# STATISTICAL ANALYSIS PLAN

For:

AstraZeneca AB

PROTOCOL No. D7460C00002

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of Multiple Ascending Doses of AZD4041 in Healthy Adult Subjects

Altasciences Project No. AZN-P3-000

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## STATISTICAL ANALYSIS PLAN APPROVAL

We have carefully read this statistical analysis plan and agree it contains the necessary information required to handle the statistical analysis of study data.

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Altasciences PPD

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On behalf of the Sponsor:

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PPD Statistician

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Date

## VERSION CONTROL

| Version | Date | Author | Description of Changes |
|---|---|---|---|
| 1.0 | 12-05-2022 | PPD | Not applicable |
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| | | | |
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## ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CSF | Cerebrospinal Fluid |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CV% | Coefficient of Variation |
| CCI | [redacted] |
| dECG | Digital Electrocardiogram |
| DSMB | Data Safety Monitoring Board |
| DMP` | Data Management Plan |
| ECG | Electrocardiogram |
| EOS | End of Study |
| ET | Early Termination |
| CCI | CCI [redacted] |
| ICF | Informed Consent Form |
| ICH | International ~~conference on~~ Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| LN | Natural Log |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PK | Pharmacokinetic(s) |
| PR(PQ) | ECG interval measured from the onset of the P wave to the onset of the QRS complex |
| PT | Preferred Term |
| 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 |

| | |
|---|---|
| SD | Standard Deviation |
| SE | Standard Error |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| TEAE | Treatment-emergent Adverse Event |
| TFLS | Tables, Figures, and Listings |
| CCI | CCI |
| WHO-DDE | World Health Organization Drug Dictionary- enhanced |

# 1 INTRODUCTION

This statistical analysis plan (SAP) provides a detailed description of the statistical methods and procedures to be implemented for the analyses of data from protocol D7460C00002. Pre-planning of analyses reduces the potential for bias and often reduces disputes between sponsor and the regulatory authority regarding the validity of the results. The same principles apply to supportive and/or sensitivity analyses. These analyses must be prospectively specified. (Good Review Practice: Clinical Review of Investigational New Drug Applications, December 2013).

The analyses described in the SAP are based upon the final protocol version 2.0 (Amendment 1) dated 2022/02/03.

## 2 STUDY OBJECTIVES

The objectives of the study and corresponding study endpoints are detailed in Table 1.

**Table 1: Objectives and Related Endpoints**

| Objective | Endpoint | Analysis |
|---|---|---|
| **Primary** | | |
| To evaluate the safety and tolerability of orally administered AZD4041 in healthy subjects following daily doses for 14 days (or to steady state). | • Adverse events (AEs)<br>• Vital signs<br>• Clinical laboratory tests<br>• 12-lead electrocardiogram (ECG) (digital ECG [dECG] and safety ECG) and telemetry<br>• Columbia Suicide Severity Rating Scale (C-SSRS) questionnaire<br>• Physical and neurological examination<br>• Measurement of male hormone levels: testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and inhibin B. | Refer to Section 8 |
| **Secondary** | | |
| • To characterize the multiple dose pharmacokinetics (PK) of AZD4041 in plasma and urine and assess the time required to reach steady state, the degree of accumulation, and the time dependency of its PK. | The following AZD4041 PK endpoints will be estimated, data permitting:<br>• Plasma: $C_{max}$, $T_{max}$, $AUC_{0-24}$, $AUC_{0-t}$, $AUC_{0-inf}$, $AUC_{ss}$, $C_{trough}$, $C_{\tau}$, $t_{1/2,z}$, $t_{1/2Eff}$, CL/F, $V_z$/F, $R_{AC}(C_{max})$, and $R_{AC}(AUC)$, $\lambda_z$<br>• Urine: $C_{maxU}$, $T_{maxU}$ $AUC_{0-infU}$, $Ae_{\tau}$, fe/F, and $CL_R$<br>Additional PK parameters may be estimated as appropriate to support the main PK endpoints. | Refer to Section 7 |

| Objective | Endpoint | Analysis |
|---|---|---|
| • CCI [redacted] | CCI [redacted] | |
| • To assess the central nervous system (CNS) penetration potential of AZD4041 by quantification of AZD4041 concentration in the cerebrospinal fluid (CSF) at plasma steady state. | CSF (Cohorts 2 and 3 only): CSF concentration (ng/ml) reported as a percentage of total and free plasma concentration | |
| **Exploratory** | | |
| CCI [redacted] | | |

| Objective | Endpoint | Analysis |
|---|---|---|
| CCI | | |

# 3 STUDY DESIGN

## 3.1 General Description

This is a Phase 1, single-centre, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study in healthy male and female adult subjects.

The study will include up to 48 subjects (12 subjects per cohort) who will be randomized 9:3 to active drug or placebo. Each cohort will receive AZD4041 or placebo in a MAD study. Screening will occur within 28 days prior to the first study drug administration. Screening data will be reviewed to determine subject eligibility prior to the first study drug administration.

