Clinical Study Report

1 TITLE PAGE

A Phase I Randomized, Single-blind, Placebo-controlled, First-in-Human and Sequential Group Study to Assess Safety, Tolerability, and Pharmacokinetics of AZD0186 Following Single Ascending Doses via Oral Administration

Investigational Medicinal Product:	AZD0186
Indication Studied:	Type 2 Diabetes (T2DM)
Parexel Study Number:	PXL278634
Sponsor Study Number:	D8740C00001
IND Number:	IND 163977
Development Phase:	Phase I
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Investigator Name and Address:	PPD
Study Duration:	20 December 2022 (first subject first visit) to 11 May 2023 (last subject last visit)
Version and Date of Report:	Version 1.0, dated 01 Dec 2023

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines. The essential documentation related to this study has been retained by relevant parties.

2 SYNOPSIS

Title of Study:	A Phase I Randomized, Single-blind, Placebo-controlled, First-in-Human and Sequential Group Study to Assess Safety, Tolerability, and Pharmacokinetics of AZD0186 Following Single Ascending Doses via Oral Administration	
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Indication Studied:	Type 2 Diabetes (T2DM)	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit - Los Angeles	
Publication:	Not applicable	
Study Duration:	First subject first visit: 20 December 2022	Last subject last visit: 11 May 2023

Study Objectives:

Primary objective [a]:

To assess the safety and tolerability of AZD0186 following oral single ascending doses in healthy subjects (Part 1 and Part 4), in healthy Japanese subjects (Part 2), and in healthy Chinese subjects (Part 3).

Secondary objective [a]:

To characterize the pharmacokinetics (PK) of AZD0186 following oral single ascending doses.

The results of the exploratory objectives outlined in the CSP will not form part of the Clinical Study Report (CSR) for this study.

[a] The study was terminated early after Cohort 4 of Part 1. Therefore, this objective was only evaluated for Part 1 Cohorts 1 to 4.

Study Design:

This was a first-in-human, randomized, single-blind, placebo-controlled, SAD sequential group design study in healthy male and female subjects, performed at a single study center. The study was planned to have consisted of 4 parts: Part 1, Part 2, Part 3, and Part 4:

- Part 1: the planned number of cohorts were up to 6 cohorts; additional cohorts could be included if the Safety Review Committee (SRC) considered it necessary to repeat a dose level or if additional dose steps were required. Within each cohort, the aim was to have 6 subjects on AZD0186 and 2 subjects receiving placebo.
  - Sentinel dosing was conducted for the first 2 subjects in each cohort: 1 subject was randomized to receive AZD0186 and 1 subject was randomized to receive placebo. The safety data from the sentinel subjects (up to 48-hours post-dose) were reviewed by the Investigator before the remaining subjects in the cohort were dosed. If a dose level was to be repeated, there was to be sentinel dosing at that repeated dose level.
- Part 2: the planned number of Japanese cohorts was 1, but more than 1 cohort could be included if the SRC considered it necessary to repeat a dose level or if additional dose steps were required. No sentinel dosing was planned to be performed for the Japanese cohort.
- Part 3: the planned number of Chinese cohorts was 1, but more than 1 cohort could be included if it was considered necessary to repeat a dose level or if additional dose steps were required. No sentinel dosing was planned to be performed for the Chinese cohort.
- Part 4: one of the Part 1 cohorts was planned to continue into the food-effect part after a washout period of at least 7 days. Part 4 was planned to be initiated after SRC review of all available data from preceding cohorts in this study.

The study was terminated early after completion of Cohort 4 of Part 1; thus, Parts 2 to 4 did not occur. The decision to discontinue the study was based on the overall data for AZD0186 which did not show significant differentiation from standard of care or other drugs in development. Only data from Part 1 Cohorts 1 to 4 are described in this CSR.

Part 1 of the study consisted of:

- A Screening Period of maximum 28 days.
- A Treatment Period during which subjects were resident at the Clinical Unit from 2 days before investigational medicinal product (IMP) administration (Day -2) until at least 48 hours after IMP administration; discharged on Day 3.
- A Follow-up Visit within 7 ± 1 day after the last IMP dose.

Study Subjects:

Planned for Inclusion:	Randomized:	Completed Study:
64 subjects	31 subjects	31 subjects

Main Inclusion Criteria:

- Healthy male and female (of non-child-bearing potential) subjects, 18 to 55 years of age, who had a body mass index of 18 to 32 kg/m^2 (inclusive) and weighed at least 50 kg.

Investigational Medicinal Products:

Intervention name	AZD0186 Oral Suspension	AZD0186 Oral Suspension Placebo
Type	Drug	Drug
Dose formulation	Suspension	Suspension
Unit dose strengths	CCI [redacted]	Matching volume

Dosage levels	Starting dose: CCI mg Doses for subsequent cohorts: CCI and CCI mg	Matching volume
Route of administration	Oral	Oral
Use	Experimental	Placebo
IMP or Non-Investigational Medical Products	IMP	IMP
Sourcing	Manufactured and provided by AstraZeneca	Manufactured and provided by AstraZeneca
Packaging and labeling	CCI	CCI
Batch/Manufacturing Lot Numbers:	CCI CCI	CCI
Expiry Dates:	CCI CCI	CCI

Duration of Treatment:

Each subject in Part 1 was involved in the study for up to approximately 5 weeks (35 days).

