2 SYNOPSIS

Title of Study:	A Phase I Randomized, Single-blind, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD8233 Following Single Ascending Dose Administration to Healthy Male Subjects with Elevated LDL-C Levels	
Study Numbers:	Parexel Study No.: Pxl238221 Sponsor Study No.: D7990C00001	
Investigational Medicinal Product:	Study Drug: AZD8233	
Indication Studied:	Hypercholesterolemia	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	PPD	
Publication:	None	
Study Duration:	First subject first visit: 03 Aug 2018	Last subject last visit: 19 Dec 2020

Study Objectives:

Primary objective:

To assess the safety and tolerability of AZD8233 following SC administration of single ascending doses (Part 1) and a single CCI dose in the Chinese and Japanese cohorts (Part 2).

Secondary objectives:

- To characterize the PK of AZD8233 following SC administration of single ascending doses (Part 1) and a single CCI dose in the Chinese and Japanese cohorts (Part 2).
- To assess the effect of AZD8233 on levels of LDL-C following SC administration of single ascending doses (Part 1) and a single CCI dose in the Chinese and Japanese cohorts (Part 2).
- To assess the effect of AZD8233 on levels of PCSK9 following SC administration of single ascending doses (Part 1) and a single CCI dose in the Chinese and Japanese cohorts (Part 2).

Exploratory results are not reported in this clinical study report (CSR).

Title of Study:	A Phase I Randomized, Single-blind, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD8233 Following Single Ascending Dose Administration to Healthy Male Subjects with Elevated LDL-C Levels

Study Design:

This study consisted of 2 parts. Part 1 was a randomized, single-blind, placebo-controlled study in healthy male subjects with elevated LDL-C levels to assess the safety, tolerability, PK and PD of AZD8233 following single ascending doses (ascending doses consisted of CCI AZD8233). Part 2 was a randomized, single-blind, placebo-controlled study in healthy male Chinese and Japanese subjects with elevated LDL-C levels to assess the safety, tolerability, PK and PD of AZD8233 in these populations, following a single CCI dose of AZD8233. CCI was the second highest dose that was given in Part 1 of the study and was predicted to be the highest monthly dose in future repeated dosing studies in the further clinical development program of AZD8233.

During Part 1, 7 cohorts, each consisting of 8 subjects, participated in the study. During Part 2, 1 cohort of 9 Chinese subjects and 1 cohort of 8 Japanese subjects was enrolled in parallel after completion of Part 1. The study was performed at a single clinical unit. A total of 73 male subjects, aged 18 to 60 years, were randomized into this study.

Within each cohort, 6 subjects were randomized to receive a single SC dose of AZD8233 and at least 2 subjects were randomized to receive placebo. Dosing for each ascending dose cohort in Part 1 was proceeded with 2 subjects in a sentinel cohort, such that 1 subject was randomized to receive placebo and 1 subject was randomized to receive AZD8233.

For both Part 1 and Part 2, the study comprised of:

- Screening Period of maximum 28 days;
- Treatment Period:
  - during which the sentinel subjects (Part 1 only) were resident at the Clinical Unit from the day before Investigational Medicinal Product (IMP) administration (Day -1) until at least 72 hours after IMP administration; discharged on Day 4.
  - during which the non-sentinel subjects were resident at the Clinical Unit from the day before IMP administration (Day -1) until at least 48 hours after IMP administration; discharged on Day 3.
- Follow-up Period of 16 weeks that consisted of:
  - Ten Follow-up Visits for sentinel subjects, the subjects returned for Follow-up Visits 1, 2, 3, 4, 6, 8, 10, 12, 14 and 16 weeks post-dose.
  - Eleven Follow-up Visits for non-sentinel subjects, the subjects returned for Follow-up Visits on Day 4 and 1, 2, 3, 4, 6, 8, 10, 12, 14 and 16 weeks post-dose.

