2. SYNOPSIS

STUDY TITLE: 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

INVESTIGATORS: [redacted]

STUDY SITES: [redacted]

PUBLICATION (REFERENCE): None

STUDY PERIOD:

15 October 2019 (date of first subject informed consent) to

02 November 2021 (date of last subject contact)

PHASE OF DEVELOPMENT: 1

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.

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

METHODOLOGY: This was a Phase I, 2-center (planned as single-center, but conducted at 2 centers), FIH, randomized, double-blind, placebo-controlled, single ascending dose, sequential group study.

The study enrolled 48 healthy subjects across 6 cohorts as shown in **Table 1**.

Table 1 Dose-Level Cohorts

Cohort	Actual Dose Level of AZD4041
Cohort 1	[redacted]
Cohort 2	[redacted]
Cohort 3	[redacted]
Cohort 4	[redacted]
Cohort 5	[redacted]
Cohort 6	[redacted]

Eight subjects were enrolled in each cohort. Within each cohort, 6 subjects were randomized to receive AZD4041 and 2 subjects were randomized to receive placebo. Dosing for each ascending dose cohort proceeded with 2 subjects in an initial sentinel cohort, such that

1 subject was randomized to receive placebo and 1 subject was randomized to receive AZD4041 in a blinded fashion.

The blinded safety data from the 2 sentinel subjects through at least 24 hours postdose were reviewed by the PI, PPD medical monitor, and AstraZeneca study physician before the remaining subjects in the cohort were dosed. The remaining 6 subjects in each cohort were dosed at least 24 hours after the sentinel cohort.

The study comprised a screening period of up to 28 days (4 weeks), a 4-day in-patient period during which a single oral dose of AZD4041 or placebo was administered, and an outpatient follow-up period. The overall study duration (screening, treatment, and follow-up periods) was approximately 6 weeks.

Number of subjects (planned and analyzed): A total of 48 subjects were planned and enrolled across 6 cohorts in the study. All 48 subjects (100.0%) completed the study and were included in the safety analysis set and PK analysis set.

Diagnosis and main criteria for inclusion: Subjects in this study were healthy males and females of nonchildbearing potential aged 18 to 65 years (Cohorts 1, 2, and 3), and healthy vasectomized male and female subjects of nonchildbearing potential aged 18 to 65 years (Cohort 4 and first 5 subjects of Cohort 5) and aged 18 to 55 years (remaining 3 subjects of Cohort 5 and all subjects of Cohort 6), who weighed ≥50 kg and had a BMI of 18.0 to 30.0 kg/m^2, inclusive.

Test product, dose, and mode of administration, lot number:

- [redacted]
- [redacted]

Reference therapy, dose, and mode of administration, lot number:

- Placebo, lot number not applicable, administered as a single oral solution
- Vehicle for placebo [redacted] lot number not applicable.

Duration of treatment: [redacted]

CRITERIA FOR EVALUATION:

Safety: Safety and tolerability of AZD4041 were evaluated by the frequency and severity of AEs, clinical laboratory test results (hematology, clinical chemistry, and urinalysis), vital sign measurements (systolic and diastolic BP, pulse rate, respiratory rate, and body temperature), and 12-lead ECG and telemetry results.

Pharmacokinetics: The following PK parameters were calculated: C_{max}, T_{max}, AUC_{0-t}, AUC_{0-inf}, $t_{1/2\,\lambda z}$, CL/F, and V_z/F.

Pharmacodynamics: To characterize the PD relationship between drug exposure and QT interval, an E-R analysis may be conducted with data from this study and other studies, with a prespecified 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 PD analysis will be conducted later, and the results will be reported in a separate report.

STATISTICAL METHODS:

Safety: All safety assessments, including AEs; liver diagnostic investigations; liver risk factors/lifestyle events; liver signs and symptoms data; clinical laboratory test results (hematology, chemistry, and urinalysis); vital sign measurements; and pECG, dECG, and telemetry monitoring data are presented in data listings.

All AEs were coded by SOC and PT using the Medical Dictionary for Regulatory Activities Version 22.1. The number and percentage of subjects with AEs are presented in summary tables. A subject with 2 or more AEs within the same SOC and PT was counted once in the summarization level.

An overview of AEs, including number of subjects with at least 1 AE, with at least 1 TEAE, with at least 1 treatment-related TEAE, with at least 1 moderate TEAE, with at least 1 treatment-related moderate TEAE, with at least 1 severe TEAE, with at least 1 treatment-related severe TEAE, with at least 1 SAE, with at least 1 treatment-related SAE, with at least 1 TEAE leading to early discontinuation, and death are presented by treatment and overall. Summary tables are also provided for all TEAEs by SOC, PT, treatment, and overall.

