A 12-week, multi-center, double-blinded, parallelgroup, randomized, placebo-controlled phase IIb study to evaluate the safety, tolerability and efficacy of IZD334 to reduce CRP in cardiovascular high-risk patients.

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To evaluate the safety, tolerability and efficacy of IZD334 to reduce CRP in cardiovascular high-risk patients.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON49686

Source
ToetsingOnline

Brief title
IZD334-002

Condition

- Coronary artery disorders

Synonym
artherosclerosis; coronary artery disease (CAD)

Research involving
Human

Sponsors and support

Primary sponsor: Inflazome Ltd.
Source(s) of monetary or material Support: Inflazome Ltd.

Intervention

Keyword: cardiovascular high-risk, c-reactive protein CRP

Outcome measures

Primary outcome

To assess the safety and tolerability of oral IZD334 in patients with high

cardiovascular risk

To evaluate the efficacy of IZD334 measuring the percent change from baseline

of 450mg IZD334 compared to placebo in plasma CRP after 12 weeks of treatment

Secondary outcome

To evaluate the percent change from baseline of 150mg IZD334 compared to

placebo in plasma CRP after 12 weeks of treatment

To evaluate the percent change from baseline of 50mg IZD334 compared to placebo

in plasma CRP after 12 weeks of treatment

To evaluate the percentage of participants achieving a reduction from baseline

in plasma CRP to <2 mg/L with 450mg IZD334 compared to placebo after 12 weeks

of treatment

To evaluate the percentage of participants achieving a reduction from baseline

in plasma CRP to <2 mg/L with 150mg IZD334 compared to placebo after 12 weeks

of treatment

To evaluate the percentage of participants achieving a reduction from baseline

in plasma CRP to <2 mg/L with 50mg IZD334 compared to placebo after 12 weeks of

treatment

Exploratory objectives:

To characterize the pharmacokinetics (PK) of IZD334

To evaluate levels of inflammatory biomarkers in plasma (such as IL-6, IL-1b,

IL-18, ASC, caspase-1 and TNFa)

To explore biomarkers of cardiac damage, glucose and lipid meta

To explore responder analysis based on IL-1b genetic pattern

Study description

Background summary

Coronary Artery Disease (CAD) develops when coronary arteries become too narrow. The coronary arteries are the blood vessels that supply oxygen and blood to the heart. CAD is usually caused by hardening of the arteries, creating plaques.
Plaques cause the arteries to narrow and this results in reducing the blood and oxygen flow to the heart. Patients with hardening of the arteries are at high risk of developing major cardiovascular events, including heart attack and stroke. Such events can lead to death.
IZD334 is expected to stop and prevent hardening of the arteries. IZD334 is expected to reduce the risk of future occurrence of major cardiovascular events in patients with a coronary arterial disease.
Inflammation triggers the liver to produce certain proteins, so called c-reactive proteins (CRP). Measuring the CRP level in the blood is a non-specific indicator to detect inflammation and to evaluate the severity of it.

Study objective

To evaluate the safety, tolerability and efficacy of IZD334 to reduce CRP in cardiovascular high-risk patients.

Study design

The study will explore three dose levels of IZD334 compared to placebo to lower

plasma CRP levels in high-risk CV patients over 12 weeks of treatment, followed by a 4-week follow-up period.
During the treatment period patients will visit the study centre 6 times and will receive study treatment or placebo for the period until the next visit.
Both study drug and placebo come in capsules. Patients are instructed to take 3 capsules daily by mouth in the morning 1 hour before breakfast. This is a double-blind study, which means that neither the patient, nor the investigator will know which group the patient is in.

