A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIXED SEQUENCE STUDY TO ASSESS THE EFFECT ON RESPIRATORY DRIVE OF MULTIPLE DOSES OF AZD4041 WHEN CO-ADMINISTERED WITH A SINGLE DOSE OF MORPHINE IN HEALTHY RECREATIONAL OPIOID USERS

Protocol Number:	D7460C00003
Altasciences Project Number:	AZN-P1-265
Investigational Product:	AZD4041
Phase of Development:	Phase 1
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden

COMPLIANCE

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation and all applicable federal and local regulations.

Protocol Version		Date
1.0	**(Original)**	**August 09, 2022**
2.0	**(Amendment 01)**	**September 16, 2022**

PROTOCOL AMENDMENT 01 – SUMMARY OF CHANGES

Description of Change Made	Section/Location	Rationale
Changed manufacturer, concentration and volume of administration of opioid treatment (morphine).	• Study Synopsis (Opioid, Dose, and Mode of Administration) • Section 3.2 (Study Treatments) • Section 5.1.2 (Morphine)	Lack of supply by original manufacturer.
Clarified a discrepancy in exclusion criterion #23. Changed: *'Positive test result for alcohol and/or drugs of abuse upon admission on **Day -1**.'* To: *'Positive test result for alcohol and/or drugs of abuse upon admission on **Day -2**.'*	Section 4.2 (Exclusion Criteria)	To be consistent with the accurate information presented in Table 6-1 (Schedule of Activities)

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STUDY SYNOPSIS

Name of Sponsor/Company:	AstraZeneca AB
Name of Product:	AZD4041
Title of Study:	A Randomized, Double-blind, Placebo-controlled, Fixed Sequence Study to Assess the Effect on Respiratory Drive of Multiple Doses of AZD4041 When Co-administered With a Single Dose of Morphine in Healthy Recreational Opioid Users
Study Development Phase:	Phase 1
Objectives:	**Primary objective:** • To assess the effect on respiratory drive of morphine administered after multiple doses of AZD4041 compared to morphine administered alone in healthy recreational opioid users **Secondary objectives:** • To assess the safety and tolerability of multiple doses of AZD4041 when co-administered with a single dose of morphine in healthy recreational opioid users • To assess the pharmacokinetics (PK) of AZD4041 and morphine in healthy recreational opioid users • To assess the impact of multiple dose administrations of AZD4041 on the PK of morphine and its metabolites • To assess the impact of morphine on steady-state PK of AZD4041 • To assess the renal clearance of AZD4041
Endpoints:	**Safety:** *Primary* Incidence of clinically significant changes in respiratory parameters, defined as: • Incidence of increased end tidal carbon dioxide ($EtCO_2$) of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) • Incidence of reduction in SpO_2 to <92% (sustained for at least 30 seconds) *Secondary* • SpO_2 (%) ▪ Mean time to reduction in SpO_2 to <92% (sustained for at least 30 seconds) ▪ Mean duration of reduction in SpO_2 to <92% (sustained for at least 30 seconds)

	▪ Maximum postdose reduction of SpO_2 adjusted for baseline ▪ Mean postdose SpO_2 • $EtCO_2$ (mmHg) ▪ Mean time to each increased $EtCO_2$ episode of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) ▪ Mean duration of each increased $EtCO_2$ episode of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) ▪ Maximum postdose increase in $EtCO_2$ adjusted for baseline ▪ Mean postdose $EtCO_2$ • Respiratory rate (breaths/min) ▪ Incidence of reduced respiratory rate to <6 breaths/min (sustained for at least 30 seconds) ▪ Mean time to each reduced respiratory rate episode of <6 breaths/min (sustained for at least 30 seconds) ▪ Mean duration of each reduced respiratory rate episode of <6 breaths/min (sustained for at least 30 seconds) ▪ Maximum postdose decrease in respiratory rate adjusted for baseline ▪ Mean postdose respiratory rate • Incidence, frequency, severity and relationship of AEs • Vital signs (blood pressure, heart rate, and oral temperature) • ECGs (12-lead safety ECGs, 12-lead digital ECGs, ECG telemetry) • Clinical laboratory test results (clinical chemistry, hematology, coagulation, urinalysis) • Physical examination findings • Neurological examination findings • Columbia-Suicide Severity Rating Scale (C-SSRS) findings • Type of medical intervention used, summarized for each event of significantly increased $EtCO_2$, reduced SpO_2, or respiratory rate **Pharmacokinetic:** Plasma samples will be analyzed to determine concentrations of AZD4041, morphine, morphine-6-glucuronide and morphine-3-glucuronide. <u>Pharmacokinetic parameters for morphine, morphine-6-glucuronide and morphine-3-glucuronide include, but are not limited to, the following:</u> Day 1 and Day 15 : • C_{max}: Maximum observed plasma concentration • t_{max}: Time to maximum observed plasma concentration • AUC_{0-t}: Area under the plasma concentration vs time curve from time 0 to the time of the last measurable concentration

	• $AUC_{0-\infty}$: Area under the concentration time curve extrapolated to infinity, calculated as $AUC_{0-T} + C_{last}/\lambda_Z$, where C_{last} is the last quantifiable concentration at time T_{last} • $t_{1/2,z}$: Terminal elimination half-life, calculated as $\ln(2)/\lambda$ • T_{last}: Time of last measurable observed concentration • CL: Total body clearance, calculated as $Dose/AUC_{0-\infty}$ (parent drug only) • Vz: Volume of distribution based on terminal phase (parent drug only) <u>Pharmacokinetic parameters for AZD4041 include, but are not limited to, the following:</u> Days 2 to 7 and 9 to 14: • C_{trough}: Predose concentration observed immediately prior to the next successive dose Days 8 and 15: • $C_{max,ss}$: Maximum observed plasma concentration • $t_{max,ss}$: Time to maximum observed plasma concentration • C_{trough}: Predose concentration observed immediately prior to the next successive dose • AUC_τ: Area under the concentration time curve over the dosing interval at steady-state, calculated from 0 to 24 hours (dosing interval) • C_{av}: Average concentration during a dosing interval, after the last dose of a multiple dose regimen, calculated as $AUC\tau/\tau$ • $t_{1/2,z}$: Terminal elimination half-life, calculated as $\ln(2)/\lambda$ (Day 15 only) • CLss/F: Apparent clearance at steady-state, calculated as $Dose/AUC_\tau$ • Vzss/F: Apparent volume of distribution at steady-state (based on terminal phase) Urine samples will be analyzed to determine concentrations of AZD4041. <u>Pharmacokinetic parameters for AZD4041 include, but are not limited to, the following:</u> Day 15: • $Ae\tau$: Amount of drug excreted in urine • fe/F: Cumulative fraction of unchanged drug excreted in urine over the dosing interval • CL_R: Apparent renal clearance • $t_{1/2}$: Elimination half-life

Investigational Product, Dose, and Mode of Administration (proposed):	AZD4041 oral solution CCI (active drug dissolved in vehicle) Manufacturer of Drug Substance: AstraZeneca Dose: CCI Mode of administration: Oral
Placebo, Mode of Administration:	Vehicle (CCI) without active drug (AZD4041) Manufacturer: MEDISCA Mode of administration: Oral
Opioid, Dose, and Mode of Administration	Morphine for intravenous (IV) use (Duramorph PF®), CCI Manufacturer of Drug Substance: Hikma Pharmaceuticals USA Inc. Dose: CCI Mode of administration: IV
Study Design:	This is a Phase 1, randomized, double-blind, placebo-controlled, 2 fixed sequence multiple dose study in healthy male and female recreational opioid users. This study will consist of 3 phases: Screening and Qualification phase, Treatment phase, and Follow-up/Early Termination (ET). After a Screening period of up to 27 days (Day -30 to Day -3), eligible subjects will be admitted to the clinical research unit (CRU) on Day -2. Subjects will be randomized to 1 of 2 fixed treatment sequences (28 subjects in Sequence 1, and 16 subjects in Sequence 2) on Day -1. Subjects will be required to present a negative urine drug and alcohol screen upon admission on Day-2, except for tetrahydrocannabinol (THC). If THC is positive at admission, a cannabis intoxication evaluation will be done by an Investigator, and subjects may be permitted to continue in the study at the discretion of an Investigator. Subjects will then undergo a naloxone challenge where an initial 0.2 mg IV dose of naloxone hydrochloride (HCl) will be administered. The subject will be observed for signs or symptoms of opioid withdrawal. If there is no evidence of withdrawal within 1 minute (as assessed by a Clinical Opioid Withdrawal Scale [COWS] score of <5), an additional 0.6 mg IV dose of naloxone HCl will be given, and the subject will be observed for signs and symptoms of withdrawal for 5 minutes (as assessed by COWS). Subjects who present symptoms of withdrawal during the qualification process will be excluded from the study and will not be eligible to enter the Treatment phase. In total, subjects will be confined to the CRU for approximately 20 days from Day -2 to Day 18 (until approximately 72 hours following the last study drug administration). On Day 1, subjects will receive a single CCI IV dose of morphine. From Day 2 to Day 15, subjects will receive a CCI oral dose of AZD4041 or placebo once daily for 14 consecutive administrations. On the morning of Day 15, the CCI oral dose of AZD4041 or placebo will be combined with a single CCI IV dose of morphine. In order to limit the number of subjects being treated with investigational product

	on any single day, eligible subjects will be assigned to different subgroups. Subgroup sizes should be limited to no more than 8 subjects. Dosing of subgroups should be staggered to occur on different days, with at least 2 days between the start of dosing for sequential subgroups. A Follow-up visit will occur approximately 7 days after the last drug administration.
Duration of Treatment and Subject Confinement:	Duration of clinical trial (per subject): Screening: Day -30 to Day -3 (up to 27 days) Qualification: Day -2 to Day -1 (2 days) Treatment: Subjects will be confined to the clinical site for approximately 20 days, from Day -2 until Day 18 (ie, until 72 hours following the last study drug administration) Follow-up visit: Subjects will be followed-up approximately 7 days after the last drug administration. Total study duration: up to 54 days (including Screening)
Study Population:	Healthy, male and/or female recreational opioid users
Planned Number of Subjects:	Approximately 44 subjects will be randomized (28 AZD4041 + morphine and 16 Placebo + morphine) to ensure completion of at least 36 subjects (24 AZD4041 + morphine, and 12 Placebo + morphine on Day 15).
Bioanalysis:	Plasma concentrations of AZD4041, morphine, morphine-6-glucuronide and morphine-3-glucuronide will be measured by validated bioanalytical methods. Urine concentrations of AZD4041 will also be measured by a validated bioanalytical method.
Safety Analysis:	The safety analysis will be fully detailed in a statistical analysis plan (SAP).
Pharmacokinetic Analysis:	The PK parameters will be determined by non-compartmental analysis using appropriate software. The PK analysis will be fully detailed in a SAP.
Statistical Analysis:	The statistical analyses will be fully detailed in a SAP.

STUDY ADMINISTRATIVE STRUCTURE

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1. INTRODUCTION

1.1. Background

Opioid use disorder (OUD) is a public health crisis responsible for significant morbidity, mortality, and productivity loss. In 2019, approximately 70% of deaths from drug overdose involved opioids (CDC, 2020), and seven out of 1000 babies (~90 babies each day) were born with neonatal abstinence syndrome because their mothers had OUD (Healthcare Cost and Utilization Project, 2016). OUD presents an enormous economic burden in the US estimated to be $170-215 billion per year (Society of Actuaries, 2019), with the total annual costs to the healthcare system in 2018 alone estimated at over $89 billion (Murphy, 2020). These economic burdens and costs to health, quality of life, and public assistance programs are all directly or indirectly related to OUD. There are only 3 Food and Drug Administration (FDA) approved treatments for OUD, all of which target μ opioid receptors, which are the major targets for opioid actions in the brain. Methadone, buprenorphine, and naltrexone act as an agonist, partial agonist, and antagonist, respectively, at μ opioid receptors. While each is effective with supervised use and accessory support services, such as counselling, they have limited clinical efficacy and utility (Leslie et al, 2019, Mancher et al, 2019). Limitations include intrinsic rewarding properties that lead to misuse/diversion (Hall et al, 2008, Leslie et al, 2019, Mancher et al, 2019), unpleasant side effects (Chen and Ashburn, 2015) that reduce compliance, such as withdrawal symptoms (Mancher et al, 2019), and high residual rates of relapse to drug use (Leslie et al, 2019, Wakeman et al, 2020). Since OUD and its deleterious consequences are a dire national health crisis, the US National Institute on Drug Abuse (NIDA) has identified several high priority drug targets for rapid therapeutic development (Rasmussen et al, 2019). OX_1 receptor antagonists are high on this list and are considered one of the most promising targets for the development of novel OUD treatments (Rasmussen et al, 2019).

The neuropeptides orexin A and orexin B (also known as hypocretin 1 and hypocretin 2, respectively) are hypothalamic neuropeptides that act through 2 closely related G protein coupled receptors, the OX_1 and OX_2 receptors. Orexin A has high affinity for both receptors whereas orexin B has higher affinity for OX_2 over OX_1 receptors. Orexin transmission has been implicated in a diverse range of physiological functions, including feeding and energy homeostasis (Sakurai et al, 1998), the sleep/wake cycle (Gotter et al, 2016), neuroendocrine homeostasis, cardiovascular functions (Samson et al, 2007), and motivated behaviours (Kodadek and Cai, 2010). A considerable body of preclinical studies suggests that orexin transmission at OX1 receptors plays a major role in the motivation to seek and consume opioids and other drugs of abuse (Quarta et al, 2009; Porter-Stransky et al, 2017; Fragale et al, 2019). Indeed, pharmacological blockade of OX_1 receptors or genetic deletion of the gene encoding this receptor markedly decreases the consumption of opioids and other addictive drugs such as nicotine and cocaine in laboratory animals without altering their willingness to engage in and seek natural reinforces such as food or sex (Kohlmeier et al, 2013).

Based on these findings, it has been proposed that excessive orexin transmission at OX1 receptors may play a fundamental role in the development and maintenance of OUD. Recent human brain studies provide compelling support for this hypothesis. Post-mortem human brain studies have revealed that the numbers of orexin neurons detected in the lateral hypothalamus of those suffering from OUD are markedly upregulated compared with non-OUD patients

(Pantazis et al, 2020). Rodents treated with opioids also show increased numbers of orexin neurons in the brain (Thannickal et al, 2018). This response is thought to reflect the de novo production of orexin peptides by neurons in the hypothalamus in response to opioid use, which contributes to the excessive orexin transmission hypothesized to drive the pathologically elevated motivation to seek and consume opioids (Thannickal et al, 2018). Based on compelling preclinical studies and clinical literature, OX_1 receptor antagonists are considered one of the most promising novel therapeutic strategies to treat OUD (Rasmussen et al, 2019). Importantly, OX_1 receptors play a similar role in regulating the addiction-related actions of nicotine, psychomotor stimulants, and alcohol, raising the possibility that OX_1 receptor antagonists may have utility for the treatment of addiction across different classes of abused drugs.

1.2. Study Rationale

AstraZeneca (AZ), in partnership with Eolas Therapeutics, Inc, is developing an OX_1 receptor antagonist, AZD4041, which demonstrates favourable drug-like physiochemical properties. The half maximal inhibitory concentration (IC_{50}) for AZD4041 at OX_1 and OX_2 receptors is 5 nM and > 5000 nM, respectively. The high level of selectivity between the OX_1 and OX_2 receptors substantially reduces the potential for hypnotic effects of this OX_1 antagonist since it is thought that the OX_2 receptor is primarily responsible for the effects of orexin on arousal (Boutrel et al, 2005). Consistent with this possibility, AZD4041 does not induce sleep-like electroencephalogram (EEG) waveforms in rodents across a broad range of doses. AZD4041 does not measurably inhibit the activity of cytochrome P450 enzymes or human ether-a-go-go-related gene (hERG) channels nor does it have significant actions at any non-OX_1 receptor targets so far screened. AZD4041 is highly brain penetrant in nonhuman primates and has relatively slow rates of clearance and high levels of oral bioavailability in dogs. AZD4041 demonstrates in vivo efficacy, as measured by reduced oxycontin-seeking behaviours, in rodents - at relatively low exposures. Further details of these studies are provided in the Investigator's Brochure (AZD4041 Investigator's Brochure).

AZD4041 may therefore provide an attractive treatment option for OUD.

This study is being primarily conducted to assess the effect on respiratory drive of morphine administered after multiple doses of AZD4041 compared to morphine administered alone in healthy recreational opioid users. This study will also assess the safety, tolerability, and pharmacokinetics (PK) of multiple doses of AZD4041when co-administered with single dose of morphine in healthy recreational opioid users. The PK of AZD4041 and morphine in healthy recreational opioid users will be assessed. Moreover, the impact of multiple dose administrations of AZD4041 on the PK of morphine and metabolites will also be assessed, including the impact of morphine on steady-state PK of AZD4041.

1.3. Risk/Benefit Assessment

1.3.1. Known Potential Benefits

AZD4041 has shown significant efficacy in oxycodone self-administration studies in rats. In addition, AZD4041 reduces cue-induced reinstatement of oxycodone seeking behaviours and blocks craving-like behaviours in a rat model of oxycodone withdrawal. Supporting the feasibility of developing a safe and potent OX1 receptor antagonist for OUD is the fact that two dual OX1/OX2 receptor antagonists (suvorexant and lemborexant, so-called DORAs) have

already received FDA approval as sleep-promoting agents. The sleep-promoting actions of DORAs primarily reflect their ability to block the OX2 receptors. Neither of these DORAs show any evidence of concerning side-effects in the general population despite their wide-spread use. This suggests that novel OX1 receptor selective antagonists, devoid of the sleep-promoting effects that limit the utility of DORAs for non-sleep-related disorders such as OUD, are unlikely to be associated with mechanism related toxicity in humans (O'Connor et al, 2010). It therefore appears that AZD4041 could represent a novel strategy in the treatment of addictive disorders such as OUD, where it has the potential to address a significant unmet need. It is thought unlikely that the recreational opioid users participating in the current study will benefit from taking the AZD4041 study treatment. However, it is anticipated that the study will provide important safety and PK data that will inform the scientific rationale for further development of AZD4041 as a potential treatment of OUD.