Actual results and changes from baseline are summarized for clinical laboratory test results (hematology, chemistry, and urinalysis) and vital sign measurements. Shift tables for clinical laboratory test results are summarized. Descriptive statistics of smoothed PR, RR, QRS, QT values and derived QTcF, and HR values, as well as change from baseline, are summarized by treatment group (pooled placebo, dose level of AZD4041, and pooled AZD4041) and nominal time point. The number and percent of subjects whose worst (ie, highest) postbaseline smoothed QTcF value according to the following categories are tabulated by visit, time point, 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; and increase from baseline >60 msec. The tabulations are presented separately for the subgroups who may have had an elevated QTcF (>450 msec) at baseline and those who did not.

The liver diagnostic investigations, liver risk factors/lifestyle events, and liver signs and symptoms data, telemetry monitoring data, and physical and neurological examination findings are presented in data listings.

Pharmacokinetics:

AZD4041 plasma concentration data are summarized using descriptive statistics by treatment and nominal sampling time. Individual and mean AZD4041 plasma concentration versus time data are plotted by treatment. For ease of presentation, mean plasma concentrations of AZD4041 are plotted by nominal time by treatment on both linear and semilogarithmic scales.

Plasma PK parameters for AZD4041 are presented in data listings and summarized by treatment using descriptive statistics.

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

Dose proportionality for AZD4041 is evaluated for C_{max}, AUC_{0-t}, and AUC_{0-inf}. A power model using Statistical Analysis System (SAS®) software (SAS Institute Inc., Cary, North Carolina) Version 9.4 is fitted to describe the relationship between Y (C_{max}, AUC_{0-t}, and AUC_{0-inf}) and X (dose) that used 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, are presented along with the 90% CI of the slope. Dose proportionality is concluded if the 90% CI of the slope β lay entirely within [1+ln(0.8)/ln(r), 1+ln(1.25)/ln(r)], where r is a ratio that described the dose range and is defined as the ratio of highest dose/lowest dose. If the proportionality is not demonstrated over the entire dose range, the lowest or highest dose is removed, and the analysis is repeated until a range of proportionality is determined. Dose proportionality is assessed with at least 3 dose levels.

The statistical analyses are based on the PK analysis set.

Pharmacodynamics:

The results of the E-R analysis are not included in this main CSR. The specifications of the E-R modeling were not included in the SAP.

RESULTS:

Safety Results:

- Overall, 12 subjects (25.0%) reported a total of 17 TEAEs: 5 subjects (41.7%) had 8 TEAEs in the pooled placebo cohort; [redacted] There were no apparent dose-related trends observed with respect to TEAE reporting. All TEAEs resolved by the end of the study.
- [redacted]
- Overall, 6 of 17 TEAEs were considered to be related to study drug by the investigator: [redacted]

- The majority of TEAEs were mild in severity. [redacted]
- There were no severe TEAEs, deaths, SAEs, or TEAEs leading to study discontinuation reported during the study.
- [redacted]
- [redacted]
- No subject met the criteria for Potential Hy's Law or Hy's Law during the study.
- Only 1 of the abnormal testosterone, LH, FSH, and inhibin B test results for individual subjects was considered clinically significant: high testosterone levels (>52.1 nmol/L) were considered clinically significant for 1 subject from check-in until Day 4.
- No apparent treatment- or dose-related trends were observed in clinical laboratory test results, vital sign measurements, 12-lead ECG results, or physical and neurological examination findings. No individual abnormal hematology, serum chemistry, or urinalysis result value was considered clinically significant or reported as a TEAE by the investigator.

Pharmacokinetic Results:

Following single oral dose administration of AZD4041, plasma AZD4041 peak and total exposures increased as the dose increased from [redacted]. The $t_{1/2\,\lambda z}$ ranged from [redacted] Mean CL/F values ranged from [redacted] and V_z/F values ranged from [redacted] with consistent values across the evaluated dose range. Overall, the variability in exposure parameters was moderate across dose groups. Dose proportionality was not confirmed statistically; however, in general AZD4041 PK was approximately dose proportional over the dose range of [redacted] as the estimate for the slope approximated 1 for all parameters.

CONCLUSIONS:

Safety Results:

AZD4041 was found to be generally well tolerated and to have a good safety profile when administered as a single oral ascending dose over the range [redacted] in healthy subjects during this study.

Pharmacokinetics:

- AZD4041 mean C_{max} and AUC values increased with increasing dose from [redacted].
- Exposure parameters (C_{max} and AUC) of AZD4041 increased in an approximately dose proportional manner from [redacted]; however, the 90% CIs of the slopes were not fully contained within the criteria to make a statistical claim of dose proportionality.

- The $t_{1/2\ \lambda z}$ ranged from [redacted] across the dose range explored. Mean CL/F values ranged from [redacted] and V_z/F values ranged from [redacted] with consistent values across the evaluated dose range.

DATE OF REPORT: 18 March 2022