Pemafibrate to Reduce cardiovascular OutcoMes by reducing triglycerides IN patiENts with diabeTes

Published: 07-02-2017
Last updated: 15-04-2024

The primary scientific aim of the PROMINENT study is to assess whether treatment with the selective peroxisome proliferator activated receptor modulator alpha (SPPARM-α), pemafibrate, will prevent myocardial infarction (MI), ischemic stroke,...

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

Summary

ID

NL-OMON53131

Source
ToetsingOnline

Brief title
PROMINENT

Condition

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

Synonym
heart and vascular disease, increased TriGluceridеglyceride (type of fat)

Research involving
Human

Sponsors and support

Primary sponsor: Kowa Research Institute, Inc.

Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Cardiovascular, Efficacy, Pemafibrate, Safety

Outcome measures

Primary outcome

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the clinical composite endpoint of:

• Nonfatal MI

• Nonfatal ischemic stroke

• Coronary revascularization

• Cardiovascular death

Secondary outcome

The group A (clinical) endpoints are time to first occurrence of:

-The 4-component composite endpoint of non-fatal MI, non-fatal ischemic stroke, hospitalization for unstable angina requiring unplanned ischemic stroke, hospitalization for unstable angina requiring unplanned coronary revascularization or cardiovascular death

- The 3-component composite endpoint of non-fatal MI, non-fatal ischemic stroke, or cardiovascular death

-Any component of the primary endpoint or hospitalization for HF

-Any component of the primary endpoint or all-cause mortality

-Any component of the primary endpoint, any coronary revascularization, or hospitalization for HF

-Any new or worsening PAD, defined as incidence of lower extremity

revascularization, intermittent claudication, rest pain, lower extremity ischemic ulceration, or major amputation with either ankle-brachial index <= 0.9 or other diagnostic testing (eg, toe-brachial index, angiogram, or other imaging study)

- Time of first occurrence of individual endpoints and an analysis of total events (evaluating time to occurrence of the first and all recurrent nonfatal MI, non-fatal ischemic stroke, coronary revascularization, or cardiovascular death).
- Additionally, as a prespecified secondary analysis, evidence of any genetic effect modification that may relate to pemafibrate and incident cardiovascular events will be evaluated. In particular, whether the effect of pemafibrate as compared with placebo on cardiovascular events differs according to known genetic polymorphisms in the PPARA gene (such as, but not limited to rs6008845), will be assessed.

The group B (lipid) endpoints are:

• The change from Screening/Enrollment Visit (Visit 1) to Month 4 Visit (Visit 5) for the following lipid biomarkers: TC, TG, HDL-C, non-HDL-C (calculated), VLDL-C (calculated), ApoA1, ApoC3, and ApoE; and

• The change from Randomization Visit (Visit 2) to Month 6 Visit (Visit 6) for non-fasting remnant cholesterol

* VLDL-C will be calculated as TC minus HDL-C minus LDL-C, where LDL-C is measured by a direct homogenous method.

Tertiary Efficacy Endpoints:

Tertiary endpoints include microvascular endpoints (ie, diabetic retinopathy and diabetic nephropathy as defined below) as well as exploratory mechanistic studies evaluating differences in average achieved levels and change from baseline between pemafibrate and placebo arms in:

• Core lipid parameters (total cohort): TG, HDL-C, calculated and directly measured LDL-C, calculated VLDL C and non-HDL C, TC, ApoB, ApoE, and directly measured remnant cholesterol

• Advanced lipid parameters (total cohort): ApoA1, ApoC3, LDL-C by beta quantification (PUC), lipoprotein particles (nuclear magnetic resonance [NMR] size, concentrations, and subfractions), HDL-TG and LDL-TG by PUC, and directly measured sdLDL-C and LDL-TG

• Inflammatory and glycemic parameters (total cohort): hsCRP, fasting glucose, HbA1c, and FGF-21

• Expanded exploratory lipid and non-lipid parameters (US/Canada subcohort): ApoA5, ApoB48, ANGPTL3, ANGPTL4, PCSK9 mass, CK-18, and type IV collagen

Microvascular endpoints will also be examined. These will include diabetic retinopathy, defined as use of retinal laser treatment, anti-vascular endothelial growth factor therapy, or vitrectomy due to development of and/or deterioration in diabetic retinopathy and blindness; and diabetic nephropathy, defined as an increase in microalbumin/creatinine ratio to > 30 mg/g among those without microalbuminuria at baseline, or categorical change from baseline albuminuria (normo-, micro-, or macroalbuminuria), doubling of creatinine from baseline, creatinine level > 6.0 mg/dL, eGFR < 15 mL/min/1.73 m2, or initiation

of renal replacement therapy (dialysis or transplant) among all participants.