For each cohort, 9 subjects will be randomly assigned to receive AZD4041 and 3 subjects will be assigned to receive placebo. Within each cohort, 2 subjects will be randomized initially to AZD4041 or placebo (1:1 ratio) to allow a sentinel dosing approach. Providing no clinically significant issues have been noted after the first 3 doses of the initial 2 (sentinel) subjects in a cohort and provided the Day 2 safety laboratory tests for the 2 subjects have been reviewed, the remaining 10 subjects will be randomised to AZD4041 or placebo in a 8:2 ratio and will be dosed in 2 separate groups with at least 24 hours between groups to monitor for safety and tolerability. All subjects will receive either AZD4041 or placebo administered CCI for 14 days.

## 3.2 Treatments

All investigational products *(*IPs*)* will be provided by the Sponsor. The study treatments are presented in Table 2*:* *Cohort and Treatment Information* .

**Table 2: Cohort and Treatment Information**

| Cohort[a] | Treatment | N | Dose[b] |
|---|---|---|---|
| 1 | AZD4041 or Placebo | 12 (9:3) | Adaptive |
| 2 | | | |
| 3 | | | |

a. = An additional cohort may be added if the maximum tolerated dose has not been defined and the maximum allowed exposure has not been reached after 3 cohorts.
b. = Or until maximum tolerated dose is defined.

## 3.3 Study Procedures

For complete details on the study assessments to be performed for each study period, refer to APPENDIX A.

## 3.4 Randomization and Unblinding Procedures

The CRU will generate the randomization code with a computer program according to the study design, the number of subjects, and the number of treatments. Eligible subjects within each cohort will be randomly assigned in a ratio of 9:3 to Active: Placebo. Once generated, the randomization code will be final and will not be modified.

Subjects who sign the ICF, are randomized, receive the study treatment, and subsequently withdraw, or are withdrawn or discontinued from the study, should not generally be replaced. However, consideration may be given to the replacement of such subjects in order to enable the

completion of at least 10 subjects for the purposes of Safety Review Committee and dose escalation decisions. Replacement of subjects under these circumstances 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 cohort stopping rules (Section 4.4.2.1) or otherwise jeopardise the safe conduct of the study.

**Blinding**

The treatment assignment will not be known by the study participants; however, the taste between the IP and placebo is distinguishable and unable to be masked. Therefore, it is possible that subjects will know the treatment to which they have been assigned.

The randomization code will not be available to the personnel of the bioanalytical facility until the bioanalytical phase of the study has been completed. 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, including the pharmacokineticist(s) and statistician(s) (or delegate), until all the 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). In the event of a medical emergency requiring identification of the study drug administered to an individual subject, an Investigator will make every attempt to contact the Sponsor's Study Physician to explain the need for breaking the blind within 24 hours of doing so. The date and reason for breaking the blind must be recorded.

The results of the PK and safety analyses will be made available only to the personnel responsible for evaluating the safety data before proceeding with the next dose level. The bioanalytical facility will preserve the blind by reassigning alternative subject numbers to the interim data before they are made available to the PK facility and Sponsor; these alternative subject numbers will be assigned by the lab at the time of sample analysis.

# 4 ANALYSIS POPULATIONS

The following populations will be defined:

- **Safety population***:* The safety population will include all subjects who received at least 1 dose of the IP or placebo.
- **Pharmacokinetic Population:** The PK population will include all subjects who have received at least 1 dose of AZD4041 and have at least 1 PK concentration after dosing. Subjects administered matching placebo will not be included in the PK population.

  Subjects who do not complete the sampling schedule may be included in the PK analysis for only the PK parameters that are judged not to be affected by the missing sample(s).
- CCI [redacted]

# 5 STUDY SUBJECTS

Disposition data, analysis population information and protocol deviations will be listed and summarized as described in Table 3.

**Table 3: Data Presentations for Study Subject Information**

| Data | Variables | Presentation |
|---|---|---|
| Disposition and analysis population | Subject, completion status (i.e., completed or withdrawn), reason for withdrawal, analysis population determination | Listings:<br>• Randomization<br>• Disposition<br>• Analysis population<br>Table:<br>• Disposition |
| Protocol deviations | Protocol deviations | Listings:<br>• Protocol deviations<br>• Pharmacokinetic (PK) sample collection time deviations |

## 5.1 Disposition

Subject disposition will be summarized for all subjects randomized. The following will be presented:

- Number (N) of subjects screened
- N of subjects randomized
- N and % of subjects who completed the study
- N and % of subjects who withdrew from the study by primary reason for withdrawal
- N and % of subjects included in each analysis population

The percentages will be calculated using the number of randomized subjects as the denominator. The summary will be presented by treatment (dose level of AZD4041 and pooled placebo).

## 5.2 Protocol Deviations

Deviations identified at the site will be collected in the clinic deviation tracking system (DTS) and presented in a protocol deviation listing. Protocol deviations will be reviewed by the Sponsor, principal investigator, lead statistician and study scientist(s) and finalized before unblinding the study. Protocol deviations will be listed for the Safety Population.

