AstraZeneca

AZD4041 – D7460C00001

A Phase I, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of AZD4041 Following Single Ascending Dose Administration to Healthy Volunteers

07AUG2020

Final Statistical Analysis Plan

Version 1.0

[redacted]

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LIST OF ABBREVIATIONS

λ_z	apparent terminal phase elimination rate constant
$\%AUC_{extrap}$	percentage of the area extrapolated for calculation of $AUC_{0\text{-inf}}$.
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
$AUC_{0\text{-t}}$	area under the plasma concentration versus time curve from time zero to the last quantifiable concentration in plasma
$AUC_{0\text{-inf}}$	extrapolation of the area under the curve from time 0 to infinity
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	observed maximum plasma concentration
CRU	clinical research unit
CSR	clinical study report
CV	coefficient of variation
dECG	digital electrocardiogram
ECG	electrocardiogram
E-R	exposure-response
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 Center
eCRF	electronic case report form
GLP	Good Laboratory Practice
HL	Hy's Law
HR	heart rate
MedDRA	Medical Dictionary for Regulatory Activities
OX1	orexin 1 receptor
OX2	orexin 2 receptor
PD	pharmacodynamics
pECG	paper electrocardiogram
PK	pharmacokinetic
PR	pulse rate
PR(PQ)	electrocardiogram interval measured from the onset of the P wave to the onset of the QRS complex
QRS	electrocardiogram interval measured from the onset of the QRS complex to the J point
QT	electrocardiogram interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula

RR	time elapsed between 2 consecutive R waves as measured by electrocardiogram
Rsq	r^2, the coefficient of determination (goodness of fit statistic); visual inspection of the terminal slope will be performed. In general, λ_z may only be retained if $r^2 \geq 0.80$
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis software
SD	standard deviation
SoA	schedule of activities
SOC	system organ class
SRC	safety review committee
$t_{1/2\,\lambda z}$	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum (peak) plasma concentration following drug administration
ULN	upper limit of normal
V_{ss}/F	apparent volume of distribution at steady state
WHO	World Health Organization

1. Introduction

Smoking is an epidemic of global proportions. It is the leading cause of morbidity and mortality in virtually every country in the world (Lim et al 2010). Smoking increases the risk of death by three-fold in smokers, compared with non-smokers (Jha et al 2013). It is predicted that approximately 0.6 billion current smokers worldwide will die from smoking-related illnesses, such as chronic obstructive pulmonary disease, cardiovascular disease and lung cancer (Ezzati and Lopez 2003, Doll et al 2004, Coe et al 2005, Mathers and Loncar 2006).

Pharmacotherapy is an effective strategy to aid smoking cessation efforts, but there is considerable risk of relapse even when treated with the most efficacious medications currently available. Further, medications that are effective aids to smoking cessation are associated with a range of adverse effects. This highlights the pressing need to develop safer and more effective smoking cessation therapeutics.

The neuropeptides orexin A and orexin B (also known as hypocretin 1 and hypocretin 2 respectively) are hypothalamic neuropeptides that act through two closely related G protein coupled receptors (GPCRs), the OX1 and OX2 receptors. Orexin A has high affinity for both receptors whereas orexin B has higher affinity for OX2 over OX1 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 (Willie et al 2003; Gotter et al 2016), neuroendocrine homeostasis, cardiovascular functions (Samson et al 2007), and motivated behaviors (Kodadek and Cai 2010). The OX1 receptor signals almost exclusively through Gq coupling. Nicotine, which is the principal reinforcing component in tobacco smoke responsible for addiction (Stolerman and Jarvis 1995), activates orexin (hypocretin) neurons in the brain. This increase in orexinergic transmission is thought to play a crucial role in regulating the motivational properties of the drug that results in tobacco dependence (Kenny 2011). Further, OX1 receptors regulate the reinstatement of extinguished drug-seeking responses in abstinent rats (Boutrel et al 2005, Harris et al 2005, Kenny 2011) and mice, considered animal models with heuristic value for understanding relapse in abstinent human drug addicts. As such, OX1 receptor antagonists are considered one of the most promising novel therapeutic strategies to facilitate smoking cessation. Importantly, OX1 receptors play a similar role in regulating the addiction-related actions of opioids, psychomotor stimulants and alcohol, raising the possibility that OX1 receptor antagonists may have utility for the treatment of addiction across different classes of abused drugs.

This study is conducted to assess the safety, tolerability, and pharmacokinetics (PK) of single doses of AZD4041 in a small number of healthy subjects, prior to advancing AZD4041 into larger clinical trials of longer duration.

2. Objectives

2.1. Primary Objectives

The primary objectives of this study were as follows:

- To assess the safety and tolerability of AZD4041 following oral administration of single ascending doses
- To characterize the PK of AZD4041 following oral administration of single ascending doses of AZD4041

2.2. Secondary Objective

The secondary objective of this study was to characterize the pharmacodynamic (PD) relationship between drug exposure and QT interval.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase I, first-in-human, single-center, randomized, double-blind, placebo-controlled, single ascending dose, sequential group study in healthy male and female subjects of non-childbearing potential (Cohorts 1, 2, and 3), or healthy vasectomized male and female subjects of non-childbearing potential (Cohorts 4, 5, and 6), aged 18 to 65 years.

