. Additional trainings may occur, as needed.
15. The opioid craving VAS will be performed on day -1. The opioid craving VAS will be performed predose on days 11, at the following postdose time point on day 11: 2 hours, predose on day 12 and at the following postdose time point on day 12: 2 hours.
16. On day 12, ASP8062 or placebo ASP8062 will be administered orally under fasting conditions (i.e., no food or beverage will be allowed from at least 10 hours predose through at least 4 hours postdose) with approximately 240 mL water. Water intake will be prohibited from at least 1 hour predose through at least 2 hours postdose except for the approximately 240 mL water to swallow the investigational product. ASP8062 or placebo ASP8062 will be administered with the approximately 240 mL of water and the buprenorphine/naloxone will be administered immediately after the subject has consumed the ASP8062 or placebo with the approximately 240 mL of water.
17. On all dosing days (excluding days 11 and 12), buprenorphine/naloxone will be administered sublingually under standardized fed conditions (i.e., meals will be served up to 1 hour predose or at least 2 hours postdose). Water will be allowed ad libitum. On days 11 and12, buprenorphine/naloxone will be administered sublingually under fasting conditions (i.e., no food or beverage will be allowed from at least 10 hours predose through at least 4 hours postdose). On days 11 and 12, water intake will be prohibited from at least 1 hour predose through at least 2 hours postdose, except for the approximately 240 mL water provided to administer the IP. On day 11, the subject will consume approximately 240 mL of water and then place the buprenorphine/naloxone sublingually to match the dosing condition on day 12. On day 12, buprenorphine/naloxone will be administered concomitantly with ASP8062 or placebo ASP8062.

Footnotes continued on next page

18. Blood samples for ASP8062 pharmacokinetics will be collected predose on day 12 and at the following postdose time points on day 12: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120, 144, 168, 216 and 264 hour(s).
19. Blood samples for buprenorphine and its metabolite (norbuprenorphine) and naloxone pharmacokinetics will be collected predose on day 11 and at the following postdose time points on day 11: 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12 and 16 hour(s). Blood samples for buprenorphine and its metabolite (norbuprenorphine) and naloxone pharmacokinetics will be collected predose on day 12 and at the following postdose time points on day 12: 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 16, 24, 168, 216 and 264 hour(s).
20. The blood sample for biomarker and PGx analysis (biobanking) can be collected on day -1 or predose on day 1.

1.3.1 Sample Collection Schedule

Table 2 Sample Collection Schedule

Day	Time Point	Pharmacokinetics ASP8062	Pharmacokinetics and Metabolite Profiling Buprenorphine/ naloxone	Clinical Laboratory Tests		Vital Signs	Continuous Pulse Oximetry	12-lead ECG	Physical Examination	C-SSRS	SpO_2	End Tidal CO_2	COWS	Opioid Craving VAS
				Blood	Urine									
Day -28 to -2	Screening			X	X	X		X	X	X				
-1				X	X	X		X	X	X	X		X	X
1	Predose			X	X	X							X	
2														
3														
4	Predose					X								
5														
6														
7														
8	Predose					X								
9														
10														
11	Predose		X	X	X	X	X	X			X	X		X
	0.25 hours		X											
	0.50 hours		X											
	1 hour		X			X					X	X		
	1.5 hours		X											
	2 hours		X	X	X	X		X			X	X		X
	3 hours		X											
	4 hours		X			X		X			X	X		
	8 hours		X			X					X	X		
	12 hours		X			X		X			X			
	16 hours		X											

Table continued on next page

Day	Time Point	Pharmacokinetics ASP8062	Pharmacokinetics and Metabolite Profiling Buprenorphine/ naloxone	Clinical Laboratory Tests		Vital Signs	Continuous Pulse Oximetry	12-lead ECG	Physical Examination	C-SSRS	SpO_2	End Tidal CO_2	COWS	Opioid Craving VAS
				Blood	Urine									
12	Predose	X	X	X	X	X	X	X			X	X		X
	0.25 hours	X	X											
	0.50 hours	X	X											
	1 hour	X	X			X					X	X		
	1.50 hours	X	X											
	2 hours	X	X	X	X	X		X			X	X		X
	2.50 hours	X												
	3 hours	X	X											
	4 hours	X	X			X		X			X	X		
	6 hours	X												
	8 hours	X	X			X					X	X		
	12 hours	X	X			X		X			X			
	16 hours	X	X											
13	24 hours postdose day 12	X	X	X		X								
	36 hours postdose day 12	X												
14	48 hours postdose day 12	X		X		X								
	60 hours postdose day 12	X												
15	72 hours postdose day 12	X		X		X								

Table continued on next page

Day	Time Point	Pharmacokinetics ASP8062	Pharmacokinetics and Metabolite Profiling Buprenorphine/ naloxone	Clinical Laboratory Tests		Vital Signs	Continuous Pulse Oximetry	12-lead ECG	Physical Examination	C-SSRS	SpO_2	End Tidal CO_2	COWS	Opioid Craving VAS
				Blood	Urine									
16	96 hours postdose day 12	X		X		X								
17	120 hours postdose day 12	X		X		X								
18	144 hours postdose day 12	X		X		X								
19	168 hours postdose day 12	X	X			X								
20	192 hours postdose day 12					X								
21	216 hours postdose day 12	X	X			X								
22	240 hours postdose day 12					X								
23	264 hours postdose day 12	X	X			X								
24						X								
25						X								
26				X	X	X								

Table continued on next page

Day	**Time Point**	**Pharmacokinetics** ASP8062	**Pharmacokinetics and Metabolite Profiling** Buprenorphine/ naloxone	**Clinical Laboratory Tests**		**Vital Signs**	**Continuous Pulse Oximetry**	**12-lead ECG**	**Physical Examination**	**C-SSRS**	**SpO_2**	**End Tidal CO_2**	**COWS**	**Opioid Craving VAS**
				Blood	**Urine**									
27 (ESV)	After completion of down-titration period					X		X	X	X	X			

COWS: clinical opiate withdrawal scale; C-SSRS: Columbia-Suicide Severity Rating Scale; CO_2: carbon dioxide; ECG: electrocardiogram; ESV: end-of-study visit; SpO_2: blood oxygen saturation; VAS: visual analogue scale

2 INTRODUCTION

2.1 Background

ASP8062 is a novel compound with positive allosteric modulator (PAM) activity on the γ-aminobutyric acid type B ($GABA_B$) receptor that is intended for oral administration and is currently being developed for the treatment of opioid use disorder (OUD) and alcohol use disorder (AUD). ASP8062 is a crystal, which is practically insoluble in water and slightly soluble in ethanol (EtOH).

2.1.1 Substance-use Disorders

An estimated 2.1 million Americans had an OUD in 2017 [Substance Abuse and Mental Health Services Administration, 2018]. Overdose deaths due to opioid use have skyrocketed to over 47600 in 2017 [Scholl et al, 2018]. National Institute on Drug Abuse (NIDA) data show that use of opioids can lead to neonatal abstinence syndrome [NIDA, 2019a] as well as the spread of infectious diseases like human immunodeficiency virus (HIV) and hepatitis [NIDA, 2019b]. Medication assisted treatment with buprenorphine (with or without naloxone), methadone or naltrexone is the current standard of care, and has resulted in decreases in opioid use, overdose deaths, criminal activity and infectious disease transmission [Mattick et al, 2014; Schwartz et al, 2013; Mattick et al, 2009]. However, buprenorphine can induce withdrawal on first administration, has an overdose potential, induces withdrawal symptoms and a loss of tolerance on cessation, is also subject to abuse and diversion and can cause respiratory suppression. Buprenorphine's ceiling effect may limit its effectiveness in patients with ongoing opioid use [Bart, 2012].

The Diagnostic and Statistical Manual of Mental Disorders, edition 5 (DSM-5) defines substance use disorders as a constellation of recurrent pathological cognitive, behavioral and physiological symptoms arising from the ongoing use of a substance. The DSM-5 has combined the DSM-4 categories of substance abuse and substance dependence under the single heading of substance use disorders, which is classified by severity based on the number of symptom criteria (out of a total of 11) that are met: mild (2 to 3 criteria), moderate (4 to 5 criteria) and severe (more than 6 criteria) [Hasin et al, 2013]. Different drugs produce different effects on the user, but important shared features include a dysregulation of brain reward pathways and an overactive brain stress system, which together reinforce use of the substance to achieve a pleasurable high, even if pursuing this high incurs great cost or negative consequences for the user.

2.1.2 Background on Pharmacological Concept

Gamma-aminobutyric acid (GABA), the most abundant inhibitory neurotransmitter, activates 2 types of receptors: ionotropic GABA type A receptors [Olsen & Sieghart, 2008] and metabotropic $GABA_B$ receptors [Bowery et al, 2002]. Studies with GABAergic drugs and drugs of abuse have indicated that the $GABA_B$ receptor mediates suppression of craving/self-administration across several drug modalities. Drugs triggering abuse act by enhancing dopamine release in the ventral tegmental, striatal, and prefrontal cortical areas of the brain. The effects of GABAergic compounds on decreasing drug self-administration and

drug seeking behavior act by either directly or indirectly decreasing dopamine release in the aforementioned brain areas [Filip et al, 2015].

$GABA_B$ agonists or PAMs have been found to attenuate opioid-, alcohol-, cocaine- and nicotine-seeking behavior [Augier et al, 2017; Vlachou et al, 2011; Franklin et al, 2009; Filip & Frankowska, 2007; Paterson et al, 2004; Di Ciano & Everitt, 2003b; Di Ciano & Everitt, 2003a] and also attenuate the drugs of abuse-evoked changes during intracranial self-stimulation [Vlachou et al, 2011; Paterson et al, 2008; Slattery et al, 2005]. However, activation of $GABA_B$ receptors by orthosteric agonists such as baclofen induces side effects such as sedation, somnolence, excessive weakness, vertigo and cognitive impairment. The sedative properties of baclofen limits its potential widespread therapeutic utility [Dario & Tomei, 2004]. Accordingly, activation of $GABA_B$ receptors by PAMs is one of the prioritized medication treatment approaches for NIDA in response to the opioid crisis [Rasmussen et al, 2019].

2.1.3 Nonclinical and Clinical Data

ASP8062 is an orally available, new molecular entity discovered by Astellas Pharma Inc. ASP8062 is a $GABA_B$ receptor PAM with activity in the central nervous system (CNS).

ASP8062 (1, 3 and 10 mg/kg orally) decreased self-administration of EtOH in male and female rats (Study 8062-PH-9054). Intragastric administration of ASP8062 (0.3, 1 and 3 mg/kg) to rhesus monkeys decreased self-administrations with morphine (Study 8062-PH-9052). In a rat conditioned place preference (CPP) study, ASP8062 (1, 3 and 10 mg/kg orally) decreased cocaine-induced elevation of CPP score in a dose-related manner (Study 8062-PH-9051). Intragastric administration of ASP8062 (0.1, 0.3 and 1 mg/kg) to rhesus monkeys significantly decreased the mean number of self-administrations with cocaine in 1 of the 3 animals (Study 8062-PH-9053). Overall, the findings in rats and rhesus monkeys indicate ASP8062 has potential suppressing effects on substance use disorders such as alcohol, morphine and cocaine in humans.

ASP8062 did not affect the retention time in the rotarod test in rats up to 30 mg/kg (Study 8062-PH-9035). ASP8062 at doses of 10, 30 and 100 mg/kg orally had no synergistic effect on motor coordination when combined with EtOH at doses of 0.5, 1 and 2 g/kg orally, but may have antagonistic effects in a mouse accelerating rotarod performance test (Study 8062-PH-9038). γ-hydroxybutyrate (GHB) at doses of 0.1, 0.2 and 0.4 g/kg orally had an additive effect with EtOH. These results suggest that ASP8062 has no stronger additive interaction with EtOH compared to GHB (Study 8062-PH-9039).

The 4-week toxicity studies in rats and dogs and 13-week toxicity study in rats showed mainly monitorable, mild and reversible changes driven by exaggerated pharmacology. ASP8062 showed no effects on motor coordination using an accelerating rotarod test in rats at doses up to 30 mg/kg orally. ASP8062 at doses of 10, 30 and 100 mg/kg orally had no synergistic effect on motor coordination when combined with EtOH at doses of 0.5, 1 and 2 g/kg orally in a mouse accelerating rotarod performance test. ASP8062 at 3 and 10 mg/kg did not potentiate respiratory suppression induced by morphine in cynomolgus monkeys.

Potential ASP8062-related toxicities, based on nonclinical studies, are described in [Section 2.3 Risk Benefit Assessment].

Six clinical studies (5 phase 1 studies and 1 phase 2a study) of ASP8062 have been completed prior to initiation of this study. The phase 1 studies include the single ascending dose study (8062-CL-0001, including food effect), the multiple ascending dose study (8062-CL-0002, including cerebrospinal fluid distribution), the single dose polysomnography study (8062-CL-0003), the sequential single and multiple dose study in Japanese subjects (8062-CL-0004) and the single dose crossover study comparing ASP8062 new tablet (tablet B formulation) and reference tablet (tablet A formulation, which was used previously in 5 phase 1 studies and 1 phase 2a study) (8062-CL-0005, including food effect). In addition, 20 healthy subjects were exposed to single oral doses of ASP8062 (60 mg) together with a single dose of alcohol (EtOH dose: 0.6 g/kg for females and 0.7 g/kg for males) in Study 8062-CL-2001 (report in progress). All these studies were in healthy male and/or female subjects. The phase 2a study includes an efficacy and safety study (8062-CL-0101). This study was in male and female fibromyalgia (FM) patients. The reference tablet (used in phase 1 and phase 2a FM studies) is referred to as "tablet A formulation" and the new tablet (used in OUD/AUD studies) is referred to as "tablet B formulation". Clinical data has been summarized in [Section 2.1.3.1 Clinical Pharmacokinetics/Pharmacodynamics] and [Section 2.1.3.2 Clinical Safety].