For PK sampling time deviations, information will be derived programmatically and presented in a separate listing. Allowable windows for PK blood samples are shown in Table 4.

**Table 4: Acceptable Windows for Timed PK Blood Specimen Collection Procedures**

| Elapsed Time | Accepted Window |
|---|---|
| Predose | No window specified |
| > 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 |

# 6 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Unless otherwise specified, all available data will be listed, summarized, for demographics and other baseline characteristics and presented for the safety population as detailed in Table 5.

**Table 5: Data Presentations for Demographic and Other Baseline Characteristics**

| Data | Variables | Presentation |
|---|---|---|
| Demographic and Other Baseline Characteristics | Sex, age, ethnicity, race, height, weight and body mass index (BMI) | Listing<br>Table |
| Medical history | All medical history findings | Listing |
| Prior and Concomitant medications | All medications taken prior to study drug administration and concomitant medications (including vaccines, prescription medications, nonprescription medications, dietary supplements, vitamins, or herbal medications) | Listing |
| Contraception | Contraceptive method | Listing |

# 7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

The PK analysis will be carried out according to Altasciences Standard Operating Procedures (SOPs). Unless otherwise specified, all available PK data and analysis results will be presented for the PK Population.

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## 7.1 Missing Values

The lack of concentration values due to failure to collect the sample, a lost or compromised sample, or due to the subject's early termination from the study will be termed "missing" in the dataset, and no imputation will be done. For urine data, if a subject has failed to void over a particular collection interval, the amount excreted will be set to zero.

If the actual collection time of a postdose plasma PK sample is unknown, but a valid concentration value has been measured, the sample will be set to missing in the PK analysis and will be presented in listings but excluded from descriptive statistics. Unknown predose collection times will be handled on a case-by-case basis.

## 7.2 Measurements Below the Lower Limit of Quantitation

Concentration values below the lower limit of quantitation (LLOQ) associated with predose collection times will be replaced with zero for the non-compartmental analyses (NCA); however, postdose collection times will be replaced using conditional substitutions that considers zero before Tmax and likelihood estimations after Tmax.

Concentration values below the LLOQ will be replaced with zero for mean PK profile representations as well as for descriptive statistic calculations.

## 7.3 Actual Time

The plasma NCA analysis will be based on the actual sampling times, except for predose samples, which will always be reported as zero, regardless of time deviations.

The individual plasma concentration/time profiles will be presented using actual sampling times whereas the mean plasma concentration/time profiles and tables presenting summary statistics of concentration -time series will be presented using nominal sampling times.

Actual times for plasma PK sample collections will be listed in the report.

Urine PK analysis and data presentation will utilize the nominal collection interval times; CSF concentration and biomarker data will be presented based on nominal collection time.

## 7.4 Baseline Reference Timepoint

Unless otherwise specified, the baseline value will be defined as the last non-missing evaluation prior to the first study drug administration.

## 7.5 Non-Compartmental Analysis

The following configuration for the NCA analysis (with Phoenix® WinNonlin® version 8, or higher) will be used:

- Data: Serial sampled data

- Model/Dose options Type: Plasma (200 202) and Urine (210 – 212)/Extravascular
- AUC Calculation Method: Linear up/Log down (applicable to plasma only)
- Lambda $_Z$ ($\lambda_z$) calculation: Best fit method for $\lambda_z$ Linear-Log regression

Reasons for excluding PK parameters will include the following:

- AUC: AUC parameters will not be estimated if less than 3 consecutive measurable concentrations are observed.
- PK parameters requiring λz estimation (eg, $AUC_{0\text{-inf}}$ and $t_{1/2}$) will be set to Not Reported (NR) in the Tables and Listings if they meet one of the following:
  - $R^2 < 0.8$
  - Extrapolated area > 20%

The PK parameters for AZD4041 are presented in Table 6

**Table 6: Pharmacokinetic Parameters of AZD4041 in Plasma**

| PK Parameter | Definition |
|---|---|
| **Plasma, Day 1** | |
| $C_{max}$ | Maximum observed concentration |
| $T_{max}$ | Time of maximum observed concentration |
| $AUC_{0\text{-}24}$ | Area under the concentration time curve from time 0 (dose administration) to 24 hours<br>*(The **nominal time** will be used to estimate partial AUC using the NCA built-in tool in Phoenix® WinNonlin®. This means that actual times off by more than 1 minute from the partial end-hour timepoint will be extrapolated/interpolated as per Phoenix® WinNonlin®'s built-in formulas. If extrapolation/interpolation is not possible, then no value is reported by the software.)* |
| $AUC_{0\text{-}t}$ | Area under the concentration time curve from time 0 (dose administration) to the time of last quantifiable concentration ($t_{last}$) |
| $AUC_{0\text{-inf}}$ | Area under the concentration time curve extrapolated to infinity, calculated as $AUC_{0\text{-}t} + C_{last}/\lambda_Z$, where $C_{last}$ is the measured concentration at time $t_{last}$ |
| $t_{1/2,z}$ | Terminal elimination half-life, calculated as $\ln(2)/\lambda_Z$ |
| CL/F | Apparent total clearance, calculated as $Dose/AUC_{0\text{-inf}}$ |
| $V_z/F$ | Apparent volume of distribution, calculated as $Dose/\lambda_Z * AUC_{0\text{-inf}}$ |
| $C_{max}/D$ | Dose-normalized $C_{max}$ |
| $AUC_{0\text{-}t}/D$ | Dose-normalized $AUC_{0\text{-}t}$ |
| $AUC_{0\text{-inf}}/D$ | Dose-normalized $AUC_{0\text{-inf}}$ |
| **Plasma, Day 14:** | |
| $C_{max}$ | Maximum observed concentration |