The study plans to enroll 48 healthy subjects across 6 cohorts as shown in Table 3-1.

Table 3-1: Dose-Level Cohorts

Cohort	Dose Level of AZD4041
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Eight subjects will participate in each cohort. Within each cohort, 6 subjects will be randomized to receive AZD4041 and 2 subjects will be randomized to receive placebo. Subjects that drop out before dosing will be replaced. Dosing for each ascending dose cohort will proceed with 2 subjects in a sentinel cohort, such that 1 subject will be randomized to receive placebo and 1 subject will be randomized to receive AZD4041 in a blinded fashion.

The safety data from the sentinel subjects up to 24 hours post-dose will be reviewed by the principal investigator (PI), clinical research organization (CRO) medical monitor, and AstraZeneca study physician before the remaining subjects in the cohort are dosed. The remaining 6 subjects for each cohort will be dosed at least 24 hours after the sentinel cohort.

The study comprises a screening period of up to 28 days (4 weeks), a 4-day in-patient period for Cohorts 1 to 3 and a 6-day in-patient period for Cohorts 4 to 6 during which a single oral dose of AZD4041 or placebo will be administered, and an out-patient follow-up period. The overall study duration (screening, treatment, and follow-up periods) will therefore be approximately 6 weeks. The general study design is summarized in Figure 3-1.

Figure 3-1: Study design (Cohorts 1 to 3)

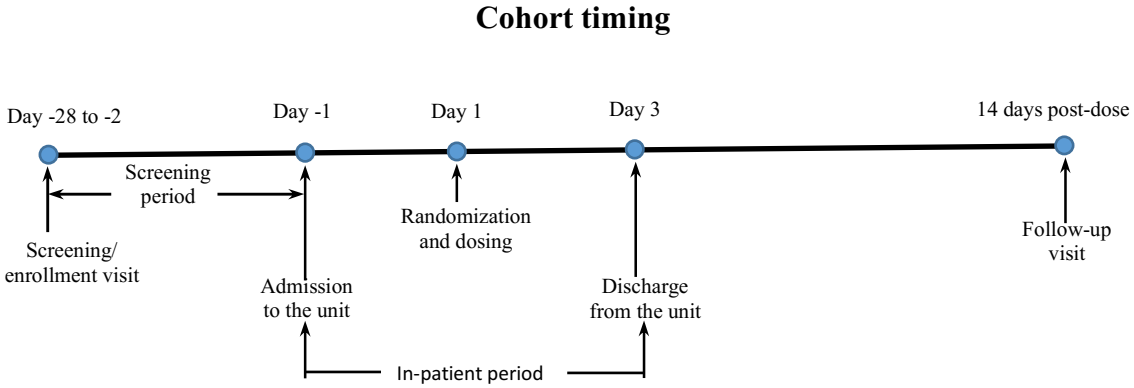
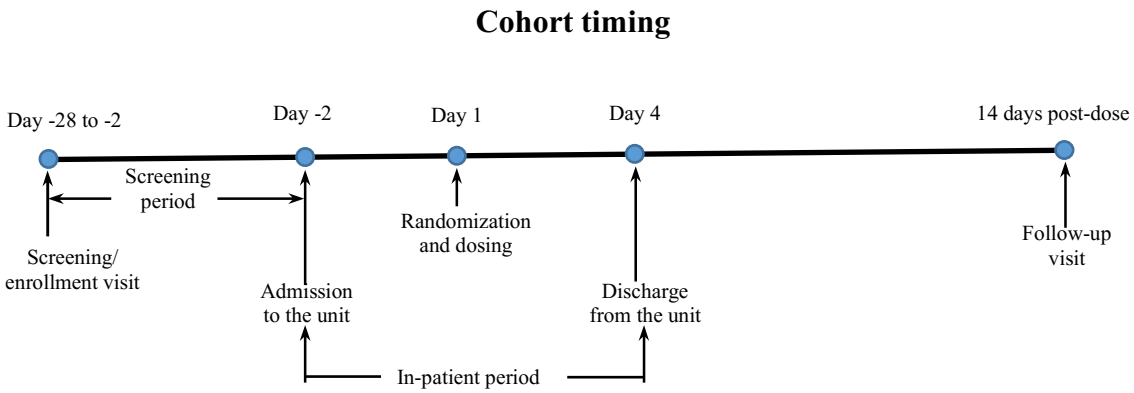


Figure 3-2: Study design (Cohorts 4 to 6)



The end of study is defined as the last expected visit/contact of the last subject undergoing study treatment. A subject is considered to have completed the study when the subject has completed his/her last scheduled visit or last scheduled procedure, presented in Appendix 14.1 Schedule of Activities (SoA).