Detailed information from nonclinical and clinical studies can be found in the [Investigator's Brochure].

2.1.3.1 Clinical Pharmacokinetics/Pharmacodynamics

In general, pharmacokinetic properties of ASP8062 1 to 30 mg administered once daily for 14 days were similar to ASP8062 0.3 to 70 mg administered as single doses. Median t_{max} values after multiple doses on day 14 (2 to 3 hours) were in the same range as single doses (1 to 4 hours). Accumulation following multiple doses was predictable and was approximately 2 to 3-fold for AUC. Steady-state conditions were observed for all dose levels by day 14. There was no dose dependency, nor was there evidence for either auto-induction or auto-inhibition. AUC for the tablet B formulation (tablets to be used in the current study) was approximately 8% to 13% higher than the tablet A formulation and C_{max} was approximately 60% higher.

Suboxone® sublingual film contains buprenorphine, a partial-opioid agonist, and naloxone, an opioid antagonist. Buprenorphine is metabolized and eliminated in urine and feces. Norbuprenorphine is the major metabolite which has been found to bind opioid receptors in vitro. Naloxone undergoes metabolism as well. Naloxone has no clinically significant effect when administered by the sublingual route, although blood levels of drug were measurable. When Suboxone® sublingual film is administered sublingually or buccally, buprenorphine has a mean elimination half-life ranging from 24 to 42 hours and naloxone has a mean elimination half-life ranging from 2 to 12 hours [Suboxone Package Insert].

There was a significant and likely dose-related increase in slow-wave sleep (SWS) over the whole night for single doses of 35 mg and 70 mg ASP8062 compared to placebo. This increase in SWS was mainly observed during the first third of the night where SWS was most prevalent. However, there was no consistent or dose-related effect of ASP8062 compared to placebo on rapid eye movement sleep. With regards to pharmacodynamics, growth hormone release was generally greater in the ASP8062 treatment groups and appeared to be dose-related.

An in vitro cytochrome P450 (CYP) study suggested ASP8062 is mainly metabolized by CYP3A4. Neither naloxone nor buprenorphine are listed as an inhibitor or inducer of CYP3A4 in the regulatory guidance. Buprenorphine is metabolized by multiple CYPs (CYP3A4; major, CYP2C8 and 2C9; minor) and multiple UDP-glucuronosyltransferases (UGTs) [Rouguieg et al, 2010; Picard et al, 2005]. Naloxone is metabolized by multiple UGTs [Di Marco et al, 2005; Cheng et al, 1999]. An in vitro CYP study suggested ASP8062 is mainly metabolized by CYP3A4 (IND 125639 study 8062-ME-9001). The half-maximal inhibitory concentration values of ASP8062 were 9.25 μmol/L for CYP2C9 and > 10 μmol/L for all other CYP isoforms tested (IND 125639 study 8062-ME-0003). In addition, ASP8062 did not show more than dose proportional pharmacokinetics or time variant pharmacokinetics in humans. These data suggest that there is no significant inhibitory effect of ASP8062 for CYPs under the proposed clinical dose/exposure. Assessments based on the relevant data of ASP8062, literature and regulatory guidance (the FDA's 2020 Final Guidance for Industry on in vitro Cytochrome P450- and transporter- mediated drug-drug interaction (DDI) studies, the 2018 MHLW Guideline on drug interactions for drug development and appropriate provision of information and the 2012 EMA Guideline on the investigation of drug interactions) indicate no remarkable concerns of a pharmacokinetic DDI between ASP8062 and opioids (e.g., morphine and buprenorphine) and naloxone.

2.1.3.2 Clinical Safety

A total of 117 healthy subjects were exposed to single oral doses of ASP8062 (fasted 0.3, 1, 3, 10, 30, 35 or 70 mg, or fed 10 or 30 mg), including 26 subjects who also received multiple doses (3, 10 or 30 mg) over 14 days (Study 8062-CL-0004). Thirty-six additional healthy subjects were exposed to multiple doses of ASP8062 (1, 3, 10 or 30 mg) over 14 days. Ninety-five FM patients were exposed to multiple doses of 30 mg ASP8062 over 8 weeks. Overall, ASP8062 was well tolerated in healthy subjects at single doses up to 70 mg and multiple doses (once daily) for 14 days up to 30 mg. In addition, 20 healthy subjects were exposed to single oral doses of ASP8062 (60 mg) together with a single dose of alcohol (EtOH dose: 0.6 g/kg for females and 0.7 g/kg for males) in Study 8062-CL-2001 (report in progress). There were no deaths or serious treatment-emergent adverse events (TEAEs) reported in any study. All adverse events (AEs) were transient and mild or moderate in severity. Dizziness and headache, within the SOC nervous system disorders, were the only TEAEs occurring in all 6 phase 1 studies (most of these events were considered by the investigator to be related to study drug). Safety findings were generally similar for the 30 mg ASP8062 tablet A formulation and the 30 mg ASP8062 tablet B formulation. In FM patients administered ASP8062 30 mg once daily for 8 weeks, dizziness was the most commonly

reported TEAE (28 [29.5%] patients), almost 13 times the incidence of patients administered placebo (2 [2.3%] patients). Dizziness resulted in discontinuation of 8 (8.4%) FM patients treated with 30 mg ASP8062. Potential ASP8062-related safety considerations, based on clinical studies, are described in [Section 2.3 Risk Benefit Assessment].

Detailed information from clinical studies can be found in the [Investigator's Brochure].

Clinical safety information of buprenorphine/naloxone can be found in [Section 2.3 Risk Benefit Assessment].

2.1.4 Summary of Key Safety Information for Investigational Product(s)

Based on available safety information with ASP8062, there are currently no expected serious adverse reactions for ASP8062.

Detailed reference safety information (RSI) for ASP8062 can be found in the [Investigator's Brochure].

Detailed safety information of buprenorphine/naloxone can be found in the [Suboxone Package Insert].

2.2 Study Rationale

While the pharmacokinetic DDI potential of ASP8062 with opioids is considered to be low [Section 2.1.3.1 Clinical Pharmacokinetics/Pharmacodynamics], potential interaction such as opioid effects on respiratory depression is theoretically possible because both ASP8062 and opioids are centrally active [Pattinson, 2008]. In addition, for future studies in OUD patients, ASP8062 will be co-administered with opioids, including standard medication-assisted treatments such as buprenorphine/naloxone. This DDI/safety study will provide relevant safety, tolerability and pharmacokinetic data in order to assess potential risk of ASP8062 co-administered with buprenorphine/naloxone for future studies in this patient population.

2.3 Risk Benefit Assessment

ASP8062 has a potential to decrease use of illicit opioid drugs and improve the quality of life in patients with OUD. In the present study however where only a single 60 mg oral dose of ASP8062 will be administered, there is no likelihood of a therapeutic effect. Given the safety profile of ASP8062 when administered to healthy subjects there appears to be relatively minimal risk to subjects taking a single 60 mg oral dose.

The risks of buprenorphine-naloxone from a number of formulations are well known and comfortably administered on an outpatient basis. Once subjects show minimal withdrawal symptoms they will be started on an upward titration of buprenorphine/naloxone sublingual film from an initial dose of 4 mg/1 mg (buprenorphine-naloxone) to a daily dose of 16 mg/4 mg by at least day 5. Risks of buprenorphine-induced TEAEs are minimized by virtue of the fact the final daily dose that subjects are stabilized on is below the maximal dose of 24 mg/6 mg described in [Suboxone Package Insert]. Risks are also minimized because the subjects are confined at a research unit that has given a range of opioids, including buprenorphine/naloxone. Side effects of opioids in general include respiratory depression,

CNS depression, dependence, hepatitis with or without jaundice, allergic reactions, impairment in the ability to drive, orthostatic hypotension, elevation of cerebrospinal fluid pressure and intracholendochal pressure. These AEs are minimized due to the relatively weak partial agonist effects of buprenorphine at μ-opioid receptors and the combination with the non-selective opioid antagonist naloxone (which especially reduces the likelihood of respiratory depression based on the naloxone terminal half-life. The most common AE (> 1%) associated with sublingual administration of buprenorphine-naloxone film was oral hypoesthesia. Other AEs included constipation, glossodynia, oral mucosal erythema, nausea, vomiting, palpitations, hyperhidrosis and blurred vision. Buprenorphine/naloxone will be down-titrated from days 19 through 26 in a manner known to be safe and well-tolerated. The site has appropriately trained staff and required equipment available to treat subjects presenting with both opioid withdrawal and buprenorphine/naloxone associated AEs.

There is no expected benefit to the subjects from the administration of buprenorphine/naloxone other than the potential that subjects may gain insight that this may be a useful treatment for them. All subjects will be provided with referrals for treatment of OUD before planned discharge.

This will be the first study where a single oral dose of ASP8062 is administered in subjects stabilized on a buprenorphine/naloxone sublingual film. Risks are minimized by confining subjects in an experienced research unit testing the effects of approved medications or new chemical entities when combined with buprenorphine formulations or other opioids. Continuous pulse oximetry for at least 8 hours will be employed on day 12 when ASP8062 is given with buprenorphine/naloxone so that the low potential for respiratory depression will be noted immediately, and appropriate medical treatment may be given. Patients will also be monitored by experienced staff for signs of opioid withdrawal. Vital signs will be monitored on a daily basis and electrocardiograms (ECGs) will be monitored on day 12 to detect potential cardiovascular symptoms. AEs will be assessed on a daily basis for early detection of untoward effects with the combination of treatments administered on day 12. Potential hepatic toxicity will be monitored with clinical laboratory testing on a daily basis through day 14 to 17 of the investigational period. Prior to discharge, subjects will be provided with local buprenorphine and methadone providers for their reference.

There is not expected to be a benefit from a single oral dose of ASP8062 provided on top of stabilized treatment with buprenorphine-naloxone.

3 STUDY OBJECTIVE(S) AND ENDPOINT(S)

The primary, secondary and exploratory objectives and endpoints for this study are listed in [Table 3].

Table 3 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
• To assess the safety and tolerability of multiple doses of buprenorphine/naloxone alone and buprenorphine/naloxone in combination with a single dose of ASP8062	• Nature, frequency and severity of AEs • Clinical laboratory tests (hematology, biochemistry and urinalysis) • Vital signs (blood pressure, pulse and respiratory rate) • 12-lead ECG • C-SSRS • SpO_2 • End tidal CO_2
Secondary	
• To assess the potential for pharmacokinetic interaction between ASP8062 and buprenorphine/naloxone	• Plasma ASP8062: AUC_{inf}, AUC_{last} and C_{max} • Plasma buprenorphine and its metabolite (norbuprenorphine): AUC_{24} and C_{max} • Plasma naloxone: AUC_{24} and C_{max}
Exploratory	
• CCI	• CCI
• CCI	• CCI
• CCI	• CCI • CCI • CCI

AE: adverse event; C-SSRS: Columbia-Suicide Severity Rating Scale; CO_2: carbon dioxide; ECG: electrocardiogram; SpO_2: blood oxygen saturation; VAS: visual analogue scale

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Study Design

This is a randomized, subject- and investigator-blinded, placebo-controlled, single sequence study comprising of male and female subjects with OUD. The study is planned to be performed at 1 study site in the US.

Subjects will be screened for up to 28 days prior to first investigational product (IP) administration. Eligible subjects will be admitted to the clinical unit on day -1 and will be residential for a single period of 27 days/26 nights. Subjects will receive multiple sublingual doses of buprenorphine/naloxone on days 1 through 26. Buprenorphine/naloxone dosing will

begin once a clinical opiate withdrawal scale (COWS) ≥ 5 is achieved. Titration may be extended based on subject tolerability; however, subjects must be on a stable dose of 16/4 mg buprenorphine/naloxone by day 5. Subjects will be on a stable, total daily dose of 16/4 mg buprenorphine/naloxone on days 5 through 18. After randomization on day 12, subjects will receive a single oral dose of 60 mg ASP8062 or placebo ASP8062 (2:1 ratio) concomitantly with buprenorphine/naloxone and undergo repeat intensive safety assessment on day 12 with continued safety and pharmacokinetic assessments up to day 23 (264 hours postdose of ASP8062 or placebo ASP8062). The stable dose of buprenorphine/naloxone (16/4 mg) will be down-titrated from days 19 through 26. Subjects are to remain awake, seated or semirecumbent and avoid lying on either the left or right side for at least 4 hours postdose on days 11 and 12.

Subjects will be discharged from the clinical unit after completion of down-titration on the condition that all required assessments have been performed and that there are no medical reasons for a longer stay in the clinical unit; which is the end-of-study visit (ESV). Prior to discharge, subjects will be provided with local buprenorphine and methadone providers for their reference.

