A Randomised, Parallel, Double-Blind, Placebo-Controlled Phase 2b Study to Assess the Safety, Tolerability and Efficacy of AZD8233 Treatment in Participants with Hyperlipidaemia (SOLANO)

Published: 20-05-2021
Last updated: 05-04-2024

To assess the safety and tolerability of AZD8233 as compared with placebo in participants with hyperlipidaemia receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON52196

Source
ToetsingOnline

Brief title
SOLANO

Condition

- Cardiac disorders, signs and symptoms NEC
- Lipid metabolism disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
High Blood Cholesterol levels, Hyperlipidaemia

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: AstraZeneca

Intervention

Keyword: AZD8233, Hyperlipidaemia, LDL-C, PCSK-9 targeted antisense oligonucleotide

Outcome measures

Primary outcome

- Primary safety and tolerability will be evaluated in terms of AEs, vital

signs, ECG, and clinical laboratory evaluations, including platelet count.

- Primary efficacy will be evaluated in terms of the relative change in serum

LDL-C from baseline to the end of Week 28.

Secondary outcome

- Secondary efficacy will be evaluated in terms of the relative change in PCSK9

from baseline to the end of Week 28.

- Secondary PK: Model population PK parameters to be reported in a separate

report

- Secondary immunogenicity: Development of ADA (anti-drug antibodies) and titre

(if participants are ADA positive) during treatment and follow-up

Study description

Background summary

Elevated plasma LDL-C, is a main risk factor for cardiovascular disease and is typically caused by a combination of environmental and genetic factors. Statin

therapy is the standard lipid lowering medication for both primary and secondary prevention of cardiovascular disease. Reduction of LDL-C by statins leads to a significant reduction in cardiovascular events. Statins reduce LDL-C by inhibiting HMG CoA reductase, the rate limiting enzyme of hepatic cholesterol synthesis. However, despite the substantial benefits of statin therapy, many patients do not reach LDL-C target goals.
Genetic studies have identified PCSK9 as an important HMG-CoA-independent circulating regulator of LDL-C. Circulating PCSK9 is derived mainly from the liver and increases LDL-C by promoting degradation of hepatic LDL receptors. Gain of function mutations in PCSK9 cause familial dominant hypercholesterolemia; loss of function is associated with low circulating levels of LDL-C and a reduced risk of major vascular events.
Based on the significant clinical benefit of PCSK9 inhibition, AstraZeneca is developing a human PCSK9-targeted, GalNAc conjugated ASO that specifically inhibits PCSK9 expression in the liver. Severe, reversible thrombocytopenia has been observed in some ASO programs in clinical trials, but it is not known whether all members of the class have this characteristic (Crooke et al 2017). This study will evaluate platelet count, over time, in AZD8233-treated participants with hyperlipidaemia, receiving maximally tolerated statin and/or ezetimibe therapy, compared with placebo. The aim of the study is to see if any thrombocytopenia signal is observed, and whether it is feasible to reduce platelet monitoring frequency and maintain patient safety. AZD8233 may provide novel treatment options for patients with hyperlipidaemia.

Study objective

To assess the safety and tolerability of AZD8233 as compared with placebo in participants with hyperlipidaemia receiving maximally tolerated statin and/or ezetimibe therapy as defined by the investigator.

Study design

This is a randomised parallel, double blind, placebo controlled Phase 2b study to evaluate the safety and tolerability of AZD8233 as compared with placebo. The study is planned to be carried out across approximately 100 clinical sites in around 8 countries. Approximately 376 participants with hyperlipidaemia will be randomly assigned to AZD8233 60 mg or matching placebo in a 1:1 ratio. Participants will be treated with AZD8233 or placebo SC, Q4W for 28 weeks, to provide data to guide platelet monitoring for future programs. The aim is that, of the participants randomised to AZD8233 doses, at least 150 should complete the 28 weeks of planned treatment. The effect of AZD8233 60 mg, administered SC, Q4W for 28 weeks, on concentrations of LDL-C in serum will also be evaluated.
There will be an initial screening period starting up to 28 days before and ending on the day before the randomisation visit (ie, Day -1). The study is divided into a planned treatment period of 28 weeks followed by a safety

follow-up of 12 weeks. Overall, this makes a total study participation time of 40 weeks once participants are randomly assigned into the trial.

Intervention

The intervention group receives AZD8233 60 mg, administered SC, Q4W for 28 weeks. The placebo group receives placebo, administered SC, Q4W for 28 weeks.

