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Clinical Study Report Synopsis	
Drug Substance	AZD4041
Study Code	D7460C00002
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A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of Multiple Ascending Doses of AZD4041 in Healthy Adult Subjects

Study dates: First participant enrolled: 17 December 2021
Last participant last visit: 07 June 2022
The analyses presented in this report are based on a clinical data lock date of 19 September 2022

Phase of development: Clinical pharmacology (I)

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Sponsor's Responsible Medical Officer: PPD
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted at 1 site in 1 country.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of orally administered AZD4041 in healthy participants following daily doses for 14 days (or to steady state)	• AEs • Vital signs • Clinical laboratory tests • 12-lead ECG (dECG and safety ECG) and telemetry (bedside cardiac monitoring) • C-SSRS questionnaire • Physical and neurological examination • Measurement of hormone levels: testosterone, LH, FSH, and inhibin B
Secondary	
• To characterize the multiple dose PK of AZD4041 and assess the time required to reach steady state, the degree of accumulation, and the time dependency of its PK • CCI [redacted] • To assess the CNS penetration potential of AZD4041 by quantification of AZD4041 concentration in the CSF at plasma steady state	The following AZD4041 PK endpoints were to be estimated, data permitting: • Plasma: C_{max}, T_{max}, AUC_{0-24}, AUC_{0-t}, AUC_{τ}, C_{trough}, C_{τ}, $t_{1/2,z}$, $t_{1/2Eff}$, CL/F, V_z/F, $R_{AC}(C_{max})$, $R_{AC}(AUC)$, and λ_z • Urine: Ae_{τ}, fe/F, and CL_R • CSF (Cohorts 2 and 3 only): CSF concentration (ng/ml) reported as a percentage of total and free plasma concentration Additional PK parameters could be estimated as appropriate to support the main PK endpoints. CCI [redacted]
Exploratory	

Objectives	Endpoints
CCI	

Abbreviations: AE = adverse event; CNS = central nervous system; C-SSRS = Columbia Suicide Severity Rating Scale; CSF = cerebrospinal fluid; CYP = cytochrome P450; dECG = digital electrocardiogram; ECG = electrocardiogram; CCI FSH = follicle stimulating hormone; CCI LH = luteinizing hormone; CCI PK = pharmacokinetics; CCI CCI

Study design

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

The study was designed to include up to 48 participants (12 participants per cohort; up to 4 cohorts) who were randomized 9:3 to active drug or placebo, respectively. The fourth cohort was optional and was to be added at the discretion of the Safety Review Committee (SRC) if the maximum tolerated dose (MTD) had not been defined and the maximum allowed exposure had not been reached after 3 cohorts. The dose administered in Cohort 3 was deemed the maximum allowable dose for repeat dosing and Cohort 4 was therefore not needed.

Target participant population and sample size

The study included 36 participants (12 participants per cohort) who were randomized 9:3 to active drug or placebo, respectively.

Main inclusion criteria included:

1. Healthy adult males or females. Female participants were of non-childbearing potential (postmenopausal and/or surgically sterile)

2. Aged at least 18 years but not older than 55 years on the day of randomization

3. Men who were biologically capable of fathering children agreed and committed to use an adequate form of contraception for the duration of the treatment period and for no less than 120 days (4 months) after the last administration of study intervention. Men also agreed to refrain from sperm donation for the duration of the treatment period and for at least 90 days after the last administration of study intervention.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Table S2 CCI

CCI

Duration of treatment

Screening: Day -28 to Day -1 (up to 28 days)

Participant confinement: Day -2 to Day 17

Follow-up visit: Days 27 to 31

Total study Duration: 59 days (including Screening)

Statistical methods

Safety Analysis

Safety assessments included measurement and monitoring of adverse events (AEs), vital signs, clinical laboratory tests, 12-lead electrocardiograms (ECGs) (digital ECG [dECG] and safety ECG), telemetry (bedside cardiac monitoring), CCI [redacted] Columbia Suicide Severity Rating Scale (C-SSRS) questionnaires, and physical and neurological examinations.

Pharmacokinetic and Pharmacodynamic Analyses

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

CCI [redacted]

Concentration data are 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). The PK parameters are summarized using these same statistics, as well as geometric mean and geometric CV.

Inferential statistical analysis was performed with SAS® Version 9.4.

For dose-proportionality evaluation, dose–normalized PK parameters (C_{max} and appropriate AUCs) were assessed graphically and natural log-transformed (ln) PK parameters (C_{max} and appropriate AUCs) were assessed statistically using a power model.

Steady state assessment was evaluated graphically and in tabular form based on C_{trough} measurements.

Study population

A total of 36 participants (100.0%) were included in the safety population and 35 participants (97.2%) were included in the PD population. The PK population included all participants on active treatment (27 participants [75.0%]) and excluded all participants on placebo (9 participants [25.0%]).

Participants were recruited from 1 study centre. The first participant was enrolled on 17 December 2021 and the last participant's last visit was on 07 June 2022.

Summary of pharmacokinetic results

- CCI
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- CCI [redacted]

Summary of pharmacodynamic results

CCI [redacted]

Summary of safety results

Based on the results in this study, the following safety conclusions can be made:

- No serious AEs (SAEs), Grade 3 treatment-emergent adverse events (TEAEs), or deaths occurred during the study
- CCI PPD CCI [redacted]
  CCI [redacted]
- The majority of the TEAEs were not drug-related
- Most TEAEs were assessed as Grade 1 in intensity
- CCI [redacted]
- No clinically significant abnormal findings in laboratory values, vital signs, physical examinations, ECGs, or telemetry occurred during the study
- No suicidal ideation or behavior was reported during the study

Conclusions

- Overall, AZD4041 was safe and well -tolerated
- There were no evident findings in the ECG complexes that preceded the onset of non-sustained VTs, nor in the VTs themselves, in any of the above presented cases that would have indicated a drug induced pro arrhythmic effect.

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]