4.2 Dose Rationale

The primary objective of this study is to assess the safety and tolerability of multiple doses of buprenorphine/naloxone alone and buprenorphine/naloxone in combination with a single dose of ASP8062. ASP8062 is primarily metabolized by CYP3A4. Buprenorphine and naloxone are not CYP3A4 inhibitors or inducers at clinically relevant dose/exposure and therefore, not expected to affect ASP8062 pharmacokinetic profiles. In the 8062-CL-0005 study, the AUCs of 30 mg ASP8062 with tablet B formulation (provided as a 30 mg tablet) were approximately 10% higher than 30 mg ASP8062 with the tablet A formulation (provided as a 25 mg tablet plus a 5 mg tablet) with the 90% CI within the standard bioequivalence limits (80.00, 125.00); C_{max} was approximately 60% higher. With this finding, multiple doses of 25 mg ASP8062 with tablet B formulation will be proposed for future clinical trials for OUD. For this study, a single dose of 60 mg ASP8062 with tablet B formulation is expected to achieve comparable exposures after multiple doses of 25 mg ASP8062 and exposures in the previous clinical studies. Based on the preliminary pharmacokinetic data in the 8062-CL-2001 study, C_{max} and AUC_{24} after single dose of 60 mg were 218 ng/mL and 1820 ng•hr/mL, which did not exceed mean exposure limit set in previous phase 1 studies (247 ng/mL for C_{max} and 2339 ng•hr.mL for AUC_{24}). The exposures achieved in this study is also expected to be pharmacologically active (as seen in study 8062-CL-0003) and safe and tolerated based on data from previous clinical studies in total of 137 healthy subjects and 95 fibromyalgia patients as reviewed in [Section 2.1.3.1 Clinical Pharmacokinetics/Pharmacodynamics and Section 2.1.3.2 Clinical Safety].

The buprenorphine/naloxone dosage and administration is per the Suboxone® label [Suboxone Package Insert]. For down-titration of buprenorphine/naloxone, [Ling et al, 2009] has reported no difference between 7-day and 28-day taper group in terms of providing urine

samples free of illicit opioids. In the light of safety, 9-day down-titration was selected for this study.

4.3 End of Study Definition

The study start is defined as the date the first subject signs informed consent. End of the study is defined as the last visit or scheduled procedure shown in Schedule of Assessments [Table 1] for the last subject in the study.

5 STUDY POPULATION

The study population will consist of male and female subjects (18 to 60 years of age, inclusive) with moderate or severe OUD according to the DSM-5, who are willing to take buprenorphine/naloxone.

All screening assessments must be completed and reviewed to confirm the potential subject meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

5.1 Inclusion Criteria

Subject is eligible for participation in the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act authorization for US study sites) must be obtained from the subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is a male or female subject between 18 to 60 years of age, inclusive at screening.
3. Subject has a body mass index (BMI) range of 18 to 36 kg/m^2, inclusive and weighs at least 50 kg at screening.
4. Subject has a diagnosis of moderate or severe OUD according to the DSM-5 at screening.
5. Subject tests positive for opioids at screening and/or on day -1 or subject shows signs of opioid withdrawal on day -1.
6. Subject is willing to take buprenorphine/naloxone and is not taking buprenorphine or buprenorphine/naloxone at screening.
7. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
    a. Not a woman of childbearing potential (WOCBP) (see [Appendix 12.3 Contraception Requirements])
    b. WOCBP who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent through at least 30 days after final IP administration.
8. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 30 days after final IP administration.

9. Female subject must not donate ova starting at first dose of IP and throughout the study period and for 30 days after final IP administration.
10. Male subject with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception (see [Appendix 12.3 Contraception Requirements]) throughout the study period and for 90 days after final IP administration.
11. Male subject must not donate sperm during the treatment period and for 90 days after final IP administration.
12. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom and spermicide for the duration of the pregnancy throughout the study period and for 90 days after final IP administration.
13. Subject agrees not to participate in another interventional study while participating in the present study.
14. Participant must be willing to abstain from smoking (including use of tobacco-containing products and nicotine or nicotine-containing products [e.g., electronic vapes] from at least 1 hour predose through at least 8 hours postdose on days 11 and 12.

5.2 Exclusion Criteria

Subject will be excluded from participation in the study if any of the following apply:

1. Subject has received any investigational therapy within 28 days or 5 half-lives, whichever is longer, prior to screening.
2. Subject has any condition which, in an investigator's opinion, makes the subject unsuitable for study participation.
3. Female subject who has been pregnant within 6 months prior to screening or breastfeeding within 3 months prior to screening.
4. Subject has a known or suspected hypersensitivity to ASP8062, buprenorphine, naloxone or any components of the formulations used.
5. Subject has had previous exposure with ASP8062.
6. Subject has any of the liver function tests (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase and total bilirubin [TBL]) > 2 × upper limit of normal (ULN) on day -1. In such a case, the assessment may be repeated once.
7. Subject has any clinically significant history of allergic conditions (including drug allergies, asthma or anaphylactic reactions, but excluding untreated, asymptomatic, seasonal allergies) prior to first IP administration, as judged by an investigator.
8. Subject has any history or evidence of any clinically significant cardiovascular, gastrointestinal, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal and/or other major disease or malignancy, as judged by the investigator, with exception of history of cholecystectomy.
9. Subject has current or recent diagnosis (within the last 12 months) of moderate or severe alcohol, sedative, hypnotic, anxiolytic, cocaine or any other substance use disorder (except for opioids, caffeine, tobacco or nicotine) according to the DSM-5 at screening.

10. Subject has a history or presence of any clinically significant psychiatric disorders such as, bipolar 1, schizophrenia, schizoaffective disorder or major depressive disorders, as judged by an investigator.
11. Subject tests positive for alcohol, benzodiazepine or methadone on day -1. Subject tests positive for buprenorphine on day -1.
12. Subject has had recent suicidal ideation within the last 12 months or subject who is at significant risk to commit suicide, as judged by the investigator, using the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening or since the last visit on day -1.
13. Subject has/had febrile illness or symptomatic, viral, bacterial (including upper respiratory infection) or fungal (noncutaneous) infection within 1 week prior to day -1.
14. Subject has any clinically significant abnormality following the investigator's review of the physical examination, ECG and protocol-defined clinical laboratory tests at screening or on day -1.
15. Subject has a mean pulse < 45 or > 110 beats per minute (unless out of range [> 110 beats per minute] pulse is deemed to be secondary to opioid withdrawal, as judged by the investigator); mean systolic blood pressure (SBP) > 150 mmHg; mean diastolic blood pressure (DBP) > 95 mmHg (unless out of range blood pressure is deemed to be secondary to opioid withdrawal, as judged by the investigator) (measurements taken in duplicate after subject has been resting in the supine position for at least 5 minutes; pulse will be measured automatically) on day -1. If the mean blood pressure exceeds the limits above, 1 additional duplicate may be taken.
16. Subject has a mean corrected QT interval using Fridericia's formula (QTcF) of > 450 msec (for male subjects) and > 470 msec (for female subjects) on day -1. If the mean QTcF exceeds the limits above, 1 additional duplicate ECG may be taken.
17. Subject has used any prescribed drugs, vitamins and natural or herbal remedies (including, St. John's Wort) in the 2 weeks prior to first IP administration, except for rescue medications, milk of magnesia, acetaminophen, topical dermatological products, including corticosteroid products, hormonal contraceptives and hormone replacement therapy (HRT).
18. Subject has used any inducer of CYP2C8, 2C9 or 3A4-related metabolism (e.g., barbiturates, rifampin, aprepitant, ritonavir, apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, phenobarbital, primidone, armodafinil, modafinil, and rufinamide) in the 3 months prior to day -1.
19. Subject has had significant blood loss or donated approximately 500 mL of whole blood (excluding plasma donation) within 56 days prior to screening or donated plasma within 7 days prior to day -1.
20. Subject has a positive serology test for antibodies to HIV type 1 and/or type 2, acute hepatitis B virus infection or acute hepatitis C virus infection, excluding asymptomatic hepatitis C virus infection at screening.
21. Subject has loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

22. Criterion removed.
23. Subject is an employee of Astellas, the study-related contract research organizations (CROs) or the clinical unit.

5.3 Restrictions During the Study

5.3.1 Exercise

Subjects will refrain from strenuous exercise from 48 hours prior to admission to the clinical unit up to and including the ESV.

Subjects are encouraged to walk and stretch while in the clinical unit to avoid AEs associated with the sedentary environment.

5.3.2 Dietary and Fluid Restrictions

To avoid false-positive results of the drugs of abuse test, no food or drinks containing poppy seeds (e.g., specialty breads and muffins) will be allowed from 48 hours prior to admission to the clinical unit up to and including the ESV.

Subjects will not be allowed to consume food and drinks which may interact with circulatory, gastrointestinal, liver or renal function from at least 24 hours for alcohol or xanthine-containing products and 72 hours for grapefruit/Seville orange or grapefruit/Seville orange-containing products prior to admission to the clinical unit up to and including the ESV.

Subjects will be served normal balanced caloric drinks and meals at consistent times during their stay in the clinical unit. Total daily caloric intake will preferably not exceed normal daily limits (approximately 2800 kcal/male and female subjects). Dietary and fluid restrictions apply to administration conditions as specified in [Section 6.1 Investigational Product(s)]. The menu and nutritional information will be documented in the clinical study file.

Standardized lunch and dinner will be served at fixed time points on day 1. On other days, the subjects will receive standard meals.

5.3.3 Smoking Restrictions

Participants will not be allowed to smoke (including using tobacco-containing products and nicotine or nicotine-containing products [e.g., electronic vapes]) from at least 1hour predose through at least 8 hours postdose on days 11 and 12 during measurements for continuous pulse oximetry and end tidal CO_2.

5.4 Screen Failures

A screen failure is defined as a potential subject who signed the informed consent form (ICF), but did not meet 1 or more criteria required for participation in the study and was not randomized.

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the electronic case report form (eCRF).

5.4.1 Rescreening

Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, vital signs, physical examination, ECG, etc.) may be repeated once within the 28-day screening period without the need to register the participant as a screen failure. If the participant meets exclusion criteria that cannot resolve during the screening period, or more than 28 days elapse from the date of signing the ICF, the participant must be documented as a screen failure. In order to re-screen after prior screen failure, a new ICF must be signed and the participant entered into screening with a new participant identification number. Rescreening is only allowed once for an individual participant.

6 INVESTIGATIONAL PRODUCT(S)

6.1 Investigational Product(s) Administered

Table 4 Investigational Product(s)

Name	**ASP8062**	**Placebo ASP8062**	**Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride)**
Use	Test Product	Placebo	Test Product
Dosage Formulation	Tablet	Tablet	Film
Physical Description	Round, reddish-yellow film-coated tablet	Round, reddish-yellow film-coated tablet	Orange rectangular sublingual film
Dose Strength	Single dose of 60 mg ASP8062 (2 × 30 mg tablets)	Single dose of placebo ASP8062 (2 × tablets)	See [Section 6.6 Dose Modification]
Packaging and Labeling	1 × aluminum/aluminum blister strips (2 × 7 configuration per strip in carton	1 × aluminum/aluminum blister strips (2 × 7 configuration per strip in carton	2 mg/0.5 mg sublingual film (30 films per box) 8 mg/2 mg sublingual film (30 films per box) 4 mg/1 mg sublingual film in foil pouch (30 films per box) 12 mg/3 mg sublingual film in foil pouch (30 films per box)
Route of Administration	Oral	Oral	Sublingual

Table continued on next page

Name	ASP8062	Placebo ASP8062	Suboxone® (buprenorphine hydrochloride/naloxone hydrochloride)
Administration Instruction	On day 12, ASP8062 will be administered orally under fasting conditions (i.e., no food or beverage will be allowed from at least 10 hours predose through at least 4 hours postdose) with approximately 240 mL water. Water intake will be prohibited from at least 1 hour predose through at least 2 hours postdose except for the approximately 240 mL water to swallow the investigational product.	On day 12, placebo ASP8062 will be administered orally under fasting conditions (i.e., no food or beverage will be allowed from at least 10 hours predose through at least 4 hours postdose) with approximately 240 mL water. Water intake will be prohibited from at least 1 hour predose through at least 2 hours postdose except for the approximately 240 mL water to swallow the investigational product.	On all dosing days (excluding days 11 and 12), buprenorphine/naloxone will be administered sublingually under standardized fed conditions (i.e., meals will be served up to 1 hour predose or at least 2 hours postdose). Water will be allowed ad libitum. On days 11 and 12, buprenorphine/naloxone will be administered sublingually under fasting conditions (i.e., no food or beverage will be allowed from at least 10 hours predose through at least 4 hours postdose). On day 11, the subject will consume approximately 240 mL of water and then place the buprenorphine/naloxone sublingually to match the dosing conditions on day 12.
IMP or Non-IMP	IMP	IMP	Non-IMP
Sourcing	Provided centrally by sponsor	Provided centrally by sponsor	Provided locally by investigator site

IMP: Investigational medicinal product

Refer to the pharmacy manual for detailed information regarding preparation, handling and storage of the IP.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All IP used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at Astellas Pharma Global Development Inc. (APGD) or sponsor's designee in accordance with APGD or sponsor's designee standard operating procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Each carton will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

Refer to the pharmacy manual for detailed information regarding packaging and labeling of the IP.

6.2.2 Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
2. Only subjects enrolled in the study may receive IP and only authorized study site personnel may supply or administer IP. Only IP with appropriate expiry/retest dating may be dispensed.
3. All IP must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions and access must be limited to the investigator and authorized study site personnel.
4. The investigator, institution or the head of the medical institution (where applicable) is responsible for accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records).
5. Further guidance and instruction on final disposition of used and unused IP is provided in the pharmacy manual.

Refer to the pharmacy manual for detailed information regarding handling, storage and accountability of the IP.

6.3 Randomization and Blinding

6.3.1 Blinding Method

The study will be conducted as subject- and investigator-blinded.

In order to maintain the blind, the subjects will receive the same number of tablets. The pharmacist will provide the investigator or designee with blinded IP to subjects.