| | |
|---|---|
| $T_{max}$ | Time of maximum observed concentration; if it occurs at more than one timepoint, $t_{max}$ is defined as the first timepoint with this value |
| $C_\tau$ | Concentration at the end of the dosing interval. Observed concentration, otherwise the predicted concentration value will be calculated as per Phoenix® WinNonlin®'s built-in rules for interpolation/extrapolation, and subject to the criteria for PK parameters requiring $\lambda_z$ estimation. |
| $AUC_{ss}$ | Area under the concentration time curve over the dosing interval at steady state, calculated from 0 to 24 hours (dosing interval)<br>*(The **nominal time** will be used to estimate $AUC_{ss}$ using the NCA built-in tool in Phoenix® WinNonlin®. This means that actual times off by more than 1 minute from the dosing interval end-hour timepoint will be extrapolated/interpolated as per Phoenix® WinNonlin®'s built-in formulas. If extrapolation/interpolation is not possible, then no value is reported by the software.)* |
| $AUC_{0-t}$ | Area under the concentration time curve from time 0 (dose administration) to the time of last quantifiable concentration ($t_{last}$) |
| $t_{1/2,z}$ | Terminal elimination half-life, calculated as $\ln(2)/\lambda_Z$ |
| $t_{1/2Eff}$ | Effective half-life, calculated as<br>$\tau * \ln2 /\ln(Rac_{(AUC)}/( Rac_{(AUC)}-1))$, where $\tau$ is 24 hours[1] |
| $CL/F_{ss}$ | Apparent total clearance at steady state, calculated as $Dose/AUC_\tau$ |
| $Vz/F_{ss}$ | Apparent volume of distribution at steady state, calculated as $Dose/\lambda_Z * AUC_\tau$ |
| $C_{max}/D$ | Dose-normalized $C_{max}$ |
| $AUC_\tau/D$ | Dose-normalized $AUC_\tau$ |
| $AUC_{0-t}/D$ | Dose-normalized $AUC_{0-T}$ |
| $R_{AC}(C_{max})$ | Accumulation ratio evaluated by comparing Day 14 $C_{max}$ to Day 1 $C_{max}$ |
| $R_{AC}(AUC)$ | Accumulation ratio evaluated by comparing Day 14 $AUC_\tau$ to Day 1 $AUC_{0-24}$*<br>**Day 1 $AUC_{0-t}$ may be used if $AUC_{0-24}$ cannot be estimated, provided that the 24-hour sample was collected within 10% of nominal time.* |
| **Plasma, Various Days:** | |
| $C_{trough}$ | Observed concentration at the end of the dosing interval (predose concentrations on Day 2 [Day 1, 24-hours] through Day 14) |
| **The following plasma PK parameters will be used for PK calculation and presented in the PK listings only** | |
| $t_{last}$ | Time of last measurable observed concentration |
| $C_{last}$ | Observed concentration corresponding to $t_{last}$ |
| $\lambda_Z$ | Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration *versus* time curve |
| $\lambda_{Z\ Upper}$ | Upper limit on time for values included in the calculation of $\lambda_z$ |
| $\lambda_{Z\ Lower}$ | Lower limit on time for values included in the calculation of $\lambda_z$ |

| | |
|---|---|
| Number of Points | Number of data points in computing $\lambda_Z$ |
| $R^2$ | Goodness of fit for the terminal phase |
| Residual area | Extrapolated area (ie, percentage of $AUC_{0-\infty}$ due to extrapolation from $t_{last}$ to infinity: $AUC_{0-\infty} - AUC_{0-t}$/ $AUC_{0-\infty}$*100) |
| **Urine, Day 1, and Day 14:** | |
| $Ae_\tau$ | Amount of drug excreted in urine<br>The Ae at each urine collection interval will be calculated as follows: Concentration * Volume of urine during that time interval (t1 to t2)<br>Cumulative Ae will be calculated as the sum of all urine collection interval Aes<br>*Note: The Ae at pre-dose will not be included in the calculation of cumulative Ae.* |
| fe/F | Cumulative fraction of unchanged drug excreted in urine over all time intervals, calculated as<br>(Ae / Dose)*100 (expressed in %)<br>*Note: The Ae at pre-dose will not be included in the calculation of fe.* |
| $CL_R$ | Apparent renal clearance, calculated as:<br>$Ae_{(0-24)}$ / $AUC_{0-24}$ on Day 1 and as $Ae_{(0-24)}$ / $AUC_\tau$ on Day 14<br>A different time interval may be used providing not all single intervals are usable.<br>**Day 1 $AUC_{0-t}$ may be used if $AUC_{0-24}$ cannot be estimated, provided that the 24-hour sample was collected within 10% of nominal time.* |
| **CSF, Day 14:** | |
| $C_{CSF}$% | AZD4041 CSF concentration (Cohorts 2 and 3 only), calculated as a percentage of plasma concentration (i.e. Kp(CSF) = CSF /total plasma concentration *100 and $Kp_{,u}$(CSF) = CSF/free plasma concentration *100) |