1.3.2. Important Potential Risks

Potential risks of AZD4041 based on data observed in animal studies include thymus effects (including atrophy), male reproductive tract effects, and arrhythmias.

In nonclinical studies, AZD4041 has been evaluated in repeat dose toxicity studies of 1 month duration in rats, and in studies of 1- and 3-months duration in dogs; in in vitro and in vivo genotoxicity studies; and in an in vitro phototoxicity study. Safety pharmacology studies assessing effects on the respiratory, cardiovascular, central and peripheral nervous systems, and in vitro effects on hERG have also been conducted.

AZD4041 was negative in the Good Laboratory Practice (GLP) in vitro Ames and chromosome aberration studies and in the GLP in vivo micronucleus study. AZD4041 was also negative in an in vitro 3T3 phototoxicity assay.

No significant effects of AZD4041 were noted on the central nervous system (CNS), locomotor function, or motor coordination in rats. In the sleep/wake and EEG study in rats, AZD4041 significantly increased wakefulness at the expense of non-rapid eye movement sleep when compared with control. In a respiratory study conducted in rats, no significant effects were seen except at the highest dose of 100 mg/kg where lower tidal volume (11% below) was noted when compared with vehicle control at baseline. A similar effect was noted with AZD4041 alone in a study with a morphine challenge; increased respiratory depression was also noted following morphine administration after AZD4041. For the current clinical study, effects on sleep/wakefulness will be assessed via AE reporting. Only healthy subjects will be enrolled in the current study and subjects with respiratory co-morbidities will be excluded. In addition, vital signs will be assessed at regular intervals after dosing (See Schedule of Activities, Table 6-1).

In the hERG assay, the IC_{50} for AZD4041 was calculated to be 219.3 µM. In a panel of in vitro electrophysiological assays of recombinant human voltage-gated cardiac ion channels (hKv4.3/hKChIP2.2 – ITO; hKv7.1/hKCNE1 – IKS; hNav1.5 – INa; hKV1.5; hCav3.2; hHCN4), AZD4041 had no activity. Therefore, a risk of QT prolongation is not expected with AZD4041. In the dog cardiovascular study, sustained durations of premature ventricular contractions, beginning approximately 7 hours after dosing and continuing up to 24 hours after dosing, were noted in 1 dog only at the highest dose of 100 mg/kg. The onset of the changes was soon after the approximate T_{max} (average of 4.6 hours) in the dog study. Hemodynamic

parameters were largely unaltered and were maintained in the physiological range of heart rate (HR) and blood pressure (BP). In a dog 14-day investigative study, lower HR, with associated longer PR and QT intervals, were recorded at 60 mg/kg/day; there were no changes in the rate-corrected QT interval and no arrhythmias were noted. There were no changes in ECG rhythm or waveform morphology attributable to AZD4041. Furthermore, there were no effects on ECG parameters or morphology in the 1-month dog study in which dogs received up to 60 mg/kg/day.

In the 1-month GLP toxicity studies, the key findings were lower thymus weights and thymic atrophy in female dogs, and effects on the male reproductive tract in dogs. Other findings were increased liver weight, attributed to hepatocellular hypertrophy in rats and dogs; and increased thyroid weight, attributed to follicular cell hypertrophy and recorded in rats only. Due to the minimal severity and adaptive nature of the changes, the hepatic and thyroid changes were considered not adverse. Lower thymus weights were noted for female dogs and correlated with increased severity of thymic atrophy, characterized by decreased thickness of the cortex relative to the medulla, at the high dose. Taken together, the effect on thymus weight combined with the microscopic finding of atrophy was considered to be adverse. There were no effects on organ weight or microscopic pathology noted for the thymus at the end of the recovery period, indicating recovery. Effects on the thymus were not recorded in the dog 3-month study.

In the dog 1-month study, effects in the form of tubular degeneration/atrophy of the testes, reduced luminal sperm in the epididymides, and immaturity and/or single cell necrosis of the prostate glands, with associated effects on organ weight, were noted. There was some evidence of recovery at the end of the 4-week recovery period, in that findings were of a lesser severity compared to the main test and/or of a similar incidence/severity to the concurrent controls. In the 3-month dog study, there were changes in the prostate (atrophy and lower weight) and testes (vacuolation of Leydig cells) and epididymides (epithelial vacuolation). In comparison to the 1-month study, these changes were generally not as marked, considered to be non-adverse and followed longer term administration at generally higher exposures. Following 1 month of administration, the no-observed-adverse-effect-level (NOAEL) was established as 100 mg/kg/day in the rat and 10 mg/kg/day in the dog. The NOAEL in the dog 3-month study was 60 mg/kg/day. There is evidence that OX_1 receptors are expressed in dog seminiferous tubules (Ligouri, 2018) and are involved in the regulation of spermatogenesis (Barreiro et al, 2005, Hakovirta et al, 1999, Yan et al, 1999, Yan et al, 2000), which may demonstrate a potential link between the pharmacological action of AZD4041 and the findings in the dog. It should be noted that similar findings were not seen after 14 days in the dog dose range finding study, albeit with smaller numbers. No effects on the male reproductive tract were seen in the rat 1-month GLP toxicity study.

The AZD4041 single ascending dose (SAD) study (Protocol D7460C00001) was completed for 6 cohorts of healthy volunteer with N= 8 subjects per cohort randomly assigned to receive either AZD4041 or placebo (N= 6 AZD4041 and N=2 placebo). Single oral doses explored in the SAD study were CCI [redacted]. There were no severe treatment emergent adverse events (TEAEs), severe adverse events (SAEs) or TEAEs leading to study discontinuation over the course of the study. There were no apparent dose-related trends with respect to the reporting of AEs. The most common TEAEs to be reported in subjects treated with AZD4041 include ventricular tachycardia (5.6%), back pain (5.6%), nausea (2.8%), vomiting

(2.8%) and dyspnea (2.8%). No clinically significant changes have been reported for laboratory safety, vital sign, or 12-lead ECG parameters.

Two short episodes of non-sustained ventricular tachycardia (NSVT) were observed in the SAD study in subjects who had received AZD4041, 1 each in Cohort 4 (CCI) and Cohort 5 (CCI), observed at 8 hours and 6.5 hours postdose, respectively. The NSVT events were asymptomatic and resolved spontaneously. Across the full dose range of the study, no trends for changes or prolongations in ECG parameters including QTcF, QRS, and PR interval; or changes in the QRS and T-wave morphology that would indicate, for example, hERG-related potassium or sodium channel effects. There was no evidence for systematic changes in HR. In 12-lead ECG telemetry files of the 2 subjects with NSVT, no notable QTcF prolongation or QRS interval prolongation, or changes in QRS or T wave morphologies were found. No subject in the study has had a QTcF > 450 msec. Only 1 subject in the study had an increase in QTcF > 30 msec (32 msec), which occurred at 6 hours postdose. Neither subject appears to be different from the rest of the subjects in their cohort based on exposure parameters (Area under the curve, C_{max}, T_{max}, concentration at 6 and 8 hours).

The multiple ascending dose (MAD) study of AZD4041 (Protocol D7460C00002) has recently completed in Canada and interim data [blinded to treatment assignment] are available pending database lock. Three dose levels of AZD4041 were explored (CCI) in healthy volunteers, who received repeat once-daily doses for 14 days (N=12 subjects per cohort with N=9 receiving AZD4041 and N=3 receiving placebo). Cardiac monitoring included extended periods of ECG telemetry and Holter ECG recording. Dose escalation proceeded uneventfully across the cohorts. Exposures for AZD4041 (C_{max} and AUC) increased in an approximate dose proportionate manner from CCI and remained within the range predicted. Maximum exposures (T_{max}) were observed between 0.5 to 3.0 hours postdose. The effective half-life for AZD4041 ranged from 18.6 to 21.3 hours, comparable to that observed in the SAD study. Accumulation ratios over the dosing period ranged from 1.27 to 1.59 for C_{max} and from 1.66 to 1.81 for AUC. Steady state exposures (C_{trough}) were achieved at Day 6 for the CCI dose and Day 8 for the CCI dose levels. With respect to the pre-defined limits of human exposure and exposure predictions for potential doses higher than CCI , further dose escalation was not undertaken. No medically important tolerability or safety issues were raised by the dose escalation committee with respect to any of the safety endpoints (including vital signs, 12-lead ECGs, safety blood tests and urinalysis) during the course of the study. There were no observed SAEs or dose-limiting toxicities. Adverse events were mild in nature and were mostly resolved by checkout. The most common TEAEs, reported in two or more subjects, were NSVT (observed for two subjects in Cohort 1 [CCI placebo] and one subject in Cohort 3 [CCI placebo]), post lumbar puncture syndrome, medical device site reaction, headache, and nausea. The NSVT events were detected on Holter ECG monitoring; they were non-sustained and resolved spontaneously. One of the subjects with NSVT in Cohort 1 reported palpitations on Day 2 and was withdrawn by the Investigator before dosing on (Day 3) for safety reasons due to these adverse events. In Cohort 3 CCI placebo), one episode of NSVT was observed on Day 2, ~7.5 hours after dosing. The event was asymptomatic and resolved without intervention or recurrence. No clinically significant changes or trends for changes were observed for laboratory safety assessments, vital sign parameters, or ECG intervals in the MAD study. Overall, AZD4041 was considered to have a good safety and tolerability profile when

administered to healthy volunteers in repeat oral doses (once daily for 14 days) up to CCI in the MAD study. A detailed summary of the available human safety and PK data is provided in the Investigator's Brochure (AZD4041 Investigator's Brochure).

There is limited class information on the safety profile of selective OX1 receptor antagonists in humans. While two DORA (suvorexant and lemborexant) are approved for the treatment of insomnia, no selective OX1 receptor antagonists have been approved for any indication so far. Limited safety data are available for the single and multiple dosing studies with 2 selective OX1 receptor antagonists (ACT-539313 [Kaufmann et al, 2019, Kaufmann et al, 2021] and JNJ-61393215 [Salvadore et al, 2019]). Both appeared to be well tolerated in these initial studies with the most common reported AEs being somnolence and headache.

The following safety measures will be monitored continuously for signs of respiratory depression from up to 1 hour prior to dosing up to approximately 6 hours following dosing in the Treatment phase:

- End-tidal carbon dioxide ($EtCO_2$) monitoring
- Blood oxygen saturation (SpO_2) monitoring
- Respiratory rate monitoring

Safety measurements of $EtCO_2$ and SpO_2 are accepted endpoints for the evaluation and monitoring of respiratory function, change in oxygenation, and change in ventilation (Linko and Paloheimoi, 1989, Jabre et al, 2009, Manifold et al, 2013, and Waugh et al, 2011). Monitoring $EtCO_2$ has been shown to be more sensitive in the detection of respiratory depression than monitoring respiratory rate and pulse oximetry alone (Goli et al, 2012). In the clinical setting, respiratory depression is usually described in terms of decreased respiratory rates, decreased SpO_2 levels, (Cashman et al, 2004) or elevated $EtCO_2$ levels and, therefore, these measures are appropriate to monitor for respiratory depression in the context of this study.

Serious, life-threatening, or fatal respiratory depression may occur with use of morphine (Infumorph Label 2019). Subjects will be monitored for respiratory depression in a fully equipped and staffed environment. Details of mitigating signs of respiratory depression and medical interventions are provided in Sections 6.1.15 and 6.1.16.

Additional safety measures implemented at predose and specified timepoints postdose will include the collection and documentation of AEs and vital signs (ie, systolic and diastolic BP, HR, and oral temperature), respiratory rate, and SpO_2. Cardiovascular risk mitigations include appropriate eligibility criteria, individual and study-level stopping criteria; and a sufficiently stringent level of cardiac monitoring will be retained for the current clinical study protocol, similar to MAD study protocol; 12-lead safety ECGs, alongside extended periods of ECG telemetry and Holter monitoring have been implemented to monitor for any arrhythmias. Subjects will be determined as eligible for inclusion into the study based on measures of clinical laboratory testing, vital signs, medical history, Columbia-Suicide Severity Rating Scale (C-SSRS), physical examination, and ECG.

1.3.2.1. Justification for Dose selection

The rationale for the planned AZD4041 dose level (CCI) for the current study is based on an understanding of data accumulated across non-clinical studies and clinical experience to-date and summarised as follows:

- AZD4041 was found to have a good safety profile and to be well tolerated by healthy volunteer subjects administered single oral doses up to CCI in the completed single - dose study (D7460C00001) and up to CCI administered once daily for 14 days in the repeat-dose study (D7460C00002). The observed PK data in the studies indicate dose-related and approximately dose-proportional exposures. Steady state exposures were achieved after 6 to 8 days of repeat dosing. The observed steady-state exposures are aligned with those previously predicted from simulations and modelling. Exposures observed at the CCI repeat dose level in the MAD study do not exceed those previously achieved at the highest (CCI) single dose level explored in the SAD study (see Investigator's Brochure for details of human safety and PK).
- Safety margins for AZD4041 have been based on PK data observed in the MAD study at the CCI dose level and calculated with respect to exposure data achieved at the NOAEL exposures observed in the 3-month dog GLP study (60 mg/kg) and the 1-month rat GLP study (100mg/kg). The 3-month study is considered to provide the most robust and comprehensive assessment of the effects of AZD4041 in the dog. The lowest NOAEL exposures from the repeat dose toxicology studies are from the rat 1-month study (see Table 1-1 and Table 1-2). The relevant safety margins at the proposed CCI dose level are therefore considered to be 22-fold and 13.2-fold for maximum observed concentration (free $C_{max, ss}$) and total exposure at steady-state (free $AUC_{tau.ss}$), respectively.
- Concentrations of AZD4041 that are predicted to be therapeutically efficacious and relevant to humans with opioid-use disorder have been estimated by extrapolation of exposures at a dose level which is effective in a rat oxycodone withdrawal model. In the rodent model, a total plasma exposure of 523 nM and a free plasma exposure of 147 nM were estimated at an efficacious AZD4041 dose of CCI (PO). Analysis of PK data from the human MAD study indicates that it is possible to achieve comparable systemic exposures that are predicted to achieve efficacy. In humans, once daily repeat CCI doses of AZD4041 for 14 days provided a mean total C_{max} of 1828 nM (941 ng/mL) and free C_{max} of 327 nM (168.4 ng/mL). Likewise, human study provided a mean total C_{trough} concentration of 697 nM (359 ng/mL) and free C_{trough} concentration of 125 nM (64ng/mL) for CCI dose at steady-state. Preliminary evaluation of AZD4041 steady CNS penetration at the CCI dose level in the MAD study indicate a total brain-to-unbound plasma drug partition coefficient ($K_{p,uu}$) of 0.295. Corresponding estimates for the brain free concentrations (mean $C_{max.ss}$ = 97 nM and $C_{trough.ss}$ = 39 nM) are comparable to the estimated free brain exposure of AZD4041 (25 nM) predicted to confer efficacy in the rodent oxycodone withdrawal model. Furthermore, measured free brain concentrations in humans following dosing of CCI to steady state exceed the in vitro inhibitory constant for AZD4041 at the human orexin 1 receptor (Ki = 1.5 to 7.9 nM) and

are in line with exposures where OXR1 target engagement would be expected (see Investigator's Brochure for details).

- The proposed CCI dose level for AZD4041 is considered appropriate for the current study, because (1) the expected steady-state exposures at CCI provide coverage over a range of exposures that are predicted to be therapeutically efficacious for the treatment of opioid use disorder in humans, and (2), therefore provides for a robust evaluation of the potential for AZD4041 to interact with single doses of morphine at a dose level that is considered to be at the higher limit of plausible efficacious and therapeutically-relevant doses.

Table 1-1 Observed MAD study Exposures and Calculated Margins to Dog NOAEL (3-month GLP study)

Clinical dose (mg)	Total $C_{max.ss}$ (ng/mL)	Human Free $C_{max.ss}$ (ng/mL)	Total $AUC_{tau.ss}$ (ng·h/mL)	Human Free $AUC_{tau.ss}$ (ng·h/mL)	Free $C_{max.ss}$ margin to dog NOAEL	Free $AUC_{tau.ss}$ margin to dog NOAEL
CCI	232	41.5	3030	540	91	105
	478	85.6	6290	1125.9	44	50
	941	168.4	12609	2257.1	22	25

A human plasma protein binding value of 17.9% has been applied to calculate human free C_{max} and AUC_{tau}.
For the NOAEL values, combined sex (male and female) toxicokinetic data have been utilized.
Dog NOAEL (60 mg/kg) exposures for free C_{max} (3,764 ng/mL) and free AUC_{last} (56,883 ng.h/mL) were used to calculate safety margins.
Human exposures for the planned CCI dose level should not exceed 1/10th of the NOAEL in the 3-month dog study. Based on observed human exposures, free $C_{max.ss}$ is not expected to exceed 376 ng/mL and free $AUC_{tau.ss}$ is not expected to exceed 5688 ng.h/mL.