Study description

Background summary

Treatment of dyslipidemia for cardiovascular disease (CVD) prevention has traditionally focused on mitigating the atherogenic potential of elevated low-density lipoprotein cholesterol (LDL-C), which today is the chief lipid target in clinical practice. While statins are the mainstay of therapy for lowering LDL-C in the majority of patients, many individuals retain a high CVD risk despite achieving LDL-C goals.
In efforts to ameliorate this residual CVD risk, the last decade in lipid research has been dominated by investigations into the potential added vascular benefits of raising high-density lipoprotein cholesterol (HDL-C). However, despite seemingly concordant in vitro and in vivo experimental data, consistent evidentiary support for the pharmacologic strategy of raising plasma HDL-C levels is currently lacking. Indeed, results from several recent interventional trials with a cholesteryl ester transfer protein inhibitor or with nicotinic acid to increase HDL-C levels have failed to show a reduction in cardiovascular (CV) events, and low HDL-C remains a potent marker of increased vascular risk after statin therapy8 and improving HDL functionality may ultimately prove to be a promising therapeutic strategy.
As described below, the recognition that hypertriglyceridemia (HTG) commonly accompanies low HDL-C, a plausible pathobiology, associative prospective epidemiologic data, showing consistent benefits in subgroup analyses of completed triglyceride (TG) reduction trials, and more recent Mendelian randomization and other genetic studies supporting a causal link have all fueled renewed interest in HTG as a secondary lipid target, especially in the context of type 2 diabetes (T2D).
Yet, no clinical trial has examined the effect of TG reduction on hard CVD outcomes among patients most likely to benefit, that is, those with established dyslipidemia (elevated TG and low HDL-C). This knowledge gap is especially disconcerting, given that mean TG levels have risen in the United States (US), as elsewhere, along with the growing global pandemic of obesity and T2D.

Study objective

The primary scientific aim of the PROMINENT study is to assess whether treatment with the selective peroxisome proliferator activated receptor modulator alpha (SPPARM-α), pemafibrate, will prevent myocardial infarction (MI), ischemic stroke, coronary revascularization, and cardiovascular (CV) death in adults with type 2 diabetes (T2D) who have elevated triglycerides (TG) and low highdensity lipoprotein cholesterol (HDL-C) levels and are at high risk

for future CV events.

Specifically, the primary objective of the study is to determine whether pemafibrate administered at a dose of 0.2 mg twice daily will delay the time to first occurrence of any component of the clinical composite endpoint of:
• nonfatal MI;
• nonfatal ischemic stroke;
• coronary revascularization; or
• CV death.

The secondary scientific aim of this study is to investigate 1) the efficacy (time to first occurrence) of a number of secondary CV and diabetes related vascular and nonvascular endpoints in the study population, and 2) the efficacy (as measured by the percent change from baseline) for a number of lipid measures.

Study design

The (PROMINENT) study is a randomized, double-blind, placebo-controlled, international study evaluating the ability of Pemafibrate to prevent CV events among 10,000 male and female adults with T2D and moderate hypertriglyceridemia with low HDL-C, on background moderate- to high-intensity statin therapy. PROMINENT will be conducted in 20-25 countries to ensure generalizability and allow for the enrollment and follow-up period to complete in approximately 5 years.
The study is event-driven such that after 1,092 events have been confirmed, with a minimum of 200 events accrued in women.

This study will include the following: a Pre-Screening Visit (Visit 0), a Screening/Enrollment Visit (Visit 1), a 21-day (maximum 35 day) Placebo Run-In Period, a Randomization Visit (Visit 2), a Treatment Period consisting of approximately 30 visits (post-randomization Visits 3 through 33, as applicable), a Common Study End Date (CSED) Visit, and a Post-Study Safety Call.

Participants who continue to be eligible, are compliant with medication during the Placebo Run In Period, and have completed submission of relevant medical records will return for the Randomization Visit (Visit 2; Week 0) to be randomly allocated in a 1:1 ratio to receive either pemafibrate at a dose of 0.2 mg twice daily or a matching placebo tablet to be taken twice daily

Throughout the treatment period, beginning with Month 10 (Visit 8), telephone visits will alternate with in-person visits occurring approximately every 2 months after Month 10
At the Months 2, 4 and 12 visits, at annual visits thereafter and at the CSED Visit, fasting blood samples and urine sample will be collected for safety and efficacy assessments. After Month 12, blood samples will also be collected for

safety assessment (chemistry panel only) at each intervening in-person visit

Participants will be followed for an average period of approximately 4 years after randomization (estimated study duration: 5 years). Participants who discontinue their medication for any reason and are not able to recommence therapy should still continue to be followed for the collection of data and samples.