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit Los Angeles.

The administration of all study intervention was recorded in ClinBase™ system.

Compliance was assured by direct supervision and witnessing of study intervention administration. After administration, a check of the subjects' mouth and hands was performed.

Placebo samples were not analyzed, unless there was a need to confirm that correct treatment had been given to study subjects.

Criteria for Evaluation:

Safety Variables:

Safety endpoints included adverse events (AEs), serious adverse event (SAEs), clinical laboratory evaluations (hematology, biochemistry, and urinalysis), vital signs (including systolic and diastolic blood pressure [BP], and heart rate), 12-lead safety and digital electrocardiograms (ECGs), telemetry, physical examination, and ophthalmological examination.

Pharmacokinetic Parameters:

Primary PK parameters included AUCinf, AUClast, and Cmax.

Statistical Methods:

Determination of Sample Size:

This was a Phase I study to investigate the safety and tolerability of a novel compound.

The sample sizes for this study were chosen to obtain reasonable evidence of safety and tolerability without exposing undue numbers of subjects to the compound at this phase of clinical development. 8 evaluable subjects per cohort were required to complete the study (6 receiving AZD0186 and 2 receiving placebo). Previous experience in Phase I studies had shown that the sample sizes proposed for this study were reasonable to accomplish the objectives of the study.

Presentation and Analysis of Safety Data:

All safety summaries and analyses were based upon the Safety set unless otherwise specified. All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) by cohort, dose level, and visit. Categorical variables were summarized in frequency tables (frequency and proportion) by cohort, dose level, and visit.

Presentation and Analysis of Pharmacokinetic Data:

The analysis of PK data was based on the PK set. The plasma and urine concentrations of AZD0186 and the PK parameters were listed and presented in tabular and graphical form by visit. PK parameters were calculated by non-compartmental analyses and summarized using descriptive statistics by visit. A power model approach was used to assess dose proportionality for Cmax, AUClast, and AUCinf by fitting least squares linear regressions using logarithmic transformations of PK parameters as the dependent variables and logarithmic transformations of doses as the independent variables. For each parameter, an estimate of the slope and intercept of the regression line and corresponding 90% CIs were obtained.

Protocol Deviations:

No important protocol deviations were identified in Part 1 of this study.

Safety Results:

- No AEs with an outcome of death, other SAEs, AEs leading to IMP discontinuation or withdrawal from the study were reported.
- A total of 8 subjects (34.8%) who received AZD0186 and 2 subjects (25.0%) in the pooled placebo group experienced at least 1 AE.
- The most frequently reported AEs belonged to the System Organ Class 'Gastrointestinal disorders' (8 subjects [34.8%] in the pooled AZD0186 group). Nausea was the most commonly reported AE (6 subjects [26.1%] in the pooled AZD0186 group) followed by vomiting (2 subjects [8.7%] in the pooled AZD0186 group).
- AEs of moderate intensity were reported in 2 subjects (8.7%) in the pooled AZD0186 group and 1 subject (12.5%) in the pooled placebo group. All other reported AEs were considered mild in intensity.
- AEs that were considered related to the IMP by the Investigator were reported in 8 subjects (34.8%) in the pooled AZD0186 group and 1 subject (12.5%) in the pooled placebo group.
- No clinically relevant trends were observed for laboratory parameters, vital signs, ECGs, physical examination, or ophthalmological examination.
- Single oral doses up to CCI mg of AZD0186 were tolerated in the studied population and there were no safety concerns.

Pharmacokinetic Results:

- Median tmax was similar between all the cohorts between 1.00 and 1.51 h post-dose.
- Geometric mean t1/2λ appeared to increase with dose from 1.947 h to 7.581 h across the [CCI] to [CCI] mg dose range.
- Across the [CCI] mg to [CCI] mg dose range, Cmax appeared to increase in a less than dose-proportional manner, whilst AUClast and AUCinf appeared to increase in an approximately dose-proportional manner.
- Between-subject variability for Cmax and all AUC parameters was moderate to high across the dose range (gCV% 13.25 to 64.77%).
- Urinary excretion of AZD0186 was low with less 1% of dose being excreted unchanged.

Discussion and Conclusion:

- Single oral doses of up to [CCI] mg AZD0186 were tolerated in the studied population and there were no safety concerns.
- Median tmax was similar between all the cohorts at between 1.00 and 1.51 h post-dose. Across the [CCI] mg to [CCI] mg dose range Cmax appeared to increase in a less than dose-proportional manner, whilst AUClast and AUCinf appeared to increase in an approximately dose-proportional manner. Urinary excretion of AZD0186 was low with less than 1% of the dose excreted unchanged.

Version and Date of Report: Version 1, 01 Dec 2023

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