Intervention

In this study patients will receive study drug IZD334 or placebo for 12 weeks. A placebo looks identical to the study drug but does not contain any active ingredient. Patients have equal chance to be randomized in 1 of 4 treatment groups:
* IZD334 50mg
* IZD334 150mg
* IZD334 450mg
* Placebo

Study burden and risks

Inflammation driven by IL-1b has been shown to be an independent risk factor for atherosclerotic diseases and major cardiovascular events. Given that canakinumab, by inhibiting IL-1b, demonstrated a risk-reduction in the large outcome trial CANTOS, it is expected that a NLRP3 inhibitor is similarly effective. The fact that IZD334 also inhibits IL-18 production may add additional value over canakinumab. It is further assumed that IZD334 lacks an increased risk of severe infectious episodes during long-term treatment. In addition, IZD334 is free of major drug-drug interaction issues and the drug may be admimistered as a once daily oral therapy. This makes IZD334 an attractive novel drug for the patient population of interest. The herein proposed study has been designed as a multi-center, randomized, parallel group, placebo controlled, double-blind trial to provide evidence on dose-dependent effects of IZD334 on surrogate markers of cardiovascular risk such as CRP and to study the safety and tolerability profile in the target population over 12 weeks of treatment. The safety and tolerability profile of IZD334 was found to be unremarkable during phase I clinical testing in human subjects exposed at the highest dose of 450 mg qd for one week. The proposed treatment duration of 12 weeks in light of a favourable safety profile as determined in 13 week toxicology studies in rats and monkeys with exposure levels above those predicted under the highest dose of 450 mg QD seems justifiable. Further, PK/PD modelling data derived from the first in man study in healthy subjects allowed to propose a dose-rationale.
In summary, the benefit-risk assessment is considered positive and supportive of conducting the herein proposed study in patients with CAD and increased

systemic inflammation.

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

1. Signed and dated informed consent form obtained before any study assessment is performed
2. Male or female patients aged *18 years
3. Stable coronary artery disease (CAD) where stable coronary artery disease refers to any of the following:
a. a reversible supply/demand mismatch related to ischemia or
b. a history of myocardial infarction (minimum 30 days prior to randomization) or
c. the presence of coronary artery plaque of any severity documented by cardiac

catheterization or computed tomography angiography.
Patients are considered stable if they are asymptomatic or their symptoms are adequately controlled by medications or revascularization.
4. Elevated plasma CRP level of * 2 mg/L at screening visit 1 (local lab) and confirmed at screening visit 2 by central lab
5. Negative pregnancy test for females of child-bearing potential (premenopausal, * 2 years post-menopausal, not surgically sterile)
6. Stable concomitant medication for at least 4 weeks prior to randomization
7. Patients with creatinine clearance * 30 mL/min/1.73m2 by the MDRD (modification of diet in renal disease) equation may be included

Exclusion criteria

1. Any use of NSAIDs or steroids or cholchicine or anti-IL-1 inhibitors within 4 weeks prior to randomization (ASS 100mg as part of SOC treatment is allowed / topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted)
2. Any investigational drugs or participation in a clinical trial within 4 weeks or five half-lives (whichever is longer) prior to randomization
3. Active systemic infections (other than common cold) during the two weeks prior to randomization
4. Positive test for hepatitis B virus surface antigen (HBsAg) or Hepatitis C virus RNA at screening
5. Positive test for HIV at screening
6. History of severe hypersensitivity according to the investigator*s judgement to previous drugs of similar chemical classes
7. Any severe, progressive or uncontrolled medical condition at baseline that in the judgment of the investigator prevents the patient from participating in the study including uncontrolled hypertension, uncontrolled diabetes and severe hepatic disease
8. Symptomatic patients with Class IV heart failure (HF) (New York Heart Association)
9. Planned Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG)
10. Any clinically significant abnormal laboratory tests at screening
11. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial
12. Inability or unwillingness to undergo repeated venipunctures (e.g., due to poor tolerability or lack of access to veins)
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (HCG) laboratory test (> 5 mIU/mL)
14. Women of childbearing potential unwilling or unable to practice effective

method of contraception

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:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	132
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	IZD334
Generic name:	IZD334

Ethics review

Approved WMO Date:	10-06-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2020
Application type:	First submission

Review commission: METC Amsterdam UMC

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	EUCTR2020-000942-32-NL
CCMO	NL73726.018.20