3.2. Study Endpoints

3.2.1. Primary Endpoints

Safety endpoints include the following:

- The frequency and severity of adverse events (AEs)
- Clinical laboratory test results (hematology, biochemistry, and urinalysis)
- Vital sign measurements (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature)
- 12-Lead ECG (paper ECG and digital ECG) and telemetry results
- Testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and inhibin B (male subjects in Cohorts 4, 5, and 6 only)

PK endpoints include the following:

- Maximum (peak) plasma drug concentration (C_{max})
- Time to reach maximum (peak) plasma concentration following drug administration (T_{max})
- Area under the plasma concentration versus time curve from time zero to the last quantifiable concentration in plasma (AUC_{0-t})
- Extrapolation of the area under the curve from time 0 to infinity (AUC_{0-inf})
- Terminal half-life ($t_{1/2\lambda z}$)
- Apparent total clearance of the drug from plasma after oral administration (CL/F)
- Apparent volume of distribution at steady state after oral administration (V_{ss}/F)

3.2.2. Secondary Endpoints

An exposure-response (E-R) analysis may be conducted with data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document, for the QT interval corrected for heart rate using Fridericia's formula (QTcF) parameter, as part of the cardiac safety evaluation and with the intention to obtain a Thorough QT (TQT) study substitute. The results of the E-R analysis may not be included in the main study report.

4. General Statistical Considerations

All statistical analyses will be performed using Statistical Analysis System (SAS®) software (SAS Institute Inc., Cary, North Carolina) Version 9.4 or higher.

For categorical variables, number and percentage of subjects will be presented. Percentage will be rounded to 1 decimal place and will be suppressed when the corresponding number of subjects is zero.

Continuous variables will be summarized using descriptive statistics and will include number of subjects, mean, median, standard deviation (SD), minimum, and maximum, unless otherwise specified. Geometric mean and coefficient of variation (CV) will also be presented for PK parameters. Minimum and maximum will be presented to the same precision as the original data, mean, median, and geometric mean will be presented to 1 more decimal place than the original data, and SD and CV will be presented to 2 more decimal places than the original data.

Study day will be calculated as follows:

- If assessment date is on or after the date of study drug administration, then Study Day = Assessment Date – Dose Date + 1
- Otherwise, Study Day = Assessment Date – Dose Date

All data collected on the electronic case report form (eCRF) will be presented in data listings by cohorts and subject where applicable.

Baseline will be defined as the last non-missing assessment prior to the study drug administration, including assessments from unscheduled visits. Unscheduled visits will not be included in summaries except for determining baseline. If there are repeated assessments at a post-dose time point, the first non-missing assessment will be included in the summary tables.

For blood pressures summaries, the average of triplicate measurements obtained at predose on Day 1 will be used as the baseline, and the average of triplicate measurements at post dose timepoints will be used.

Missing or partial date values will not be imputed unless otherwise stated.

Subjects who received placebo will be pooled across cohorts for summary purpose.

4.1. Randomization, Stratification, and Blinding

Approximately 48 subjects will be randomized in this study (8 subjects in each cohort). Within each cohort, 2 sentinel subjects will be randomized in 1:1 ratio to receive AZD4041 or placebo, and the remaining 6 subjects will be randomized to receive AZD4041 or placebo in 5:1 ratio, following review of sentinel safety data up to 24 hours post-dose. Subjects that drop out before dosing will be replaced.

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by use of active and placebo dosage forms of similar appearance. Access to the randomization code will be strictly controlled according to the standard operating procedures of PPD.

Blind breaking envelopes will be prepared. A subject or subjects may be unblinded in the event of a dose-limiting toxicity, serious adverse event (SAE), or other event, or if there is a medical emergency where the identity of the drug must be known to properly treat a subject. Data will be reviewed blinded by the safety review committee (SRC), but if the PI or the SRC consider it necessary due to a safety concern, data from individual subjects or the entire cohort may be unblinded to enable decision-making. If a subject becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of opening

the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

4.2. Sample Size

Due to the exploratory nature of the study, sample size is not based on formal statistical considerations but is based primarily on a desire to obtain sufficient safety and tolerability information while exposing as few subjects as possible to the investigational treatment.

4.3. Analysis Population

The safety analysis set will include all subjects who receive AZD4041 or placebo and have any post-dose safety data.

The PK analysis set will include all subjects who receive AZD4041 and have any PK data.

5. Subject Disposition

5.1. Disposition

Number and percentage of subjects who were screen failures, who were randomized, who completed the study, and who did not complete the study, along with the reason for not completing the study, and the number and percentage of subjects included in each analysis population, will be summarized by treatment and overall for all screened subjects.

Subject disposition will be presented in a data listing. Subjects excluded from the analysis populations and the reasons for exclusion will be presented in a data listing.

5.2. Protocol Deviations

Protocol deviations will be summarized by treatment and overall for the safety analysis set and presented in a data listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

The demographics information, including age, sex, ethnicity, race, screening weight, screening height, and screening body mass index (BMI) will be summarized by treatment and overall for the safety analysis set.

Subject demographics and baseline characteristics will be presented in a data listing.

6.2. Medical History

Medical history will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version to be delineated in the clinical study report (CSR).

Medical history data will be presented in a data listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

A prior medication is defined as any medication that ends prior to the study drug administration. A concomitant medication is defined as any medication that starts on or after the time of study drug administration. Medications that started prior to the study drug administration but ends after the study drug administration or are ongoing will be considered both prior and concomitant.

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary, version to be delineated in the CSR, and will be presented in a data listing.