6.3.2 Confirmation of the Indistinguishability of the Investigational Product

The appearance of both the dosage form and packaging of ASP8062 are identical to those of its placebo.

6.3.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list will be stored with the clinical unit pharmacist in a locked storage facility. The individual emergency code envelopes (ECEs) will be stored with medical staff for medical emergency use.

6.3.4 Breaking the Treatment Code for Emergency

For every randomized subject, an individual ECE will be stored in a secure location with access by designated personnel, in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. A code break can only be requested by the investigator or subinvestigators designated to have access to perform blind-breaking. In case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of the subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such determination. If the investigator decides that unblinding is

warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment for the subject.

The investigator must have a designated backup to support emergency unblinding requirements.

Prior to randomization, subjects should be provided with information that includes the study site emergency contact number and backup contact number in case of a medical emergency. Any unblinding by the investigational personnel must be reported immediately to the sponsor and include an explanation of why the IP was unblinded. Personnel who will be unblinded will not convey information regarding treatment assignments in the study, whether informally or formally, to any other person, unless required for medical reasons. The time and date of opening, any of these ECEs must be documented in the study file and the medical monitor should be contacted to discuss the case, if possible, before unblinding. If unblinding is associated with a serious adverse event (SAE), the investigator is to follow the instructions in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

All unopened ECEs will be destroyed at the end of the study. Opened ECEs will remain at the study site with the subject's study records.

6.3.5 Breaking the Treatment Code by the Sponsor

The sponsor may break the treatment code for subjects who experience a suspected unexpected serious adverse reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual emergency codes will be provided to the limited personnel who are responsible to break the codes for all SUSAR cases for reporting purposes.

6.3.6 Assignment and Allocation

6.3.6.1 Subject Number

Subjects will be assigned a subject number at study entry (i.e., signing of informed consent). The subject numbers will be sequential and rising.

The subject number will comprise of a 5-digit clinical unit number and 5-digit screening number.

6.3.6.2 Randomization

Prior to dosing on day 12, subjects will be assigned a randomization number in accordance with the randomization code generated by the sponsor's Data Science department or designee. Subjects will be randomized in a 2:1 ratio to ASP8062 or matching placebo.

Once a randomization number has been allocated to a subject, it will not be assigned to another subject. If a subject withdraws prematurely from the study and is replaced under the direction of the sponsor, then a replacement randomization number will be assigned. A replacement randomization code will be generated such that replacement subjects are assigned to the same cohort and treatment as the discontinued subject.

6.4 Investigational Product Compliance

Dosing will take place in the clinical unit. The administration of IP will be supervised to ensure treatment compliance. After IP administration, a check of the subject's mouth and hands will be performed. The exact day and time of IP administration will be documented.

6.5 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

6.5.1 Previous Treatment (Medication and Nonmedication Therapy)

All medicinal products, including prescribed or nonprescribed drugs, used prior to first IP administration will be considered previous medication.

The subjects must abstain from use of any prescribed drugs, vitamins and natural or herbal remedies (including St. John's Wort) in the 2 weeks prior to first IP administration, except for:

- Rescue medications [Section 6.5.3 Rescue Drugs]
- Milk of magnesia
- Acetaminophen
- Topical dermatological products, including corticosteroid products
- Hormonal contraceptives
- HRT

At screening, subjects will be questioned regarding the medicinal products that they have been using over the past 3 months. All medication used within 4 weeks prior to admission to the clinical unit will be documented.

6.5.2 Concomitant Treatment (Medication and Nonmedication Therapy)

All medicinal products other than the IPs, including prescribed or nonprescribed drugs (including vitamins and natural and herbal remedies, e.g., St. John's Wort), used from first IP administration until the ESV will be considered concomitant medication.

Subjects will only be allowed to use the following concomitant medication(s), if needed, from first IP administration until the ESV:

- Rescue medications [Section 6.5.3 Rescue Drugs]
- Milk of magnesia (except for days 11 and 12)
- Acetaminophen (up to 2 g/day)
- Topical dermatological products, including corticosteroid products
- Hormonal contraceptives
- HRT

If a subject's health condition necessitates the use of any medication other than the permitted medications during the study, the investigator and medical monitor, or designee(s), will discuss the case and determine if the subject should be withdrawn from the study and/or excluded from analysis sets, depending on if, and how, the medication(s) used influence(s) the study outcome. The nonpermitted concomitant medication will be recorded as a protocol deviation (see [Section 10.3 Major Protocol Deviations], protocol deviation 4).

All concomitant treatments (medication and nonmedication therapy) will be documented.

6.5.3 Rescue Medications

Buprenorphine/Naloxone

- Hydroxyzine pamoate: 50 mg (1 or 2 × tablets) every 6 hours, as needed
- Mylanta/Maalox: 10 to 20 mL, per product instruction, as needed
- Loperamide: 2 mg, per product instruction, as needed
- Methocarbamol: 750 mg (1 or 2 × tablets) every 6 hours, as needed
- Ibuprofen: 200 mg (2 × tablets) every 6 hours, as needed
- Promethazine: 25 mg oral or intramuscular, every 6 hours, as needed
- Clonidine: 0.1 mg, every 12 hours, as needed

6.6 Dose Modification

There will be no modification for the single planned ASP8062 dose of 60 mg.

On day 1, subjects will receive a 4/1 mg buprenorphine/naloxone dose in the morning and a 4/1 mg buprenorphine/naloxone dose in the afternoon. On day 2, subjects will receive an 8/2 mg buprenorphine/naloxone dose in the morning and a 4/1 mg buprenorphine/naloxone dose in the afternoon. On day 3, subjects will receive a 12/3 mg buprenorphine/naloxone dose in the morning. On day 4, subjects will receive a 16/4 mg buprenorphine/naloxone dose in the morning. Titration may be extended based on subject tolerability; however, subjects must be on a stable dose of 16/4 mg buprenorphine/naloxone by day 5. Subjects not on a stable dose of 16/4 mg buprenorphine/naloxone by day 5 will be discontinued from the study. Subjects will be on a stable, total daily dose of 16/4 mg buprenorphine/naloxone on days 5 through 18. The stable dose of buprenorphine/naloxone (16/4 mg) will be down-titrated from days 19 through 26, according to [Table 5].

Table 5 Schedule of Down-titration of Buprenorphine/Naloxone Dose

Day(s)	Subjects with Stabilized Buprenorphine/Naloxone Dose of 16/4 mg
18	16/4 mg
19	8/2 mg
20	8/2 mg
21	8/2 mg
22	4/1 mg
23	4/1 mg
24	4/1 mg
25	2/0.5 mg
26	2/0.5 mg
27	(Discharge/ESV)

ESV: end-of-study visit

6.7 Criteria for Continuation of Treatment

Not applicable.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Efficacy Assessments

7.1.1 Opioid Craving Visual Analogue Scale

The opioid craving visual analogue scale (VAS) will be used to measure subjects' opioid craving. Ratings will be performed as indicated in the Schedule of Assessments [Table 1] using the opioid craving VAS [Appendix 12.9 Opioid Craving Visual Analogue Scale].

All subjects will undergo a scripted training and practice regimen. Additional training sessions will be done as needed and will be documented in source document.

7.2 Safety Assessments

7.2.1 Adverse Events

See [Section 7.3 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

7.2.2 Laboratory Assessments

Clinical laboratory tests will be performed at a local laboratory apart from drugs of abuse and alcohol tests performed at the clinical unit.

Blood samples will be collected via a peripherally placed intravenous cannula or by direct venipuncture in a suitable vein.

Blood samples for serology, hematology and biochemistry and urine samples for urinalysis will be collected as indicated in the Schedule of Assessments [Table 1]. The clinical laboratory tests to be performed in the study are listed in [Appendix 12.7 Laboratory Assessments].

Drugs of abuse and alcohol tests will be performed according to the clinical site's preferred method. Drugs of abuse and alcohol tests will be performed as indicated in the Schedule of Assessments [Table 1].

Pregnancy tests (female subjects only) will be performed according to the clinical site's preferred method. Pregnancy tests will be performed as indicated in the Schedule of Assessments [Table 1].

A blood sample will be collected for follicle-stimulating hormone (FSH) tests (postmenopausal female subjects only) as indicated in the Schedule of Assessments [Table 1].

If any of the clinical laboratory tests results are outside the normal range at any scheduled time point during the study, the investigator may decide to repeat the test(s) on new samples. The clinical relevance of the abnormal results will be documented. Clinically relevant changes will be recorded as AEs (see [Section 7.3 Adverse Events and Other Safety Aspects]).

7.2.3 Vital Signs

Blood pressure (SBP and DBP), pulse, respiratory rate and oral temperature measurements will be taken as indicated in the Schedule of Assessments [Table 1]. Measurements will be taken after the subject has been resting in the supine position for at least 5 minutes. Measurements will be taken in duplicate with approximately 2-minute intervals at screening and on day -1. At all other time points, single measurements will be taken. Oral temperature will be taken as a single measurement at all time points.

7.2.4 Physical Examination

Physical examination will be performed as indicated in the Schedule of Assessments [Table 1] and whenever there is a medical indication.

The investigator should examine the body systems as described in the clinical site's SOP for physical examination. New or worsening clinically significant physical examination findings after IP administration will be recorded as AEs if they meet the criteria in [Section 7.3 Adverse Events and Other Safety Aspects].

7.2.5 Electrocardiogram

7.2.5.1 12-lead Electrocardiogram

12-lead ECGs will be taken as indicated in the Schedule of Assessments [Table 1]. 12-lead ECGs will be taken after the subject has been resting in the supine position for at least 5 minutes. 12-lead ECGs will be taken in duplicate with approximately 1-minute intervals and both ECGs will be completed within 5 minutes.

The investigator will use the system at the phase 1 unit to review, sign and date the ECG after recording to ensure subject safety. The time of the ECG, the interval measurements, as well as an overall conclusion, will be documented. This overall conclusion will be recorded as normal, abnormal not clinically significant, or abnormal clinically significant. If the overall conclusion is abnormal, the applicable abnormality code as provided by the sponsor must be recorded. Considering their relatively rare occurrence in healthy subjects, an ECG judged as abnormal clinically significant by a local physician for phase 1 studies must be further evaluated by another physician, and if confirmed will be recorded as an AE.

Per time point, the ECGs printouts will be reviewed in a timely manner by the investigator. Paper ECGs will be stored with the subject source. The time of the ECG, the interval measurements and the overall conclusion will be transcribed into the eCRF.

7.2.6 Continuous Pulse Oximetry and Spot Blood Oxygen Saturation

Continuous pulse oximetry will be taken as indicated in the Schedule of Assessments [Table 1]. Continuous pulse oximetry will be measured using a pulse oximeter placed on the subject's fingertip.

Blood oxygen saturation (SpO_2) levels will be measured as indicated in the Schedule of Assessments [Table 1]. SpO_2 will be measured using a pulse oximeter placed on the subject's fingertip.

7.2.7 Columbia-Suicide Severity Rating Scale

The C-SSRS [Posner et al, 2009] is a feasible, low-burden rating scale that assesses the full spectrum of suicidality: suicidal ideation, intensity of ideation, suicidal behaviors and actual attempts. Ratings will be performed as indicated in the Schedule of Assessments [Table 1] using the C-SSRS [Appendix 12.10 Columbia-Suicide Severity Rating Scale].

7.2.8 Continuous End Tidal Carbon Dioxide and Spot End Tidal Carbon Dioxide

Continuous monitoring of end tidal carbon dioxide (CO_2) will be taken as indicated in the Schedule of Assessments [Table 1]. End tidal CO_2 measurements will be obtained per subject utilizing a portable bedside capnography device. Timepoints for recorded measurements will be performed as indicated in the Schedule of Assessments [Table 1].

7.2.9 Clinical Opiate Withdrawal Scale

The COWS [Wessen & Ling, 2003] will be used to assess subjects' symptoms for opiate withdrawal over a period of time. Ratings will be performed as indicated in the Schedule of Assessments [Table 1] using the COWS [Appendix 12.11 Clinical Opiate Withdrawal Scale].

7.2.10 Order of Assessments

All predose procedures, e.g., 12-lead ECG, vital signs, opioid craving VAS, spot pulse oximetry, spot end tidal CO_2, and blood or urine sampling for clinical laboratory tests, will be performed within 60 minutes prior to dosing. All other measurements for 12-lead ECG and vital signs, will be performed within 15 minutes of the nominal time point. Opioid craving VAS will be performed within 10 minutes of the nominal time point. Pharmacokinetic sampling will be collected within 5 minutes from the nominal time point. When time points for procedures overlap, they should be performed in the following order: 12-lead ECG, vital signs (including SpO_2, if applicable), blood sampling for pharmacokinetics collected (including blood for clinical laboratory tests, if applicable) at the nominal time point and opioid craving VAS.

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that met the definition of an AE or SAE.

7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received IP. AE collection begins after the signing of the ICF and will be collected until 12 days for ASP8062 and 1 day for Suboxone® after the final IP administration or when the subject is determined to be a screen failure.

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The methods of recording, evaluating and assessing seriousness, causality and severity of AEs and SAEs are described in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting]. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

An AE with a change in severity is recorded as a new AE.

7.3.3 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If after the protocol-defined AE collection period (see [Section 7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information]), an AE progresses to an SAE, or the investigator learns of any serious adverse event or adverse event ([S]AE) including death, where he/she considers there is reasonable possibility it is related to the IP or study participation, the investigator must promptly notify the sponsor.

7.3.4 Reporting of Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential, so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

In the case of an SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

Procedures for reporting SAEs to the sponsor are described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

7.3.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Not applicable.