Table 1-2 Observed MAD study Exposures and Calculated Margins to Rat NOAEL (1-month GLP study)

Clinical dose (mg)	Total $C_{max.ss}$ (ng/mL)	Human Free $C_{max.ss}$ (ng/mL)	Total $AUC_{tau.ss}$ (ng·h/mL)	Human free $AUC_{tau.ss}$ (ng·h/mL)	Free $C_{max.ss}$ margin to dog NOAEL	Free $AUC_{tau.ss}$ margin to dog NOAEL
CCI	232	41.5	3030	540	90	55
	478	85.6	6290	1125.9	44	26
	941	168.4	12609	2257.1	22	13.2

A human plasma protein binding value of 17.9% has been applied to calculate human free C_{max} and AUC_{tau}.
For the NOAEL values, combined sex (male and female) toxicokinetic data have been utilized.
Rat NOAEL (100 mg/kg) exposures for free C_{max} (3,751 ng/mL) and free AUC_{last} (29,793 ng.h/mL) were used to calculate safety margins.
Human exposures for the planned CCI dose level should not exceed 1/10th of the NOAEL in the 1-month rat study. Based on observed human exposures, free $C_{max.ss}$ is not expected to exceed 375 ng/mL and free $AUC_{tau.ss}$ is not expected to exceed 2979 ng.h/mL.

- The dose of morphine administered in this study is not expected to present any significant risk to the subjects (Duramorph Label 2010). In adults, the recommended initial IV

morphine dose is between 2 mg to 10 mg/70 kg of body weight. Doses of morphine of up to [redacted] have been safely administered intravenously in non-dependent, recreational opioid users (Stoops et al, 2010, Webster et al, 2011). A supratherapeutic dose of morphine was selected for this study to increase the likelihood of evaluating effects on respiratory parameters. The dose of [redacted] IV was selected for this study as it has been safely administered in prior studies of opioid experienced, non-dependent recreational users (Osterlund et al, 2001, Osterlund et al, 1999, Thompson et al. 1999, Skarke et al, 2003, Bailey et al, 1991).

- The potential for AZD4041 ([redacted] administered once daily for 14 days) to interact with single doses of morphine at a metabolic level is considered to be low in this study. In vitro studies indicate that AZD4041 shows minimal or no inhibition across a panel of cytochrome P450 (CYP) enzymes with IC_{50} values all determined to be > 30 µM. AZD4041 is considered to pose a low risk as a perpetrator of drug-drug interactions via inhibition of transporters such as OATP1B1 (IC_{50} = 38 µM), BCRP (IC_{50} = 48 µM) or P-glycoprotein (IC_{50} = 282 µM) and poses a low risk as a perpetrator via induction of CYP enzymes (4-fold and 100 fold induction of CYP1A2 and CYP34 at 30 µM, respectively). While CYP3A4 contributes to >90% of AZD4041 metabolism in vitro, it is not expected that single doses of morphine ([redacted]) will appreciably affect the metabolism or clearance of AZD4041.

1.3.3. Risk/Benefit Conclusion

The hepatic and thyroid effects observed in the preclinical studies were considered minimal and adaptive; and thymic atrophy was noted to have fully recovered at the end of the recovery period. On the basis of data observed in the safety pharmacology study, the effects of AZD4041 co-administered with single doses of morphine, on respiratory drive will be evaluated and monitored in the clinical study by measuring $EtCO_2$, O_2 saturation, and respiratory rate.

Cardiac arrhythmia remains a *potential* risk during the ongoing exploratory clinical development of AZD4041 and appropriate risk mitigation measures have been implemented into the protocol.

Women of non-childbearing potential may be enrolled into the study. Inclusion of fertile (non-vasectomised) males in the study is justified on the basis that the 3-month dog GLP study provides the most robust and comprehensive evaluation of AZD4041 on the male reproductive tract in this species. A NOAEL has been identified in the dog study with respect to toxicologic effects seen in the prostate, testes and epididymides. Human exposures to AZD4041 at steady-state for the planned dose level ([redacted], once daily for 14 days) are not expected to exceed $1/10^{th}$ of the NOAEL in the 3-month dog study. These exposures are also significantly lower than those identified at the NOAEL in the rat 1-month study. No reproductive effects have been seen in the rat 1-month GLP study. In addition, the planned dose of AZD4041 has been evaluated previously in a 14-day MAD clinical study; the dosing regimen was generally well tolerated and no significant medical or safety concerns were raised by the dose escalation committee.

Based on the considerations regarding the potential risks of AZD4041, exposure of healthy volunteer subjects with a history of recreational opioid use to repeat doses of AZD4041 is considered justifiable in relation to the significant unmet need to develop improved efficacious

treatments for opioid-use disorder. It is expected that the safety, tolerability and PK data acquired in the current study in healthy volunteer who are opioid users, will provide a scientific basis and rationale for the subsequent evaluation of AZD4041 in patients with OUD.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of AZD4041 may be found in the Investigator's Brochure (AZD4041 Investigator's Brochure).

2. STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To assess the effect on respiratory drive of morphine administered after multiple doses of AZD4041 compared to morphine administered alone in healthy recreational opioid users	• $EtCO_2$ (mmHg): Incidence of increased $EtCO_2$ of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) • SpO_2 (%): Incidence of reduction in SpO_2 to <92% (sustained for at least 30 seconds)
Secondary	
To assess the safety and tolerability of multiple doses of AZD4041 when co-administered with a single dose of morphine in healthy recreational opioid users	• SpO_2 (%) ▪ Mean time to reduction in SpO_2 to <92% (sustained for at least 30 seconds) ▪ Mean duration of reduction in SpO_2 to <92% (sustained for at least 30 seconds) ▪ Maximum postdose reduction of SpO_2 adjusted for baseline ▪ Mean postdose SpO_2 • $EtCO_2$ (mmHg) ▪ Mean time to each increased $EtCO_2$ episode of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) ▪ Mean duration of each increased $EtCO_2$ episode of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds) ▪ Maximum postdose increase in $EtCO_2$ adjusted for baseline ▪ Mean postdose $EtCO_2$ • Respiratory rate (breaths/min) ▪ Incidence of reduced respiratory rate to <6 breaths/min (sustained for at least 30 seconds) ▪ Mean time to each reduced respiratory rate episode of <6 breaths/min (sustained for at least 30 seconds) ▪ Mean duration of each reduced respiratory rate episode of <6 breaths/min (sustained for at least 30 seconds) ▪ Maximum postdose decrease in respiratory rate adjusted for baseline

OBJECTIVES	ENDPOINTS
	▪ Mean postdose respiratory rate • Incidence, frequency, severity, and relationship of AEs • Vital signs (blood pressure, heart rate, and oral temperature) • ECGs (12-lead safety ECGs, 12-lead digital ECGs, and ECG telemetry) • Clinical laboratory test results (clinical chemistry, hematology, coagulation, urinalysis) • Physical examination findings • Neurological examination findings • C-SSRS findings • Type of medical intervention used, summarized for each event of significantly increased $EtCO_2$, reduced SpO_2, or respiratory rate
To assess the PK of AZD4041 and morphine in healthy recreational opioid users	Plasma concentrations as well as PK parameters for AZD4041 and morphine and its metabolites as described in Section 8.4
To assess the impact of multiple dose administrations of AZD4041 on the PK of morphine and its metabolites	Plasma concentrations as well as PK parameters for AZD4041 and morphine and its metabolites as described in Section 8.4
To assess the impact of morphine on steady-state PK of AZD4041	Plasma concentrations as well as PK parameters for AZD4041 and morphine and its metabolites as described in Section 8.4
To assess the renal clearance of AZD4041	Urine concentrations as well as PK parameters for AZD4041 as described in Section 8.4

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram EtCO2 = end tidal carbon dioxide; PK = pharmacokinetic; SpO2 = oxygen saturation.

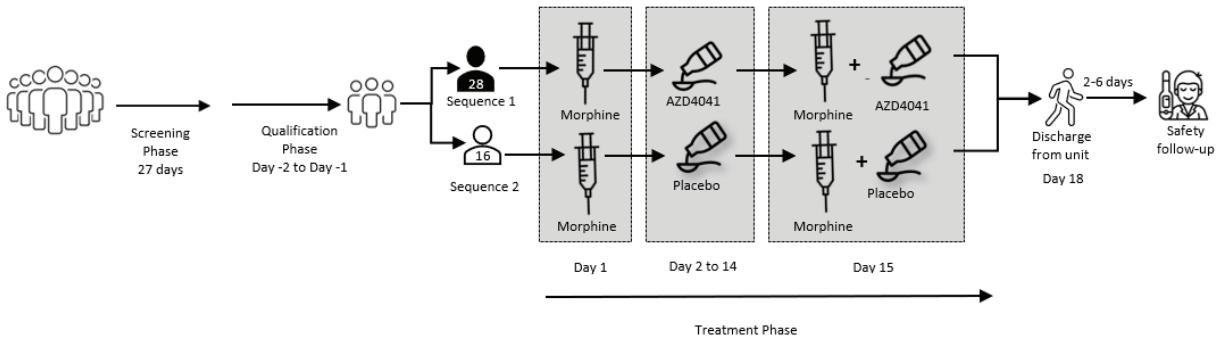
3. STUDY DESIGN

3.1. Overall Study Design

This is a Phase 1, randomized, double-blind, placebo-controlled, 2 fixed sequences, multiple dose study in healthy male and/or female recreational opioid users.

This study will consist of 3 phases: Screening and Qualification, Treatment phase, and Follow-up (see Figure 3-1).

Figure 3-1 Study Design



After a Screening period of up to 27 days (Day -30 to Day -3), eligible subjects will be admitted to the clinical research unit (CRU) on Day -2. Subjects will be randomized to 1 of 2 fixed treatment sequences (28 subjects in Sequence 1, and 16 subjects in Sequence 2) on Day -1.

Subjects will be required to present a negative urine drug and alcohol screen upon admission on Day-2, except for tetrahydrocannabinol (THC). If THC is positive at admission, a cannabis intoxication evaluation will be done by an Investigator, and subjects may be permitted to continue in the study at the discretion of an Investigator. Subjects will then undergo a naloxone challenge where an initial 0.2 mg intravenous (IV) dose of naloxone hydrochloride (HCl) will be administered. The subject will be observed for signs or symptoms of opioid withdrawal. If there is no evidence of withdrawal within 1 minute (as assessed by a Clinical Opioid Withdrawal Scale [COWS] score of <5), an additional 0.6 mg IV dose of naloxone HCl will be given, and the subject will be observed for signs and symptoms of withdrawal for 5 minutes (as assessed by COWS). Subjects who present symptoms of withdrawal during the qualification process will be excluded from the study and will not be eligible to enter the Treatment phase.

In total, subjects will be confined to the CRU for approximately 20 days from Day -2 to Day 18 (until approximately 72 hours following the last study drug administration).

On Day 1, subjects will receive a single CCI IV dose of morphine. From Day 2 to Day 15, subjects will receive a CCI oral dose of AZD4041 or placebo once daily for 14 consecutive days. On the morning of Day 15, the CCI oral dose of AZD4041 or placebo will be combined with a single CCI IV dose of morphine.

In order to limit the number of subjects being treated with investigational product (IP) on any single day, eligible subjects should be assigned to different subgroups. Subgroup sizes should be limited to no more than 8 subjects. Dosing of subgroups should be staggered to occur on different days, with at least 2 days between the start of dosing for sequential subgroups.

A Follow-up visit will occur approximately 7±2 days after the last study drug administration.

The schedule of activities of the study is described in Table 6-1.

3.2. Study Treatments

The following treatments will be administered according to Table 3-1.

- **Test**: A single [redacted] of AZD4041 oral solution will be administered once daily from Day 2 to Day 15 according to the randomization schedule.
- **Placebo**: Vehicle without active drug (AZD4041) will be orally administered once daily from Day 2 to Day 15 according to the randomization schedule.
- **Morphine**: A [redacted] of morphine will be intravenously administered on Days 1 and Day 15 only.

Table 3-1 Treatment Sequences

	Day 1	Days 2 to 14	Day 15[a]
Sequence 1 (n=28)	[redacted] Morphine	[redacted] AZD4041 once daily	[redacted] AZD4041 + [redacted] Morphine
Sequence 2 (n=16)	[redacted] Morphine	Placebo once daily	Placebo + [redacted] Morphine

a. The assigned treatment (AZD4041 or Placebo) will be administered orally immediately (within 1 minute) after the end of morphine infusion.

4. SUBJECT POPULATION

Subjects meeting all the inclusion criteria and none of the exclusion criteria at Screening may be eligible for participation in this study. Continued eligibility will be assessed upon admission to the clinical site, prior to the first study drug administration.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or enrolled in the study.

4.1. Inclusion Criteria

1. Recreational opioid user, not currently considered to have moderate or severe substance use disorder for opioids (based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [DSM-5] criteria) and has experience with opioid use for non-therapeutic purposes (ie, for psychoactive effects) on at least 10 occasions in their lifetime and at least 1 occasion in the last 12 weeks prior to Screening
2. Provision of signed and dated informed consent form (ICF) prior to the initiation of any protocol-specific procedures
3. Stated willingness to comply with all study procedures and availability for the duration of the study
4. Healthy adult male or female, 18 to 55 years of age, inclusive, prior to the first study drug administration
5. Body mass index (BMI) within 18.0 kg/m^2 to 35.0 kg/m^2, inclusive, and body weight at least 50 kg at Screening

6. A female study subject of non-childbearing potential must meet 1 of the following criteria:

   (1) Physiological postmenopausal status, defined as the following:

   a) absence of menses for at least 1 year prior to the first study drug administration (without an alternative medical condition); and
   b) Follicle stimulating hormone (FSH) levels ≥ 40 mIU/mL at Screening

   AND/OR

   (2) Surgical sterile, defined as those who have had hysterectomy, bilateral oophorectomy and/or bilateral salpingectomy, or bilateral tubal ligation. Women who are surgically sterile must provide documentation of the procedure by an operative report, ultrasound, or other verifiable documentation.

7. If male, must agree to use a highly effective method of contraception (see APPENDIX10 for contraception guidance) when engaging in sexual activity and must not donate sperm during the study and for at least 4 months (120 days) after the last dose of study medication

8. Healthy in the opinion of an Investigator, as determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs, oxygen saturation (SpO_2), respiratory rate, or clinical laboratory (including hematology, coagulation, clinical chemistry, urinalysis, and serology [Screening visit only]) at Screening visit and/or prior to the first study drug administration

4.2. Exclusion Criteria

1. Female who is pregnant according to the pregnancy test at Screening or prior to the first study drug administration
2. Male subjects with a history of oligospermia or azoospermia or any other disorder of the reproductive system
3. Male subjects who are undergoing treatment or investigation for infertility
4. History of moderate or severe substance or alcohol use disorder (excluding nicotine and caffeine) within the past 2 years, as defined by the DSM-5
5. History of any significant psychiatric disorder according to the criteria of the DSM-5 which, in the opinion of the Investigator, could be detrimental to subject safety or could compromise study data interpretation.
6. History of significant hypersensitivity to AZD4041, morphine and/or other opioids, naloxone, or any related products (including excipients of the study formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs
7. History of any significant disease, including [but not necessarily limited to] significant hepatic, renal, cardiovascular, pulmonary, hematologic, neurological, psychiatric, gastrointestinal, endocrine, immunologic, ophthalmologic, or dermatologic disease of any etiology (including infections) identified at Screening

8. Presence or history of significant gastrointestinal, liver or kidney disease, or any other condition [including those that may result from surgery] that is known to interfere with drug absorption, distribution, metabolism, or excretion, or known to potentiate or predispose to undesired effects.
9. Oxygen saturation (SpO_2) below 95% at Screening or prior to first study drug administration
10. Any abnormal vital signs, after no less than 5 minutes rest (supine position), as defined in the list below, at Screening and/or prior to the first study drug administration. Out of range test may be repeated once for each visit at the discretion of the Investigator.
    - Systolic BP < 90 mmHg or > 140 mmHg
    - Diastolic BP < 50 mmHg or > 90 mmHg
    - HR < 45 or > 90 beats per minute (bpm)
11. Any clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG and any clinically important abnormalities in the 12-lead ECG, which in the Investigator's opinion, may interfere with the interpretation of QTc interval changes, including abnormal ST-T-wave morphology, particularly in the protocol-defined primary lead, or left ventricular hypertrophy at Screening or prior to the first study drug administration (out of range test may be repeated once for each visit at the discretion of the Investigator)
12. Prolonged QT interval corrected for HR using Fridericia's formula (QTcF) > 450 ms at Screening or prior to first study drug administration
13. Shortened QTcF < 340 ms at Screening or prior to first study drug administration
14. Family history of long QT syndrome
15. ECG interval measured from the onset of the P wave to the onset of the QRS complex (PR [PQ]) interval shortening < 120 ms (PR > 110 ms but < 120 ms is acceptable if there is no evidence of ventricular preexcitation) at Screening or prior to first study drug administration.
16. PR (PQ) interval prolongation (>220 ms), persistent or intermittent second (Wenckebach block while asleep is not exclusive) or third degree atrioventricular (AV) block, or AV dissociation at Screening or prior to first study drug administration.
17. Persistent or intermittent complete bundle branch block, incomplete bundle branch block, or intraventricular conduction delay with ECG interval measured from the onset of the QRS complex to the J point (QRS) > 110 ms. Subjects with QRS > 110 ms but < 115 ms are acceptable if there is no evidence of ventricular hypertrophy or preexcitation at Screening or prior to first study drug administration.
18. In the predose 24-hour telemetry, presence of ≥10 ventricular premature contractions (VPCs) during 1 hour, or ≥ 100 VPCs during 24 hours of telemetry, or any occurrence of paired VPCs (ventricular couplets) or other repetitive ventricular rhythms, including non-sustained or sustained (> 30 second duration), slow (< 100 bpm), or fast (≥ 100 bpm) ventricular tachycardias.