Intervention

Patients will be randomized 1:1 to receive either double-blind Pemafibrate 0.2 mg or placebo twice a day. The estimated enrollment period is approximately 30 months. It is estimated the mean treatment duration will be approximately 48 months (4 years), and some patients remaining in the study for up to approximately 60 months (5 years). at least 1,092 participants who meet a component of the primary endpoint are required, with a minimum of 200 events accrued in women. Depending on the rates of accumulating endpoints in this study, the study duration may be shorter or longer.

Study burden and risks

Subject participation in the study will be approximately 4 years. The exact duration of the study will be determined during the study, but will be approximately 5 years.

Subjects are asked to take either Pemafibrate or placebo twice a day.

Subjects participating in this study are expected to visit the study center maximun of 20 times. After visit 11, the subject is expected to come every 4 months. The subject will be contacted by phone to assess how they are doing. Whenever the subject stops the study medication, he/she will have an end of treatment or Early Termination visit.

For some of the blood tests, it is recommended that the subject fasts for at least 8 hours before coming to the study center. This involves visits 1,1.1, 2, 4, 5, 9, 11 and from than once a year.

Female patients of childbearing potential must agree to use effective contraception.

There may be risks involved in taking this study drug (for side effects see E9) that have (not) been identified in the studies completed so far.

Taking part in this study does not guarantee that the subject will receive any medical benefit. However the subjects cardiovascular risk may be reduced as a result of taking part in this study. The close medical attention the subject

gets during the study may result in him/her gaining new information about his/her health which may provide benefits for his/her general health and wellbeing.

Contacts

Public
Kowa Research Institute, Inc.

430 Davis Dr. Suite 200
Morrisville NC27560
US
Scientific
Kowa Research Institute, Inc.

430 Davis Dr. Suite 200
Morrisville NC27560
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Fasting TG >= 200 mg/dL (2.26 mmol/L) and < 500 mg/dL (5.65 mmol/L) at Visit 1 (Screening/Enrollment Visit) or Visit 1.1 (Retest)
2. HDL-C <= 40 mg/dL (1.03 mmol/L) at Visit 1 (Screening/Enrollment Visit) or Visit 1.1 (Retest)
3. Type 2 diabetes of longer than 12 weeks duration documented in medical records, for example: local laboratory evidence through medical record review of elevated HbA1c (>= 6.5% [48 mmol/mol]), elevated plasma glucose (fasting >=

126 mg/dL [7.0 mmol/L], 2-hour >= 200mg/dL [11.1 mmol/L] during oral glucose tolerance testing, or random value >= 200 mg/dL with classic symptoms, or currently taking medication for treatment of diabetes; AND either
a) Age >= 50 years if male or >= 55 years if female (primary prevention cohort); OR
b) Age >= 18 years and established systemic atherosclerosis (secondary prevention cohort), defined as any 1 of the following:
i. Prior MI or ischemic (non-hemorrhagic) stroke
ii. Coronary angiographic lesion of >= 60% stenosis in a major epicardial vessel or >= 50% left main stenosis
iii. Asymptomatic carotid disease with >= 70% carotid artery stenosis
iv. Symptomatic carotid disease with >= 50% carotid artery stenosis
v. Symptomatic lower extremity peripheral artery disease (PAD) (ie, intermittent claudication, rest pain, lower extremity ischemic ulceration, or major amputation with either ankle brachial index <= 0.9 or other diagnostic testing [eg, toe-brachial index, angiogram, or other imaging study])
vi. Prior arterial revascularization procedure (including coronary,carotid, or peripheral angioplasty/stenting, bypass, or atherectomy/endarterectomy)
4. In addition, by Visit 1 (Screening/Enrollment Visit), participants must be either:
a) Receiving treatment with a stable dose (ie, for at least 12 weeks) of a qualifying moderate- to high intensity statin (atorvastatin >= 40 mg/day, rosuvastatin >= 20 mg/day, simvastatin >= 40 mg/day*, or pitavastatin 4 mg/day); or
b) Have evidence of LDL-C <= 70 mg/dL (1.81 mmol/L) by local laboratory determination within the previous 12 months#, or
c) Statin intolerant+ and have evidence of LDL-C <= 100 mg/dL (2.59 mmol/L) by local laboratory determination within the previous 12 months.
* Participants enrolled on simvastatin > 40 mg/day must have been taking and tolerating that dose for at least 12 months.
# If untreated or on stable dosing (ie, for at least 12 weeks) of another lipid-lowering regimen that may include a statin with or without ezetimibe and/or a PCSK9 inhibitor
+ Statin intolerance is defined as: the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that begins or increases during statin therapy and stops when statin therapy is discontinued. Participants not receiving a daily regimen of a statin (e.g., 1-3 times weekly) could also be considered "statin intolerant" if they cannot tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size, and the criteria outlined above are also met.
5. Ability to understand and comply with study procedures and give written informed consent.

