A Phase 2, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 in Patients With Heterozygous Familial Hypercholesterolemia

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lipid metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON45499

Source
ToetsingOnline

Brief title
MGL9606

Condition

- Lipid metabolism disorders

Synonym
Heterozygous Familial Hypercholesterolemia

Research involving
Human

Sponsors and support

Primary sponsor: Madrigal Pharmaceuticals, Inc.

Source(s) of monetary or material Support: Madrigal Pharmaceuticals;Inc.

Intervention

Keyword: Heterozygous Familial Hypercholesterolemia (HeFH), LDL-C, MGL-3196

Outcome measures

Primary outcome

The primary efficacy parameter is mean percent change from baseline in LDL-C.

Secondary outcome

The secondary efficacy parameters include the following:

o Mean percent change from baseline in non-HDL-C, ApoB, TC/HDL-C ratio,

triglycerides,

lipoprotein(a), ApoA1/ApoB ratio, and lipoprotein particle assessment; and

o Absolute percent change from baseline in LDL-C.

Safety variables to be assessed include safety laboratory tests, vital signs,

12-lead ECG with

rhythm strip, physical examinations, assessment of adverse events, and clinic

assessments.

Study description

Background summary

Despite advances in treatment, approximately 70% of high-risk cardiovascular (CV) patients do not achieve low-density lipoprotein cholesterol (LDL-C) goals, and as many as 10% of hypercholesterolemic patients do not tolerate statins.1,2 Elevated LDL-C levels are associated with CV disease, including myocardial infarctions and strokes, and drugs such as statins that lower LDL-C also reduce CV morbidity and mortality. Heterozygous familial hypercholesterolemia (HeFH)

and homozygous familial hypercholesterolemia (HoFH) are genetic disorders characterized by severe debilitating dyslipidemia and early onset CV disease. The prevalence of HeFH is estimated to be 1 in 500 and may be as high as 1 in 200. Despite treatment with newer therapies (ie, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) and standard care (which includes statins and ezetimibe), some HeFH patients are not achieving their LDL-C goal.3 MGL-3196 is a liver-directed, orally active, partial agonist for the thyroid hormone receptor (THR), with approximately 28-fold selectivity for the beta receptor compared to the active thyroid hormone, triiodothyronine (T3). Selectivity for a thyroid agonist at thyroid hormone receptor beta isoform (THR-*), the predominant liver thyroid hormone receptor, has the potential of providing metabolic benefits of thyroid hormone that are mediated in the liver, while avoiding unwanted systemic actions of thyroid hormone in heart and bone that are largely mediated through THR alpha (THR-*).4 Thyroxine (T4) via its active derivative, T3, provides beneficial metabolic effects on cholesterol, triglycerides, and liver triglyceride levels, primarily through action at the THR-*, the predominant hepatocyte THR.5,6,7,8,4 However, excessive levels of thyroid hormone can lead to adverse effects, particularly in the heart and bones that are primarily mediated by the THR- * receptor which is the major systemic thyroid hormone receptor.9,10 MGL-3196 is a selective THR-* agonist with actions in the liver that is designed to avoid those systemic actions mediated through THR- * and the central thyroid action suppression observed with previous analogues.

Study objective

The primary objective of this study is to determine the effect of once-daily oral MGL-3196 60 mg
or 100 mg versus placebo for 12 weeks on the percent change from baseline in low-density
lipoprotein cholesterol (LDL-C) in patients with HeFH.
The secondary objectives of this study are the following:
o To evaluate the safety profile, including any changes in thyroid axis hormones, and tolerability
of once-daily oral MGL-3196 60 mg or 100 mg versus placebo after 12 weeks in patients with
HeFH;
o To determine the effect of once-daily oral MGL-3196 60 mg or 100 mg versus placebo for
12 weeks on the percent change from baseline on the following assessments in patients with
HeFH:
o Non-high-density lipoprotein cholesterol (non-HDL-C),
o Apolipoprotein B (ApoB),
o Total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio,
o Triglycerides,
o Lipoprotein(a),

o Apolipoprotein A1 (ApoA1)/ApoB ratio, and
o Lipoprotein particle assessment; and
o To determine the effect of once-daily oral MGL-3196 60 mg or 100 mg versus placebo for
12 weeks on the absolute change from baseline in LDL-C in patients with HeFH.