[1] Sources: **Error! Reference source not found.** and **Error! Reference source not found.**

## 7.6 Cerebrospinal Fluid

For Cohorts 2 and 3 only, AZD4041 CSF concentrations (ng/ml) on Day 14 will be calculated as a percentage of plasma concentration collected at the corresponding time.

## 7.7 CCI

CCI [redacted]

### 7.7.1 CCI

CCI [redacted]

### 7.7.2 CCI

CCI [redacted]

## 7.8 Summary Statistics

All tables, figures, and listings, when appropriate, will be stratified by cohort (dose level) and by study day, as applicable.Summary statistics of the individual AZD4041 plasma, urine, and CSF concentration data and derived parameters as well as biomarker data will be calculated for the PK population. Summary statistics will be calculated for concentration at each individual timepoint and for all PK parameters.

Concentration data will be summarized by group using the following statistics: number of observations (N), arithmetic mean (mean), standard deviation (SD), minimum (min), median, maximum (max), and coefficient of variation (CV). PK parameters will be summarized using these same statistics, as well as geometric mean and geometric mean CV.

If PK parameters can only be estimated in a limited number of subjects, the following criteria will be applied for reporting descriptive statistics:

- If a PK parameter value is reportable in less than 3 subjects for a given study part and day, then SD, CV, and geometric mean CV will be considered not reportable
- If a PK parameter value is only reportable in 1 subject for a given study part and day, only minimum and maximum will be reported

## 7.9 Statistical Analysis

**Dose Proportionality for Day 1 and Day 14**

Inferential statistical analysis will be performed with SAS.

Appropriate dose–normalized PK parameters ($C_{max}$ and appropriate AUCs) will be assessed graphically for dose-proportionality.

Natural log-transformed PK parameters ($C_{max}$ and appropriate AUCs) will be assessed statistically for proportionality. Proportionality analysis will be done using a power model. The power model is defined as:

$$\ln(\text{PK parameter}) = \alpha + \beta \bullet \ln(\text{Dose}) + \varepsilon$$

where $\alpha$ is the intercept, $\beta$ is the slope and $\varepsilon$ is the normal error term. A linear model with ln-transformed dose as a continuous effect will be fitted. A point estimate and a 90% confidence interval (CI) will be derived for the slope ($\beta$).

Dose proportionality may be assessed within different dose ranges if deemed appropriate with at least three doses.

**Steady State**

$C_{trough}$ will be displayed graphically and summarized descriptively by day to assess for steady state.

# 8 SAFETY ANALYSIS

Unless otherwise specified, all available data will be listed and summary tables for safety assessments will be presented by treatment (dose level of AZD4041 and pooled placebo) per cohort for the Safety population as detailed in Table 7.

Continuous variables will be summarized (absolute values) using descriptive statistics (n, mean, SD, minimum, median and maximum).

**Table 7: Data Presentations for Safety Assessments**

| Data | Variables | Presentation |
|---|---|---|
| Adverse events | Adverse event (AE) description, date and time (start and end), intensity, relationship to study drug, action taken, study days and outcome | Listing<br>Table |
| Extent of exposure | Study drug administration dose, units, date, time, Cohort | Listing |
| Clinical laboratory evaluations | Laboratory results (refer to section 8.2 for parameters) | Listing<br>Table |
| Vital signs | Blood pressure, pulse, and body temperature | Listing<br>Table |
| Physical and neurological examinations | Physical and neurological examinations findings | Listings |
| 12-Lead Electrocardiograms (ECGs) | ECG interpretations and findings | Listings<br>Table |
| Digital Electrocardiograms (ECGs) | Digital ECG interpretations and findings | Listings<br>Table<br>Figures |
| Telemetry | Telemetry findings | Listings |
| Columbia-Suicide Severity Rating Scale (C-SSRS) | C-SSRS Suicide Ideation score | Listing for individual items |

## 8.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are adverse events (AEs) that are not present prior to the exposure to study treatment or AEs that are already present that worsen in intensity or frequency following exposure to study treatment. All AEs reported following exposure to study treatment are considered TEAEs.