Exclusion criteria

1. Current or planned use of fibrates or agents with potent peroxisome proliferator activated receptor (PPAR)-α agonist activity (eg, saroglitazar) within 6 weeks (42 days) of Visit 1 (Screening/Enrollment Visit). Note: PPAR-γ agonists (eg, glizatones such as pioglitazone and rosiglitazone) are allowed
2. Known sensitivity to PPAR-α agonists or tablet excipients
3. Initiation of, or change in, current TG-lowering therapy within 12 weeks of Visit 1 (if applicable). Note: TG-lowering therapy is defined as niacin > 100 mg/day or dietary supplements or prescription omega-3 fatty acids > 1 g/day
4. Type 1 diabetes mellitus
5.Uncontrolled diabetes mellitus as defined by a HbA1c > 9.5% [80 mmol/mol] at Visit 1 (Screening/Enrollment Visit)
6.Untreated or inadequately treated hypothyroidism [thyroid stimulating hormone (TSH) > 2.0 X the upper limit of normal (ULN) or free thyroxine (T4) <= the lower limit of normal] or hyperthyroidism; controlled thyroid disease (permitted) requires normal TSH and stable therapy for at least 4 weeks
7. Recent CVD event (eg, MI or stroke) within 8 weeks of Visit 2 (Randomization Visit)
8. Recent or planned vascular intervention within 8 weeks of Visit 2
9. New York Heart Association Class IV heart failure (HF)
10. Known homozygous familial hypercholesterolemia (heterozygous is permitted) or familial hypoalphalipoproteinemia
11.Documented previous occurrence of myositis/myopathy
12.Unexplained creatine kinase (CK) > 5 X ULN
13.Liver disease defined as cirrhosis or Child-Pugh class B and C, or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 X ULN
14.Biliary obstruction or hyperbilirubinemia (ie, total bilirubin > 2 X ULN, except with a documented diagnosis of Gilbert's disease)
15.Chronic renal insufficiency, defined by an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m2 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or kidney transplant, regardless of renal function
16.Unexplained anemia (hematocrit <= 30%)
17.Uncontrolled hypertension (seated systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg) at Visit 2 (Randomization Visit).
18.History of chronic active hepatitis B or hepatitis C, or known infection with HIV; participants with documented hepatitis C resolution after treatment are permitted
19.Active malignancy, except non-melanoma skin cancer or carcinoma in situ of the cervix, within the last 2 years.
20.Prior organ transplant or any condition likely to lead to organ transplantation in the next 5 years
21.Current or anticipated chronic use of cyclosporine, rifampicin, or other inhibitors of organic anion transporting polypeptides (OATP)1B1, or OATP1B3
22.History of alcoholism or unwillingness to limit alcohol intake to < 15

alcoholic beverages (or units) per week or < 5 alcoholic beverages (or units) during a single occasion for men and < 8 alcoholic beverages (or units) per week or < 4 alcoholic beverages (or units) during a single occasion for women during the study period. Note: One alcoholic beverage (unit) is defined as 12 oz. (350 mL) of beer, 5 oz. (150 mL) of wine, or 1.5 oz. (45 mL) of liquor
23.History of hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
24.Women who are pregnant, lactating, planning to be pregnant or lactating during the study period, or WOCP who are not using an acceptable method of contraception
25.A medical condition, other than vascular disease, with life expectancy < 3 years, which might prevent the participant from completing the study
26.Any factors likely to limit adherence to the study medications and procedures, such as substance abuse, dementia, plans to move within the next 2 years, and/or history of noncompliance with medication or scheduled appointments, and
27.Participation in another clinical study at the time of informed consent, or has received an investigational drug within 90 days before signing the informed consent for this study.

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:	Recruitment stopped
Start date (anticipated):	28-08-2017
Enrollment:	231
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PEMAFIBRATE
Generic name:	SPPARM-&alfa;

Ethics review

Approved WMO Date:	07-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2018
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	06-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-003818-26-NL
ClinicalTrials.gov	NCT03071692
CCMO	NL60527.056.17