7.2. Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures which occur during the study will be presented in a data listing.

7.3. Study Treatments

Study drug administration data will be presented in data listings. Overdose information will be presented in a data listing as well.

8. Safety Analysis

All safety analyses will be based on the safety analysis set unless otherwise specified.

8.1. Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

All AEs will be coded by SOC and preferred term using MedDRA, version to be delineated in the CSR.

8.1.1. Incidence of Adverse Events

Number and percentage of subjects with AEs will be presented in summary tables. A subject with 2 or more AEs within the same SOC and preferred term will be counted once in summarization level.

An overview of AEs, including number of subjects with at least one AE, with at least one TEAE, with at least one treatment-related TEAE, with at least one moderate TEAE, with at least one treatment-related moderate TEAE, with at least one severe TEAE, with at least one treatment-related severe TEAE, with at least one SAE, with at least one treatment-related SAE, with at least one TEAE leading to early discontinuation, and death will be presented by treatment and overall.

Summary tables will also be provided for all TEAEs by SOC, preferred term, treatment and overall.

All AEs will be presented in a data listing.

8.1.2. Relationship of Adverse Events to Study Drug

The relationship of AEs to study treatment will be assessed by the investigator as not related or related.

All TEAEs will be summarized by SOC, preferred term, relationship to study treatment, treatment, and overall. A subject with 2 or more events at each level of summarization will be counted once using the most related event. Events with missing relationship will be considered as related in the summaries but will be presented as missing in the data listings.

8.1.3. Severity of Adverse Event

The severity of an AE will be evaluated by the investigator as mild, moderate, or severe.

All TEAEs will be summarized by SOC, preferred term, severity, treatment, and overall. A subject with 2 or more events at each level of summarization will be counted once using the most severe event. Events with missing severity will be considered as severe in the summaries but will be presented as missing in the data listings.

8.1.4. Serious Adverse Events

An SAE is an AE occurring during any study phase (screening [from the time of signature of informed consent form], treatment, follow-up), that fulfils one or more of the following criteria:

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical treatment to prevent one of the outcomes listed above.

All SAEs including death will be presented in a data listing.

8.1.5. Treatment-Emergent Adverse Events Leading to Study Discontinuation

All TEAEs leading to study discontinuation will be presented in a data listing.

8.2. Liver Events

The liver diagnostic investigations, liver risk factors/lift style events, and liver signs and symptoms data as collected in eCRF will be presented in data listings.

8.3. Clinical Laboratory Evaluations

The clinical chemistry, hematology, and urinalysis will be performed at visits specified in Appendix 14.1 SoA.

Other laboratory tests include testing for immunodeficiency virus (HIV), hepatitis B and C at screening, urine drug screen and alcohol screen at screening and on Day -1, pregnancy test at screening and on Day -1, and follicle stimulating hormone (FSH) testing in women at screening.

The details of clinical laboratory assessments to be performed are listed in Table 8-1.

Table 8-1 Laboratory Safety Variables

Hematology (whole blood)	White blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), neutrophils absolute count, monocytes absolute count, eosinophils absolute count, basophils absolute count, platelets, and reticulocytes absolute count
Clinical chemistry (serum or plasma)	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT), total bilirubin, unconjugated bilirubin, C-reactive protein (CRP), blood urea nitrogen, creatinine, glucose (fasting), albumin, phosphate, potassium, calcium, sodium, bicarbonate, thyroid stimulating hormone (TSH)[a], thyroxine (T_4)[b], and follicle stimulating hormone (FSH)[c]
Urinalysis	Glucose, protein, hemoglobin, microscopy (if positive for blood or protein)
Viral serology	Human immunodeficiency virus (HIV I and II), hepatitis B surface antigen (HBsAg) and hepatitis C Virus antibody
Pregnancy test (females only)	Human beta chorionic gonadotrophin
Urine drug screen	Alcohol and cotinine, amphetamines (includes methamphetamines and ecstasy/3,4 methylenedioxymetamphetamine), barbiturates, benzodiazepines, cannabinoids (includes tetrahydrocanabinol), cocaine metabolites, methadone, tricyclic antidepressants, opiates (includes heroin, codeine, and oxycodone), and phencyclidine.

a Screening only
b Reflex only (if TSH is abnormal)
c Screening for post-menopausal women

The clinical laboratory that will perform the tests will provide the reference ranges for all clinical laboratory parameters. Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter and evaluated as clinically significant or not clinically significant by the investigator. All laboratory results along with the abnormal flag and clinical significance will be presented in data listings. The potentially clinically significant (PCS) values will also be flagged. The PCS criteria are defined in Appendix 14.2.

Actual results and changes from baseline will be summarized for hematology, chemistry, quantitative urinalysis laboratory tests by treatment and visit. Shift tables with categories of low, normal, and high for quantitative results, and normal and abnormal for qualitative results will be provided by treatment and visit.

8.4. Testosterone, Luteinizing Hormone, Follicle Stimulating Hormone, and Inhibin B Assessments

For Cohorts 4 to 6, in order to monitor for effects on testicular function in male subjects, samples for assessment of testosterone, LH, FSH, and inhibin B levels will be collected at 0 hour (0800 or 1000) and at 4, 6, 8, 12, and 22 hours on Day -1 and at 0 hour (0800 or 1000) and at 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours on Day 1, as listed in the SoA (Appendix 14.1).