7.3.6 Adverse Events of Special Interest

AEs related to potential substance abuse and suicide (serious or nonserious) are considered to be of scientific and medical concern specific to ASP8062 and Suboxone®, for which ongoing monitoring and reporting is required.

Additional information around AEs of special interest will be collected to complete subject narratives. AEs of special interest related to potential substance abuse are listed in [Appendix 12.12 Adverse Events of Interest Related to Potential Substance Abuse].

One of the most clinically salient AEs of special interest for Suboxone® is respiratory depression. Respiratory depression following administration of only Suboxone® is very rare but is more common when administered with known CNS depressants such as

benzodiazepines. For this reason, continuous monitoring of blood oxygen saturation will be performed on day 12 when ASP8062 is administered with Suboxone®. In addition to this monitoring, clinically significant decreases in blood oxygen saturation requiring medical information will lead to stopping the study [Section 8.4 Discontinuation of the Study].

7.3.7 Special Situations

Certain special situations observed in association with the IP, such as incorrect administration (e.g., wrong dose of IP or background therapy) are collected in the eCRF, as protocol deviation per [Section 10.3 Major Protocol Deviations] or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE in the eCRF. If the AE meets the definition of an SAE, the SAE is to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on the SAE worksheet.

The special situations are:

- Pregnancy
- Medication error, overdose and “off-label use”
- Misuse/abuse
- Occupational exposure

Instructions and procedures for reporting special situations are provided in [Appendix 12.4.6 Reporting Procedures for Special Situations].

7.3.8 Supply of New Information Affecting the Conduct of the Study

When new information becomes available that is necessary for conducting the study properly, the sponsor will inform all investigators involved in the study as well as the appropriate regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated ICF in order to continue participation in the study.

7.3.9 Urgent Safety Measures

An urgent safety measure (USM) is an intervention that is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant competent authorities and IRB/IEC, where applicable, in order to protect subjects from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

7.3.10 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the study physician (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be a USM, the sponsor will take appropriate action to ensure the safety and welfare of the subjects. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

7.4 Pharmacokinetics

7.4.1 Analysis of ASP8062, Buprenorphine/Naloxone and Metabolite (Norbuprenorphine) in Plasma

Blood samples for the analysis of ASP8062 and buprenorphine/naloxone in plasma will be collected as indicated in the Schedule of Assessments [Table 1] for the evaluation of pharmacokinetics.

The actual date and time of each blood sample collection will be documented. Blood sample collection, handling and storage will be described in the laboratory manual. Analysis will be performed using a validated assay method at a bioanalytical laboratory specified by the sponsor.

When deemed appropriate, plasma samples remaining after the pharmacokinetic analysis may be used for exploratory metabolic profiling or exploratory biomarker analysis after the study. These tests will be described in a separate report and will not be incorporated in the integrated clinical study report (CSR).

7.5 Pharmacodynamics

Not applicable.

7.6 Electronic Clinical Outcome Assessment

Not applicable.

7.7 Other Assessments

7.7.1 Sample for the Analysis of Genes Related to Efficacy/Safety

Knowledge of polymorphisms of genes $GABA_B$ receptors and/or opioid receptors may help understand/explain observed differences in efficacy/safety of ASP8062. A 2 mL whole blood sample for the analysis of these biomarker (genes) will be collected as indicated in the Schedule of Assessments [Table 1].

For detailed sample collection, sample labeling and sample shipment procedures refer to the laboratory manual. All samples will be transferred to the central laboratory and then shipped to the analytical laboratory where they will be analyzed using appropriate validated methods.

7.7.2 Sample for Banked Pharmacogenomic Sample Analysis

Pharmacogenomic (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety. A 4 mL sample of whole blood for possible banked PGx analysis will be collected as indicated in the Schedule of Assessments [Table 1]. Samples will be shipped to a sponsor-designated banking CRO.

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Appendix 12.8 Pharmacogenomic Analysis with Banked Sample] for further details on the banking procedures.

7.8 Total Amount of Blood

The approximate total blood volume taken per subject will be as follows:

Table 6 Blood Volume

Sample Type	Number of Samples	Sample Volume (mL)	Total Volume (mL)
Clinical Laboratory Tests	14	9.0 (+ 8.5)†	134.5
ASP8062 Pharmacokinetics	24	1.0	24.0
Buprenorphine/Naloxone Pharmacokinetics	26	3.0	78.0
Biomarker	1	2.0	2.0
Pharmacogenomics	1	4.0	4.0
Total			242.5

† Additional blood collection for screening.

Additional blood may be drawn for safety reasons. The maximum amount of blood drawn during the study will not exceed 500 mL.

8 DISCONTINUATION

8.1 Discontinuation of Individual Subject(s) From Study Treatment

A discontinuation from treatment is defined as a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

The reason for discontinuation from study treatment must be documented in the subject's medical records.

A subject must discontinue study treatment for any of the following reasons:

- Subject requests to stop treatment
- Any clinical AEs, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the subject
- Participation in another interventional study while participating in the present study
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- Female subject becomes pregnant

8.2 Discontinuation of Individual Subject(s) From Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in Schedule of Assessments [Table 1]. The only exception to this is when the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects not on a stable dose of 16/4 mg buprenorphine/naloxone by day 5 will be discontinued from the study.

8.2.1 Lost to Follow-up

Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments and record outstanding data.

8.3 Discontinuation of the Study Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

8.4 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

The sponsor will terminate this study if 1 of the following criteria are met. The sponsor will unblind the affected subject(s) to an investigator/delegate, before a final decision is made.

1. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12, ≥ 5 ASP8062-treated subjects experience ASP8062-related AEs of severe intensity that are considered by an investigator to be of clinical concern
2. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12, ≥ 3 ASP8062-treated subjects experience an ASP8062-related SAE and there is no plausible alternate explanation for these events

3. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12, ≥ 5 ASP8062-treated subjects show at least 1 of the following findings in 2 consecutive measurements within 24 hours postdose:
   - ALT or AST ≥ 3 × ULN and ALT or AST is ≥ 3 × day 11 (day prior to concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062) values
   - ALT or AST ≥ 2 × ULN and ALT or AST ≥ 5 × day 11 (day prior to concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062) values
   - TBL ≥ 2 × ULN and subject does not have Gilbert Syndrome
4. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12, ≥ 3 ASP8062-treated subjects have QTcF interval ≥500 msec in 2 consecutive measurements within 24 hours postdose
5. If after concomitant administration of buprenorphine/naloxone and ASP8062 or placebo ASP8062 on day 12:
   - ≥ 4 ASP8062-treated subjects experience ASP8062-related symptomatic decrease in SpO_2 requiring more than 2 liters of supplemental oxygen via nasal cannula or,
   - ≥ 1 ASP8062-treated subjects experience ASP8062-related symptomatic decrease in SpO_2 requiring intubation, for medically significant respiratory depression

9 STATISTICAL METHODOLOGY

In general, all data will be summarized with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints, unless otherwise specified. Percentages by categories will be based on the number of subjects with no missing data (i.e., will add up to 100%).

Baseline will be defined as the last nonmissing observation on or prior to first administration of IP, unless otherwise specified.

9.1 Sample Size

Approximately 30 subjects will be enrolled to complete at least 18 subjects (i.e., 12 subjects on ASP8062 and 6 subjects on placebo ASP8062). Approximagely 8 female subjects will be enrolled so that at least 25% of the enrolled subjects are female. Subjects who discontinue early from the study may be replaced at the discretion of the sponsor. No formal sample size calculation is performed as this is not a statistically powered study. The number of subjects is based on the precedent set by other studies in similar nature. The number of subjects planned is considered sufficient to achieve the study objectives.

Based on the literature, the intrasubject coefficient of variation (CV) for pharmacokinetic parameters AUC_{inf} and C_{max} of buprenorphine and naloxone are estimated to be 26%.

Assuming the underlying variability is similar to 26% and the true underlying ratio is 100%, the 90% CI will lie within (77.0 129.0) with > 80% probability.

9.2 Analysis Sets

For each treatment group, the number and percentage of subjects will be characterized for all randomized subjects and by each analysis set.

9.2.1 Full Analysis Set

The full analysis set (FAS) will consist of all subjects who are randomized, received at least 1 dose of IP and all of the opioid craving VAS measurement. The FAS will be used set for the efficacy analysis.

9.2.2 Safety Analysis Set

The safety analysis set (SAF) consists of all subjects who receive at least 1 dose of IP.

The SAF will be used for all summaries and analysis of the safety data.

9.2.3 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PKAS) consists of all subjects who receive at least 1 dose of IP for which concentration data are available to facilitate derivation of at least 1 primary pharmacokinetic parameter. Inclusion of subjects in the PKAS with missing data or major protocol deviations will be considered by the pharmacokineticist on a case-by-case basis.

The PKAS will be used for all summaries and analyses of the pharmacokinetic data.

9.3 Demographics and Baseline Characteristics

9.3.1 Demographics

Demographics and baseline characteristics (age, sex, race, ethnicity, body weight, height and BMI) will be provided separately for all subjects in the SAF and by treatment (buprenorphine/naloxone in combination with ASP8062 [B/N + ASP] and buprenorphine/naloxone in combination with placebo [B/N + Pbo]) for all randomized subjects.

9.3.2 Subject Disposition

The number and percentage of subjects with screening disposition and reasons for screening disposition will be presented for all subjects with informed consent. Similar tables will be provided for subjects with run in disposition and reasons for run in disposition will be presented for all subjects in the SAF. The number and percentage of subjects who completed and discontinued treatment and reasons for treatment discontinuation will be provided for all subjects in the SAF and by treatment (B/N + ASP and B/N + Pbo) for all randomized subjects. Similar summaries will be created for investigational period and down-titration period disposition presented by treatment (B/N + ASP and B/N + Pbo) for all randomized subjects. All disposition details and dates of first and last evaluations for each subject will be listed.

9.3.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

All previous and concomitant treatment (medication and nonmedication therapy) will be listed.

9.3.4 Medical History

Medical history for each subject will be listed.

9.3.5 Investigational Product Exposure

The exposure tables will be presented for each IP (buprenorphine, naloxone and ASP8062). The number and percentage of subjects exposed to buprenorphine and naloxone, total daily dose will be summarized by treatment group (buprenorphine/naloxone alone [B/N alone], B/N + ASP and B/N + Pbo). The buprenorphine/naloxone in combination with ASP8062 (active and placebo) treatment groups will be summarized by period (Investigational period [day 12 to 18] and Down-titration period [day 19 to 26]). The number and percentage of subjects exposed to ASP8062 will be summarized by treatment group (B/N + ASP and B/N + Pbo).

All IP exposure data will be listed.

9.4 Analysis of Efficacy

9.4.1 Opioid Craving Visual Analogue Scale

To characterize preliminary efficacy, descriptive statistics will be provided for the opioid craving VAS results and change from baseline by treatment group (B/N + ASP and B/N + Pbo) and time points.

Opioid craving VAS data will be displayed in listings.

9.5 Analysis of Safety

For analysis of safety, the treatment groups are B/N alone, B/N + ASP and B/N + Pbo.

9.5.1 Adverse Events

AEs will be coded using MedDRA. An AE with onset at any time from first dosing until last scheduled procedure will be classified as a TEAE for inclusion in the summary tabulations. An IP-related TEAE is defined as any TEAE with a causal relationship assessed as “yes” by the investigator, or records where the relationship is missing.

An overview and separate summaries of the number and percentage of subjects with TEAEs, IP-related TEAEs, TEAEs leading to withdrawal of treatment, IP-related TEAEs leading to withdrawal of treatment and TEAEs excluding SAEs that equal or exceed a threshold of 5% in any treatment group will be presented by SOC, preferred term and treatment group. Also included in the overview are the number and percentage of subjects with serious TEAEs, IP-related serious TEAEs, TEAEs leading to death and IP-related TEAEs leading to death.

The number and percentage of subjects who have a TEAE within the drug abuse dependence SMQ (MedDRA v23.0) as classified by SOC and preferred term will be summarized by treatment group. In addition, the number and percent of subjects who have drug abuse related TEAEs as classified by preferred term and lowest level term will be summarized by treatment group.

The number and percent of subjects who have a TEAE with the drug withdrawal SMQ (MedDRA v23.0) as classified by SOC and preferred term will be summarized by treatment group. In addition, the number and percentages of subjects who have withdrawal related TEAEs as classified by SOC and preferred term will be summarized by treatment group.

For all the mentioned above summaries, the buprenorphine/naloxone in combination with ASP8062 (active or placebo) treatment groups will be split into periods (Investigational period [day 12 to 18] and Down-titration period [day 19 to 26]).

AE data will be listed.

9.5.2 Laboratory Assessments

For quantitative clinical laboratory measurements (hematology and biochemistry), descriptive statistics will be used to summarize results and change from baseline by treatment group and time point.

The number and percentage of subjects with potentially clinically significant values in liver enzymes and TBL will be tabulated.

Laboratory data will be listed.

9.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign (blood pressure, pulse and respiratory rate) results and changes from baseline for subjects in the SAF by treatment group and time point.

Vital signs data will be listed.

The number and percent of subjects with a respiratory rate < 6 breaths per minute (bpm), < 8 bpm and < 10 bpm and the number and percent of subjects with a respiratory rate > 24 bpm, > 28 bpm, > 32 bpm and > 36 bpm at any time point will be summarized by treatment group. The lowest and highest respiratory rate, respectively, will be used in the analysis.

9.5.4 Electrocardiogram

9.5.4.1 12-lead Electrocardiogram

12-lead ECG data and interpretations will be listed.