Study design

This is a multi-center, double-blind, randomized, placebo-controlled study to evaluate the safety
and efficacy of MGL-3196 in patients with HeFH. Patients who qualify for study inclusion will
be randomized to receive one of three 12-week treatments: MGL-3196 60 mg, MGL-3196
100 mg, or placebo given orally once daily. Patients will self-administer MGL-3196 once daily
each morning, and their statin medication each evening, during the 12-week treatment period.
To participate in the study, patients must be diagnosed with HeFH using standard accepted
procedures and meet the study criteria. Patients must first provide written, informed consent and
then undergo screening procedures within 14 days prior to randomization.
Following randomization, patients will undergo a 12-week treatment period and will periodically
return to the study site (visits are planned at Weeks 2, 4, 8, 12 and 16) for assessment of vital signs
(oral temperature, pulse rate, respiratory rate, and seated blood pressure). Chemistry (including
calcium and phosphorus) and hematology will be assessed at all study visits; a 12-lead ECG will
be performed at all study visits; and coagulation and urinalysis will be performed at baseline and
end of study. At all study site visits, blood samples will be collected for the assessment of thyroid
hormone parameters including TSH, total triiodothyronine (T3) and thyroxine (T4), and free T3
(FT3) and FT4. Lipids (as described in the secondary objectives) will be assessed at all study visits
except for LDL particle analyses, which will be assessed at baseline, Week 12, and Week 16;
LDL-C will be determined by ultracentrifugation at baseline and Week 12. Other biomarker
assessments will include sex hormone-binding globulin (SHBG) and high-sensitivity C-reactive
protein (hsCRP), assessed at all study visits. Follicle-stimulating hormone (FSH), total and free

testosterone, luteinizing hormone (LH), creatine kinase MB isoenzyme (CKMB), troponin I,
reverse T3, fibrinogen, alkaline phosphatase (ALP) isoenzymes, procollagen type 1 N-terminal
propeptide (P1NP), and C-terminal telopeptide (CTX) will be assessed at baseline, Week 12, and
Week 16; free testosterone will be calculated from total testosterone, SHBG, and serum albumin.
Patients will be evaluated for adverse events throughout the study.
Following the first dose of MGL-3196 and thereafter, the dose of MGL-3196 will be down-titrated
if TSH is below the lower limit of normal (LLN) with a >50% change from baseline confirmed
on 2 consecutive assessments. Down-titrations will be as follows: the 100 mg dose would be
decreased to 60 mg. Following down-titration,
TSH testing will resume according to the schedule of procedures. A second down-titration is
permitted (eg,the 60 mg dose would be decreased to 40 mg). If TSH remains following the second decrease, the patient will be
discontinued from the study and Early Termination assessments will be performed. Dose increases
are not permitted.
A Data Safety Monitoring Board (DSMB) will oversee the study to ensure patient safety and to
advise if any dosing alterations are recommended. The DSMB will review safety including thyroid
hormone effects, liver-related events (ie, clinically meaningful elevations in liver enzymes ALT,
aspartate aminotransferase [AST], and bilirubin), and other efficacy (lipid parameters) and safety
data as needed. The DSMB will perform regularly scheduled reviews.

Intervention

MGL-3196 60 mg, MGL-3196 100 mg, or placebo given orally once daily.

Study burden and risks

Risks: possible side effects of the study medication Burden: blood draws, fasting state before each visit

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

Patients who meet all of the following criteria will be eligible to participate in the study:
1. Must be willing to participate in the study and provide written informed consent;
2. Male and female adults *18 years of age;
3. Female patients of child bearing potential with negative serum pregnancy (beta human chorionic gonadotropin) test who are not breastfeeding, do not plan to become pregnant during the study, and agree to use effective birth control (ie, condoms, diaphragm, non-hormonal intrauterine device [IUD], or sexual abstinence [only if this is in line with the patient*s current lifestyle]) throughout the study and for at least 1 month after study completion; hormonal contraception (estrogens stable *3 months) and hormonal IUDs are permitted if used with a secondary birth control measure (eg, condoms); OR female patients of non-child bearing potential (ie, surgically [bilateral oophorectomy, hysterectomy, or tubal ligation] or naturally sterile [>12 consecutive months without menses]); male patients who have sexual intercourse with a female partner of child bearing potential from the first dose of study drug until 1 month after study completion must either be surgically sterile (confirmed by documented azoospermia >90 days after the procedure) OR agree to use a condom with