The results of these assessments will be presented in a data listing for safety population.

8.5. Vital Sign Measurements

Vital signs will be measured at specified timepoints in Appendix 14.1. Height will be measured at screening, and weight and BMI will be measured/calculated at specified timepoints in Appendix 14.1 SoA.

Vital signs will include systolic and diastolic blood pressure (BP), pulse rate (PR), respiratory rate (RR), and body temperature. Vital signs will be measured in a semi-supine position after 5 minutes rest. Supine and standing BP and PR will be measured using a semiautomatic recording device. Supine BP and PR will be taken after at least 5 minutes supine rest. Standing BP and PR will be taken approximately 3 minutes after the respective supine measurements. Three consecutive BP readings will be recorded at intervals of at least 1 minute. The average of the 3 BP readings will be recorded on the eCRF, and these records will be used in statistical summaries.

Orthostatic BP will be calculated as:

BP in supine position – BP in standing position

Orthostatic PR will be calculated as:

PR in standing position – PR in supine position

Actual results and changes from baseline in vital sign, weight, and BMI measurements will be summarized by treatment and timepoint. Vital sign measurements including the orthostatic BP and orthostatic PR, weight, and BMI results., along with PCS flags will be presented in a data listing. The PCS criteria are defined in Appendix 14.3.

8.6. Electrocardiograms

Twelve-lead paper ECGs (pECG) allow the investigator to review the ECG tracings at bedside and determine any potential risks. Digital 12-lead ECGs (dECG) are collected and electronically

submitted to the AstraZeneca ECG Center for expert review and reporting of ECG intervals. Telemetry is used for continuous monitoring of ECG activity as a safety measure.

8.6.1. Twelve-Lead Paper ECG

Twelve-lead pECGs will be obtained after the subject has been resting in the supine position for at least 10 minutes at specified timepoints in Appendix 14.1 SoA. All pECGs will be evaluated for heart rate, PR, RR, QRS, QT, and QTcF intervals. 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 in the eCRF.

All pECG data including investigator findings will be presented in a listing.

8.6.2. Digital ECG

The AstraZeneca ECG Center will perform the digital ECG (dECG) analysis and interpretation in this study, using the EClysis© system, version 4.0, or higher. The following dECG variables will be reported by the AstraZeneca ECG Center: RR, PR, QRS and QT intervals from the lead defined as the primary analyses lead. Heart rate will be derived as 60/(RR in seconds) and QTcF will be derived as QT (msec)/(RR in seconds)$^{1/3}$.

The dECG data will be smoothed on an individual subject basis before performing the derivations above and before 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 for nominal time-point recordings. At least 4 measurements with the time between the first and last record greater than 2.75 minutes for a nominal time-point should be present or else, the smoothed value at the corresponding nominal time-point will be set to missing.

Digital ECG results will be listed by treatment (pooled placebo, dose level of AZD4041) 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. The changes from baseline for smoothed and derived parameters will be listed as well.

Descriptive statistics of smoothed PR, RR, QRS, QT values and derived QTcF and HR values as well as change from baseline will be summarized by treatment group (pooled placebo, dose level of AZD4041, and pooled AZD4041) and nominal time-point. The baseline for the dECG measurements will be the smoothed pre-dose assessment on Day 1.

The number and percent of subjects whose worst (i.e. highest) post-baseline smoothed QTcF value, according to the following categories, will be tabulated by visit, timepoint, and treatment group (pooled placebo, dose level of AZD4041, and pooled AZD4041):
- Absolute value >450 msec and ⩽480 msec
- Absolute value >480 msec and ⩽500 msec
- Absolute value >500 msec
- Increase from baseline >30 msec and ⩽60 msec

- Increase from baseline >60 msec

The above tabulations will be presented separately for the subgroups who have an elevated QTcF (>450 msec) at baseline and those who do not.

All dECG data will be presented in a listing.

8.6.3. Telemetry

To allow a real-time assessment of cardiac safety at the study site, subjects will be monitored by telemetry (for real-time assessment of cardiac rate and rhythm) for 4 to 6 hours at specified timepoints in Appendix 14.1 SoA. Any clinically significant change noted on telemetry will be followed up with a 12-lead ECG. Further evaluation and treatment will be performed as deemed appropriate by the Investigator. The telemetry monitoring data as collected in eCRF will be presented in a data listing.

8.7. Physical Examination

Physical examination will be conducted at specified timepoints in Appendix 14.1 SoA.

A complete physical examination will be performed and includes an assessment of the following systems: cardiovascular, chest/lungs/respiratory, gastrointestinal, thyroid/neck, lymphatics, dermatological/skin, musculoskeletal/extremities, neurological, and head/ears/eyes/nose/throat (including mouth).

Physical examination results will be presented in a data listing.

9. Pharmacokinetics

9.1. Data Handling

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of descriptive statistics. When all concentrations are BLQ for a timepoint, mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable, otherwise the calculated mean will be presented.

For PK parameter calculations, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

Missing concentrations will be excluded from summaries and PK parameter calculations.