19. Any clinically significant illness in the 28 days prior to the first study drug administration
20. Heavy smoker (>20 cigarettes per day) and/or is unable to abstain from smoking or unable to abstain from the use of prohibited nicotine containing products for at least 1 hour before and at least 6 hours after study drug administration (including e-cigarettes, pipes, cigars, chewing tobacco, nicotine topical patches, nicotine gum, or nicotine lozenges)
21. Regularly consumes excessive amounts of caffeine or xanthines within 30 days prior to Screening, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, or other caffeinated beverages per day
22. History of suicidal ideation within 1 year of Screening (score of 4 or 5 as per the C-SSRS) or any suicidal behavior (as per C-SSRS) within 2 years of Screening, or is currently at risk of suicide in the opinion of an Investigator
23. Positive test result for alcohol and/or drugs of abuse upon admission on Day -2. Subjects with positive marijuana results at admission may be rescheduled at the discretion of an Investigator. If THC is positive at admission, a cannabis intoxication evaluation will be done by an Investigator and subjects may be permitted to continue in the study at the discretion of an Investigator. Other positive test results should be reviewed to determine if the subject may be rescheduled, in the opinion of an Investigator
24. Positive test results for HIV-1/HIV-2 Antibodies, Hepatitis B surface Antigen (HBsAg) or Hepatitis C Virus Antibody (HCVAb)
25. Any other clinically significant abnormalities in laboratory test results at Screening that would, in the opinion of an Investigator, increase the subject's risk of participation, jeopardize complete participation in the study, or compromise interpretation of study data
26. Treatment with an investigational drug within 30 days or 5 times the half-life (whichever is longer) prior to Screening
27. Use of any prescription drugs (with the exception of hormone replacement therapy) in the 14 days prior to the first study drug administration, that in the opinion of an Investigator would put into question the status of the participant as healthy
28. Use of St. John’s wort in the 28 days prior to the first study drug administration
29. Use of over-the-counter (OTC) products (including herbal preparations and supplements) within 7 days prior to the first study drug administration, with the exception of ibuprofen or acetaminophen
30. Donation of plasma in the 7 days prior to the first study drug administration
31. Donation of 1 unit of blood to American Red Cross or equivalent organization or donation of over 500 mL of blood in the 56 days prior to the first study drug administration
32. Is, in the opinion of an Investigator or designee, considered unsuitable or unlikely to comply with the Study Protocol for any reason

33. Poor venous access at Screening, as judged by an Investigator
34. Use of any prescribed or nonprescribed oral and topical inhibitors/inducers of CYP3A4 (including shampoo)
35. Is an AZ or study site employee or their close relatives

4.3. Rescreening Criteria

Subjects may be required to be rescreened as part of this study. Subject who are screen failures, due to transient exclusion criteria (ie, blood donations, consumption of products within last 28 days, etc), may be rescreened at the discretion of the Investigator, in consultation with the Sponsor.

A subject within the original screening window must meet all eligibility criteria with the following conditions:

- All Day -2 and/or Day -1 procedures (Table 6-1) must be repeated, if already done
- The subject will retain his/her original subject identification number

A subject outside of the original screening window must repeat all screening procedures, meet all eligibility criteria, and have a new subject identification number issued.

4.4. Withdrawal Criteria

4.4.1. Before First Treatment Administration

Before the first treatment administration, inclusion/exclusion criteria will govern the subjects to be dosed. If either the urine drug (except for THC) and alcohol screen or the naloxone challenge is positive, the subject will be excluded from the study. Subjects withdrawn before first treatment administration will not be followed up and will not undergo End-of-Study/Early Termination assessments. Other safety assessments may be performed if required.

Subjects are free to withdraw their consent to participate in the study at any time, without prejudice. The reason for their withdrawal or for deciding to end their participation will be documented.

4.4.2. After First Treatment Administration

Subjects may, at any time, voluntarily withdraw from the study or be removed from the study at the discretion of an Investigator or Sponsor. An Investigator may withdraw a subject at any time for any (but not limited to) of the following reasons: if it is determined that continuing the study would result in a significant safety risk to the subject or if their behavior is deleterious to the study environment. If such withdrawal occurs, or if the subject fails to return for visits, an Investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study documents.

In the case of a clinically significant illness detected during the trial (including COVID-19 diagnosis), the Principal Investigator (or delegate) will, in consultation with the Medical Monitor and Sponsor Physician, determine the most appropriate course of action on an individual basis. Evaluations will include but are not limited to:

- The safety of the subject and other study participants
- The possible effect the illness would have on the results gathered during the trial, and their ability to be appropriately analyzed or interpreted
- The possibility of suspending participation then re-initiating it after recovery
- The implication of any inclusion or exclusion criteria that would contradict possible actions
- The implication of any adherence to regulatory guidelines that may be affected by actions decided; for example group effect analysis
- The sample size calculation, current number of subjects, and possibility of replacement subjects

Evaluations and decision-making for subject removal will be documented in the study file, reported to the Sponsor, and discussed where appropriate in the Clinical Study Report.

Attempts should be made to have such subjects complete the End of Study/Early Termination assessments. End-of-Study/ET assessments should be performed as soon as possible after the last study treatment administration.

For subjects lost to follow-up (ie, those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), an Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls (at least 3), registered letters (at least 1), etc.

4.4.2.1. Stopping Rules

4.4.2.1.1. Individual Subject Stopping Rules

Participation in the clinical study may be discontinued by an Investigator (or delegate) in charge of the study or by the Sponsor for any of the following reasons, but not limited to:

- AEs (including if a subject develops any significant illness or needs to undergo any major surgery during course of the study)
- Subject non-compliance (including any violation of protocol requirements which may affect the study outcome)

Subjects will be discontinued from the clinical study for any of the following reasons, but not limited to:

- Total serum bilirubin > 2x upper limit of normal (ULN)
- Aspartate aminotransferase (AST) > 3x ULN
- Alanine aminotransferase (ALT) > 3x ULN
- Creatinine > 1.5x ULN

4.4.2.1.2. Trial Stopping Rules

Clinical trial stopping rules:

- If 2 AZD4041-related (based on Investigator or Sponsor assessment) SAEs occur (Grade 3, 4, or 5)
- Occurrence of 1 death attributable to the study treatment\
- At least 2 subjects who received AZD4041 have QTc prolongation defined as QTcF > 500 ms, or a prolongation from baseline of > 60 ms, confirmed (persistent for at least 5 minutes) and determined postdose either on 12-lead digital ECG (dECG) obtained during continuous 12-lead ECG monitoring or on a repeat 12-lead safety ECG
- At least 2 subjects who received AZD4041 have tachycardia defined as resting supine HR > 125 beats per minute persisting for at least 10 minutes
- At least 2 subjects who received AZD4041 have symptomatic bradycardia defined as resting supine HR < 40 beats per minute or asymptomatic bradycardia defined as resting supine HR < 30 beats per minute while awake persisting for at least 10 minutes
- At least 2 subjects who received AZD4041 develop hypertension defined as an increase in resting supine systolic BP > 40 mmHg and above 180 mmHg and persisting for at least 10 minutes
- At least 2 subjects who received AZD4041 develop hypotension defined as an asymptomatic fall in systolic BP > 20 mmHg and below 70 mmHg persisting for at least 10 minutes, or a symptomatic fall in resting supine systolic BP > 20 mmHg (excluding vasovagal reaction or where the Investigator considers this to be most likely related to morphine administration)

4.5. Lifestyle and/or Dietary Requirements

- Subjects will be prohibited from consuming food or beverages containing grapefruit and/or pomelo for 7 days prior to the first dosing and during the study.
- Subjects will be prohibited from consuming alcohol for 48 hours prior the first dosing and during the study. They will also be prohibited from recreational drug use from screening until the follow-up visit. In case of any doubt, a test for alcohol and/or a drug screen may be performed if requested by an Investigator. If a subject presents with a positive alcohol test or drug screen at any time after the screening visit, the subject may be rescheduled at the discretion of an Investigator. If THC is positive at check-in, a cannabis intoxication evaluation will be done by an Investigator, and inclusion will be at his or her discretion.
- Subjects will be prohibited from consuming food or beverages containing xanthines (ie, tea, coffee, cola drinks, energy drinks or chocolate) for 48 hours prior to the first dosing and during the study.
- Subjects will eat only the food provided by the study site during confinement at the CRU.
- During the study, subjects who are smokers should not smoke more than 20 cigarettes per day. Subjects will abstain from smoking for 1 hour prior and until 6 hours after each drug administration.

- Subjects will be asked to refrain from driving, operating machinery, or engaging in hazardous activities until they and an investigator are convinced the study drug is not impairing their judgment and/or ability to perform skilled tasks.

4.6. Concomitant Treatment

The naloxone challenge will consist of an initial IV dose of 0.2 mg naloxone HCl. Subjects will be observed for signs or symptoms of opioid withdrawal. If there is no evidence of withdrawal within 1 minute (as assessed by a COWS score of <5), an additional intravenous dose of 0.6 mg naloxone HCl will be given, and subjects will be observed for signs and symptoms of withdrawal for 5 minutes (as assessed by COWS). Subjects who present symptoms of withdrawal during the qualification process will be excluded from the study and will not be eligible to enter the Treatment phase.

Except for medication which may be required to treat AEs (eg, paracetamol/acetaminophen), no other treatment or medication other than the study drugs will be allowed from the first dosing until all study activities and evaluations have been completed.

Subjects will be instructed to notify the study site about any new medications (eg, those required to treat AEs) taken after the start of the study treatment. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject has received the study treatment must be listed in the subject CRF. The drug name and dose taken will be noted. An investigator or delegate and/or the Sponsor will decide whether the subject will be permitted to remain in the study, depending on the drug used, the time of drug intake, etc.

5. STUDY TREATMENTS

5.1. Investigational Products

The active IP will be provided by the Sponsor. The placebo will be provided by the CRU.

5.1.1. AZD4041 CCI and Placebo oral solution

The AZD4041 active formulation and placebo are presented in Table 5-1.

Table 5-1 Study Treatments

Study treatment name:	AZD4041
Dosage formulation:	Oral solution, with active dissolved in vehicle ([redacted])
	[redacted]
Placebo:	Vehicle ([redacted])
Route of administration:	Oral
Packaging and labelling:	[redacted]
Provider:	AZD4041: AstraZeneca UK Ltd, Macclesfield, Cheshire, United Kingdom Placebo: Altasciences Clinical Kansas Inc

5.1.2. Morphine

Morphine (Duramorph PF®, manufactured by Hikma Pharmaceuticals USA Inc., will be supplied in a concentration of [redacted] vials/ampoules (sourced by the CRU).

5.2. Investigational Product Management

5.2.1. Packaging, Labeling and Dispensing

The Sponsor will be responsible for ensuring that the IP is manufactured in accordance with applicable current Good Manufacturing Practice regulations and requirements.

The IPs will be labeled according to the requirements of local law and legislation. The IPs will be dispensed by the CRU's pharmacy, unless the Sponsor supplies the pharmacy with prelabeled individual dosing samples.

5.2.2. Storage and Handling

AZD4041 will be shipped from the client or client resources to the CRU's pharmacy.

AZD4041 should be stored under conditions as described on the label. The products should not be used if expired and should not be frozen.

The CRU's pharmacy will maintain an inventory record of the IPs received, stored (in a secure restricted area), and dispensed. IPs will be provided to study subjects only.

5.2.3. Method of Assigning Subjects to Treatment Groups

The CRU will generate the randomization code with a computer program according to the study design, the number of subjects and the sequence of treatment administration. Once generated, the randomization code will be final and will not be modified.

Subjects who sign the ICF and are randomized but do not receive the study treatment may be replaced. Subjects who sign the ICF are randomized and receive the study treatment, and subsequently withdraw, or are withdrawn or discontinued from the study, will generally not be replaced. However, consideration may be given to the replacement of such subjects in order to enable the completion of at least 36 subjects (n=24 randomized to Sequence 1 and n=12 randomized to Sequence 2) to ensure that the scientific integrity of the study is maintained. Replacement of subjects will be at the discretion of the Principal Investigator in consultation and agreement with the Medical Monitor and Sponsor Physician. Any decision to replace subjects should not conflict with the pre-defined individual subject or study stopping rules, or otherwise jeopardise the safe conduct of the study.

5.2.4. Blinding

The randomization code will not be available to the personnel of the bioanalytical facility until the bioanalytical phase of the study has been completed. The treatment assignment will not be known by the study participants.

Furthermore, the randomization code will not be available to the physician and clinical staff involved in the collection, monitoring, revision, or evaluation of AEs, as well as clinical staff who could have an impact on the outcome of the study, and including the pharmacokineticist (or delegate, until all the case report forms (CRFs) have been approved and signed and the bioanalytical phase of the study has been completed.

The preparation and/or administration of the products will be done by designated personnel that are not directly involved in the clinical aspects of the trial.

The randomization code must not be broken except in emergency situations where the identification of a subject's study treatment is required by an Investigator for further treatment to the subject or to complete a SAE report. Randomization information will be held by designated individual(s). The date and reason for breaking the blind must be recorded.

5.2.5. Study Drug Accountability

Complete and accurate inventory records of all study drugs will be maintained. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product.

The labeling, storage conditions, quantity of reserve samples for the IP, and retention period of the reserve samples shall comply with the current Food and Drug Administration (FDA) rules and regulations. Drug accountability will be performed at the completion of the trial.

5.3. Administration of Study Drug

Study treatments as described in Section 3.2 will be administered in the morning. The date and time of each dose will be recorded. For each subject, Day 1 to Day 14 scheduled postdose activities and assessments will be performed relative to the time of AZD4041/placebo administration or end of morphine infusion. From Day 15, all scheduled postdose activities will be performed relative to the end of morphine infusion, with the exception of PK sampling for AZD4041.

On Day 1, a single intravenous infusion of morphine will be administered to the subjects over a 10-minute interval (± 30 seconds) in the morning.

On Days 2 to 15, an oral dose of the assigned treatment (either AZD4041 or Placebo) once daily will be administered to subjects using a syringe for 14 consecutive days. The dose will be administered directly into the subject's mouth.

On the morning of Day 15, the oral dose of the assigned treatment (either AZD4041 or Placebo) will be combined with a single intravenous infusion of morphine. A single intravenous infusion of morphine will be administered to the subjects over a 10-minute interval (± 30 seconds). The assigned treatment (AZD4041 or Placebo) will then be administered orally immediately (within 1 minute) after the end of morphine infusion.

The study drugs will be dispensed only to eligible subjects and administered under the supervision of study personnel. Treatment compliance will be verified according to the site's standard operating procedures (SOPs).

5.4. Meals

Food intake will be controlled for the confinement period and for all subjects.

Subjects will be required to fast at least 10 hours prior to start of morphine infusion on Days 1 to 15.

On Days 1, 8, and 15, subjects will also be required to fast (abstain from food) for at least 4 hours after dosing (after end of morphine infusion on Day 15).

5.5. Fluids

Fluid intake other than water will be controlled for each confinement period and for all subjects.

On Days 1, 8, and 15, water will be permitted as needed except from at least 1 hour predose (prior to start of morphine infusion on Days 1 and 15) until 1 hour after dosing (after end of morphine infusion on Days 1 and 15).

No water restriction will be implemented for the study drug administrations on Days 2 to 7, and Days 9 to 14.

5.6. Other Protocol Restrictions

On Days 1, 8 and 15, subjects will remain seated or kept in minimal ambulatory movement for the first 4 hours following study drug administration (after end of morphine infusion on Days 1 and 15), avoiding both vigorous exertion and complete rest. On Days 2 to 7, and Days 9 to 14, subjects will remain seated or kept in minimal ambulatory movement for the first hour following study drug administration, avoiding both vigorous exertion and complete rest. However, should AEs occur at any time, subjects may be placed in an appropriate position. During these intervals, subjects will be permitted, under supervision, to get up (eg, to use the washroom facilities).

Subjects will not engage in strenuous activity at any time during the confinement period.

6. STUDY PROCEDURES

An overview of the study activities for each participant is detailed in Table 6-1.

Unless otherwise stated in the protocol, the SOPs of the study facilities, which are available for all activities relevant to the quality of the study, will be followed during this study. When the nominal time for multiple events occurs simultaneously, the events will be staggered using their acceptable windows (acceptable windows for each assessment are specified in the following sections of this protocol), with priority given to those events related to primary study endpoints. Safety procedures will be carried out in the following order if scheduled at the same time: ECG recording> vital sign assessments, respiratory rate, SpO_2, $EtCO_2$> dECG extraction> PK sampling.

Any deviation from protocol procedures should be noted in the source documentation and compiled for reporting in the Clinical Study Report.

Table 6-1 Schedule of Activities

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
Informed Consent[3]	X															
Eligibility Criteria Review (Inclusion/Exclusion)	X	X	X	X												
Demographics	X															
Height, Weight, and Body Mass Index	X														X[4]	
Medical History	X	X[5]														
Medical & Recreational Drug Uses History	X	X[6]														
Study Restrictions Review		X													X	X
Admission to CRU		X														
Clinic Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Discharge from CRU[7]															X	
Randomization			X													

[1] Individual end of study procedures may either be performed at the time of last confinement to the clinical site or at the last study visit.
[2] All predose activities will be performed within a 60-minute window prior to treatment administration
[3] The latest version of the consent form must be signed prior to a subject's inclusion (prior to any study-related procedures).
[4] Weight only
[5] Any changes since the last visit will be documented.
6 Any changes since the last visit will be documented.
[7] Discharge from the clinical site will occur approximately 72 hours after the last study drug administration.