AEs will be assessed for treatment emergence with respect to the study cohort. All TEAEs will be coded using MedDRA Version 24.0. The listing and summaries will include coded System Organ Class (SOC) and Preferred Term (PT).
An overall summary by treatment (dose level of AZD4041 and pooled placebo) will present the number and percentage of subjects with:

- At Least One TEAE
- At Least One Drug-Related TEAE
- Maximum Intensity
  - Mild
  - Moderate
  - Severe
- At Least One SAE
- At Least One Drug-Related SAE
- Death

For the study, the following AE tables will also be presented:

- TEAEs by SOC and PT
- Drug-Related TEAEs by SOC and PT
- TEAEs by SOC, PT, and Maximum Intensity (Mild, Moderate, Severe)

Events will be listed by treatment, subject and AE onset date. Treatment-emergent Adverse Event (TEAE) duration (stop date/time - start date/time) will be included in the listing; where applicable, imputed data will be used for the calculation of TEAE duration, but the original dates/time information will be presented in the listing.

## 8.2 Clinical Laboratory Evaluations

Laboratory data will be presented using units as reported by the clinical laboratory. Specific hematology, clinical chemistry, urinalysis, endocrinology, serology parameters are listed in Table 8.

**Table 8: Clinical Laboratory Evaluations**

| Clinical Laboratory Test Panel | Description |
|---|---|
| General biochemistry: | Alanine aminotransferase, albumin, alkaline phosphatase, bilirubin total and unconjugated, C-reactive protein, chloride, creatinine, creatine kinase, gamma glutamyl transferase, protein total, glucose (fasting), calcium, potassium, magnesium[a], and sodium |
| Endocrinology: | Follicle stimulating hormone[d,e], oestradiol[a,b], thyroid stimulating hormone[a] , T4[a,c], luteinising hormone[d], testosterone[d], and inhibin B[d] |
| Haematology: | White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, haemoglobin, haematocrit, mean corpuscular volume, and platelet count |
| Serology: | Human immunodeficiency virus Ag/Ab Combo, hepatitis B surface antigen, hepatitis C virus, and Severe Acute Respiratory Syndrome Coronavirus-2 |

| | |
|---|---|
| Urinalysis: | Colour, 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, cotinine, opiates, and phencyclidine |
| Pregnancy test (females only): | Serum pregnancy test |
| Alcohol screen: | Alcohol breathalyser or urine screen |

a. At Screening only
b. Postmenopausal women only
c. Reflex only (if TSH is abnormal)
d. Males only at Day -1, Day 1 and Day 14
e. FSH for females at screening only

Absolute values for 'continuous' parameters (hematology, chemistry and urinalysis) will be summarized using descriptive statistics by treatment (dose level of AZD4041 and pooled placebo).
Serology, alcohol/drug screen, Pregnancy test and Endocrinology results will be presented in separate listings.
Data listings will include out-of-range flags (L, H) and whether the abnormal values are clinically significant or not.

## 8.3 Vital Signs

Vital signs will include systolic and diastolic blood pressure, temperature and pulse.

Absolute values in vital signs measurements will be summarized descriptively by treatment (dose level of AZD4041 and pooled placebo) and time point.
Data listings will identify if values are "abnormal, clinically significant" or "abnormal, not clinically significant".

## 8.4 Physical and Neurological Examination Findings

The physical examination will include a general review of the following body systems (at minimum): head and neck, cardiovascular, respiratory, gastrointestinal, and general appearance, unless a symptom-oriented physical exam is indicated.
The neurological examination includes a review of basic mental status, cranial nerves, motor function, sensation and proprioception, reflexes, co-ordination and gait
Physical and neurological examination results will be listed as normal or abnormal. Abnormal findings of clinical significance will be included in the listings.

## 8.5 12-Lead Digital ECG Statistical Methodology

From the digital electrocardiogram (dECG) data, the following parameters will be derived:
QTcF = QT*RR-1/3, where the QT interval is in milliseconds and the RR interval is in seconds.
Heart rate (HR) = 60/RR interval, where the RR is Time Elapsed between Two Successive R-Waves of the QRS Signal on the ECG i.e. interval in seconds.
Calculation of derived parameters will be performed after smoothing of QT and RR data.
The digital electrocardiogram (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 (dose level of AZD4041 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 (dose level of AZD4041 and pooled placebo) 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) pre-dose assessment on Day 1.
Outliers with respect to QTcF will also be tabulated for the following categories:

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

Outliers in other ECG variables (absolute values either below or above the reference ranges):

PR interval < 110 ms or > 220 ms

QRS duration < 75 ms or > 115 ms

Heart rate < 50 bpm or > 100 bpm

QT < 320 ms or > 450 ms

QTcF < 320 ms or > 450 ms

CCI

[redacted]

## 8.6 12-lead Safety Electrocardiogram

Resting 12-lead Safety Electrocardiogram: Standard safety 12-lead ECGs will be performed as described in the CSP protocol section 6.2.4.

The 12-lead ECG results will be listed for each subject. All 12-lead safety 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 an Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether 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. An 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. Timepoints for 12-lead Safety ECG measurements are specified in the protocol Table 6-4 in the CSP.