Study burden and risks

Potential risks of AZD8233 are as follows: (please refer to Clinical Study Protocol Table 2 for complete overview and mitigation strategy)
- Thrombocytopenia
- Kidney injury
- Liver Toxicity - Transaminase Elevations
- Anti-drug Antibodies
- Injection Site Reactions
- Complement Activation
- Inhibition of Intrinsic Coagulation Pathway
- Hypersensitivity and Anaphylactic Reaction
- Flu-like Reactions
- Pain near SC injection site

AZD8233 is expected to lower circulating PCSK9 in this study in all AZD8233-treated participants (see Protocol Section 4.3). Pharmacologic inhibition of PCSK9 is known to increase catabolism of LDL-C and reduce circulating LDL-C. Low levels of LDL-C are associated with a lower risk of incident atherosclerotic CVD events, providing an important clinical benefit to individuals with hyperlipidaemia. A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD8233 is provided in the IB.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with AZD8233 are justified by the anticipated benefits that may be afforded to participants with hyperlipidaemia. Furthermore, findings from this study may serve to ameliorate the perception of risk potentially associated with AZD8233 around thrombocytopenia and guide recommendations for monitoring.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Participant must be 18 to 75 years of age, inclusive, at the time of signing the informed consent
- Participants who have a fasting LDL-C >= 70 mg/dL (1.8 mmol/L) but < 190 mg/dL (4.9 mmol/L) at screening
- Participants who have fasting triglycerides < 400 mg/dL (< 4.52 mmol/L) at screening
- Participants are receiving a stable dose (>= 3 months) of maximally tolerated statin and/or ezetimibe therapy at screening
- Male or female of non-childbearing potential
- Signed and dated written informed consent prior to any mandatory study specific procedures, sampling, and analyses

Exclusion criteria

- eGFR < 40 mL/min/1.73m2 using the CKD-EPI
- History or presence of gastrointestinal, hepatic or renal disease or any other conditions known to interfere with absorption, distribution, metabolism or excretion of drugs

- Any uncontrolled or serious disease, or any medical (eg,. known major active infection or major haematological, renal, metabolic, gastrointestinal or endocrine dysfunction) or surgical condition that, in the opinion of the investigator, may either interfere with participation in the clinical study and/or put the participant at significant risk (according to the investigator's judgment) if he/she participates in the clinical study
- Poorly controlled T2DM, defined as HbA1c > 10%
- Acute ischaemic cardiovascular events including stroke within 30 days, or heart failure with New York Heart Association (NYHA) Class III to IV
- Blood dyscrasias with increased risk of bleeding including idiopathic thrombocytopenic purpura and thrombotic thrombocytopenic purpura or symptoms of increased risk of bleeding (frequent bleeding gums or nose bleeds)
- High-risk of bleeding diathesis or anti-platelet therapy other than low dose aspirin (<=100mg/day).
- Malignancy within the last 10 years
- Recipient of any major organ transplant
- LDL or plasma apheresis within 12 months prior to randomisation
- Uncontrolled hypertension defined as average supine SBP > 160 mmHg or DBP > 90 mmHg
- Heart rate after 10 minutes supine rest < 50 or > 100 bpm
- Any laboratory values with the following deviations at the Screening Visit; test may be repeated at the discretion of the investigator if abnormal:
• Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus (HIV)
• ALT > 1.5 × ULN
• AST > 1.5 × ULN
• TBL > ULN
• ALP > 1.5 × ULN
• WBC < lower limit of normal (LLN).
• Haemoglobin < 12 g/dL in males or < 11 g/dL in females
• Platelet count <= LLN
• aPTT > ULN or Prothrombin Time > ULN
• UACR > 11 mg/mmol (100 mg/g)
• UPCR > 300 mg/g
-Any clinically important abnormalities in rhythm, conduction or morphology of the resting ECG and any clinically important abnormalities in the 12-lead ECG
-QTcF > 470 ms; high degree atrioventricular (AV)-block grade II-III and sinus node dysfunction with significant sinus pause untreated with pacemaker; and cardiac tachyarrhythmias
- History of drug and/or alcohol abuse or a positive screen for drugs of abuse
- use of warfarin, direct or indirect thrombin inhibitors or factor Xa inhibitors
- Mipomersen, or lomitapide within 12 months prior to randomisation
- Any fibrate therapy other than fenofibrate; if the participant is on fenofibrate therapy, the dose should be stable for at least 6 weeks prior to randomisation
- Previous administration of AZD8233/AZD6615) or inclisiran (LEQVIO ® Novartis)

- Use of evolocumab (REPATHA® Amgen) and alirocumab (PRALUENT® Regeneron) within 3 months of screening

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-08-2021
Enrollment:	35
Type:	Actual

Ethics review

Approved WMO Date:	20-05-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	04-08-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	25-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-005845-18-NL
CCMO	NL77542.000.21

Study results

Date completed:	11-07-2022
Actual enrolment:	26

Summary results
Trial is onging in other countries