Study Subjects:

Randomized:	**Received Treatment:**	**Completed Study:**
Part 1		
42 subjects (AZD8233) 14 subjects (placebo)	42 subjects (AZD8233) 14 subjects (placebo)	41 subjects (AZD8233) 14 subjects (placebo)
Part 2 (Japanese Cohort)		
6 subjects (AZD8233) 2 subjects (placebo)	6 subjects (AZD8233) 2 subjects (placebo)	6 subjects (AZD8233) 2 subjects (placebo)
Part 2 (Chinese Cohort)		
6 subjects (AZD8233) 3 subjects (placebo)	6 subjects (AZD8233) 3 subjects (placebo)	5 subjects (AZD8233) 2 subjects (placebo)

Title of Study:	A Phase I Randomized, Single-blind, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD8233 Following Single Ascending Dose Administration to Healthy Male Subjects with Elevated LDL-C Levels

Main Inclusion Criteria:

This study was conducted in healthy male subjects (Part 1) or Chinese or Japanese healthy male subjects (Part 2) with LDL-C ≥ 100 mg/dL and < 190 mg/dL, aged 18 to 60 years that weighed at least 60 kg and no more than 100 kg, inclusive.

Investigational Medicinal Product:

Formulations:	**Strength/Concentrations:**	**Batch/Manufacturing Lot Number(s):**	**Expiry Date(s):**
AZD8233 solution for injection	CCI	CCI	CCI
AZD8233 Placebo-to-Match	NA	NA	NA

Duration of Treatment:

Each subject was involved in the study for up to 20 weeks.

Treatment Compliance:

Dosing took place at the PPD. Compliance was assured by direct supervision and witnessing of IMP administration.

Administration of IMP was recorded in ClinBase™.

Criteria for Evaluation:

Safety and Tolerability Variables:

Safety and tolerability variables included adverse events (AEs), vital signs (systolic blood pressure, pulse and body temperature), 12-lead digital electrocardiogram, telemetry, physical examination, injection site reaction examinations, laboratory assessments (hematology, clinical chemistry, coagulation, renal safety biomarkers, immune activation response, complement activation panel and urinalysis).

Pharmacokinetic Parameters:

The following PK parameters were estimated where possible on plasma concentrations of AZD8233 as well as on plasma concentrations of AZD8233 full-length anti-sense oligonucleotides (ASOs).

- Plasma parameters: tlag, tmax, Cmax, AUC(0-last), AUC(0-48), AUC, CL/F, Vz/F, t½, MRT
- Urine parameters: Ae, Fe, CLR

Pharmacodynamic Parameters:

The following PD parameters were determined where possible in plasma.

- LDL-C levels
- PCSK9 levels

Statistical Methods:

Presentation and Analysis of Safety and Tolerability Data:

Subject disposition was summarized and included the following information: number of subjects randomized and dosed, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal).

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) were listed by subject. Part 1 demographic characteristics (age, gender, race and ethnicity) and subject characteristics (height, weight and BMI) were summarized (dose level of AZD8233 and pooled placebo) for all subjects in the safety analysis set. For Part 2, demographic and baseline data was summarized separately for the Chinese and Japanese cohorts, treatment (AZD8233 and placebo).

All safety data was presented in the data listings. Adverse events were summarized by Preferred Term and SOC using MedDRA vocabulary. Furthermore, listings of serious adverse events (SAEs) and AEs that led to withdrawal were made and the number of subjects who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity were summarized, if applicable. Adverse events that occur before dosing were reported separately. Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs were presented. Any new or aggravated clinically relevant abnormal medical physical examination findings compared to the baseline assessment were reported as an AE.

Vital signs measurements and laboratory results were listed and summarized including changes from baseline. Any out of range vital signs measurements and laboratory results were flagged in the individual listings.

Results of the ECGs, including normal/abnormal and specific findings were listed.

Presentation and Analysis of Pharmacokinetic Data:

Pharmacokinetic blood and urine sample collection times including derived sampling time deviations were listed. Urine amount and fraction of dose excreted (by interval and cumulative) were listed. Plasma concentrations, urine amount excreted and fraction of dose excreted (per collection interval and cumulative) and PK parameters were summarized by treatment/dose group using descriptive statistics based on the PK analysis set.

Combined individual plasma concentration versus actual times was plotted in linear and semi-logarithmic scale.