### 8.7 Telemetry Results

Telemetry results will be reviewed by the Investigator, listed by date and time, described and reported, if considered clinically significant.

### 8.8 CCI

CCI

### 8.9 C-SSRS Results

C-SSRS, results will be listed by date and time, described and reported, if considered clinically significant.

# 9 DATA HANDLING AND PRESENTATION

All safety and statistical outputs will be generated using SAS software, version 9.4.
All programs used to generate statistical analyses will be validated according to Altasciences SOPs).
Draft tables, figures and listings will be provided in RTF and PDF formats.

## 9.1 Safety Analysis Presentation

Adverse events and medical history will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) terminology as defined in the study data management plan (DMP).

Prior and concomitant medications will be coded with the WHO-DDE (March 2021) as defined in the study DMP.
Generally, summaries will be presented by treatment (dose level of AZD4041 and pooled placebo). Some summaries will also be presented to include all subjects (i.e., subject disposition and demographics).

Summaries for data collected at scheduled times specified by the protocol will be presented by treatment (dose level of AZD4041 and pooled placebo), visit and, where applicable, time point.

In general, the data listings will include data from all subjects who receive at least one dose of either AZD4041 or placebo.

Study days will be included in adverse event and concomitant medication listings in addition to dates. Study days will be calculated relative to the first day of double-blind treatment (Day 1) derived as (event date - first day of AZD4041 or placebo dosing) +1 for events after the first day of dosing and (event date - first day of AZD4041 or placebo dosing) for events before the first day of dosing.
The following general comments also apply to all statistical analyses and data presentations:

- Duration variables will be calculated using the general formula: (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as ‘<10’ or ‘≤5’ will be treated as ‘10’ or ‘5’ respectively, and a value such as ‘>100’ will be treated as ’100’. However, the actual values as reported in the database will be presented in data listings.
- When assessments are repeated for a given time point or performed at unscheduled times, only the result which is the closest to the dosing time will be included in summary tables.

In general, summary statistics for raw variables (i.e., variables measured at the study site or central laboratory) will be displayed as follows:

- Minima and maxima will be displayed to the same number of decimal places as the raw data.
- Means, medians, and quartiles will be displayed to 1additional decimal place.
- Standard deviations will be displayed to 2 additional decimal places.

- Percentages will be displayed to 1 decimal place. Percentages between 0 and 0.1 (exclusive) will be displayed as '<0.1'.
- P-values will be displayed to 3 decimal places. P-values that are less than 0.001 will be displayed as '<0.001'.

The number of decimal places for summary statistics of derived variables (i.e., variables that are not measured by the study site but are calculated for analysis based on other measured variables) will be determined on a case by case basis. In general:

- Minima and maxima will be displayed to the commonly used unit of precision for the parameter.
- Means, medians, quartiles, and confidence limits will be displayed to 1 additional decimal place.
- Standard deviations will be displayed to 2 additional decimal places.

## 9.2 Pharmacokinetic Analysis

In general, all PK summary tables will be presented for the PK population.

Individual raw PK concentrations will be displayed with the same precision as received from the bioanalytical laboratory.

Precision for individual PK data will be displayed as follows:

- Concentration-related PK parameters (eg, $C_{max}$, AUCs) will be displayed with the same precision as the raw PK concentration data,
- Apparent clearance (CL/F, $CL/F_{ss}$) and volume of distribution ($V_z/F$, $V_z/F_{ss}$) will be reported to 3 significant figures,
- Parameters associated with time (e.g. $T_{max}$ and $t_{1/2}$) will be displayed with 2 decimal places,
- Percentages will be displayed with 2 decimal places,
- $R^2$ and $\lambda_Z$ will be displayed with 4 decimal places.

Summary statistics for concentration and PK parameters will be displayed with the same precision as the individual values, with the exception of number of observations (N) and CV% which will be presented with 0 and 1 decimal place, respectively.

## 9.3 Analysis Timepoints

Unless otherwise specified, the baseline value will be defined as the last non-missing evaluation prior to the first dose of study medication.

## 9.4 Methods for Handling Missing Data

No imputations of values for missing data (ie, blank, "Not Done", "Not Applicable", etc) will be performed and data presentations will reflect the data point as it appears in the case report form (CRF) or electronic data file.

# 10 INTERIM ANALYSES AND DATA SAFETY MONITORING

In order to inform dose selection for the next expected cohort, interim PK analysis will be performed and available at the time of the safety review meeting, prior to the next dose escalation, for Cohort 1,Cohort 2 and Cohort 3. (Note: PK analysis for Cohort 3 is required for the Cohort 3 safety review meeting in the event that a Cohort 4 is initiated for the study). These preliminary PK results will be performed on plasma concentration data only, as outlined in Section 7.1 through Section 7.5, with the exception those nominal times will be used in the analysis instead of actual times.

To preserve the study blind, bioanalytical facility will preserve the blind by reassigning alternative subject numbers to the interim data before they are made available to the PK facility and Sponsor; these alternative subject numbers will be assigned by the lab at the time of sample analysis.