The number and percentage of subjects with absolute QTcF interval > 450 msec, > 480 msec, > 500 msec, PR > 200 msec, QRS > 110 msec and heart rate > 100 bpm will be provided by treatment group, at each time point and overall by visit. Similar summary information will be provided for QTcF interval increases from baseline of > 30 msec and > 60 msec.

9.5.5 Columbia-Suicide Severity Rating Scale

The listings will include only C-SSRS assessments that show at least 1 event of suicidality (suicidal ideation and/or suicidal behavior).

9.5.6 Blood Oxygen Saturation

The spot SpO_2 levels and change from baseline will be listed and summarized by treatment group and time point. The number and percent of subjects with SpO_2 levels < 90%, < 92%, < 94% and < 96% at any time point will be summarized by treatment group. The lowest SpO_2 level across the time points will be used in the analysis. The number and percentage of participants who reach an alarm value of continuous pulse oximetry, and the number of times an alarm value was reached will be listed and summarized by treatment.

9.5.7 End Tidal Carbon Dioxide

The spot end tidal CO_2 levels, respiratory rate and change from baseline (day 11 predose) will be listed and summarized by treatment group and time point. The number and percent of subjects with an end tidal CO_2 level < 20 mm Hg, < 25 mm Hg, < 30 mm Hg and < 35 mm Hg and the number and percent of subjects with an end tidal CO_2 > 35 mm Hg, > 40 mm Hg, > 45 mm Hg and > 50 mm Hg at any time point will be summarized by treatment group. The lowest and the highest end tidal CO_2 level, respectively, will be used in the analysis. The number and percentage of participants who reach an alarm value of continuous end tidal CO_2, and the number of times an alarm value was reached will be listed and summarized by treatment.

9.6 Analysis of Pharmacokinetics

Descriptive statistics will include n, mean, SD, CV, geometric mean, and geometric CV, minimum, median, maximum. For the pharmacokinetic parameters t_{max} and t_{lag}, only n, median, minimum and maximum will be calculated.

9.6.1 Plasma Concentrations

Descriptive statistics will be presented for plasma concentrations of buprenorphine and its metabolite (norbuprenorphine) and naloxone by treatment group (B/N + ASP and B/N alone) and scheduled sample time. Standard graphics including mean plasma concentration-time profiles, overlay (spaghetti) plots and individual subject plasma concentration-time profiles for buprenorphine and its metabolite (norbuprenorphine) and naloxone by treatment group will be produced. Plasma concentrations of ASP8062 will be listed and summarized using descriptive statistics by scheduled sample time.

9.6.2 Estimation of Pharmacokinetic Parameters

Noncompartmental analysis will be used for the calculation of plasma pharmacokinetic parameters using Phoenix version 6.3 or higher (Certara LP, 100 Overlook Center, Suite 101, Princeton, NJ 08540, US).

Plasma pharmacokinetic parameters of buprenorphine, its metabolite (norbuprenorphine) and naloxone for B/N + ASP and B/N alone will be listed and summarized using descriptive statistics.

Plasma pharmacokinetic parameters of ASP8062 in combination with buprenorphine/naloxone will be listed and summarized using descriptive statistics.

9.6.3 Statistical Analysis of Pharmacokinetic Parameters

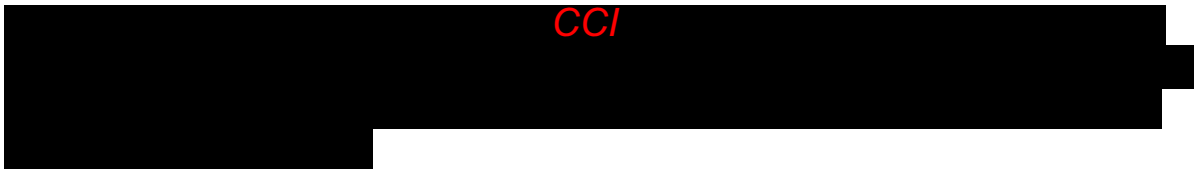
To assess the effect of ASP8062 on the pharmacokinetics of buprenorphine and its metabolite (norbuprenorphine) and naloxone, an analysis of variance (ANOVA) model with treatment (B/N + ASP and B/N alone) as a fixed effect and subject as a random effect will be fitted on natural logarithm-transformed AUC_{24} and C_{max}. Within the ANOVA, the least square (LS) mean differences between buprenorphine/naloxone in combination with ASP8062 and buprenorphine/naloxone alone, along with 90% CIs for the differences will be estimated. The LS means for AUC_{24} and C_{max} will be back-transformed to produce the geometric LS means and presented with the number of subjects for each treatment. The geometric LS mean ratios and their corresponding 90% CIs for each pharmacokinetic parameter will be presented by back-transforming and expressed as percentages.

If all subjects did not complete treatment, then the above analyses will be repeated using an ANOVA with fixed effects for treatment and subject; this analysis will only include subjects with complete data in all treatments.

9.7 Analysis of Pharmacodynamics

Not applicable.

9.8 Other Analyses



9.9 Major Protocol Deviations

Major protocol deviations as defined in [Section 10.3 Major Protocol Deviations] will listed.

9.10 Interim Analysis (and Early Discontinuation of the Study)

Not applicable.

9.11 Additional Conventions

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medications if they are missing on day of first IP administration. The imputed dates will be used to assess if the AEs or concomitant medications are treatment-emergent or concomitant, respectively.

Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

10 OPERATIONAL CONSIDERATIONS

10.1 Data Collection

All procedures conducted under the protocol must be documented.

The investigator or designee is responsible for eCRF completion and will ensure that all data and queries are accurate, complete and are verifiable with the source. The source should be appropriately maintained by the clinical unit.

Electronic data sources and any supporting documents should be available for review/retrieval by the sponsor/designee at any time.

10.2 Demographics and Baseline Characteristics

10.2.1 Demographics

Demographics and baseline characteristics will be collected as indicated in the Schedule of Assessments [Table 1]. This will include age, sex, race, ethnicity, body weight, height and BMI.

10.2.2 Medical History

A complete medical history including substance use will be collected as indicated in the Schedule of Assessments [Table 1].

10.2.3 Diagnosis of the Target Disease, Severity and Duration of Disease

Information of subject opiate use will be collected at the screening visit to determine if the subject has moderate or severe OUD. Information will also be collected to evaluate when subject OUD started. Refer to [Section 5.1 Inclusion Criteria].

10.3 Major Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. All deviations from the protocol are to be recorded. A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and well-being of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to subjects.

A major protocol deviation is 1 that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a subject. Major protocol deviations will have additional reporting requirements.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or pharmacokinetic parameters of the subject to determine subject continuation in the study.

The major protocol deviation criteria that will be summarized at the end of the study are as follows:

PD1 - Entered into the study even though the subject did not satisfy entry criteria

PD2 - Developed withdrawal criteria during the study and was not withdrawn

PD3 - Received wrong treatment or incorrect dose

PD4 - Received excluded concomitant treatment

The investigator will also assure that deviations meeting IRB/IEC and appropriate regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and appropriate regulatory authorities will be provided to the sponsor and maintained within the Trial Master File.

10.4 Study Organization

10.4.1 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be implemented for this study to monitor interim safety data. The DSMB consists of an Astellas medical doctor, a biostatistician and clinical pharmacology representative who are independent from the study team, who are not involved with day-to-day operations with the study, and do not communicate with site staff regarding the study. Additional details, including the responsibilities of the DSMB, are outlined in the DSMB charter.

10.4.2 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 Ethical, Regulatory and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.1.2 Institutional Review Board/Independent Ethics Committee/Competent Authorities

GCP requires that the protocol, any protocol amendments, investigator's brochure, ICF and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB/IEC. The IRB/IEC will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB/IEC approval of the protocol, ICF and subject information and/or advertising, as relevant, will be obtained prior to initiation of any study-specific procedures.

Any substantial amendments to the protocol will require competent authority and IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU Regulation No. 536/2014 for studies (if applicable), and all other applicable local regulations

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or nonsubstantial amendments. Depending on the nature of the amendment, either IRB/IEC or competent authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, investigator, IRB/IEC and appropriate regulatory authorities.

Amendments to this protocol must be signed by the sponsor and investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the ICF, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new ICF must also be forwarded to the sponsor.

12.1.4 Financial Disclosure

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

12.1.5 Informed Consent of Subjects

12.1.5.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF will be reviewed, signed and dated by the subject, the person who administered the ICF and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that the ICF was signed prior to any study-related procedures and that the subject received a signed copy of the ICF.

The signed ICFs will be retained by the investigator and made available (for review only) to the study monitor, auditor and appropriate regulatory authorities and other applicable individuals upon request.

12.1.5.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject verbally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participating in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update the subject's ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent subjects with the updated ICF even if relevant information was provided verbally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the reconsent process.

12.1.6 Source Documents

Source data must be available at the study site to document the existence of the subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, electronic clinical outcome assessment (eCOA) and/or drug accountability.

Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information, if applicable). All printed records must be kept in the subject file and be available for archiving.

12.1.7 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data, CRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US study sites, 2 years after approval of the NDA or discontinuation of the IND). The investigator agrees to obtain the sponsor's agreement prior to disposal, moving or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subject's medical records and/or study progress notes.

12.1.8 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the investigator or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to a subject's privacy due to direct access to source documents, or from other sources, they may not disclose the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then the sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive (DPD), and investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If the sponsor is not based in the EEA, the sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the DPD.

12.1.9 Arrangement for Use of Information and Publication of the Study

Information concerning the test product, patent applications, processes, unpublished scientific data, the investigator's brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the study agreement.

12.1.10 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final CSR that forms part of a marketing authorization application, be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator(s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for the coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database hard-lock.

12.2 Procedure for Study Quality Control

12.2.1 Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP and the study data reported by the investigator/subinvestigator are accurate, complete and verifiable with the source. The sponsor is responsible for assigning the study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO, as well as inspections from the IRB/IEC and appropriate regulatory authorities. In these instances, they must provide all study-related records including source documents when they are requested by the sponsor monitors and auditors, the CRO, the IRB/IEC or appropriate regulatory authorities. The confidentiality of the subject's identity shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2.3 Data Management

Data management will be coordinated by the Data Science department or designee of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by data management. Coding of medical terms and medications will be performed using MedDRA and the WHO Drug Dictionary, respectively. Data management is accountable for eCOA.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the study at any or all study sites and facilities. The audit may include on-site review of regulatory documents, case report forms and source documents. Direct access to these documents will be required by the auditors.

To support quality around subject safety and reliability of study results, quality tolerance limits (QTLs) are defined and monitored. QTLs represent the acceptable variation of study data, taking into consideration the current state of medical and statistical knowledge about the variables to be analyzed as well as the statistical design of the study. It is a level, point, or value associated with a parameter that should trigger an evaluation if a deviation is detected to determine if there is a possible systematic issue (i.e., a trend has occurred). The QTLs defined for this study are provided below.

Table 7 Quality Tolerance Limit

QTL #: Name and Parameter	Definition	Parameter Justification
QTL1: Subject study treatment discontinuation	Number of subjects that discontinue during run-in period	A high number of subjects that discontinue during the run-in period will impact the number of evaluable subjects for the primary endpoint

QTL: quality tolerance limit

QTL Management Activities:

- For control of risks associated with QTL1: Subject study treatment discontinuation, refer to [Section 4.1 Study Design and Section 4.2 Dose Rationale] where the buprenorphine/naloxone dose titration and ASP8062 dose rationale is described, in addition, [Section 9.1 Sample Size] discusses the planned enrollment of 30 subjects to achieve 18 evaluable subjects.

12.3 Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the Schedule of Assessments [Table 1]. Pregnancy test results must confirm that the subject is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

Females in the following categories are not considered WOCBP

- Premenopausal with 1 of the following (i.e., permanently sterile):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal

A postmenopausal state is defined as at least 12 months after last menstrual bleeding without an alternative medical cause.

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than 1 FSH measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment. Females must be on a stable dose of HRT for 2 months prior to day -1.

Documentation of any of these categories can come from the study site personnel's review of the female subject's medical records, medical examination or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

Female subjects of childbearing potential are eligible for participation in the study if they agree to use 1 of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 30 days after the final IP administration.[a]

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- Use a condom and spermicide
- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation for at least 30 days prior to first dose of IP

  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation for at least 30 days prior to first dose of IP
  - Oral
  - Injectable
  - Implantable
- Other combined (estrogen- and progesterone-containing) methods for at least 30 days prior to first dose of IP
  - Vaginal ring
  - Injectable
  - Implantable
  - Intrauterine hormone-releasing system or intrauterine device
- Bilateral tubal occlusion or ligation
- Vasectomized partner
  A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP.
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the test product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. It is not necessary to use any other method of contraception when complete abstinence is elected.

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE SUBJECTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL.

Male subjects with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 90 days after final drug administration.[a]

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator
- Use a condom and spermicide
- Female partners of male subjects who have not undergone a vasectomy or a bilateral orchiectomy should consider use of effective methods of contraception
- If sexual abstinence is practiced, sexual abstinence should be practiced from 30 days prior to screening and subject should agree to continue practicing sexual abstinence during study participation

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

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

12.4.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered an IP and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IP whether or not considered related to the IP.

12.4.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, biochemistry or urinalysis) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease, does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

12.4.1.2 Potential Cases of Drug-induced Liver Injury

Refer to [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed instructions on drug-induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Appendix 12.5 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events].