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
Vital Signs[8]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead safety ECG[9]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead continuous digital ECG and ECG extractions[10]			X[11]	X	X	X	X	X	X	X	X	X	X	X	X	
ECG telemetry[12]			X	X	X	X	X	X	X	X		X	X	X	X	
Continuous SpO_2, Respiratory Rate and $EtCO_2$ Monitoring[13]				X					X			X				
Spot SpO_2 [14]	X	X		X	X	X	X	X	X	X	X	X	X			X
Spot Respiratory rate [15]	X	X		X	X	X	X	X	X	X	X	X	X			X
Spot $EtCO_2$[16]				X	X	X	X	X	X	X	X	X	X			

[8] Vital sign measurements are detailed in Section 6.1.5.

[9] 12-lead safety ECG measurements are detailed in Section 6.1.6.1.

10 12-lead continuous digital ECG and ECG extractions are detailed in Section 6.1.6.2.

11 After the 24-hour Holter recording (starting on Day -1 and ending approximately 1 hour before the end of morphine infusion), the Holter card will be replaced with a new one.

12 ECG telemetry is detailed in Section 6.1.7.

13 Continuous SpO_2, respiratory rate and $EtCO_2$ monitoring from up to 1 hour predose (prior to start of morphine infusion on Day 1) up to at least 6 hours postdose (after end of morphine infusion on Day 1), or longer if judged medically necessary.

[14] SpO_2 measurements are detailed in Section 6.1.8.

[15] Respiratory rate measurements are detailed in Section 6.1.10

[16] $EtCO_2$ measurements are detailed in Section 6.1.9.

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
Physical Examination[17]	X	X						X			X				X	X
Neurological Examination[18]	X	X						X			X				X	X
General Biochemistry, Hematology, Coagulation, Urinalysis[19]	X	X						X			X				X	X
FSH (Females only)	X															
Serology[20]	X															
Alcohol and Drugs of Abuse Screen	X	X														
Serum Pregnancy Test (Females only)	X	X														X
C-SSRS[21]	X	X			X						X				X	X
Naloxone Challenge/COWS		X														
Morphine Administration [22]				X								X				

[17] Symptom-directed physical examination will be performed on Day 7 and Day 14 and a complete physical examination will be performed at all other timepoints. Details of the physical examination are presented in Section 6.1.3.

[18] Neurological examination is detailed in Section 6.1.4.

19 General biochemistry, hematology, coagulation tests, and urinalysis will be performed as detailed in Section 6.1.11 and APPENDIX 6.

[20] Serology will be performed as detailed in Section 6.1.11 and APPENDIX 6.

[21] The "Baseline/Screening" C-SSRS form will be completed at the Screening Visit, and the "Since Last Visit" C-SSRS form will be completed on Day 2, Day 14, at discharge or ET.

[22] On Day 1: Morphine will be intravenously administered. On Day 15: AZD4041 or Placebo will be orally administered immediately (within 1 minute) after morphine administration (end of intravenous infusion).

	Screening	Qualification		Treatment Phase												Follow-up/End of Study/Early Termination[1]
Day[2]	**-30 to -3**	**-2**	**-1**	**1**	**2**	**3**	**4-6**	**7**	**8**	**9-13**	**14**	**15**	**16**	**17**	**18**	**22 (± 2)**
AZD4041 or Placebo Administration[23]					X	X	X	X	X	X	X	X				
Blood Sampling for PK (morphine and its metabolites) [24]				X	X							X	X	X	X	
Blood Sampling for PK (AZD4041)[25]					X	X	X	X	X	X	X	X	X	X	X	
Urine Sampling for PK (AZD4041)[26]												X	X	X	X	
Adverse Event Monitoring[27]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[28]
Concomitant Medication Recording[29]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event, COWS = Clinical Opioid Withdrawal Scale, C-SSRS= Columbia-Suicide Severity Rating Scale, ECG= electrocardiogram, $EtCO_2$ = end tidal carbon dioxide, FSH = Follicle-Stimulating Hormone, PK = pharmacokinetics, SpO_2 = oxygen saturation
Note: On Day 1 and Day 15, predose time points are relative to start of morphine infusion and postdose time points are relative to end of morphine infusion with the exception of the PK sampling time points for AZD4041 which are relative to AZD4041/placebo administration.

[23] On Days 2 to 14, AZD4041 or Placebo will be orally administered once daily. On Day 15, AZD4041 or Placebo will be orally administered immediately (within 1 minute) after morphine administration (end of intravenous infusion).
24 Blood samples for morphine and its metabolites will be collected as detailed in Section 6.2.1.
25 Blood samples for AZD4041 will be collected as detailed in Section 6.2.1.
26 Urine samples for AZD4041 will be collected as detailed in Section 6.2.2.
27 Spontaneous AE reporting is continuous throughout the study, beginning with the time the subject gives informed consent; however, at regular intervals, AE checks will be performed using non-leading questions.
28 Adverse events check must be done at the last scheduled study visit.
[29] Medications taken within 30 days prior to Screening and throughout the duration of study participation will be recorded.

6.1. Safety Assessments

Safety assessments will include physical examination, neurological examination, vital signs (systolic and diastolic BP, HR, and oral temperature), 12-lead safety ECGs, 12-lead dECGs, ECG telemetry, C-SSRS questionnaires, clinical laboratory tests, $EtCO_2$, SpO_2, respiratory rate, and AE monitoring. At the discretion of an Investigator, additional safety assessments may be performed as needed to ensure subject safety.

6.1.1. Medical History

The medical history at Screening will include all queries by the medical and clinical staff related to the subject's well-being and history of relevant past medical events/experiences. Medical history will include all demographic data (age, sex, race, body weight, height, and BMI) and baseline characteristics. Alcohol and smoking habits will also be recorded.

6.1.2. Recreational Alcohol/Drug Use

A lifetime history of all drug use, including alcohol, will be collected as scheduled in Table 6-1. For drug use (except alcohol), history, including drug preference (ie, drug of choice), frequency of use, and date of last use will be collected using reported drug names and drug class (eg, cannabinoids, depressants, dissociative anesthetics, hallucinogens, opioids and morphine derivatives, and stimulants). DSM-5 modules will be included as a part of the recreational drug/alcohol use history and used to screen for alcohol and substance use disorder.

6.1.3. Physical Examination

A physical examination will be performed by a medically qualified and licensed individual as outlined in Table 6-1.

The physical examination will include a general review of the following body systems (at minimum): head and neck, cardiovascular, respiratory, gastrointestinal, brief neurological (if a full neurological examination is not scheduled), and general appearance, unless a symptom-oriented physical exam is indicated.

A Sponsor-provided form will be used to facilitate a standardized approach to the physical examination (APPENDIX 11).

6.1.4. Neurological Examination

Neurological examination (assessments of basic mental status, cranial nerves, motor function, reflexes, sensation, proprioception, coordination, and gait) will be performed as scheduled in Table 6-1.

A Sponsor-provided form will be used to facilitate a standardized approach to the physical examination (APPENDIX 12).

6.1.5. Vital Signs

Vital signs will be measured as outlined in Table 6-1 and specifically in Table 6-2.

Table 6-2 Vital Sign Recording Schedule

Vital Sign Recording - Scheduled Timepoints
Screening
Day -2
Days 1: predose and 1, 2, 3, 4, 6, 8, and 12 hours postdose
Days 2 to 14: predose, and 1 hour postdose
Day 15: predose and 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose
Follow-up visit/ET

Abbreviations: ET = Early Termination

Vital signs will include BP, HR, and oral temperature (at Screening, Day -2, discharge, and Follow-up visit/Early Termination only).

Vital signs will be taken while subjects are rested and supine for at least 5 minutes.

The acceptable windows for vital sign assessments are presented in Table 6-3.

Table 6-3 Acceptable Windows for Vital Sign Assessments Procedures

Elapsed Time	Accepted Window
Predose	within 60 minutes
> 0 hour and ≤ 24 hours	± 30 minutes
> 24 hours and ≤ 72 hours	± 60 minutes

6.1.6. 12-Lead Electrocardiogram

6.1.6.1. 12-Lead Safety Electrocardiogram

The 12-lead safety ECGs will be performed as outlined in Table 6-1 and specifically in Table 6-4. Additional safety ECGs may be performed at the Investigator's discretion. The 12-lead ECGs will be obtained after the subject has been resting in the supine position for at least 10 minutes. All 12-lead ECGs will be evaluated for HR, and for PR, time elapsed between two successive R-waves of the QRS signal on the ECG (RR), QRS, QT, and QTcF intervals, and the Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant, and the reason for the abnormality will be recorded. The date/time, physician interpretation (normal, abnormal clinically significant, abnormal not clinically significant), and all evaluated parameters and intervals will be recorded in the electronic CRF (eCRF), and the paper printouts will be stored at the site. The Investigator (or designee) will evaluate the printout of the 12-lead ECG in real time, and with particular attention to the effects of clinical importance on the PR, QRS, and QTcF intervals.

Table 6-4 Safety ECG Recording Schedule

Safety ECG Recording - Scheduled Timepoints[a]
Screening
Day -2
Days 1[b]: predose and 1, 2, 4, 6, and 12 hours postdose
Days 2 to 14[b]: predose and 1 hour postdose
Day 15[b]: predose and 1, 2, 4, 6, 12, 24, 48, and 72 hours postdose
Follow-up visit/ET

Abbreviations: ET = Early Termination
a. Safety procedures will be carried out in the following order: ECG recording>Vital sign assessments>PK sampling
b. Predose safety ECGs should be recorded within 60 minutes of the scheduled dosing time and BEFORE vital sign assessments and PK sampling.

The acceptable windows for 12-lead safety ECG assessments are presented in Table 6-5.

Table 6-5 Acceptable Windows for 12-Lead Safety Electrocardiogram Assessments Procedures

Elapsed Time	Accepted Window
Predose	within 60 minutes
> 0 hour and ≤ 24 hours	± 30 minutes
> 24 hours and ≤ 72 hours	± 60 minutes

6.1.6.2. Electronic Capture of 12-lead Continuous Digital Electrocardiogram

The AZ ECG Center will perform the dECG analysis, using the EClysis© system, version 4.0, or higher. Lead V2 will be used as the primary analysis lead, with lead V5 as the primary backup lead and lead II as the secondary back-up lead, for all time points when lead V2 is found to be unsuitable for analysis.

At clinical study protocol-indicated time points in Table 6-6, 12-lead continuous dECG files will be recorded using the 12-lead Mortara Holter equipment (H12+) according to AZ ECG Center's standard procedures for settings/configuration, recording and transfer of dECGs. The 12-lead Holter memory cards will be sent to the AZ ECG Center with an agreed courier.

It is to be noted that the 12-lead Holter recordings will serve multiple purposes. It will be the source for 12-lead dECG extractions. In addition to providing 12-lead dECG extractions, the recordings will be used for prolonged arrhythmia monitoring as part of the safety data collection (these data will be analyzed at a later stage and will not be available for the bedside safety monitoring at site). The first ECG recording with Holter device starts on Day -1 (approximately 24 hours before dosing) and continues to 72 hours postdose (Day 4). On Day 8, recording will start at least 1 hour before dosing and continue to 24 hours postdose. On Day 15, recording will start at least 1 hour before dosing and continue to 72 hours postdose (Day 18). Specific extraction times for dECG are presented in Table 6-6.

The same recording device will be used for each subject at all time points, when possible. Date and time settings must be checked on the Mortara Holter equipment, at the start of each study

day and aligned with an official timekeeper. The metadata of each file will be checked by the responsible personnel at the study site to ensure that the cards sent to the AZ central dECG files repository have correct metadata.

Skin preparation must be thorough and electrode positions must be according to standard 12-lead ECG placement. Permanent electrodes will be applied at least 30 minutes before first study recording and left in place for the duration of each relevant study day. Electrode positions for dECG take precedence over those for telemetry. Subjects will rest in a supine position for at least 5 to 10 minutes before the start of each recording. A shorter resting period (at least 5 minutes) may be done in certain cases, depending on competing procedures in the study.

The subject should be in the same supine body position (maximum 30 degrees flexion of the hip and feet not in contact with the footboard) at each recording time point during the study.

From the continuous dECG files received at the AZ ECG Centre, the EClysis© system will extract continuous files of at least 5 minutes length at clinical study protocol-indicated time points in Table 6-6. The extraction window can be adjusted by the responsible ECG Scientific Advisor during the Metadata approval procedure, based on the 'Clinical Logs' received from the site. As standard, from each dECG extracted window, 10-second ECGs will then be extracted by the EClysis© system twice per minute and automatically analyzed by the software. The ECG Scientific Advisor will perform all necessary manual corrections of the ECG annotations provided automatically by EClysis©. All dECGs from 1 subject will be analyzed by a single reader in a blinded manner.

The AZ ECG Centre Cardiologist will finally review all data and perform all necessary adjustments before locking the data into a read-only state. From the locked data, the numerical values for the ECG intervals and amplitudes will then be made accessible on a secure file share of the AZ dECG central repository to accredited Data Management specialists for conversion into SAS® files.

The following dECG variables will be reported by the AZ ECG Centre: RR, PR, QRS, and QT intervals from the lead, defined as the primary analysis lead, as well as potential T-wave morphology changes.

Derived parameters (QTcF, HR, and others, as applicable) are calculated by the study statistician or delegate.

Table 6-6 Digital Electrocardiogram Schedule

Study Day	Visit Number	ECG Number	Time: Start of the Extraction Window, Hour:Min[a,b]	Dose	Time: Stop of the Extraction Window, Hour:Min	dECG Continuous [c, d, e]	Other[f]
1	2		-02:00		-01:30		Apply electrodes
1	2		-01:10		-01:00		Rest in bed [d]
1	2	1	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	
1	2		00:00	IP administration			

Study Day	Visit Number	ECG Number	Time: Start of the Extraction Window, Hour:Min[a,b]	Dose	Time: Stop of the Extraction Window, Hour:Min	dECG Continuous [c, d, e]	Other[f]
1	2	2	00:25		00:30	5 min	
1	2	3	00:55		01:00	5 min	
1	2	4	01:55		02:00	5 min	
1	2	5	03:55		04:00	5 min	
1	2	6	05:55		06:00	5 min	
1	2	7	07:55		08:00	5 min	
1	2	8	11:55		12:00	5 min	
2	2		-02:00		-01:30		Apply electrodes
2	2		-01:10		-01:00		Rest in bed [d]
2	2	9	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 2
2	2		00:00	IP administration			
2	2	10	00:25		00:30	5 min	
2	2	11	00:55		01:00	5 min	
2	2	12	01:55		02:00	5 min	
2	2	13	03:55		04:00	5 min	
2	2	14	05:55		06:00	5 min	
2	2	15	07:55		08:00	5 min	
2	2	16	11:55		12:00	5 min	
3	2		-02:00		-01:30		Apply electrodes
3	2		-01:10		-01:00		Rest in bed [d]
3	2	17	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 3
3	2		00:00	IP administration			
3	2	18	03:55		04:00	5 min	
3	2	19	11:55		12:00	5 min	
4	2		-02:00		-01:30		Apply electrodes
4	2		-01:10		-01:00		Rest in bed [d]
4	2	20	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 4
4	2		00:00	IP administration			
4	2	21	03:55		04:00	5 min	
5	2		-02:00		-01:30		Apply electrodes
5	2		-01:10		-01:00		Rest in bed [d]
5	2	22	-01:00 (within 60 min prior to	Predose	-00:50	10 min	Predose Day 5

Study Day	Visit Number	ECG Number	Time: Start of the Extraction Window, Hour:Min[a,b]	Dose	Time: Stop of the Extraction Window, Hour:Min	dECG Continuous [c, d, e]	Other[f]
			dosing)				
5	2		00:00	IP administration			
5	2	23	3:55		04:00	5 min	
6	2		-02:00		-01:30		Apply electrodes
6	2		-01:10		-01:00		Rest in bed [d]
6	2	24	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 6
6	2		00:00	IP administration			
7	2		-02:00		-01:30		Apply electrodes
7	2		-01:10		-01:00		Rest in bed [d]
7	2	25	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 7
7	2		00:00	IP administration			
8	2		-02:00		-01:30		Apply electrodes
8	2		-01:10		-01:00		Rest in bed [d]
8	2	26	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 8
8	2		00:00	IP administration			
8	2	27	00:55		01:00	5 min	
8	2	28	03:55		04:00	5 min	
8	2	29	05:55		06:00	5 min	
8	2	30	07:55		08:00	5 min	
8	2	31	11:55		12:00	5 min	
9	2		-02:00		-01:30		Apply electrodes
9	2		-01:10		-01:00		Rest in bed [d]
9	2	32	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 9
9	2		00:00	IP administration			
10	2		-02:00		-01:30		Apply electrodes

Study Day	Visit Number	ECG Number	Time: Start of the Extraction Window, Hour:Min[a,b]	Dose	Time: Stop of the Extraction Window, Hour:Min	dECG Continuous [c, d, e]	Other[f]
10	2		-01:10		-01:00		Rest in bed [d]
10	2	33	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 10
10	2		00:00	IP administration			
11	2		-02:00		-01:30		Apply electrodes
11	2		-01:10		-01:00		Rest in bed [d]
11	2	34	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 11
11	2		00:00	IP administration			
11	2	35	03:55		04:00	5 min	
12	2		-02:00		-01:30		Apply electrodes
12	2		-01:10		-01:00		Rest in bed [d]
12	2	36	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 12
12	2		00:00	IP administration			
13	2		-02:00		-01:30		Apply electrodes
13	2		-01:10		-01:00		Rest in bed [d]
13	2	37	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 13
13	2		00:00	IP administration			
13	2	38	03:55		04:00	5 min	
14	2		-02:00		-01:30		Apply electrodes
14	2		-01:10		-01:00		Rest in bed [d]
14	2	39	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 14
14	2		00:00	IP administration			
15	2		-02:00		-01:30		Apply electrodes
15	2		-01:10		-01:00		Rest in bed [d]
15	2	40	-01:00 (within 60 min prior to dosing)	Predose	-00:50	10 min	Predose Day 15
15	2		00:00	IP			

Study Day	Visit Number	ECG Number	Time: Start of the Extraction Window, Hour:Min[a,b]	Dose	Time: Stop of the Extraction Window, Hour:Min	dECG Continuous [c, d, e]	Other[f]
				administration			
15	2	41	00:25		00:30	5 min	
15	2	42	00:55		01:00	5 min	
15	2	43	01:55		02:00	5 min	
15	2	44	03:55		04:00	5 min	
15	2	45	05:55		06:00	5 min	
15	2	46	07:55		08:00	5 min	
15	2	47	11:55		12:00	5 min	
16	2	48	23:55		24:00	5 min	
16	2	49	35:55		36:00	5 min	
17	2	50	47:55		48:00	5 min	
18	2	51	71:55		72:00	5 min	

a. Time points for dECG may be adjusted according to emerging PK data.
b. Subjects must be in the same supine body position (maximum 30 degrees flexion in the hip) at each time point and at all visits with feet out of contact with footboard.
c. Skin must be cleaned and electrode positions marked with an indelible pen. Electrodes should be applied at least 30 minutes before the first recording.
d. The subjects must rest in bed (supine position) for at least 10 minutes prior to each dECG time point. A shorter resting period (at least 5 minutes) may be done in certain cases, depending on competing procedures in the study.
e. The subject must remain awake.
f. In some cases (when continuous monitoring is being performed), re-application of electrodes would not always be necessary. Electrodes are checked for contact and replaced if needed.

