A randomized double-blind, placebo-controlled, multicenter trial assessing the impact of lipoprotein (a) lowering with pelacarsen (TQJ230) on major cardiovascular events in patients with established cardiovascular disease (CVD).

Published: 09-12-2019
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This study has been transitioned to CTIS with ID 2023-508292-37-00 check the CTIS register for the current data. The study has two primary objectives addressing the same scientific hypothesis: one in the full study population who is at a high risk...

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

Summary

ID

NL-OMON56054

Source
ToetsingOnline

Brief title
CTQJ230A12301 trial

Condition

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

Synonym

increased lipoprotein(a), Major Adverse Cardiovascular Events (MACE)

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: cardiovascular disease, lipoprotein(a), Pelacarsen, risk reduction

Outcome measures

Primary outcome

The primary objectives of this study is to demonstrate the superiority of pelecarsen (TQJ230) compared to placebo in reducing the risk of expanded MACE (cardiovascular death, non-fatal MI, non-fatal stroke and urgent coronary re-vascularization requiring hospitalization) in 1) the overall study population with established CVD (Lp(a) >= 70 mg/dL) and/or 2) in a subpopulation with established CVD and Lp(a) >= 90 mg/dL.

See protocol 2 (p.22-23)

Secondary outcome

In the overall trial population and in the subpopulation (>= 90 mg/dL):

Demonstrate the superiority of pelacarsen (TQJ230) compared to placebo in reducing the risk of the MACE composite of CV death, non-fatal MI and non-fatal stroke.

Demonstrate the superiority of pelacarsen (TQJ230) compared to placebo in

reducing the risk of the composite of coronary heart disease (CHD) outcomes:

death due to CHD, non-fatal MI and urgent coronary re-vascularization requiring

hospitalization.

Demonstrate the superiority of pelacarsen (TQJ230) compared to placebo in

lowering the Lp(a) level at 1 year.

Evaluate the rate of all cause death.

See protocol 2 (p.23)

Study description

Background summary

Lipoprotein(a) [Lp(a)] is a lipoprotein in which the apolipoprotein B (apoB) component of lowdensity lipoprotein (LDL) is linked by a disulfide bond to apolipoprotein(a) (apo[a]) (Willeit et al 2018). Its level in humans is genetically determined and elevated levels are recognized as an independent risk factor for cardiovascular disease (CVD) (Kamstrup et al 2009, Nordestgaard et al 2010). Elevated baseline and on-statin Lp(a) were found to be independently and approximately linearly related with CVD risk, with 31% to 43%, respectively, increased risk for patients with Lp(a) 50 mg/dL or higher (Willeit et al 2018). Although screening for elevated Lp(a) is currently recommended by several scientific and medical societies, there is no specific drug treatment approved to reduce cardiovascular (CV) risk through lowering Lp(a) (Anderson et al 2016 Catapano et al 2016). Considering the magnitude of the CV risk born by patients with elevated Lp(a) it is imperative to develop new treatments which can address this unmet medical need. Such treatments should provide robust Lp(a) lowering as the clinical benefit of lowering Lp(a) is likely to be proportional to the absolute reduction in Lp(a) concentration (Burgess et al 2018). Antisense oligonucleotides (ASOs) are emerging as therapeutic agents to treat disorders where overexpression of proteins is associated with a disease process. Apolipoprotein (a) is synthesized primarily in the liver, a target organ for ASOs, where it is subsequently covalently linked to the apoB-100 component of LDL to form the Lp(a) lipoprotein. The goal of treatment with pelacarsen (TQJ230) is to reduce the production of apo(a) in the liver and thus, the level of Lp(a) lipoprotein, by using an ASO directed against the mRNA of apo(a). It has been hypothesized that a pharmacologic reduction in Lp(a) could slow down or reverse cardiovascular disease by reducing the thrombotic, atherogenic, or inflammatory effects of elevated Lp(a) levels (Nordestgaard et al 2010). The results from the Phase 2 dose-response study indicate that TQJ230 is able to achieve dose-dependent reductions in Lp(a) level up to 75,1 mg/dL from a