9.2. Plasma Concentration

Blood samples for the determination of plasma concentrations of AZD4041 will be collected on Day 1 at the following time points: predose (0), and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose. For Cohorts 4 to 6, an additional blood sample will be collected at 72 hours postdose.

Pharmacokinetic collections that have an actual sampling time that deviates from the nominal collection time more than 10% will be flagged in the data listing, but the nominal sampling time will be used for summarization.

AZD4041 plasma concentration data will be summarized using descriptive statistics (number of subjects, number of nonmissing values, arithmetic mean, SD, CV, median, minimum, and maximum) by treatment and nominal sampling time. Individual and mean AZD4041 plasma concentration versus time data will be plotted by treatment. For ease of presentation, mean plasma concentrations of AZD4041 will be plotted by nominal time by treatment on both linear and semi-logarithmic scales.

Plasma PK concentrations of AZD4041 will be reported to the precision of the raw data in listing presentations; summary statistics for arithmetic mean, median, minimum, maximum, and SD will be reported to 3 significant figures; and CV will be reported to 1 decimal place.

9.3. Pharmacokinetic Parameters

The plasma concentration-time data for AZD4041 will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® (Certara USA, Inc., Princeton, NJ) Version 8.0 or higher. Actual sampling times will be used for the estimation of all plasma PK parameters.

If data allow, the following PK parameters will be calculated:

Pharmacokinetic parameters:

PK Parameter	Definition
C_{max}	Maximum (peak) plasma drug concentration
T_{max}	Time to reach maximum (peak) plasma concentration following drug administration
AUC_{0-t}	Area under the curve from time 0 to time t
AUC_{0-inf}	Extrapolation of the area under the curve from time 0 to infinity, calculated as $AUC_{0-inf} = AUC_{0-t} + C_{last}/\lambda_z$, where C_{last} is the last quantifiable plasma drug concentration
$t_{1/2\,\lambda z}$	Terminal half-life, calculated as: $t_{1/2} = \ln(2)/\lambda_z$
CL/F	Apparent total clearance of the drug from plasma after oral administration, calculated as: $CL/F = Dose/AUC_{0-inf}$
V_{ss}/F	Apparent volume of distribution at steady state

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed to document the selection of data points used to estimate $t_{1/2}$ using non-compartmental procedures:

$\%AUC_{extrap}$	Percentage of the area extrapolated for calculation of $AUC_{0-\infty}$.
λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.
Number of points	Number of data points used to estimate λ_z; a minimum of 3 data points must be used, and C_{max} must not be included.
λ_z lower	Lower bound used for the estimation of λ_z.
λ_z upper	Upper bound used for the estimation of λ_z.
Rsq	r^2, the coefficient of determination (goodness of fit statistic); visual inspection of the terminal slope will be performed. In general, λ_z may only be retained if $r^2 \geq 0.80$

Plasma PK parameters for AZD4041 will be presented in data listings and summarized by treatment using descriptive statistics (number of subjects, arithmetic mean, SD, CV%, median, geometric mean, geometric CV%, minimum, and maximum) by treatment regimen. T_{max} will be summarized using the descriptive statistics median, minimum, and maximum only.

Plasma PK parameters of AZD4041 will be displayed to 3 significant figures in all data listings and summary tables, with exception of time variables (T_{max}, λ_z lower, and λ_z upper) which will be displayed to 2 decimal places.

9.4. Pharmacokinetic Statistical Analysis

Dose-proportionality for AZD4041 will be evaluated for C_{max}, AUC_{0-t} and AUC_{0-inf}. A power model will be fitted to describe the relationship between Y (C_{max}, AUC_{0-t} and AUC_{0-inf}) and X (dose) using the least-squares linear regression model, $\ln(Y) = \ln(\alpha) + \beta \ln(X)$, which is the logarithmic form of $Y = \alpha X^{\beta}$.

The intercept of regression line, $\ln(\alpha)$, and the slope of the regression line, β, will be presented along with the 90% confidence interval (CI) of the slope. Dose-proportionality will be concluded if the 90% CI of the slope β lies entirely within $[1+\ln(0.8)/\ln(r), 1+\ln(1.25)/\ln(r)]$, where r is a ratio that describes the dose range and is defined as the ratio of highest dose/lowest dose (Smith et al 2000). If the proportionality is not demonstrated over the entire dose range, the lowest or highest dose will be removed, and the analysis will be repeated until a range of proportionality is determined. Dose proportionality will be assessed with at least 3 dose levels.

The statistical analyses will be based on the PK population.

10. Pharmacodynamics

To characterize the PD relationship between drug exposure and QT interval, an exposure-response (E-R) analysis may be conducted with data from this study alone or in combination with other studies as appropriate, with a pre-specified workflow described in a separate technical document for the QTcF parameter, as part of the cardiac safety evaluation and with the intention to obtain a Thorough QT study substitute. The results of the E-R analysis will be presented in an E-R Analysis Report and may not be included in the main study report. The specification of the E-R analysis (the E-R analysis plan) is not included in this statistical analysis plan (SAP).

11. Interim Analysis

No formal interim analysis is planned for this study.