Abbreviations: dECG = digital electrocardiogram, ECG = electrocardiogram; IP = investigational product; min = minute; PK: pharmacokinetic.
Note: On Day 1 and Day 15, predose time points are relative to start of morphine infusion and postdose time points are relative to end of morphine infusion.

Table 6-7 Window Allowance for dECG time points

Procedure	Time Point	Tolerance Window	Notes
Days 1	Predose	- 60 min to 0 h	Within max 1h predose. Start of dECG Extraction time window should occur at 5-7 min prior to nominal PK sampling timepoint. Subject should have been awake for at least 1h prior to dECG baseline in studies where ECG/QT are important
Days 2-15	Predose	- 60 min to 0 h	Within max 1h predose. Start of dECG Extraction time window should occur at 5-7 min prior to nominal PK sampling timepoint. N.B. dECG should always be sampled immediately before supine vital PK draw.

Procedure	Time Point	Tolerance Window	Notes
Days 1-15	Up to 12 h postdose	- 15 to + 15 min	Start of dECG Extraction time window should occur at 5-7 min prior to nominal PK sampling timepoint ±15 min. N.B. dECG should always be sampled immediately before supine vital PK draw
Day 2	24 h postdose	- 60 to + 60 min	Start of dECG Extraction time window should occur at 5-7 min prior to nominal PK sampling timepoint ±60 min. N.B. dECG should always be sampled immediately before supine vital PK draw
Day 16	24 and 36h postdose	- 60 to + 60 min	Start of dECG Extraction time window should occur at 5-7 min prior to nominal PK sampling timepoint ±60 min. N.B. dECG should always be sampled immediately before supine vital PK draw
Days 17 and 18	48 and 72h postdose	- 2h to + 2h	Start of dECG Extraction time window should occur at 5-7 min prior to nominal PK sampling timepoint ±2h. N.B. dECG should always be sampled immediately before supine vital PK draw
Notes:			
Start of dECG Extraction time window should occur at 5-7 min prior to nominal PK sampling time point. ECG needs to be closely coordinated with PK in ECG critical studies to maintain precision for analysis, or modelling, so the deviation from nominal time tolerance window for PK sets the frame also for dECG N.B. dECG should always be sampled immediately before supine vitals, followed by PK blood draw. Other, less rest dependent pharmacodynamic measurements follow immediately after the PK draw The tolerances for dECG reporting in this document represent those used in the clinic when ensuring the subject is prepared for the start of dECG Extraction time window. Time window deviations for actual dECG results will be calculated and provided by the AstraZeneca ECG center during analysis as these will relate to the time of extraction of each ECG. This information will not be available in the study database.			

6.1.7. ECG Telemetry

Subjects will be monitored by telemetry as outlined in Table 6-1. To allow a real-time assessment of cardiac safety (HR, rhythm, and ECG morphology) at the CRU, subjects will be monitored at least by 2-lead telemetry. Telemetry monitoring will be performed on Day -1 (starting approximately 24 hours before the start of morphine IV infusion) until 72 hours after the end of morphine IV infusion (Day 4), on Day 7 at least 30 minutes prior to AZD4041 or placebo dosing until 48 hours post Day 7 dose (Day 9), and on Day 15 at least 30 minutes before the start of morphine IV infusion and until 72 hours after the end of morphine IV infusion (Day 18). Any clinically significant change noted on telemetry will be followed up with a 12-lead safety ECG. Further evaluation including any treatment will be performed as deemed appropriate by the Investigator. Any finding of short, self-limiting, asymptomatic arrhythmia (eg, non-significant supraventricular tachycardia, atrial fibrillation or flutter, ventricular extrasystoles, ventricular tachycardia), should be documented and further evaluated in the context of the individual subject's history and clinical status. Irrespective of the intervention,

cardiac monitoring will be continued until an observed event resolves or the subject is deemed clinically stable by the Investigator.

6.1.8. Continuous and Spot Oxygen Saturation

Assessments will include continuous and spot SpO_2 monitoring, as scheduled in Table 6-1. Continuous and spot SpO_2 will be monitored using a capnography monitor except for the spot SpO_2 at Screening, Day -2, and Follow-up visit/ET which will use a portable pulse oximeter placed on the subjects' fingertip. SpO_2 will be continuously monitored for alarms from at least 1 hour prior to each study drug administration (prior to start of morphine IV infusion on Day 1 and Day 15) and will continue for up to 6 hours following each study drug administration (after the end of morphine IV infusion on Day 1 and Day 15), or longer if deemed medically necessary. Spot SpO_2 will be documented as scheduled in Table 6-8. Baseline SpO_2 will be determined at 6 timepoints predose on Day 1. The baseline value will be determined by averaging the 6 readings.

Table 6-8 Spot Oxygen Saturation Recording Schedule

Spot Oxygen Saturation Recording - Scheduled Timepoints
Screening
Day -2
Day 1: predose (at -60, -50, -40, -30, -20, and -10 minutes) and 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, and 12 postdose
Days 2 to 7: predose
Day 8: predose and 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose
Days 9 to 14: predose
Day 15: predose and 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose
Follow-up visit/ET

Abbreviation: ET = Early Termination
Note: On Day 1 and Day 15, predose time points are relative to start of morphine infusion and postdose time points are relative to end of morphine infusion.

The acceptable windows for spot SpO_2 recording are presented in Table 6-9.

Table 6-9 Acceptable Windows for SpO_2 Assessments Procedures

Elapsed Time	Accepted Window
≥ -1 hour and < 1 hour	± 10 minutes
≥ 1 hour and ≤ 24 hours	± 30 minutes

6.1.9. Continuous and Spot End-Tidal Carbon Dioxide

End-tidal carbon dioxide ($EtCO_2$) will be monitored and measured using a standardized methodology and configuration using MICROSREAM™ consumables to sample gas via nasal cannulae and the CAPNOSTREAM™20P bedside monitor according to Altasciences SOP on Capnography (CLS-5105-00, September 1st 2020). Using this configuration, for the spontaneously breathing healthy volunteer subject, baseline $EtCO_2$ measurements can be

expected to fall within the range 34-48 mmHg. Measurement of $EtCO_2$ has been applied successfully in the setting of clinical pharmacology studies for the evaluation of respiratory function (Viscusi et al, 2021). Historical data sets generated at the Altasciences clinical unit have recorded $EtCO_2$ values with acceptable variability in relatively small cohorts of healthy volunteer subjects. For example, in a cohort of N=8 subjects, mean baseline $EtCO_2$ was found to be 36.6 mmHg with SD 2.2 mmHg. In another cohort of N=15 subjects, mean baseline $EtCO_2$ was found to be 36.1 mmHg with SD 3.88 mmHg.

Assessments will include continuous and spot $EtCO_2$ through a capnography monitor, as scheduled in Table 6-1. $EtCO_2$ will be monitored continuously for alarms at least 1 hour prior to each study drug administration (prior to start of morphine IV infusion on Day 1 and Day 15) and will continue for up to 6 hours following each study drug administration (after the end of morphine IV infusion on Day 1 and Day 15), or longer if deemed medically necessary. Spot $EtCO_2$ will be recorded as scheduled in Table 6-10. Baseline $EtCO_2$ will be determined at 6 time points predose on Day 1. The baseline value will be determined by averaging the 6 readings.

Table 6-10 Spot End-Tidal CO_2 Recording Schedule

Spot End-Tidal CO_2 Recording - Scheduled Timepoints
Day 1: predose (at -60, -50, -40, -30, -20, and -10 minutes) and 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8 and 12 postdose
Days 2 to 7: predose
Day 8: predose and 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8 and 12 hours postdose
Days 9 to 14: predose
Day 15: predose and 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours postdose

Note: On Day 1 and Day 15, predose time points are relative to start of morphine infusion and postdose time points are relative to end of morphine infusion.

The acceptable windows for $EtCO_2$ assessments are presented in Table 6-11.

Table 6-11 Acceptable Windows for $EtCO_2$ Assessments Procedures

Elapsed Time	Accepted Window
≥ -1 hour and < 1 hour	± 10 minutes
≥ 1 hour and ≤ 24 hours	± 30 minutes

6.1.10. Continuous and Spot Respiratory Rate

Assessments will include continuous and spot respiratory rate as scheduled in Table 6-1. Continuous and spot respiratory rate will be monitored/measured using a capnography monitor except at Screening, Day -2, and Follow-up visit/ET where it will be measured by counting the number of breaths per minute. Respiratory rate will be continuously monitored for alarms from at least 1 hour prior to each study drug administration (prior to start of morphine IV infusion on Day 1 and Day 15) and will continue for up to 6 hours following each study drug administration (after the end of morphine IV infusion on Day 1 and Day 15), or longer if deemed medically necessary. Spot respiratory rate will be measured as scheduled in Table 6-12. Baseline

respiratory rate will be determined at 6 timepoints predose on Day 1. The baseline value will be determined by averaging the 6 readings.

Table 6-12 Spot Respiratory Rate Recording Schedule

Spot Respiratory rate Recording - Scheduled Timepoints
Screening
Day -2
Day 1: predose (at -60, -50, -40, -30, -20, and -10 minutes) and 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8 and 12 postdose
Days 2 to 7: predose
Day 8: predose (within 60 minutes) and 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8 and 12 hours postdose
Days 9 to 14: predose
Day 15: predose (within 60 minutes) and15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours postdose
Follow-up visit/ET

Abbreviation: ET = Early Termination
Note: On Day 1 and Day 15, predose time points are relative to start of morphine infusion and postdose time points are relative to end of morphine infusion.

The acceptable windows for respiratory rate assessments are presented in Table 6-11.

Table 6-13 Acceptable Windows for Respiratory Rate Assessments Procedures

Elapsed Time	Accepted Window
≥ -1 hour and < 1 hour	± 10 minutes
≥ 1 hour and ≤ 24 hours	± 30 minutes

6.1.11. Laboratory Evaluations

Laboratory evaluations will be performed as outlined in Table 6-1.

The laboratory evaluations to be conducted for this study are presented in APPENDIX 6. Additional clinical laboratory tests may be performed by the medical laboratory as part of larger standard test panels (not required for subject safety).

The Investigator or delegate will assess each abnormal value to determine if it is clinically significant. Postdose clinically significant laboratory values will be reported as AEs, if applicable, as judged by the Investigator or delegate.

Only test results required by the Protocol and/or abnormal results will be entered in the clinical database and reported in the Clinical Study Report, based on report requirement.

6.1.12. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire designed for the assessment of suicidal ideation and behaviour in adolescents and adults.

The C-SSRS will assess suicidality over the month preceding Screening as well as over the subject's lifetime. At Screening, the "Baseline/Screening" version of the scale will be used, and at subsequent visits the "Since Last Visit" version of the scale will be used. Versions of the instrument relevant to the subject's native language (ie, English) should be used. C-SSRS evaluations will be undertaken at the timepoints indicated in Table 6-1.

The questionnaire must be administered by an Investigator or other individual that is suitably qualified by education or training. See APPENDIX 7 for a sample C-SSRS –Baseline/Screening version assessment and APPENDIX 8 for a sample C-SSRS-Since Last Visit version assessment.

If there is a positive result for suicidality on the C-SSRS after Screening (defined by a subject answering "yes' to questions 4 or 5 on the suicidal ideation portion of the C-SSRS), the subject will be evaluated by an Investigator or medically qualified Sub-investigator for continuation in the study.

If a subject becomes suicidal during the study, an Investigator should provide the appropriate treatment to the subject.

6.1.13. Clinical Opioid Withdrawal Scale (COWS)

The naloxone HCl challenge will be conducted as indicated in Table 6-1 for eligible subjects. Clinical Opioid Withdrawal Scale is a clinician-administered, pen and paper instrument that rates 11 common opiate withdrawal signs or symptoms. The summed score of the eleven items can be used to assess a subject's level of opiate withdrawal and to make inferences about their level of physical dependence on opioids (Wesson and Ling, 2003). The scale must be administered by an Investigator or other individual that is suitably qualified by education or training. See APPENDIX 9 for a sample of COWS.

6.1.14. Assessment of Respiratory Depression

Capnography alarms will be set to evaluate for respiratory depression and will include:

- An increase in $EtCO_2$ of at least 10 mmHg compared to baseline or >50 mmHg, whichever value is the lowest
- A reduction in O_2 saturation to <92%
- A reduction in respiratory rate to <6 breaths per minute

All alarms will be assessed for clinical significance and reported as AEs, as applicable. Supplemental oxygen will be given as medically necessary. Events will be timed using a stopwatch or equivalent to confirm clinical relevance. Interventions used to treat respiratory depression will be documented.

6.1.15. Medical Interventions for Signs of Respiratory Depression

In the event that subjects show signs and symptoms of respiratory depression, the Investigator or study staff will begin intervention procedures that may escalate in the degree of intervention as follows:

- Verbal stimuli: Call the subject's name loudly. If no response and/or no improvement in respiratory depression, proceed to physical stimuli.
- Physical stimuli: Apply sternal rub to subject and/or apply nail bed pressure. If subject is unable to be aroused and/or there is no improvement in signs of respiratory depression, proceed to O_2 administration and prepare for possible naloxone administration (if there is no improvement with verbal or physical stimuli, there is a high likelihood of requiring naloxone administration).
- O_2 administration: Administer oxygen with a target SpO_2 of 95-100%. Prepare naloxone for administration if no improvement in respiratory depression clinical parameters or as per Investigator discretion.
- Naloxone administration: Administer naloxone (eg, 4 mg/spray IN every 2-3 minutes; 0.4 mg IV every 2-3 minutes to a maximum of 10 mg) and titrate until adequate oxygenation/ventilation is achieved.

The Investigator or designee will choose the appropriate level of intervention as deemed medically necessary. Subjects who receive intervention will be evaluated to determine if further intervention (eg, hospitalization) is warranted. Subjects who show significant signs of respiratory depression that requires naloxone administration or poses significant safety concerns may be withdrawn from the study at the discretion of the Investigator or designee.

6.1.16. Rescue Therapy

The clinical study site is equipped with emergency equipment and supplies that correspond with the level of risk associated with this study. In case of a medical emergency or an SAE requiring medical intervention, emergency equipment and supplies will be available and will include, but may not be limited to, stocked crash carts, oxygen source, suction pump, and defibrillator. Emergency medication (eg, naloxone) or rescue medication required for advanced cardiac life support may be administered if deemed necessary by an Investigator or designee. If required, subjects will be transported to a hospital.

During the Qualification and Treatment periods, the PI or designee will be on-site at the time of study drug administration until at least 6 hours postdose. Advanced cardiac life support-certified staff will be present on site and an Investigator will be readily available by telephone.
When not available on-site, the PI or designee will be on-call until the end of the study. While confined in the CRU, subjects will be supervised by staff nurses and/or paramedics. Dedicated nurses and/or paramedics will be available to monitor AEs and perform safety measures. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication will be recorded.

6.2. Pharmacokinetic Assessments

6.2.1. Pharmacokinetic Blood Sampling

The complete blood sampling schedule for morphine and its metabolites is presented in Table 6-14. The complete blood sampling schedule for AZD4041 is presented in Table 6-15.

Table 6-14 Pharmacokinetic Blood Sampling Schedule for Morphine and its Metabolites

Pharmacokinetic Blood Sampling - Scheduled Timepoints[a]
Day 1: predose, 5, 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours postdose
Day 15: predose, 5, 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose

a Predose is relative to the start of morphine intravenous infusion. Nominal times listed are relative to the end of morphine intravenous infusion.

Table 6-15 Pharmacokinetic Blood Sampling Schedule for AZD4041

Pharmacokinetic Blood Sampling - Scheduled Timepoints[a]
Days 2 to 7: predose
Day 8: predose, 5, 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, and 12 hours postdose
Days 9 to 14: predose
Day 15: predose, 5, 15, 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose

a. Nominal times listed are relative to the time of AZD4041 administration.

Blood samples will be collected by direct venipuncture into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. As an option to the subject or if judged necessary by the clinical staff, blood samples may be collected from an indwelling cannula which will be placed in the vein of the subject.