Figures for the arithmetic mean (SD) concentration-time data was presented for all doses on both a linear and semi-logarithmic scale. Individual concentration-time data was graphically presented on linear and semi-logarithmic scales.

AZD8233 is a N-acetylgalactosamine (GalNAc) conjugated chemically modified 16-mer oligonucleotide which is cleaved in the hepatocytes to generate the unconjugated anti-sense oligonucleotide (ASO) resulting in the pharmacologically active compound inhibiting PCSK9 mRNA translation. Dose proportionality of AZD8233 and AZD8233 full length ASOs were assessed graphically and analysed using the power model approach with the logarithm of PK parameters AUC and Cmax as the dependent variables and the logarithm of the dose as the independent variable.

Figures with individual and dose-normalized Cmax, AUC and AUC(0-last) were also presented graphically versus dose.

Pharmacokinetic data was summarized separately for Part 1 and Part 2.

Presentation and Analysis of Pharmacodynamic Data:

The effect of AZD8233 on levels of LDL-C, PCSK9, lipid panel (total cholesterol, HDL-C, LDL-C, triglycerides) and lipoprotein profile (particle size and number by nuclear magnetic resonance) was evaluated. The results were listed and summarized by treatment (dose level of AZD8233 or pooled placebo) including changes from baseline.

The followings figures were presented:

Title of Study:	A Phase I Randomized, Single-blind, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD8233 Following Single Ascending Dose Administration to Healthy Male Subjects with Elevated LDL-C Levels

- Individual levels of LDL-C, PCSK9, lipid panel and lipoprotein profiles versus actual time points in linear and semi-logarithmic scale showing a subject in each plot and displaying reference ranges per parameter.
- Arithmetic mean (observed and change from baseline values, when applicable) of LDL-C, PCSK9, lipid panel and lipoprotein profiles versus nominal time points in linear (± SD) scale. All treatments were overlaid on the same plot and reference ranges displayed.
- Figures displaying simultaneously different parameters were generated if considered appropriate.

Separate analysis sets applied for each study part. Pharmacodynamic data was summarized separately for Part 1 and Part 2.

Determination of sample size

This was a Phase I study to investigate the safety and tolerability of a novel compound. The sample size was chosen to obtain reasonable evidence of safety and tolerability without exposing undue numbers of subjects to the compound at this phase of clinical development. Part 1 consisted of 56 subjects, while Part 2 (Japanese Cohort) include 8 subjects and Part 2 (Chinese Cohort) consisted of 9 subjects. Previous experience in Phase I studies had shown that the sample size being proposed is reasonable to accomplish the objectives of the study.

Protocol Deviations:

There were no subjects with important protocol deviations.

CCI

[redacted]

Title of Study:	A Phase I Randomized, Single-blind, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD8233 Following Single Ascending Dose Administration to Healthy Male Subjects with Elevated LDL-C Levels

Pharmacodynamic Results:

- A significant and dose dependent decrease in PCSK9 and LDL-C levels from baseline was observed at all doses of AZD8233 except for at the CCI dose which was not different from placebo. At the low-to-medium dose range (CCI), a significant reduction of LDL-C was evident by week 1 and lasted up to week 10; while at the high doses (CCI), a significant reduction of LDL-C was evident sooner at 72 hours post-dose and lasted longer and up to week 16. The reduction of PCSK9 was evident 72 hours post-dose at low-to-medium doses (CCI) and 24 hours post-dose at high dose levels (CCI) with effect lasted up to week 10 and week 16, respectively. At the highest dose, the reduction in PCSK9 and LDL-C from baseline was estimated to > 90% and around 70%, respectively. The maximum effect was observed between week 2 and week 6. After reaching max reduction the PCSK9 and LDL-C levels slowly returned towards baseline levels over the 16 weeks Follow-up Period.
- Similar to the CCI , non-Asian cohort in Part 1, AZD8233 at CCI dose, induced a significant reduction of LDL-C and PCSK9 in both the Japanese and Chinese cohorts. A significant reduction of LDL-C and PCSK9 was evident 72 hours post-dose and 24 hours post-dose, respectively, in both the Japanese and Chinese cohorts. Overall, the PCSK9 and LDL-C reduction over time followed the same pattern in the Japanese and Chinese cohorts as compared to the non-Asian CCI cohort with a slow return to baseline levels over the 16 weeks Follow-up Period.
- No ethnic difference in effect on PCSK9 and LDL-C reduction over time could be concluded between the Japanese and Chinese cohorts analysed either as separate cohorts or combined as one Asian cohort compared to the non-Asian cohort administered the same dose (CCI) in Part 1.