mean 99,3 mg/dL with the highest dose, 20 mg QW s.c. Treatment with pelacarsen (TQJ230) was also associated with dose-dependent statistically significant reductions in apoB, oxidized phospholipids (OxPL)-apo(a) and OxPL-apoB in all (aside from the lowest dose 20 mg Q4W) pelacarsen (TQJ230) -treated cohorts, compared to pooled placebo group. The most efficacious cohort, 20 mg QW, achieved 24%, 62%, and 89% decrease from baseline at the primary endpoint analysis compared to pooled placebo for apoB, OxPL-apo(a), and OxPL-apoB, respectively. In conclusion, the efficacy data generated to date indicate that the drug is potent enough to improve CV outcomes in patients with elevated Lp(a). The most noteworthy safety finding with administration of TQJ230 or similar ASOs in nonclinical studies was thrombocytopenia (Henry et al 2017). In the Phase 2 program, there were no clinically meaningful TQJ230-related changes in platelet counts in humans at doses ranging from 20 mg Q4W to 20 mg QW (total dose ranging from 260 to 1040 mg) relative to placebo. The intensive monitoring of platelet counts in the Phase 2b study did not show a dose-response for a decrease in platelets and no patient had confirmed decrease in platelet count below 100,000/mm3. There was no imbalance in the incidence of any two occurrences of platelet counts < 140,000/mm3 between any of the individual pelacarsen (TQJ230) treatment groups or pooled pelacarsen (TQJ230) groups, and pooled placebo. There was no imbalance in the overall incidence of bleeding episodes. There were no clinically significant differences in the incidence of liver function tests (LFTs) increases, mean serum creatinine or eGFR over time between treatment groups in the Phase 2b study. Overall, pelacarsen (TQJ230) has shown an acceptable safety and tolerability profile to support further development in a phase 3 study. Additional details on the efficacy and safety of pelacarsen (TQJ230) are available in the Investigator Brochure (IB). Rationale for the selected dose, 80 mg s.c. QM is provided in Section 4.2. Study TQJ230A12301 is planned to investigate if treatment with pelacarsen (TQJ230) 80 mg QM vs placebo reduces major adverse cardiovascular events (MACE) and characterize further the safety profile of the drug. See protocol 1 (p.21-22)

Study objective

This study has been transitioned to CTIS with ID 2023-508292-37-00 check the CTIS register for the current data.

The study has two primary objectives addressing the same scientific hypothesis: one in the full study population who is at a high risk of a CV event, and the other one in a subpopulation expected to be at higher risk, i.e patients with Lp(a) value >= 90 mg/dL. Successful achievement of the primary objectives requires meeting one of the two, or both primary objectives. An independent Clinical Endpoint Committee (CEC) will adjudicate all primary and secondary endpoints. Definitions of all endpoints will be included in the CEC Charter and Endpoints Manual, which will be provided to CEC and investigators, respectively.

See protocol 2 (p.22)

Study design

CTQJ230A12301 is a randomized, double- blind, parallel group,

placebo-controlled, multicenter study comparing pelacarsen (TQJ230) 80 mg s.c. QM to placebo in subjects with established CVD as evidenced by history of myocardial infarction, history of ischemic stroke or symptomatic peripheral artery disease (PAD) and elevated levels of Lp(a). Recruitment will target approximately 30% of randomized subjects to have had index myocardial infarction (Section 5.1) between >= 3 month and approximately 12 months prior to Randomization.
The study consists of a screening period of approximately 30 days, followed by a period of CV risk factor therapy optimization of approximately 30-90 days, if required, and a double-blind treatment period. The minimum follow-up in double-blind period is required to be 2.5 years,
the overall trial duration is expected to be approximately 4.25 years during which 993 primary endpoint events are expected to accumulate (Figure 3-1). The study will end when either 993 CEC confirmed primary CV events have accumulated or all subjects have had at least 2.5 years of follow-up time - whatever comes later.

See protocol 3 (p.24-25)

Intervention

Subjects will be randomized 1:1 to administer subcutaneous injections of pelacarsen (TQJ230) 80 mg or placebo QM. Injections will be self-injected or administered by a caregiver with the injection device TQJ230 Needle Safety Device (NSD), or by the study site personnel. For details on how injections should be performed, please refer to Section 6.7.2. Instructions for prescribing and taking the study treatment.

See protocol 6 (p.33)

Study burden and risks

The risk of developing thrombocytopenia was identified during administration of pelacarsen (TQJ230) or similar ASOs in nonclinical studies. However, exposure to pelacarsen) (TQJ230) for up to 12 months in the phase 2b study and intensive monitoring of platelet count did not show any confirmed decrease in platelets below 100,000/mm3, nor was there an imbalance in the incidence of any two occurrences of platelet counts < 140,000/mm3 between pelacarsen (TQJ230) treatment groups, including the highest dose pelacarsen (TQJ230) 20 mg QW, and pooled placebo. While 80 mg QM was not directly evaluated in the phase 2b study (20mg QW was evaluated), it is re-assuring that safety margins for the exposure to pelacarsen (TQJ230) 80 mg QM are well below the NOAEL in chronic monkey studies (Section 4.2). To ensure that regular follow-up is performed during the initial period after initiation of treatment with the study drug, platelet count will be monitored on monthly intervals during the first 6 months. This will be followed by monitoring every 3 months up to the end of year 2, and every 6 months thereafter up to the end of the study. If thrombocytopenia occurs, and depending on its severity and/or occurence of bleeding events, respective rules for individual