The actual time of all PK blood draws will be recorded and reported for all subjects.

Windows for timed PK blood sample collections are presented in Table 6-16. PK samples collected outside of the pre-specified windows will be documented as protocol deviations. Since actual times are to be used for the PK analysis, deviations will be reflected in the analysis unless indicated otherwise upon review of the data.

Table 6-16 Acceptable Windows for Timed PK Blood Specimen Collection Procedures

Elapsed Time	Accepted Window
Predose	within 5 minutes[a]
> 0 hour to ≤ 30 minutes	± 1 minute
> 30 minutes to ≤ 4 hours	± 2 minutes
> 4 hours to ≤ 12 hours	± 5 minutes
> 12 hours to ≤ 24 hours	± 10 minutes
> 24 hours to 72 hours	± 2 hours

a. On Day 1 and Day 2, the accepted window can be increased to within 60 minutes.

AZD4041, morphine, morphine-6-glucuronide, and morphine-3-glucuronide concentrations for PK assessments will be obtained through bioanalysis of the plasma derived from the blood samples drawn during this study, using validated bioanalytical methods.

6.2.2. Pharmacokinetic Urine Sampling

The complete urine sampling schedules are presented in Table 6-17 for AZD4041.

Table 6-17 Pharmacokinetic Urine Sampling Schedule for AZD4041

Pharmacokinetic Urine Sampling - Scheduled Timepoints[a]	
Day 15	Predose spot collection, 0-6 hours, 6-12 hours, 12-24 hours, 24-48 hours, and 48-72 hours postdose

a. Urine will be collected at the specified intervals (-60 minutes for predose spot collection and ±20 minutes for postdose spot collections)

AZD4041 concentrations for PK assessments will be obtained through bioanalysis of the urine collected during this study, using a validated bioanalytical method.

6.2.3. Pharmacokinetic Sample Processing, Storage and Shipping

Blood and urine samples for PK determination will be processed, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

7. ADVERSE EVENTS DOCUMENTATION

7.1. Definitions

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

A suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study drug including comparator; it could be an abnormal clinical laboratory value as well as a significant shift from baseline within normal range which an Investigator considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of an Investigator)

An AE of special interest (AESI: serious or non-serious) is one of scientific and medical concern specific to the Sponsor's drug product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. An AESI is a noteworthy event for the particular product or class of products that a Sponsor may want to monitor carefully. It could be serious or non-serious (eg, hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. Such events may require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Sponsor to other parties (eg, regulatory authorities) might also be warranted.

The following AESI(s) has been specified for the study intervention(s) in this protocol:

- Cardiac arrhythmia (including NSVT)

Non-serious AESIs are to be recorded in electronic data capture (EDC) within 72 hours, and serious AESIs are to be reported to the sponsor within 24 hours.

7.2. Severity Assessment

All AEs will be graded per the current National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Every effort will be made to obtain an adequate evaluation of the severity.

7.3. Causality Assessment

An Investigator will determine the relationship of any AE to the study drug using the guidelines presented in Table 7-1.

Table 7-1 Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the IP that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the IP. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.
No Reasonable Possibility	Evidence exists that the AE has an etiology other than the IP. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

AE = adverse event; IP = investigational product; SAE = serious adverse event

7.4. Adverse Event Monitoring

For the purposes of this study, the monitoring period for AEs extends from the pre-trial evaluation until the follow-up visit. Registration of new AEs will start from the moment of ICF signature and will stop 7 days after the last study drug administration (ie, stop registration on new AEs on follow-up visit in case last AZD4041 dose was administered on Day 15).

Subjects will be questioned on their health status from the beginning of the study, before departure from the clinical site, and at the follow-up visit. Open-ended questions will be asked.

During the study, all AEs reported by the subject, observed by the clinical staff, or elicited by general questioning will be recorded for all subjects and reported in the CRF.

From the signing of the ICF until the first study drug administration, AEs will be recorded as screening events or as part of on the medical history eCRF page, as applicable. AEs occurring after study drug administration will be recorded on AE eCRF page and indicated as TEAEs in the Clinical Study Report, as well as non-serious AESI (defined in Section 7.1).

Any AE which remains unresolved as of the last study visit will require an evaluation and follow-up until the AE has been resolved, stabilized or a reasonable explanation for its persistence found, or is deemed mild and safely resolving.

In the case of AEs deemed related to the IP, every effort will be made to determine the final outcome.

If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw from the study, they will be advised of the safety precautions to be taken. For those subjects whose status is unclear because they fail to appear for study visits

without stating an intention to withdraw, Investigator should show "due diligence" by documenting in the source records steps taken to contact the subject, (eg, dates of at least three telephone call attempts, registered letters, etc).

It is an Investigator's responsibility to ensure subjects experiencing AEs receive appropriate follow-up, treatment where required, and that every action is well documented.

Classification of AEs will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1 or higher.

Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE March 2021 or later).

7.5. Reporting of Pregnancy

Any pregnancy in a female partner of a male subject and the subsequent outcome of any conception (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality/birth defect) that occurs from the first study drug administration until 5 half-lives of AZD4041 (or 4 months [whichever is longer]) after the last study drug administration will be recorded and should be reported to the Sponsor's designee within 24 hours of the knowledge of its occurrence by the clinical site:

- MMS Holdings, Inc.
- Email: PPD
- Facsimile: PPD

Pregnancy reports should be made using the MMS Pregnancy Notification and Outcome Form.

Pregnancies should be followed until resolution of pregnancy with any abnormal outcomes of the mother or the child being reported. Outcomes can be categorized into the following (1. Normal Outcome before end of the Study, 2. Abnormal outcome before end of study, 3. Normal outcome after end of study, or 4. Abnormal outcome after end of study). Congenital abnormalities/birth defects, spontaneous miscarriages, and any other SAEs experienced during pregnancy should be recorded and reported as an SAE according to Section 7.6.

7.6. Serious Adverse Event Reporting

The CRU will report all SAEs to the Sponsor, which includes the AZ study physician (or designee) and MMS Holdings, Inc., without regard to causality, within 24 hours after becoming aware of its occurrence using the SAE Report Form provided by MMS Holdings. The study-specific Safety Management Plan (SMP) will provide further details on SAE distribution. For the purposes of this study, the monitoring period for SAEs extends from the pre-trial evaluation until the follow-up visit. From the signing of the ICF until the first study drug administration, SAEs will be recorded as screening events or as part of the medical history, as applicable. SAEs occurring after study drug administration will be indicated as such in the Clinical Study Report. SAEs will be followed until resolution or stabilization. In order to deem subjects lost to follow-up, the study staff must contact each subject 3 times.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the IP(s). Information not available at the time of the initial report (eg, an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant information is available.

The appropriately completed SAE Report Form should be directed to the Sponsor's designee:

- MMS Holdings, Inc.
- Email: PPD
- Facsimile: PPD

Any SAE reports should be made using the SAE Report Form provided by MMS Holdings. It is **not** acceptable for an Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the SAE report forms. There may be instances when copies of medical records for certain cases are requested by AZ. In this case, all subject identifiers, with the exception of protocol number, site number and the subject number, will be redacted on the copies of the medical records before submission to AZ. A SAE will be considered "unexpected" if the AE is not listed in the reference safety information section of the Investigator's Brochure or is not listed at the specificity or severity that has been observed. "Unexpected", as used in this definition, also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the AZD4041.

If reports of any new suspected unexpected serious adverse reactions (SUSARs) become available to the Sponsor or their designee during the clinical portion of this study (related or not to the present study), the Sponsor or their designee has to advise the CRU, through its clinical Investigator, of those events.

The CRU will determine whether suspected unexpected serious adverse reactions (SUSARs) must be reported to the Institutional Review Board (IRB). If so, the event will be reported via fax or email according to the IRB's reporting policy.

All details on SUSAR reporting to regulatory authorities will be specified in the SMP.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Analysis Populations

8.1.1. Randomized Population

The Randomized Population will include all subjects who are randomized to the Treatment phase.

8.1.2. Safety Population

The Safety Population will include all randomized subjects who receive at least 1 dose of morphine.

The number of subjects who were included, who discontinued, and who completed the study will be tabulated. The primary reasons for discontinuation will be provided.

8.1.3. Completer Population

The Completer Population will include all subjects in the Safety Population who complete the entire Treatment phase and the follow-up period (up to at least Day 22). This population will be used for inferential analysis of maximum postdose increase in $EtCO_2$ ($E_{max\ (postdose - predose)}$), maximum postdose reduction in SpO_2 ($E_{max\ (predose - postdose)}$), and maximum postdose decrease in respiratory rate ($E_{max\ (predose - postdose)}$).

8.1.4. Pharmacokinetic Population

All subjects in the Safety Population who receive at least 1 dose of morphine or AZD4041 and have at least 1 PK concentration after dosing will be included in the PK Population.

The PK population will be further described in a SAP.

8.2. Demographic Data and Other Baseline Characteristics

Listings and descriptive summary statistics of demographic (age, height, weight and BMI) and baseline data will be presented.

Statistics for demographic and baseline data will be detailed in a Statistical Analysis Plan (SAP).

8.3. Safety

Statistics for summary of AEs and safety results will be detailed in a SAP.

8.3.1. Safety Endpoints

The primary safety endpoints are:

- Incidence of increased $EtCO_2$ of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds)
- Incidence of reduction in SpO_2 to <92% (sustained for at least 30 seconds)

The secondary safety endpoints are:

- Mean time to reduction in SpO_2 to <92% (sustained for at least 30 seconds)
- Mean duration of reduction in SpO_2 to <92% (sustained for at least 30 seconds)
- Maximum postdose reduction of SpO_2 adjusted for baseline
- Mean postdose SpO_2
- Mean time to each increased $EtCO_2$ episode of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds)
- Mean duration of each increased $EtCO_2$ episode of at least 10 mmHg compared to baseline or >50 mmHg (sustained for at least 30 seconds)
- Maximum postdose increase in $EtCO_2$ adjusted for baseline
- Mean postdose $EtCO_2$
- Incidence of reduced respiratory rate to <6 breaths/min (sustained for at least 30 seconds)
- Mean time to each reduced respiratory rate episode of <6 breaths/min (sustained for at least 30 seconds)

- Mean duration of each reduced respiratory rate episode of <6 breaths/min (sustained for at least 30 seconds)
- Maximum postdose decrease in respiratory rate adjusted for baseline
- Mean postdose respiratory rate
- Incidence, frequency, severity and relationship of AEs
- Vital signs measurements (BP, HR, and oral temperature)
- ECGs (12-lead safety ECGs, 12-lead dECGs, and ECG telemetry)
- Clinical laboratory test results (clinical chemistry, hematology, coagulation, urinalysis)
- Physical examination findings
- Type of medical intervention used, summarized for each event of significantly increased $EtCO_2$, reduced SpO_2 or respiratory rate

8.3.2. Safety Analysis

8.3.2.1. Respiratory Depression Analysis

Summary statistics and inferential analysis for respiratory depression endpoints will be done using the Completer Population.

Incidence of increased $EtCO_2$ of at least >50 mmHg will be summarized by treatment and time point using frequency tables. Mean time to each increased $EtCO_2$ episode of at least >50 mmHg, mean duration of each increased $EtCO_2$ episode of at least >50 mmHg, and mean postdose $EtCO_2$ will be summarized by treatment and time point using descriptive statistics. Maximum postdose increase in $EtCO_2$ $E_{max\ (postdose - predose)}$ will be summarized by treatment using descriptive statistics and inferential analysis. $EtCO_2$ averages (predose average from Days 2 to 15), and postdose average on Day 15 will also be summarized by treatment using descriptive statistics and inferential analysis. For each event of significantly increased $ETCO_2$, type of medical intervention used will be listed.

Incidence of reduction in SpO_2 to <92% will be summarized by treatment and time point using frequency tables. Mean time to reduction in SpO_2 to <92%, mean duration of reduction in SpO_2 to <92%, and mean postdose SpO_2 will be summarized by treatment and time point using descriptive statistics. Maximum postdose reduction of SpO_2 $E_{max\ (predose - postdose)}$ will be summarized by treatment using descriptive statistics and inferential analysis. SpO_2 averages (predose average from Days 2 to 15), and postdose average on Day 15 will also be summarized by treatment using descriptive statistics and inferential analysis. For each event of significantly reduced SpO_2, type of medical intervention used will be listed.

Incidence of reduced respiratory rate to <6 breaths/min will be summarized by treatment and time point using frequency tables. Mean time to each reduced respiratory rate episode of < 6 breaths/min, mean duration of each reduced respiratory rate episode of <6 breaths/min, and mean postdose respiratory rate will be summarized by treatment and time point using descriptive statistics. Maximum postdose decrease in respiratory rate $E_{max\ (predose - postdose)}$ will be summarized by treatment using descriptive statistics and inferential analysis. Respiratory rate averages

(predose average from Days 2 to 15), and postdose average on Day 15 will also be summarized by treatment using descriptive statistics and inferential analysis.

For $EtCO_2$, SpO_2, and respiratory rate the following figures will be generated:

1) Mean (± SD) treatment by time point for Day 1 Morphine alone matched to Day 15 Morphine + AZD4041
2) Mean (± SD) treatment by time point for Day 1 Morphine alone matched to Day 15 Morphine + Placebo
3) Mean (± SD) treatment by time point for Days 2-15 predose AZD4041 vs. Days 2-15 predose Placebo
4) Boxplot for E_{max} Day 1 Morphine alone matched to Day 15 Morphine + AZD4041
5) Boxplot for E_{max} Day 1 Morphine alone matched to Day 15 Morphine + Placebo
6) Boxplot for E_{max} Day 15 Morphine + AZD4041 vs. Day 15 Morphine + Placebo

For all inferential analysis on $EtCO_2$, SpO_2, and respiratory rate, mixed-effects models will be used for E_{max} and averaged measures. The models will include treatment as a fixed effect, and baseline as a covariate. Homogeneity of treatment variances will be explored to determine if subject may be considered a random effect.

For maximum postdose increase in $EtCO_2$ ($E_{max\ (postdose - predose)}$), maximum postdose reduction in SpO_2 ($E_{max\ (predose - postdose)}$), and maximum postdose decrease in respiratory rate ($E_{max\ (predose - postdose)}$), the following contrasts will be explored in the mixed-effects models:

1) E: Morphine + AZD4041 (Day 15) vs A: Morphine alone (Day 1)
2) F: Morphine + Placebo (Day 15) vs B: Morphine alone (Day 1)
3) E: Morphine + AZD4041 (Day 15) vs F: Morphine + Placebo (Day 15)

For $EtCO_2$, SpO_2, and respiratory rate averages (predose average from Days 2 to 15), and postdose average on Day 15, the following contrasts will be explored in the mixed-effects models:

1) E (postdose): Morphine + AZD4041 (postdose average Day 15) vs C + E (predose): AZD40401 (predose average Days 2-15)
2) C + E (predose): Morphine + AZD4041 (predose average Days 2-15) vs D + F (predose): Morphine + Placebo (predose average Days 2-15)

8.3.2.2. 12-lead digital ECG Statistical Methodology

From the dECG data, the following parameters will be derived:

1) QTcF will be calculated as QTcF = QT*RR-1/3, where the QT interval is in milliseconds and the RR interval is in seconds.
2) Heart rate will be calculated, based on the RR interval as HR = 60/RR interval, where the RR interval is in seconds.
3) Calculation of derived parameters will be performed after smoothing of QT and RR data.

The dECG data will be smoothed on an individual basis before performing the derivations above and prior to calculation of any changes from baseline or descriptive statistics. For each subject it will be done as follows: the mean value of all the measurements will be taken provided that at least 4 measurements are present and the time between the first and last is greater than 2.75 minutes or else, the smoothed value at the corresponding target time point will be set to missing.

Digital ECG results will be listed by treatment (Morphine and AZD4041 vs Morphine and placebo) for each subject and time point and will include all individual and smoothed values of PR, RR, QRS, QT interval, and the derived values of QTcF and HR. All smoothed and derived parameters will have changes from baseline derived and presented.

Descriptive statistics will be presented by treatment and time point for smoothed values and changes from baseline of smoothed values of PR, RR, QRS, QT; derived values and changes from baseline for QTcF and HR will also be included. The baseline for the dECG measurements will be the (smoothed) predose assessment on Day 1.

Outliers with respect to PR, QRS, HR, RR and QTcF will also be tabulated for the following categories:

For QTcF:

- Absolute value > 450 ms and ≤ 480 ms
- Absolute value > 480 ms and ≤ 500 ms
- Absolute value > 500 ms
- Increase from baseline > 30 ms and ≤ 60 ms
- Increase from baseline > 60 ms

The maximum postdose values for PR interval will be summarized by treatment according to the following categories:

- ≤220 ms
- >220 and ≤ 240 ms (all instances flagged in the listing*)
- >240 ms (all instances flagged in the listing **)

The maximum postdose values for QRS duration will be summarized by treatment according to the following categories:

- ≤115 ms
- >115 ≤ 119 ms (all instances flagged in the listing*)
- >119 ms (all instances flagged in the listing**)

The maximum/min postdose values for HR will be summarized by treatment according to the following categories:

- <40 bpm (all instances flagged in the listing**)
- 40 - <50 bpm (all instances flagged in the listing*)
- ≥50 bpm and ≤100 bpm
- >100 - ≤120 bpm (all instances flagged in the listing*)
- >120 bpm (all instances flagged in the listing**)

The maximum/min postdose values for RR will be summarized by treatment according to the following categories:

- <500 ms (all instances flagged in the listing**)
- 500 ms - < 600 ms (all instances flagged in the listing*)
- ≥ 600 ms ≤ 1200 ms
- > 1200 ms ≤ 1500 ms (all instances flagged in the listing*)
- >1500 ms (all instances flagged in the listing**)

All calculations of dECG parameters and reporting described in this section will be performed by AltaSciences.