The SRC will review data from each cohort before progression to the next cohort can occur. The blinded safety, PK concentration, and PK parameter data will be reviewed by the investigators, medical monitor, and sponsor's representative as described in the SRC plan to ensure that it is safe to proceed with the planned dose escalation.

12. Changes in the Planned Analysis

There are no changes in this statistical analysis plan compared to the protocol.

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14. Appendices

14.1. Schedule of Activities (SoA)

Cohorts 1 to 3

	Screening Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Follow–up Visit[a] (14 days post-dose)
Informed consent	X					
Inclusion/exclusion criteria	X	X	X			
Demographic data	X					
Medical history	X					
Urinary drug screen	X	X				
Alcohol screen	X	X				
Testing for HIV, hepatitis B and C	X					
Pregnancy testing[b]	X	X				
FSH testing in women	X					
Randomization			X			
Admission to CRU		X				
Discharge from CRU					X	
Height, body weight, and BMI[c]	X	X			X	X
Study drug administration			X			
Adverse event recording	X	X	X	X	X	X
Blood pressure, temperature, respiratory rate, and pulse rate	X	X	X[d]	X	X	X
12-lead paper safety ECG	X	X	X[e]	X[e]	X[e]	
12-lead digital ECG			X[e]	X[e]	X[e]	
Telemetry[f]		X	X			
Clinical laboratory evaluations[g]	X	X		X		X
Physical examination	X	X			X	X
Blood sampling for PK[h]			X	X	X	

[a] Tests will be performed at follow-up and also in cases of discontinuation.
[b] Serum pregnancy test will be performed at screening and check-in.
[c] Height will be measured at screening only.
[d] Blood pressure, temperature, respiratory rate, and pulse rate will be measured at pre-dose, then at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours post-dose.
[e] Paper and digital ECGs will be collected at the same time points as PK sampling. Recording of ECGs will precede PK sampling and check of vital signs at each time point.

[f] Telemetry for 4 to 6 hours on Day -1 to establish a baseline. Pre-dose to 24 hours post-dose.
[g] Clinical laboratory assessments must be repeated if first collected more than 2 weeks before dosing.
[h] Blood samples will be collected at pre-dose, then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours.

BMI body mass index; CRU Clinical Research Unit; ECG electrocardiogram; FSH follicle stimulating hormone; HIV human immunodeficiency virus; PK pharmacokinetic(s)

Cohorts 4 to 6

	Screening Day -28 to Day -2	Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Follow–up Visit[a] (14 days post-dose)
Informed consent	X							
Inclusion/exclusion criteria	X		X	X				
Demographic data	X							
Medical history	X							
Urinary drug screen	X		X					
Alcohol screen	X		X					
Testing for HIV, hepatitis B and C	X							
Pregnancy testing[b]	X		X					
FSH testing in women	X							
Randomization				X				
Admission to CRU		X						
Discharge from CRU							X	
Height, body weight, and BMI[c]	X		X				X	X
Study drug administration				X				
Adverse event recording	X	X	X	X	X	X	X	X
Blood pressure, temperature, respiratory rate, and pulse rate	X		X	X[d]	X	X	X	X
12-lead paper safety ECG	X		X	X[e]	X[e]	X[e]	X[e]	
12-lead digital ECG				X[e]	X[e]	X[e]	X[e]	
Telemetry[f]			X	X				
Clinical laboratory evaluations[g]	X		X		X			X
Physical examination	X		X				X	X
Blood sampling for PK[h]				X	X	X	X	
Blood sampling for testosterone, LH, FSH, and inhibin B (male subjects only)[i]			X	X	X	X	X	

[a] Tests will be performed at follow-up and also in cases of discontinuation.
[b] Serum pregnancy test will be performed at screening and check-in.

[c] Height will be measured at screening only.
[d] Blood pressure, temperature, respiratory rate, and pulse rate will be measured at pre-dose, then at 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours post-dose.
[e] Paper and digital ECGs will be collected at the same time points as PK sampling. Recording of ECGs will precede PK sampling and check of vital signs at each time point.
[f] Telemetry for 4 to 6 hours on Day -1 to establish a baseline. Pre-dose to 24 hours post-dose.
[g] Clinical laboratory assessments must be repeated if first collected more than 2 weeks before dosing.
[h] Blood samples will be collected at pre-dose, then at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours.
[i] Male subjects only: samples for testosterone, LH, FSH, and inhibin B will be collected at 0 hour (0800 or 1000) and at 4, 6, 8, 12, 22, and 24 hours on Day -1 and at 0 hour (0800 or 1000) and at 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours on Day 1 to Day 3. The '0' hour time point should be approximately the same time that dosing is scheduled for on Day 1. On Day 1, samples for testosterone, LH, FSH, and inhibin B will be collected at the same time as PK samples.