Mean plasma concentration-time profiles as well as parameter summary tables of the key (e.g. $C_{max}$, $T_{max}$, and AUCs) PK endpoints will be generated.

# 11 GENERAL INFORMATION RELATED TO DATA PRESENTATIONS

The formats and layouts of TFLs are provided in a separate document and are common displays. Their numbering and general content follow the International Conference on Harmonisation (ICH) E3 guidelines. Actual formats and layouts may be altered slightly from those presented as necessary to accommodate actual data or statistics.

Minor format changes will not require updates to the SAP; rather they may be documented in a Note to SAP.

# APPENDIX A STUDY SCHEDULE(S)

| Day | Screening -28 to -1 | -2 to -1[1] | 1 | 2 | 3-13 | 14 | 15 | 16 | 17[2] | Follow-up 27 to 31 |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent[3] | X | | | | | | | | | |
| Eligibility Criteria Review | X | X | X | | | | | | | |
| Demographics | X | | | | | | | | | |
| Medical History, including Height | X | | | | | | | | | |
| Body Weight | X | X | | | | X | | | | |
| Admission | | X | | | | | | | | |
| Clinic Confinement | | X | X | X | X | X | X | X | X | |
| Discharge | | | | | | | | | X[4] | |
| Study Drug Administration[5] | | | X | X | X | X | | | | |
| Randomization | | | X | | | | | | | |
| C-SSRS Questionnaire[6] | X | X | | X | | X | | | X | |
| Vital Signs[7] | X | X | X | X | X | X | X | X | X | X |
| Physical Examination[8] | X | X | | | | X | | | | X |

[1] Activities need to be completed only once and should be performed based on the order of assessments and timing defined for specific assessments.

[2] For subjects who terminate early from the study, the assessments scheduled on Day 17 will be performed as soon as possible upon termination.

[3] The latest version of the consent form must be signed prior to a subject's inclusion (prior to any study-related procedures).

[4] Subjects will be discharged from the clinical site approximately 72 hours following the last study drug administration.

[5] Subjects will be administered an oral dose of AZD4041 or placebo once daily for 14 consecutive days. Timing of clinical activities are relative to dose administration on Day 1.

[6] On dosing days, the C-SSRS questionnaire should be completed prior to AZD4041 administration and at approximately the same time each day ( ±2 hours).The Baseline/Screening version (APPENDIX 9) will be used at Screening and the 'Since Last Visit' version (APPENDIX 10) will be used at all other timepoints.

[7] Vital signs at Screening and prior to each study drug administration include blood pressure, pulse rate, and body temperature. Vital signs after each study drug administration and at the follow-up visit include blood pressure and pulse rate. Vital sign assessments timepoints are specified in Section 6.2.3.

[8] A complete physical examination and modified neurological examination will be performed on all instances except for Day -1, where a symptom-oriented physical examination will be performed.

| Day | Screening -28 to -1 | -2 to -1[1] | 1 | 2 | 3-13 | 14 | 15 | 16 | 17[2] | Follow-up 27 to 31 |
|---|---|---|---|---|---|---|---|---|---|---|
| General Biochemistry, Haematology, and Urinalysis[9] | X | X | | X | X[10] | X | | | X | X |
| Endocrinology[11] | X | X | X | | | X | | | | |
| Serology (HIV, HbsAg, and HCV) | X | | | | | | | | | |
| Serology (Severe Acute Respiratory Syndrome Coronavirus-2)[12] | | X | | | | | | | | |
| Safety 12-Lead Electrocardiogram[13] | X | X | X | X | X | X | X | X | X | X |
| 12-Lead Digital ECG[14] | | | X | X | X | X | X | X | X | |
| [redacted] CCI | | | | | | | | | | |
| Telemetry[17] | | X | X | X | X | X | X | X | | |
| Alcohol and Drugs of Abuse Screen | X | X | | | | | | | | |
| Serum Pregnancy Test (Females Only) | X | X | | | | | | | | |

[9] Clinical laboratory parameters are detailed in APPENDIX 6. On dosing days, the clinical laboratory tests will be performed prior to study drug administration.

[10] Day 7 only.

[11] Endocrinology parameters are detailed in APPENDIX 6. Male hormones (FSH, testosterone, LH, Inhibin B) are to be collected: Day-1 (1 sample preferably in the morning); Day 1 (2 samples: pre-dose and 1.5 hours post-dose); Day 14 (2 samples: pre-dose and 1.5 hours post-dose).

[12] May be done up to 72 hours prior to Day 1.

[13] The 12-lead electrocardiogram assessment timepoints are specified in Section 6.2.4. Assessments may be conducted at additional timepoints according to Principal Investigator judgment.

[14] Timepoints and extraction times for the 12-lead dECG (extracted from 12-lead Holter recordings) are specified in Section 6.2.5. 12-lead digital Holter is used for dECG extraction on Day 17

[redacted] CCI

[17] The telemetry timepoints are specified in Section 6.2.6