dose interruptions or permanent drug discontinuation are defined (Table 6-3), and possible treatment of severe events is recommended in Section 6.6.2. An independent Data Monitoring Committee (DMC) will review the safety data periodically, including changes in platelet counts and bleeding episodes, and can suggest changes in the frequency of platelet monitoring. Local injection site reactions, local erythema and bruising, were reported in the phase 2b study; however only one patient discontinued treatment due to this. To minimize the impact of frequent injections, patients in study CTQJ230A12301 will inject study drug every month. In case such events occur, possible treatment is recommended in Section 6.6.2. Specific dose-limiting toxicity definitions concerning the potential risks of liver events, and flu-like reactions, with guidance for required follow-up and discontinuation of study drug, are included in this protocol (Table 6-3). Immunogenicity responses were observed in the phase 2b study, in which among 239 subjects treated with pelacarsen, 100 (41.8%) subjects tested positive for ADA, 137 (57.3%) subjects tested negative, and 2 (0.8%) subjects were unknown. The incidence of ADA was observed to be dose-dependent. The median time of onset was 1 to 3 months, with no clear relationship to dose. The phase 2b data does not suggest a potential issue with ADA as the presence of ADA had minimal impact on steady-state PK parameters and was not associated with loss of efficacy or increases of safety findings. For detailed information on immunogenicity, please consult the most recent version of the Investigator*s Brochure. The long-term effect of ADA will be evaluated in this protocol in the ADA sub-study (Section 8.5.2). Hypersensitivity, including anaphylaxis to the study drug, has been reported during this ongoing study (CTQJ230A12301) and is established as an important identified risk. In case a hypersensitivity reaction occurs, guidance for its handling and management are provided in Section 6.5.2, Table 6-3, Section 6.6.2, Section 6.7.2.2 and subject*s updated informed consent form (ICF). Guidance for prophylaxis and management of specific adverse events (AEs) are provided in Section 6.6.2. For detailed information about potential and identified safety risk please consult the most recent version of the Investigator*s Brochure. Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study. The benefit a patient might have by participating in the study is the close monitoring of their condition and optimization of treatment of known risk factors during the full duration of the study. In general, the risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, as well as periodic review of all safety data by an independent DMC. While patients with underlying CV disease have an increased risk for unfavorable outcomes (e.g. respiratory failure, death) after contracting COVID-19, the risk of being exposed to SARSCoV-2 can be mitigated, if the measures recommended or enforced by national and/or local authorities are followed. It is considered, that if the study level and the population- level requirements are followed, the pandemics-related risk of a patient participating in the study should not exceed the risk of a patient with a similar condition not participating in the study.

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

- Lp(a) >= 70 mg/dL at the screening visit
- Optimal LDL-cholesterol lowering treatment
- Optimal treatment of other CV risk factors
- Myocardial infarction: >= 3 months to <= 10 years prior to the screening visit and randomization visit
- Ischemic stroke: >= 3 months to <= 10 years prior to the screening visit and randomization visit
- Clinically significant symptomatic peripheral artery disease

Exclusion criteria

1) Uncontrolled hypertension
2) Treatment with a PCSK9 inhibitor within 12 weeks before randomization
3) Treatment with lipoprotein apheresis
4) Myocardial infarction, stroke, coronary or lower limb re-vascularization, major cardiac or non-cardiac surgery within 3 months of screening and randomization.
5) Heart failure New York Heart Association (NYHA) class IV
6) History of hemorrhagic stroke or other major bleeding
7) Severe concomitant non-CV disease that is expected to reduce life expectancy to less than 5 years, at Screening or at Randomization visit
8) Pregnant or nursing woman

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-06-2020
Enrollment:	410
Type:	Actual

Ethics review

Approved WMO

Date:	09-12-2019
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-04-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	15-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-10-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	06-01-2023
Application type:	Amendment
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Application type:	Amendment
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Approved WMO Date:	07-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
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Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-05-2023
Application type:	Amendment
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Approved WMO Date:	15-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-08-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2023

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-12-2023
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
Other	NCT04023552
EU-CTR	CTIS2023-508292-37-00
EudraCT	EUCTR2019-001076-11-NL
CCMO	NL71559.000.19