8.3.2.3. All Other Safety Analysis

Summary statistics for all other safety analysis will be done using the Safety Population.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and characterized as pre-treatment and treatment-emergent according to the intake of the study drugs. The occurrence and incidence of TEAEs will be summarized by MedDRA system organ class and preferred term and by treatment. The occurrence and incidence of TEAEs will also be summarized by severity and by relationship to the study drugs. Adverse events leading to discontinuation and SAEs will be listed.

Clinical laboratory parameters will be summarized by visit using descriptive statistics. Values within and outside the reference range will also be summarized using frequency tablets. Vital sign and ECG parameters and change from baseline (predose) will be summarized at each time point by treatment using descriptive statistics. Physical examination abnormalities and C-SSRS findings will be listed.

8.4. Pharmacokinetics

The PK analysis will be carried out according to AZ SOPs. Pharmacokinetic data handling and analysis will be further detailed in a SAP.

8.4.1. Pharmacokinetic Parameters

The PK parameters will be determined by non-compartmental analysis using appropriate software. The PK parameters for AZD4041, morphine, morphine-6-glucuronide and morphine-3-glucuronide are presented in Table 8-1.

Table 8-1 Pharmacokinetic Parameters in Plasma

Parameter[a]	Definition
For morphine, morphine-6-glucuronide and morphine-3-glucuronide (Day 1 and 15)	
C_{max}	Maximum observed concentration occurring at time t_{max}
t_{max}	Time of maximum observed concentration. If the maximum observed concentration is not unique, then the first maximum is used
AUC_{0-t}	Area under the concentration time curve from the time of last dosing to the time of last quantifiable concentration (T_{last})
$AUC_{0-\infty}$	Area under the concentration time curve extrapolated to infinity, calculated as $AUC_{0-T} + C_{last}/\lambda_Z$, where C_{last} is the last quantifiable concentration at time T_{last}
$t_{1/2,z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda$

Parameter[a]	Definition
T_{last}	Time of last measurable observed concentration
CL	Total body clearance, calculated as Dose/$AUC_{0-\infty}$ (parent drug only)
Vz	Volume of distribution based on terminal phase (parent drug only)
For AZD4041	
Days 2 to 7 and Days 9 to 14:	
C_{trough}	Predose concentration observed immediately prior to the next successive dose
Days 8 and 15	
$C_{max,ss}$	maximum observed plasma concentration
$t_{max,ss}$	time to maximum observed plasma concentration
C_{trough}	Predose concentration observed immediately prior to the next successive dose
AUC_{τ}	area under the concentration time curve over the dosing interval at steady-state, calculated from 0 to 24 hours (dosing interval)
C_{av}	average concentration during a dosing interval, after the last dose of a multiple dose regimen, calculated as AUCτ/τ
$t_{1/2,z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$ (Day 15 only)
CLss/F	Apparent total body clearance at steady-state, calculated as Dose/AUC_{τ}
Vzss/F	Apparent volume of distribution at steady-state, based on terminal phase

a. A complete list of PK parameters that will be used for PK calculation and presented in the PK listings will be included in the SAP.

Table 8.2 Pharmacokinetic Parameters in Urine for AZD4041 (Day 15 only)

Parameter	Definition
Aeτ	Amount of drug excreted in urine. The Ae at each urine collection interval will be calculated as follows: Concentration * Volume of urine during that time interval (t1 to t2). Cumulative Ae will be calculated as the sum of all urine collection interval Aes. Note: The Ae at predose will not be included in the calculation of cumulative Ae.
feτ	Cumulative fraction of unchanged drug excreted in urine over the dosing interval, calculated as (Aeτ/Dose)*100 (expressed in %), where Aeτ is the amount of drug excreted in urine during the dosing interval. Note: The Ae at predose will not be included in the calculation of fe.
CL_R	Apparent renal clearance, calculated as Aeτ/ AUCτ on Day 15. A different time interval may be used providing not all single intervals are usable.
$t_{1/2}$	Elimination half-life, calculated as ln(2)/λz on Day 15

8.4.2. Summary and Presentation of PK data

- The plasma and urine concentration data for all the analytes will be presented individually and summarized by time point by day for each treatment
- The PK parameters data for all the analytes will be presented individually and summarized by day for each treatment
- Individual as well as mean plasma and urine concentration versus time plots will be presented by day for AZD4041 as well as morphine and its metabolites (together) separately

8.4.3. Pharmacokinetic Statistical Methodology

8.4.3.1. Assessment of Steady State Achievement

C_{trough} will be compared descriptively to assess the achievement of steady-state for AZD4041.

8.4.3.2. Comparison of PK Parameters

Two-sided 90% confidence interval of the ratio of geometric LSmeans obtained from the ln-transformed PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for morphine and its metabolites; $C_{max,ss}$ and AUC_{τ} for AZD4041) will be calculated to assess the magnitude of interaction for the following comparisons:

1. Morphine and its metabolites: Morphine + AZD4041 (Day 15) *versus* Morphine alone (Day 1)
2. AZD4041: Morphine + AZD4041 (Day 15) *versus* AZD4041 (Day 8)

8.5. Determination of Sample Size

No formal sample size calculation has been performed. The number of participants is based on the precedent set by other studies of similar nature (Verbekt et al, 2017). The number of

participants planned for completion in this study is considered sufficient to achieve the study objectives. Approximately 44 subjects will be randomized (28 AZD4041 + morphine and 16 Placebo + morphine) to complete at least 36 subjects (24 AZD4041 + morphine, and 12 Placebo + morphine on Day 15).

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10. APPENDIX 1: ETHICS

10.1. Institutional Review Board

This protocol and the ICF will be submitted to an IRB (or Independent Ethics Committee[IEC]) prior to initiation of the study and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the final report.

10.2. Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the International Council for Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP), the FDA GCP Code of Federal Regulations (CFR) Title 21 (part 56), the EU Clinical Trial Directive (EC) No. 2001/20/EC, the European regulation EU 536/2014 and the Tri-Council Policy Statement (Canada).

10.3. Subject Information and Consent

Before screening activities commence, each volunteer will be given a copy of the ICF to read, as well as a full explanation of the purpose of the study, the procedures to be carried out, and the potential AE(s). Once this essential information is provided to the volunteer and the physician in charge or delegate has the conviction the volunteer understands the implications of participating in the study, and if the volunteer chooses to continue the screening process, they will be requested to sign and date a properly executed ICF prior to enrollment. Subjects will be assured they may withdraw from the study at any time without jeopardizing their medical care or future study participation (for which they qualify).

Subjects will be given a signed copy of the ICF. If an amended or revised ICF is introduced during the study, each subject's further consent must be obtained.

10.4. Subject Confidentiality

Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects should be identified by a unique subject identifier on all study documents provided to the Sponsor. In compliance with Federal regulations/ICH GCP Guidelines, it is required an Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and IRB access to review the subject's original medical records for verification of study-related procedures and data. An Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the subject's confidentiality.

11. APPENDIX 2: DATA COLLECTION, RETENTION, AND MONITORING

11.1. Case Report Forms

The subject level data is entered by the site from the source document into a study specific 21 CFR Part 11 compliant electronic clinical database to accurately collect data for each subject included in a clinical trial. Screen failure data may be entered into the database at the discretion of the Sponsor, when included in the contracted scope of work.

11.2. Data Management and Processing

Data management develops documentation to define activities performed during the data management conduct of the study trial. The EDC system is the tool used to conduct all data management data cleaning activities for monitoring, data review and queries. Data management will use a combination of automated programmed edits and manual data review listings to issue queries for non-conforming or discrepant data. Data management activities are performed in accordance with the SOPs and study-specific data management documents.

Database locking is guided by the Data Management Locking Checklist based on the concept that all site activities are complete, data are considered clean and without errors and CRF signoff by the Principal Investigator or delegate has been completed. User access is removed as part of the locking process.

Data from the clinical database will be output as SAS® datasets. All data will be included with the final report provided to the Sponsor.

11.3. Quality Control and Quality Assurance

Designated personnel from the quality assurance (QA) unit(s) of the clinical, PK and statistical facilities will be responsible for maintaining QA systems to ensure that the trial is conducted and that clinical/PK/statistical data is generated, documented and reported in compliance with the protocol and the integrated addendum to ICH E6: Guideline for Good Clinical Practice E6 (R2).

Designated personnel from each corresponding operation unit (eg, clinical, PK, and statistical facilities) will be responsible to maintain and assure the QC of all data generated and documented in compliance with the protocol.

All parts of the bioanalytical phase of the study and all its documentation will be subject to inspection by the QA unit of the bioanalytical facility to ensure that the data are generated, documented and reported in compliance with the protocol and applicable requirements as outlined in the FDA and Organization for Economic Co-Operation and Development (OECD) Principles of GLP.

11.4. Record Retention

All essential documents and records will be maintained by the clinical site in accordance with, and for the period specified in the applicable regulatory requirement(s) (FDA CFR 312.57 [C]).

11.5. Monitoring of the Study

The sponsor or its representative may monitor the study in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site will permit trial-related monitoring, audits, institutional review board (IRB)/independent ethics committee

(IEC) review, and regulatory inspection(s) by providing direct and/or virtual access, where possible, to source data/documents.

12. APPENDIX 3: ADMINISTRATIVE PROCEDURES

12.1. Liabilities

It is the Sponsor's responsibility to guarantee sufficient insurance coverage should any serious events or deaths result, either directly or indirectly, from the execution of the present protocol.

12.2. Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and the applicable regulatory requirements. Any deviation from the protocol will be recorded and explained.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB for approval.

12.3. COVID-19 Response Plan

Regulatory authorities have recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may impact the conduct of clinical trials of medical products. Challenges may arise, for example, from quarantines, site closures, travel limitations, interruptions to the supply chain for the IP(s), or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the IP or adhering to protocol-mandated visits and laboratory/diagnostic testing. To accommodate these challenges and mitigate safety risks associated with COVID-19, protocol modifications may be required which include (and are not limited to):

- Conducting the study in multiple (smaller) subject groups;
- Altering the timing of study procedures and subject confinement;
- Modification of standard inclusion or exclusion criteria;

The exact mitigations will be documented in the study Risk Assessment and Mitigation Plan.

Additional health checks including COVID-19 testing, body temperature monitoring, etc. may be performed during the trial, even if not planned within the protocol.

12.4. Statement of Investigator

The form "Qualified Investigator Undertaking" will be signed by an Investigator responsible for the medical decisions and care provided to the subjects (being also referred to as the "qualified investigator") prior to the commencement of his responsibilities with respect to the clinical trial, as required by the Food and Drug Regulations. The undertaking form will be maintained with the trial records and will be made available upon request.

The FDA 1572 form, Statement of Investigator [Title 21, CFR Part 312], will be signed by the Investigator, and will be kept on file.

12.5. Delegation of Investigator Duties

An Investigator will ensure all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

An Investigator will maintain a list of sub-investigator(s) and other appropriately-qualified persons to whom he/she delegates significant trial-related duties.

Should an Investigator delegate the supervision of the IP administration to a designated person, this individual must have the appropriate professional-legal qualifications and certifications. An Investigator should also ensure key staff personnel have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

12.6. Premature Termination or Suspension of a Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the clinical site or an Investigator (or delegate) should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority(ies) when required.

13. APPENDIX 4: PROTOCOL REVIEW AND APPROVALS

TITLE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIXED SEQUENCE STUDY TO ASSESS THE EFFECT ON RESPIRATORY DRIVE OF MULTIPLE DOSES OF AZD4041 WHEN CO-ADMINISTERED WITH A SINGLE DOSE OF MORPHINE IN HEALTHY RECREATIONAL OPIOID USERS

I have carefully read this study protocol and agree it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with GCP and the applicable regulatory requirements.

_____
Principal Investigator Name (Please Print)

_____ _____
Principal Investigator Signature Date (yyyy/mm/dd)
Altasciences Clinical Kansas Inc

TITLE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, FIXED SEQUENCE STUDY TO ASSESS THE EFFECT ON RESPIRATORY DRIVE OF MULTIPLE DOSES OF AZD4041 WHEN CO-ADMINISTERED WITH A SINGLE DOSE OF MORPHINE IN HEALTHY RECREATIONAL OPIOID USERS

On behalf of the Sponsor, I am aware of, and agree to comply with, all of the procedures contained within this protocol.

PPD _____ _____ PPD

Date (yyyy/mm/dd)

PPD
PPD
PPD , Clinical Development, Neuroscience
Neuroscience Biopharmaceuticals Research and Development
Sponsor's Representative
AstraZeneca

14. APPENDIX 5: LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interests
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AV	Atrioventricular
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per Minute
CFR	Code of Federal Regulations
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRU	Clinical Research Unit
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient Of Variation
CYP	Cytochrome P450
dECG	Digital Electrocardiogram
DORA	Dual Orexin Receptor Antagonist
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EClysis©	User-Interactive, Modular Computer-Based System for dECG Data Processing, Analysis and Measurement of ECG Intervals and Wave Amplitudes, Exports and Reports, used by the AstraZeneca ECG Centre
EDC	Electronic Data Capture
EEG	Electroencephalogram
$EtCO_2$	End Tidal Carbon Dioxide
EU	European Union
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

HBsAG	Hepatitis B Surface Antigen
HCl	Hydrochloride
HCVAb	Hepatitis C Virus Antibody
hERG	Human Ether-A-Go-Go-Related Gene
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
kg	Kilogram
L	Litre
LH	Luteinizing Hormone
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Millilitres
mmHG	Millimetre of Mercury
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
ng	Nanograms
NIDA	National Institutes on Drug Abuse
NOAEL	No-Observed-Adverse-Effect Level
NSVT	Non-Sustained Ventricular Tachycardia
OECD	Organization for Economic Co-Operation and Development
OTC	Over-The-Counter
OUD	Opioid Use Disorder
OX1/2	Orexin Receptor
PK	Pharmacokinetic
PR (PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
PT	Preferred Term

QA	Quality Assurance
QRS	ECG Interval Measured from the onset of QRS Complex to the J-Point
QT	QT Interval is the time from the start of the Q Wave to the end of the T Wave, Time Taken for Ventricular Depolarization and Repolarization
QTC	Qt Interval Corrected for Heart Rate
QTcF	Qt Interval Corrected for Heart Rate Using Fridericia's Correction Formula
RR	Time Elapsed Between Two Successive R-Waves of the QRS Signal on the ECG
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SMP	Safety Management Plan
ST	ST Segment of the ECG
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	T Wave of the ECG
TEAE	Treatment-Emergent Adverse Event
THC	Tetrahydrocannabinol
ULN	Upper Limit of Normal
VPC	Ventricular Premature Contractions
WHO-DDE	World Health Organization Drug Dictionary Enhanced

15. APPENDIX 6: CLINICAL LABORATORY EVALUATIONS

Laboratory Test Panel	Description
General biochemistry:	Alanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, bilirubin total, chloride, creatinine (including eGFR using the MDRD equation), glucose, potassium, sodium, BUN, magnesium, calcium
Endocrinology[a]	FSH
Hematology:	White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume, and platelet count
Coagulation tests:	Activated partial thromboplastin time, prothrombin time, INR
Serology[a]:	HIV Ag/Ab Combo, Hepatitis B surface antigen and Hepatitis C virus,
Urinalysis:	Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
Urine drug screen:	Amphetamines, barbiturates, cannabinoids, cocaine, opiates, benzodiazepines, ethanol, and phencyclidine
Pregnancy test:	Serum pregnancy test

Abbreviations: BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; INR = international normalization ratio; MDRD = Modification of Diet in Renal Disease

[a] Screening visit only.

16. APPENDIX 7: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION

The Columbia-Suicide Severity Rating Scale Baseline/Screening Version will be provided to the clinical site and is not included here in its entirety.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

17. APPENDIX 8: COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – SINCE LAST VISIT VERSION

The Columbia-Suicide Severity Rating Scale Since Last Visit Version will be provided to the clinical site and is not included here in its entirety.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

18. APPENDIX 9: CLINICAL OPIOID WITHDRAWAL SCALE (COWS)

Clinical Opiate Withdrawal Scale (COWS)

For each item, write in the number that best describes the patient's signs or symptom. 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

Resting Pulse Rate: (record beats per 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

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 observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Restlessness *Observation during assessment*
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 Unable to sit still for more than a few seconds

Pupil size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/ muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

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

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

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

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

Anxiety or Irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Gooseflesh skin
0 skin is smooth
3 piloerrection of skin can be felt or hairs standing up on arms
5 prominent piloerrection

Total score: _____

19. APPENDIX 10: CONTRACEPTION GUIDANCE

Non-sterilised males who are sexually active with a female partner of childbearing potential must use a condom for the duration of the treatment period and for no less than 120 days following the last administration of study drug. As a male condom is not considered to constitute a highly effective contraception method, it is recommended that female partners of a male study subject also use a highly effective method of contraception throughout the study and the protocol-specified follow-up period. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in the table below.

Table 1 Highly effective methods of contraception

Barrier methods	Hormonal methods
Intrauterine device Intrauterine hormone-releasing system (UIS)[a] Bilateral tubal occlusion Vasectomy[b] Sexual abstinence[c]	Combined (oestrogen and progestogen containing hormonal contraception) • Oral (combined pill) • Injectable • Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation[d] • Injectable • Implantable • Intravaginal

a This is also considered a hormonal method.
b With appropriate evidence of post-vasectomy surgical success.
c Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.
d Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method).

20. APPENDIX 11: PHYSICAL EXAMINATION FORM

21. APPENDIX 12: NEUROLOGICAL EXAMINATION FORM