12.4.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, the event:

- Results in death
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death; it does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect

- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE)
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.4.3 Criteria for Causal Relationship to Investigational Product

A medically qualified investigator is obligated to assess the relationship between IP and each occurrence of each (S)AE. This investigator will use medical judgment as well as the RSI [Section 2.1.4 Summary of Key Safety Information for Investigational Product(s)] to determine the relationship. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

The investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the IP and each (S)AE will be assessed by answering "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the IP?"

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a "reasonable possibility" that an (S)AE may have been caused by the IP (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the subject been administered IP?
- Plausibility (i.e., could the event have been caused by the suspect drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and study data, etc.)
- Dechallenge/dose reduction/rechallenge:
    - Dechallenge: did the (S)AE resolve or improve after only stopping the dose of the suspect drug without any treatment?
    - Dose reduction: did the (S)AE resolve or improve after reducing the dose of the suspect drug?
    - Rechallenge: did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?

- Laboratory or other test results: a specific laboratory investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of IP exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc., and strength of the alternative explanation
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible temporal relationship between exposure to the IP and (S)AE onset and/or resolution will be provided. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the sponsor. With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of "no" is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

12.4.4 Criteria for Defining the Severity of an Adverse Event

The investigator will use the following definitions to rate the severity of each AE:

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

12.4.5 Reporting Procedures for Serious Adverse Events

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by fax or email immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on delegation of authority log). Signature confirms accuracy and completeness of the SAE data as well as the investigator causality assessment including the explanation for the causality assessment.

If the SAE is associated with emergency unblinding by the investigator as outlined in [Section 6.3.4 Breaking the Treatment Code for Emergency], this is to be recorded on the SAE worksheet. On the SAE worksheet, the investigator is to include when unblinding took place in association with the SAE.

For contact details, see [Contact Details of Sponsor's Key Personnel]. Fax or email the SAE/special situations worksheet to:

Astellas Pharma Global Development Inc.
US Pharmacovigilance
North America fax number: +1-888-396-3750
North America alternate fax number: +1-847-317-1241
Email: safety-us@astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or their designee [Contact Details of Sponsor's Key Personnel].

Follow-up information for the event should be sent promptly (as soon as available but no longer than within 7 days of the initial notification.

Full details of the SAE should be recorded on the medical records, SAE/special situation worksheet and on the eCRF.

The following minimum information is required:

- International study number/study number
- Subject number, sex and age
- Date of report
- Description of the SAE (event and seriousness criteria)
- Causal relationship to the IP (including reason)
- Drug provided (if any)

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality and expectedness of the events (e.g., SUSAR reporting) according to current local/regional regulatory requirements. The sponsor or sponsor's designee will submit expedited safety reports to competent authorities and concerned ethics committee per current local regulations and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/ IEC of expedited safety reports should be retained by the study site. In the US, FDA expedited IND reporting guidelines will be followed.

The sponsor will notify all investigators responsible for ongoing clinical studies with the test product of all SUSARs, which require submission per local requirements IRB/IEC.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the rights, safety or well-being of the subject.

12.4.6 Reporting Procedures for Special Situations

12.4.6.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] using the SAE worksheet as a special situation and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 90 days from the discontinuation of dosing and report the information to sponsor according to the timelines in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Event**s**] using the SAE worksheet as a special situation.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data, etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female subject as an AE in the eCRF or SAE per [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the SAE worksheet.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the IP
- If an infant dies more than 1 month after the birth, it is to be reported if a relationship between the death and intrauterine exposure to the IP is judged as "possible" by the investigator
- Congenital anomaly (including anomaly in miscarried fetus)

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination or other means as appropriate. (S)AEs experienced by the newborn/infant should be reported via the pregnancy reporting form. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date.

12.4.6.2 Medication Error, Overdose and "Off-label Use"

If a medication error (defined as an unintended failure in the treatment process that leads to, or has the potential to lead to, harm to the subject), overdose or "off-label use" (i.e., use outside of what is stated in the protocol) is suspected, refer to [Section 10.3 Major Protocol Deviations]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Appendix 12.4.5

Reporting Procedures for Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use."

In the event of suspected ASP8062 overdose, the subject should receive supportive care and monitoring. The medical monitor/expert should be contacted as applicable.

In the event of suspected buprenorphine/naloxone overdose, refer to the approved package insert supplied by the manufacturer for IP. The medical monitor/expert should be contacted as applicable.

12.4.6.3 Misuse/Abuse

Definition of misuse: situations where the IP is/are intentionally and inappropriately used not in accordance with the intended use as defined in the protocol.

Definition of abuse: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

If misuse or abuse of the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Appendix 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the misuse or abuse of the IP.

12.4.6.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the IP of study site personnel while preparing it for administration to the subject) to the IP occurs, the investigator must forward the special situations worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the special situation are to be reported on the special situations worksheet.

12.5 Liver Safety Monitoring and Assessment

The purpose of this appendix is to provide guidance for the monitoring of drug-induced liver injury during the course of the study. It should be noted that this section does not specify the end of study analyses of liver enzymes. Any subject enrolled in a study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least ALP, ALT, AST and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN is as shown below.

Table 8 Moderate and Severe Liver Abnormalities

	ALT or AST		TBL
Moderate	> 3 × ULN	or	> 2 × ULN
Severe	> 3 × ULN	and†	> 2 × ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal

†Samples taken simultaneously or within maximum 24 hours.

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or international normalized ratio (INR) > 1.5 (if INR testing is applicable/evaluated)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

† Samples taken simultaneously or within a maximum of 24 hours.

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and clinical laboratory tests. The study site personnel are to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests should be repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the IP has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to IP are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases are to be recorded as "AEs" within the eCRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications are to be entered in the eCRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents)
    - Ultrasound or other imaging to assess biliary tract disease
    - Other clinical laboratory tests, including INR and direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or INR > 1.5) (if INR testing is applicable/evaluated)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

† Samples taken simultaneously or within a maximum of 24 hours.

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

Hy's Law definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant).

The 2 "requirements" for Hy's Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in AT elevations > 3 × ULN ("2 × ULN elevations are too common in treated and untreated subjects to be discriminating").
2. Cases of increased total bilirubin (at least 2 × ULN) with concurrent AT elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

FDA Guidance for Industry titled, "Drug-induced Liver Injury: Premarketing Clinical Evaluation" issued by the FDA on July 2009:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among subjects showing such AT elevations, often with ATs much greater than 3 × ULN, 1 or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

References

Temple R. Hy's Law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15:241-3.

12.6 List of Excluded Concomitant Medications

Not applicable.

12.7 Laboratory Assessments

Serology

Visit	Matrix	Parameters to be Analyzed
See Schedule of Assessments [Table 1]	Serum	HAV antibodies (IgM) HBc antibodies HBsAg HCV antibodies Antibodies to HIV types 1 and 2

Hematology

Visit	Matrix	Parameters to be Analyzed
See Schedule of Assessments [Table 1]	Blood	Hemoglobin Hematocrit Erythrocytes Leukocytes Differential leukocytes Neutrophils Platelets

Biochemistry

Visit	Matrix	Parameters to be Analyzed
See Schedule of Assessments [Table 1]	Serum	Sodium Potassium Calcium Chloride Magnesium Inorganic phosphorus Glucose Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Gamma-glutamyl transferase Total bilirubin Total cholesterol Triglycerides Blood urea nitrogen Creatinine Creatine kinase Lactate dehydrogenase Total protein Uric acid Albumin FSH (postmenopausal female subjects only) Carbon Dioxide

Urinalysis

Visit		Parameters to be Analyzed
See Schedule of Assessments Table 1	Dipstick	Protein Glucose pH Blood Leukocytes Urobilinogen Bilirubin Ketones Nitrite
	Microscopy (optional)	Casts Crystals Epithelial cells Leucocytes Erythrocytes Bacteria

Drugs of Abuse and Alcohol Tests

Visit	Matrix	Parameters to be Analyzed
See Schedule of Assessments Table 1	Urine	Amphetamines Barbiturates Benzodiazepines Buprenorphine Cannabinoids Cocaine Methadone Opiates Phencyclidine
	Urine	Alcohol

Pregnancy Test

Visit	Matrix	Parameters to be Analyzed
See Schedule of Assessments Table 1	Serum/urine	Human chorionic gonadotropin (female subjects only)

FSH: follicle-stimulating hormone; HAV: hepatitis A virus; HBc: hepatitis B core; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IgM: immunoglobulin M

12.8 Pharmacogenomic Analysis with Banked Sample

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring differences in a subject's gene and/or expression of genes based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and/or toxicity/safety.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study will participate in the PGx substudy. Subjects must provide written consent prior to providing any blood samples that may be used at a later time for PGx analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this substudy will provide 4 mL sample of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number. Samples will be shipped to a designated banking CRO as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis if evidence suggests that genetic variants may be influencing the drug's pharmacokinetics, efficacy and/or safety.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hard-lock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely unless otherwise specified by local regulation.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the study, if applicable. The results of the PGx analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.9 Opioid Craving Visual Analogue Scale

This document is a template from which the study-specific version will be created.

No craving _____ Strongest craving ever
[100 mm scale]

12.10 Columbia-Suicide Severity Rating Scale

12.10.1 Baseline/Screening Version

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 12 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION				
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.			**Most Severe**	**Most Severe**
Lifetime -	***Most Severe Ideation:***	_____ *Type # (1-5)* _____ *Description of Ideation*		
Past X Months -	***Most Severe Ideation:***	_____ *Type # (1-5)* _____ *Description of Ideation*		
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day			____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous			____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts			____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply			____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply			____	____

SUICIDAL BEHAVIOR		
(Check all that apply, so long as these are separate events; must ask about all types)	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____

SUICIDAL BEHAVIOR		
(Check all that apply, so long as these are separate events; must ask about all types)	**Lifetime**	**Past __ Years**
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐	**Yes No** ☐ ☐

Answer for Actual Attempts Only	**Most Recent Attempt Date:**	**Most Lethal Attempt Date:**	**Initial/First Attempt Date:**
Actual Lethality/Medical Damage: (0) No physical damage or very minor physical damage (e.g., surface scratches). (1) Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). (2) Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). (3) Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). (4) Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). (5) Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). (0) Behavior not likely to result in injury (1) Behavior likely to result in injury but not likely to cause death (2) Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

12.10.2 Since Last Visit

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.	**Most Severe**
Since Last Visit - ***Most Severe Ideation:*** _____ *Type # (1-5)* _____ *Description of Ideation*	
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR	
(Check all that apply, so long as these are separate events; must ask about all types)	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a highly floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____

SUICIDAL BEHAVIOR	
(Check all that apply, so long as these are separate events; must ask about all types)	**Since Last Visit**
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Suicide:	**Yes** **No** ☐ ☐

Answer for Actual Attempts Only	**Most Lethal Attempt Date:**
Actual Lethality/Medical Damage: (0) No physical damage or very minor physical damage (e.g., surface scratches). (1) Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). (2) Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). (3) Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). (4) Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). (5) Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality = 0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). (0) Behavior not likely to result in injury (1) Behavior likely to result in injury but not likely to cause death (2) Behavior likely to result in death despite available medical care	*Enter Code* _____

12.11 Clinical Opiate Withdrawal Scale

This document is a template from which the study-specific version will be created.

For each item, circle the number that best describes the patient's signs or symptoms. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: _____	Date and Time ____ / ____ / ____ :_____
Reason for this assessment: _____	
Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81 – 100 2 pulse rate 101 – 120 4 pulse rate greater than 120	**GI Upset:** *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past ½ hour not accounted for by room temperature or patient activity* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observed moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequently shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for roomlight 1 pupils possible larger than normal for roomlight 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional components attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscle 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5 – 12 = mild; 13 – 24 = moderate; 25 – 36 = moderately severe; more than 36 = severe withdrawal

12.12 Adverse Events of Interest Related to Potential Substance Abuse and Following Drug Withdrawal

a. Includes Adverse Events of Interest Related to Potential Substance Abuse

Preferred Term	Lowest Level Term
Euphoria-related Terms	
Euphoric mood	Feeling high
	Euphoria
	Euphoric
	Euphoric mood
	Elevated mood
	Mood elevated
	Feeling abnormal
	Feeling drunk
	Feeling of relaxation
	Thinking abnormal
	Hallucination, mixed
Dizziness	Dizziness and giddiness
Dissociative/Psychotic Terms	
Psychosis	
Aggression	
Confusion	
Disorientation	
Terms Indicative of Impaired Attention, Cognition, Mood and Psychomotor Events	
Somnolence	Somnolence
Psychomotor hyperactivity/decreased activity	Hyperactivity/hypoactivity
	Mood disorders
	Mental impairment
	Drug tolerance, habituation, drug withdrawal syndrome, substance-related disorders
Inappropriate Affect	
Inappropriate affect	Elation inappropriate
	Exhilaration inappropriate
	Inappropriate mood elevation
Product tampering	Medication tampering

b. Related Adverse Events Occurring Following Drug Withdrawal

	Higher Level Group Term	Higher Level Term	Preferred Term
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Agitation
Nervous system disorders	Neurological disorders NEC	Neurological signs and symptoms NEC	
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Anhedonia
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Anxiety
Musculoskeletal and connective tissue disorders	Muscle disorders	Muscle related signs and symptoms NEC	Chills
Musculoskeletal and connective tissue disorders	Muscle disorders	Feeling and sensations NEC	
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Depressed mood
Psychiatric disorders	Depressed mood disorders and disturbances	Depressive disorders	Depression
Gastrointestinal disorders	Gastrointestinal motility and defaecation conditions	Diarrhoea (excluding infective)	Diarrhoea
Psychiatric disorders	Mood disorders and disturbances	Emotional and mood disturbance NEC	Dysphoria
Nervous system disorders	Sleep disturbances (including subtypes)	Sleep disturbances NEC	Dyssomnia
Psychiatric disorders	Sleep disorders and disturbances	Dyssomnias	
Psychiatric disorders	Depressed mood disorders and disturbances	Depressive disorders	Dysthymic disorder
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Feeling of despair
Nervous system disorders	Headaches	Headaches NEC	Headache
Skin and subcutaneous tissue disorders	Skin appendage conditions	Apocrine and eccrine glad disorders	Hyperhidrosis
General disorders and administration site conditions	General system disorders NEC	General signs and symptoms NEC	
Psychiatric disorders	Sleep disorders and disturbances	Disturbances in initiating and maintaining sleep	Insomnia
Nervous system disorders	Sleep disturbances	Disturbances in initiating and maintaining sleep	
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Morose
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Nausea
Psychiatric disorders	Depressed mood disorders and disturbances	Mood alterations with depressive symptoms	Negative thoughts
Psychiatric disorders	Anxiety disorders and symptoms	Anxiety symptoms	Nervousness
Psychiatric disorders	Anxiety disorders and symptoms	Obsessive-compulsive disorders and symptoms	Obsessive thoughts