Safety Results:

There were no AEs with outcome of death, other SAEs, or AEs leading to withdrawal from the study.

Overall, at least 1 AE was reported in Part 1 by 21 (50.0%) subjects in the combined AZD8233 group and 4 (28.6%) subjects in the placebo group; in Part 2, Japanese Cohort, 3 (50.0%) subjects in the AZD8233 group (and none in the placebo group); and in the Chinese Cohort, by 2 (66.7%) subjects in the placebo group (and none in the AZD8233 group).

AEs assessed by Investigator as possibly related to IMP in Part 1 were upper respiratory tract infection (8 [19.0%] subjects), medical device site reaction (4 [9.5%] subjects), headache (3 [7.1%] subjects), arthralgia (2 [4.8%] subjects), and back pain (2 [4.8%] subjects) in the combined AZD8233 group and headache (2 [14.3%] subjects) in the placebo group; in Part 2, there were no AEs reported by more than 1 subject in either the Japanese or Chinese Cohort.

AEs related to IMP as per Investigator assessment in Part 1 were headache (1 [16.7%] subject) in the CCI AZD8233 group, headache and nausea (1 [7.1%] subject each) in the placebo group and in Part 2 hot flush (1 [16.7%] subject) in the Japanese Cohort, CCI AZD8233 group, and injection site bruising (1 [33.3%] subject) in the Chinese Cohort, placebo group.

All AEs were mild in intensity with the exception of 2 AEs of moderate intensity (arthralgia in Part 1 and joint swelling in Part 2, Japanese Cohort) and a single AE of severe intensity in Part 1 (gastroenteritis and panic attack). All AEs of moderate or severe intensity were resolved. No clinically relevant trends were observed for laboratory results, vital signs, or ECGs.

Title of Study:	A Phase I Randomized, Single-blind, Placebo-controlled Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AZD8233 Following Single Ascending Dose Administration to Healthy Male Subjects with Elevated LDL-C Levels

Discussion and Conclusion:

Primary objectives

- No safety or tolerability concerns were raised, no clinically relevant trends for laboratory results, vital signs, or ECG findings were reported up to the highest dose given (CCI) in this study. The maximum tolerated dose (MTD) could not be determined in this study.
- AZD8233 administered as a single dose at a range of CCI to CCI was well tolerated in the healthy male subjects included in Part 1 of the study.

Secondary objectives

- AZD8233 was rapidly absorbed with unchanged AZD8233 being the predominant circulating species at early time points, indicating that AZD8233 is mainly absorbed unchanged from the injection site.
- The full length ASOs had a biphasic plasma profile with a geometric mean terminal t½λz ranging between approximately 6 to 22 days.
- Clearance of AZD8233 full length ASOs was moderately high and predominantly non-renal with less than 0.5% of the dose excreted as full length ASOs in urine during the first 48 hours.
- AUC and Cmax for AZD8233 and full length ASOs increase in a supra-proportional manner with dose and approximately proportional above the CCI dose.
- Although exposures based upon the geometric mean AUC, AUC(0-last) and Cmax of full length ASOs of AZD8233 were higher in the Japanese and Chinese cohorts as compared to the same dose administered to the non-Asian cohort, the observed exposure of AZD8233 as well as PCSK9 reduction over time was similar in the Japanese, Chinese and non-Asian cohorts.
- A significant and dose dependent decrease in PCSK9 and LDL-C levels from baseline was observed with more than 90%, and around 70% reduction observed, respectively at the highest dose.

Version and Date of Report: Final 1.0 dated 02 July 2021

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.