spermicide. All male patients must agree not to donate sperm from the first dose of study drug until 1 month after study completion;
4. Must have a diagnosis of HeFH by genetic testing or by having met the diagnostic criteria for definite familial hypercholesterolemia outlined by the Simon Broome Register Group (Appendix C) or WHO/Dutch Lipid Network (score >8; Appendix D);
5. Must have a fasting LDL-C *2.6 mmol/L (100 mg/dL).
Any one of the following subgroups of patients with documented history of cardiovascular disease as outlined below can be included with a fasting LDL-C of * 1.8 mmol/L (70 mg/dL):
A) Coronary Artery Disease (CAD) including one or more of the following:
* Acute myocardial infarction (MI)
* Silent myocardial infarction
* Unstable angina
* Coronary revascularization procedure (e.g. percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG])
* Clinically significant CAD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging).
B) Previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin.
C) Peripheral arterial disease (one of the following criteria must be satisfied):
* Current intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) of presumed atherosclerotic origin together with ankle-brachial index equal to or less than 0.90 in either leg at rest, or
* History of intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) together with endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease,; or
* History of critical limb ischemia together with thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease.
6. Must be on a stable or maximally tolerated dose (*4 weeks prior to screening) of an approved statin (rosuvastatin *40 mg daily, atorvastatin *80 mg daily), with or without ezetimibe. Patients intolerant to statins are allowed. Refer to Section 1.2.1 Drug Interaction Studies with Statins for details.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation in the study:
1. Homozygous familial hypercholesterolemia;
2. Low-density lipoprotein (LDL) or plasma apheresis within 2 months prior to randomization;
3. New York Heart Association class III or IV heart failure, or known left ventricular ejection fraction <30%;
4. Uncontrolled cardiac arrhythmia, including confirmed QT interval corrected using Fridericia*s formula (QTcF) >450 msec for males and >470 msec for females at the screening electrocardiogram (ECG) assessment;
5. Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary

artery bypass graft, or stroke within 3 months prior to randomization;
6. Type 1 diabetes, or newly diagnosed or uncontrolled type 2 diabetes (hemoglobin A1c [HbA1c] >8%);
7. History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening; Note: Significant alcohol consumption is defined as average of >20 g/day in female patients and >30 g/day in male patients;
8. Hyperthyroidism;
9. Thyroid replacement therapy;
10. Hypothyroidism; Note: If TSH is up to 1.5 x ULN on screening with normal free T4, one repeat test is allowed to confirm the elevation in TSH. If TSH and free T4 are normal upon repeat testing, patient may be included. Patients with a history of thyroid hormone replacement therapy or patients who have discontinued thyroid hormone replacement therapy (including thyroxine) *2 months prior to randomization may be included in the study if this criterion is met;
11. Evidence of chronic liver disease;
12. Hepatitis B, as defined by the presence of hepatitis B surface antigen;
13. Hepatitis C, as defined by the presence of hepatitis C virus (HCV) antibody (anti-HCV) and HCV ribonucleic acid (RNA). Patients with positive anti-HCV who test negative for HCV RNA at screening will be allowed to participate in the study;
14. Serum alanine aminotransferase (ALT) >1.5 × ULN (one repeat allowed);
15. Estimated glomerular filtration rate <60 mL/min;
16. Creatine kinase >3 × ULN (one repeat allowed);
17. History of biliary diversion;
18. Positive for human immunodeficiency virus infection;
19. History of malignant hypertension;
20. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at screening or randomization and confirmed at an unscheduled visit;
21. Triglycerides >5.7 mmol/L (500 mg/dL) at screening and confirmed by repeat assessment;
22. Active, serious medical disease with likely life expectancy <2 years;
23. Active substance abuse, including inhaled or injection drugs within the year prior to screening;
24. Use of any excluded medications or procedures listed in Section 5.6.1;
25. Participation in an investigational new drug trial within the 30 days prior to randomization; or
26. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, or compromise the well-being of the patient

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:	Recruitment stopped
Start date (anticipated):	19-04-2017
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MGL-3196
Generic name:	MGL-3196

Ethics review

Approved WMO Date:	01-12-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2017
Application type:	Amendment
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	EUCTR2016-002315-17-NL
CCMO	NL58872.018.16

Study results

Date completed: 15-01-2018

Actual enrolment: 24

Summary results

Trial is onging in other countries