Table continued on next page

	Higher Level Group Term	**Higher Level Term**	**Preferred Term**
General disorders and administration site conditions	General system disorders NEC	Pain and discomfort NEC	Pain
Nervous system disorders	Sleep disturbances (including subtypes)	Sleep disturbances NEC	Poor quality sleep
Psychiatric disorders	Sleep disorders and disturbances	Dyssomnias	
Cardia disorders	Cardiac disorder signs and symptoms	Cardia signs and symptoms NEC	Syncope
Vascular disorders	Decreased and nonspecific blood pressure disorders and shock	Circulatory collapse and shock	
Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC	
Psychiatric disorders	Sleep disorders and disturbances	Disturbances in initiating and maintaining sleep	Terminal insomnia (lower level term of interest: early morning awakening)
Nervous system disorders	Sleep disturbances	Disturbances in initiating and maintaining sleep	
Nervous system disorders	Movement disorders (including parkinsonism)	Tremor (excluding congenital)	Tremor
Gastrointestinal disorders	Gastrointestinal signs and symptoms	Nausea and vomiting symptoms	Vomiting

NEC: not elsewhere classified

c. Analysis Search Strategy for Adverse Events of Interest Related to Potential Substance Abuse

MedDRA v23.0 SOC	Higher Level Group Term	Higher Level Term	Preferred Term	Lowest Level Term
Nervous system disorder	Neurological disorder NEC	Neurological signs and symptoms	Dizziness	Dizziness and giddiness
Psychiatric disorders	Psychosis	Psychosis	Psychosis	
	Deleria	Confusion and Disorientation	Disorientation	
			Confusion	
	Personality disorder	Behavior and socializing disturbance	Aggression	
	Cognitive and attention disorders and disturbances	Cognitive and attention disorders and disturbances NEC	Mental impairment	Mental impairment
	Sleep disorders and disturbances	Dyssomnias	Somnolence	Somnolence
	Changes in physical activity	Increased physical activity level	Psychomotor hyperactivity	Hyperactivity
		Decreased physical activity level	Decreased activity	Hypoactivity
	Mood disorders and disturbances NEC	Emotional and mood disturbances NEC	Euphoric Mood	Euphoria
				Euphoric
				Euphoric mood
				Exaggerated well-being
				Feeling high
				Felt high
				High
				High feeling
				Hyperthimic
				Laughter
			Mood altered	Mood elevated
				Affect alteration
				Affect altered
				Altered mood
				Bad mood
				Mood alteration NOS
				Mood altered
				Mood change
		Mood disorders NEC	Affective disorder	Mood disorder

Table continued on next page

MedDRA v23.0 SOC	Higher Level GT	Higher Level Term	Preferred Term	Lowest Level Term
		Affect alterations	Inappropriate affect	Elation inappropriate
				Exhilaration inappropriate
				Exhiliration inappropriate
				Inappropriate crying
				Inappropriate elation
				Inappropriate exhilaration
				Inappropriate laughter
				Inappropriate mood elevation
				Mood elevation inappropriate
	Disturbances in thinking and perception	Perception disturbances	Hallucination	Drug-induced hallucinosis
				Hallucinating
				Hallucination
				Hallucination NOS
				Hallucinations
				Hallucinations aggravated
				Kinesthetic hallucination
				Organic hallucinosis syndrome
				Pseudohallucination
				Sensory hallucinations
				Stump hallucination
			Hallucination, auditory	Auditory hallucinations
				Hallucination auditory
				Hallucination, auditory
				Verbal hallucinations
			Hallucination, visual	Hallucination visual
				Hallucination with color
				Hallucination with colour
				Hallucination, visual
				Visual hallucinations
		Hallucination	Hallucinations, mixed	Auditory and visual hallucination
General disorders and administration site conditions	General system disorders NEC	Feelings and sensations NEC	Feeling drunk	Drunk-like effect
				Drunkenness feeling of
				Feeling drunk
			Feeling abnormal	Cotton wool in head
				Feeling abnormal
				Feeling bad
				Feeling dazed
				Feeling floating
				Feeling lifeless
				Feeling miserable

Table continued on next page

MedDRA v23.0 SOC	Higher Level GT	Higher Level Term	Preferred Term	Lowest Level Term
				Feeling stoned
				Feeling strange
				Feeling weightless
				Feels awful
				Feels bad
				Feels poorly
				Felt like a zombie
				Floating feeling
				Foggy feeling head
				Funny episode
				Fuzzy
				Fuzzy head
				Muzzy head
				Neck strange feeling of
				Soft feeling
				Spaced out
				Thick head
				Unstable feeling
				Weird feeling

NEC: not elsewhere classified; NOS: not otherwise specified term

The adverse event term of sedation is mentioned in the 2010 Draft Guidance but is not included in this table.

12.13 List of Abbreviations and Definition of Key Study Terms

List of Abbreviations

Abbreviations	Description of abbreviations
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
APGD	Astellas Pharma Global Development Inc.
AST	aspartate aminotransferase
AT	aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve from the time of dosing to 24 hours
AUC_{inf}	area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{last}	area under the concentration-time curve from the time of dosing to the last measurable concentration
AUD	alcohol use disorder
BMI	body mass index
bpm	breaths per minute
B/N alone	buprenorphine/naloxone alone
B/N + ASP	buprenorphine/naloxone in combination with ASP8062
B/N + Pbo	buprenorphine/naloxone in combination with placebo
CL/F	apparent clearance
C_{max}	maximum concentration
CNS	central nervous system
CO_2	carbon dioxide
COWS	clinical opiate withdrawal scale
CPP	conditioned place preference
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{trough}	concentration immediately prior to dosing at multiple dosing
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DPD	Data Protection Directive
DSM-4	Diagnostic and Statistical Manual of Mental Disorders, edition 4
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, edition 5
ECE	emergency code envelopes
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form

Abbreviations	Description of abbreviations
EEA	European Economic Area
ESV	end-of-study visit
EtOH	ethanol
FAS	full analysis set
FM	fibromyalgia
FSH	follicle-stimulating hormone
GABA	gamma-aminobutyric acid
$GABA_B$	gamma-aminobutyric acid type B
GCP	Good Clinical Practice
GHB	γ-hydroxybutyrate
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
LA-CRF	liver abnormality case report form
LS	least square(s)
NIDA	National Institute on Drug Abuse
OUD	opioid use disorder
PAM	positive allosteric modulator
PGx	pharmacodynamics
PKAS	pharmacokinetic analysis set
PTR	peak trough ratio
QA	quality assurance
QC	quality control
QTcF	corrected QT interval using Fridercia's formula
QTL	quality tolerance limit
RSI	reference safety information
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set
SBP	systolic blood pressure
SOP	standard operating procedure
SpO_2	blood oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
SWS	slow-wave sleep
$t_{½}$	terminal elimination half-life

Abbreviations	Description of abbreviations
TBL	total bilirubin
TEAE	treatment-emergent adverse event
t_{lag}	time prior to the time corresponding to the first measurable (nonzero) concentration
t_{max}	time of maximum concentration
UGT	UDP-glucuronosyltransferases
ULN	upper limit of normal
USM	urgent safety measure
VAS	visual analogue scale
V_z/F	apparent volume of distribution during terminal phase after oral/extravascular administration
WOCBP	woman of childbearing potential

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Assessments of subjects as they enter a study before they receive any IP.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a subject into a study. Note: once a subject has received the IP or placebo, the protocol applies to the subject.
Intervention	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed and where the test product or comparative drug (sometimes without randomization) is given to a subject and continues until the last assessment after completing administration of the test product or comparative drug.
Randomization	The process of assigning subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias. Note: unequal randomization is used to allocate subjects into groups at a differential rate; for example, 3 subjects may be assigned to a treatment group for every 1 assigned to the control group.
Screen failure	Potential subject who signed the informed consent form, but did not meet 1 or more criteria required for participation in the study and was not randomized.
Screening	A process of active consideration of potential subjects for randomization in a study.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent form until just before the test product or comparative drug (sometimes without randomization) is given to a subject.
Study period	Period of time from the first study site initiation date to the last study site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

13 ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 2

I. The purpose of this amendment is:

Nonsubstantial Changes
1. Update to the rescreening language
DESCRIPTION OF CHANGE:
Edit the rescreening language.
RATIONALE:
To allow for the repeat of screening assessments within the screening window or to allow a subject to rescreen once for the study. Due to the nature of the participant population and the study design, subject safety and data integrity will not be impacted.
2. Clarify inclusion and exclusion criteria
DESCRIPTION OF CHANGE:
Move exclusion criterion 23 to the inclusion criteria and clarify the CYP450 enzymes that are excluded for exclusion criterion 18.
RATIONALE:
Previous exclusion 23 should be answered affirmatively in order for the subject to be eligible for participation; as a result, this exclusion should be listed as an inclusion. Exclusion 18 excluded all inducers of metabolism; however, after consideration, it is only necessary to exclude inducers of CYP2C8, 2C9, and 3A4.
3. **Clarify procedure for continuous end tidal CO_2**
DESCRIPTION OF CHANGE:
Add clarification that subjects may remove canula to dose or eat.
RATIONALE:
The timepoints overlap for the collection of end tidal CO_2 and it would not be possible for the subject to dose or eat with the canula in place.

II. Amendment summary of changes:

1.1 Synopsis, Inclusion Criteria & 5.1 Inclusion Criteria
ADDED:
14. Participant must be willing to abstain from smoking (including use of tobacco-containing products and nicotine or nicotine-containing products [e.g., electronic vapes] from at least 1 hour predose through at least 8 hours postdose on days 11 and 12.

1.1 Synopsis, Exclusion Criteria & 5.2 Exclusion Criteria
WAS:
18. Subject has used any inducer of metabolism (e.g., barbiturates and rifampin) in the 3 months prior to day -1.
IS AMENDED TO:
18. Subject ~~has used any inducer of metabolism (e.g., barbiturates and rifampin) in the 3 months prior to day -1.~~ **has used any inducer of CYP2C8, 2C9 or 3A4-related metabolism (e.g., barbiturates, rifampin, aprepitant, ritonavir, apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, phenobarbital, primidone, armodafinil, modafinil, and rufinamide) in the 3 months prior to day -1.**

1.1 Synopsis, Exclusion Criteria & 5.2 Exclusion Criteria
DELETED:
~~22. Participant must be willing to abstain from smoking (including use of tobacco-containing products and nicotine or nicotine-containing products [e.g., electronic vapes] from at least 1 hour predose through at least 8 hours postdose on days 11 and 12.~~

1.3 Schedule of Assessments Table 1 footnote 13
WAS:
13. Continuous end tidal CO2 to be collected starting predose on days 11 and 12 until 8 hours postdose. Timepoints will be recorded predose and 1, 2, 4 and 8 hours postdose.
IS AMENDED TO:
13. Continuous end tidal CO2 to be collected starting predose on days 11 and 12 until 8 hours postdose. Timepoints will be recorded predose and 1, 2, 4 and 8 hours postdose. **The cannula may be removed while subjects dose or eat.**

5.4.1 Rescreening
WAS:
Rescreening is allowed only in situations in which a subject underwent the screening procedures and due to logistical circumstances, the allocated time window for these tests has expired and the subject is documented as a screen failure. In order to rescreen, a new ICF must be signed and a new subject screening number assigned. Rescreening is only allowed once for an individual subject.
IS AMENDED TO:
~~Rescreening is allowed only in situations in which a subject underwent the screening procedures and due to logistical circumstances, the allocated time window for these tests has expired and the subject is documented as a screen failure. In order to rescreen, a new ICF must be signed and a new subject screening number assigned. Rescreening is only allowed once for an individual subject.~~ **Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, vital signs, physical examination, ECG, etc.) may be repeated once within the 28-day screening period without the need to register the participant as a screen failure. If the participant meets exclusion criteria that cannot resolve during the screening period, or more than 28 days elapse from the date of signing the ICF, the participant must be documented as a screen failure. In order to re-screen after prior screen failure, a new ICF must be signed and the participant entered into screening with a new participant identification number. Rescreening is only allowed once for an individual participant.**

III. Nonsubstantial amendment rationale:

Rationale for Nonsubstantial Designation
All revisions made to the protocol are administrative in nature and do not impact the safety or scientific value of the clinical study.

14 SPONSOR'S SIGNATURES

Astellas Signatories

(Electronic signatures are attached at the end of the document.)

PPD	Development Medical Science, Medical Specialties
PPD	Data Science, Medical and Development