BMI body mass index; CRU Clinical Research Unit; ECG electrocardiogram; FSH follicle stimulating hormone; HIV human immunodeficiency virus; LH luteinizing hormone; PK pharmacokinetic(s)

14.2. Potential Clinically Significant (PCS) Laboratory Values

a). Hematology:

Parameter	Conventional Unit	Low PCS Criteria	High PCS Criteria	SI Unit	Low PCS Criteria	High PCS Criteria
Hematocrit	%	< 30	> 50 (F) > 55 (M)	L/L	< 0.3	> 0.5 (F) > 0.55 (M)
Hemoglobin (male)	g/dL	< 11	> 18	g/L	110	180
Hemoglobin (female)	g/dL	< 10	> 17	g/L	100	170
Leukocyte (White Blood Cell Count)	$10^3/\mu L$	≤ 2.8	≥ 15	$10^9/L$	≤ 2.8	≥ 15
Neutrophils	cells/mm^3	1500	No upper limit	Proportion of 1.0	≤ 0.15	No upper limit
Platelet Count	$10^3/\mu L$	≤ 75	≥ 700	$10^9/L$	≤ 75	≥ 700

PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units).

b). Chemistry:

Parameter	Conventional Unit	Low PCS Criteria	High PCS Criteria	SI Unit	PCS Low Limit	PCS High Limit
Alanine aminotransferase	U/L	No lower limit	≥ 3 × ULN	U/L	No lower limit	≥ 3 × ULN
Aspartate aminotransferase	U/L	No lower limit	≥ 3 × ULN	U/L	No lower limit	≥ 3 × ULN
Albumin	g/dL	≤ 2.6	≥ 6.0	g/L	≤ 26	≥ 60
Alkaline phosphatase	U/L	No lower limit	≥ 3 × ULN	U/L	No lower limit	≥ 3 × ULN
Bilirubin, total	mg/dL	No lower limit	≥ 1.5 × ULN	µmol/L	No lower limit	≥ 1.5 × ULN
Blood urea nitrogen	mg/dL	No lower limit	≥ 30.0	mmol/L	No lower limit	≥ 10.71
Creatinine Kinase (CK)	U/L	No lower limit	≥ 3 × ULN	U/L	No lower limit	≥ 3 × ULN
Calcium, total	mg/dL	< 8.0	> 11.0	mmol/L	< 2.0	> 2.75
Chloride	mEq/L	≤ 85	≥ 120	mmol/L	≤ 85	≥ 120
Glucose	mg/dL	≤ 45.1	≥ 200.0	mmol/L	≤ 2.48	≥ 11
Gamma Glutamyl Transferase (GGT)	U/L	NA	≥ 3 x ULN	U/L	No lower limit	≥ 3 x ULN
Lactate Dehydrogenase (LDH)	U/L	No lower limit	≥ 3 x ULN	U/L	No lower limit	≥ 3 x ULN
Potassium	mEq/L	≤ 3.0	≥ 5.5	mmol/L	≤ 3.0	≥ 5.5
Protein, total	g/dL	≤ 5.0	≥ 10.0	g/L	≤ 50	≥ 100
Sodium	mEq/L	≤ 125	≥ 155	mmol/L	≤ 125	≥ 155
Serum Creatinine	mg/dL	No lower limit	> 1.5 × ULN	µmol/L	No lower limit	> 1.5 × ULN
Triglycerides	mg/dL	No lower limit	> 300	mmol/L	No lower limit	> 3.39
TSH	µU/L	below normal range	above normal range	mIU/L	below normal range	above normal range
T4, free	ng/dL	below normal range	above normal range	pmol/L	below normal range	above normal range

Parameter	Conventional Unit	Low PCS Criteria	High PCS Criteria	SI Unit	PCS Low Limit	PCS High Limit
Uric acid (Male)	mg/dL	No lower limit	≥ 10.5	µmol/L	No lower limit	≥ 624.75
Uric acid (Female)	mg/dL	No lower limit	≥ 8.5	µmol/L	No lower limit	≥ 505.75

PCS = potentially clinically significant; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal (value provided by the laboratory).

c). Urinalysis:

Parameter	PCS Low Limit	PCS High Limit
Hb/RBCs/Blood	NA	≥ +2
Protein/Albumin	NA	≥ +2
Glucose	NA	≥ +2

NA = Not Available.

14.3. Potential Clinically Significant (PCS) Vital Sign Values

Parameter	Unit	Observed Value	And/ Or	Change from Baseline	Change from Supine to Standing	Flag
Systolic Blood Pressure (supine or sitting)	mmHg	≥ 180	And	Increase of ≥ 20 mmHg	--	PCS High
		≤ 90	And	Decrease of ≥ 20 mmHg	--	PCS Low
Diastolic Blood Pressure (supine or sitting)	mmHg	≥ 105	And	Increase of ≥ 15 mmHg	--	PCS High
		≤ 50	And	Decrease of ≥ 15 mmHg	--	PCS Low
Pulse (supine or sitting)	bpm	≥ 120	And	Increase of ≥ 15 bpm	--	PCS High
		≤ 50	And	Decrease of ≥ 15 bpm	--	PCS Low
Systolic Blood Pressure (supine to standing)	mmHg	≤ 80	And	--	Decrease of ≥ 20	PCS Low
Diastolic Blood Pressure (supine to standing)	mmHg	--	--	--	Decrease of ≥ 20	PCS Low
Weight	Not Applicable			Increase of ≥ 7%	--	PCS High
				Decrease of ≥ 7%	--	PCS Low

PCS = potentially clinically significant.