A Randomized, Double-blind, Placebo-controlled, Multicenter Long-term Safety and Tolerability Study of ETC 1002 in Patients with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

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Primary Safety:* To evaluate the long-term safety and tolerability of ETC 1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic…

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

Summary

ID

NL-OMON45821

Source
ToetsingOnline

Brief title
3481/0001 (Esperion 1002-040)
Clear Harmony

Condition

- Cardiac disorders, signs and symptoms NEC
- Lipid metabolism disorders

Synonym
cardiovascular disease; hyperlipidemia

Research involving
Human

Sponsors and support

Primary sponsor: Esperion Therapeutics Inc.
Source(s) of monetary or material Support: Esperion Therapeutics

Intervention

Keyword: Cardiovascular disease, Double blind, Hyperlipidemia, Phase 3, placebo controlled study, randomized

Outcome measures

Primary outcome

The primary endpoint for this study is general safety, which includes AEs,

clinical safety laboratories, PEs, vital signs, and ECGs.

The summarization of AEs will include only treatment-emergent AEs (TEAEs),

defined as AEs that begin or worsen after randomization and ingestion of the

first dose of study drug. TEAEs and SAEs will be summarized by system organ

class (SOC), severity, and relationship to study drug for each treatment

group. Deaths, withdrawal from study treatment due to AE's, and withdrawal

from the study due to AE's will be summarized by treatment group.

Clinical safety laboratories, including hematology, blood chemistry,

coagulation, HbA1C, glucose, and urinalysis; PE findings; vital signs; ECG

readings; and weight will be summarized by the value and by change from

baseline in the value (where appropriate) at each post-baseline time point.

Hepatic Safety

Liver-associated enzymes and total bilirubin (TB) will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal values for ALT, AST, and TB will be summarized. These summaries of patients with abnormal values will be performed overall; by normal baseline; and by abnormal baseline for each of ALT, AST, and TB. Hy*s law criteria (*3 × upper limit of normal [ULN] for either ALT or AST, with accompanying TB >2 × ULN) will also be applied to the data; any potential Hy*s law cases will be listed separately. In the case of patients with Gilbert*s disease, TB will be fractionated and the determination of 2 × ULN will be based upon direct (conjugated) bilirubin.

Musculoskeletal Safety

AEs of muscle related symptoms will be summarized by treatment group. CK levels will be summarized by the value and change from baseline in the value, by treatment group and visit. In addition, the number and percent of patients with abnormal CK values will be summarized. These summaries of patients with abnormal CK will be performed overall; by normal baseline CK; and by abnormal baseline CK.

Diabetes and Glycemia

Cases of new onset of diabetes will be recorded as AEs and will be summarized using the appropriate SOC. These events will be summarized by severity and relationship to study drug for each treatment group. Glucose and HbA1C will be

monitored at baseline and at Weeks 12, 24, and 52, and be summarized.

Renal Safety

Baseline estimated glomerular filtration rate (eGFR) will be summarized by treatment group for actual value and for baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group. Shift tables of urine protein (negative/positive) from baseline over the study, will be provided by treatment group. Values of CK over the study will be summarized by treatment group and by baseline eGFR category. Finally, muscle related AEs will be summarized by treatment group and by baseline eGFR category.

Clinical Endpoints

Clinical endpoints will be monitored and adjudicated by an independent blinded expert CEC for ongoing studies the ETC 1002 program. Adjudicated clinical endpoints will be summarized by event type and treatment group. Additional details regarding clinical endpoints and clinical endpoint definitions will be included in CEC charter.

Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms and will be performed by SOC, severity, and relationship to study drug

for each treatment group.

Secondary outcome

Key Efficacy Endpoints

Percent change from baseline to Week 12 or Week 24 in LDL C, non-HDL-C, TC, apoB, and hs-CRP will be analyzed using analysis of covariance (ANCOVA), with treatment and randomization strata (patient*s CV risk and baseline statin dose) as factors and respective baseline value as a covariate. The FAS will be used. Missing data for these endpoints will be imputed using multiple imputation taking account for treatment adherence.

Other Efficacy Endpoints- see the protocol.

Study description

Background summary

ETC 1002 is a first-in-class small molecule inhibitor of ACL, an enzyme upstream of HMG CoA in the cholesterol biosynthesis pathway. ETC 1002 is a prodrug that requires activation in liver to ETC 1002 coenzyme A (ETC 1002-CoA) which mediates competitive inhibition of ACL. Inhibition of ACL by ETC 1002-CoA decreases cholesterol synthesis in liver leading to increased LDL receptor (LDLR) expression and LDL particle clearance from the blood. Therefore, inhibition of ACL by ETC 1002-CoA reduces LDL C via the same pathway as HMG CoA reductase inhibition by statins.

An important differentiating feature of ETC 1002 is that it does not inhibit cholesterol synthesis in skeletal muscle. In addition to preliminary data suggesting that only minor amounts of ETC 1002 enter skeletal muscle (<5% of systemic exposure), skeletal muscle does not express the enzyme required to activate ETC 1002 to ETC 1002-CoA and inhibit ACL. Therefore, ETC 1002 is not anticipated to mediate the adverse effects associated with inhibition of biological intermediates within the cholesterol biosynthesis pathway in skeletal muscle.

ETC 1002 has been evaluated in 15 completed clinical studies (nine Phase 1 and six Phase 2, per February 2016) among over 700 subjects receiving ETC 1002 doses from 2.5 mg/day up to 240 mg/day (multiple doses) for up to 12 weeks. All multiple-dose studies have demonstrated consistent, clinically meaningful LDL C lowering with ETC 1002 treatment and have shown a positive safety profile. This is the first study with ETC-1002 as investigational product in Europe.

Study Hypothesis:
The primary clinical hypothesis is that long-term exposure of ETC 1002 will be safe and well tolerated in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately controlled with their maximally tolerated lipid-modifying therapy, including a maximally tolerated statin.

The study will characterize the long-term safety and tolerability of ETC 1002 versus placebo in addition to maximally tolerated lipid-lowering therapy, including a maximally tolerated statin, in patients with hyperlipidemia. The randomized, double-blind, placebo controlled add-on to maximally tolerated lipid-lowering therapy design will ensure that long-term safety data are meaningful and interpretable. The extended treatment duration (52 weeks) and large patient number (n = 1950) will provide robust long-term safety in high CV risk patients who have an unmet medical need for additional lipid-lowering therapy, such as ETC 1002 once daily, orally bioavailable option.

Study objective

Primary Safety:
* To evaluate the long-term safety and tolerability of ETC 1002 versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular diseases [ASCVD]) who are not adequately controlled with their maximally tolerated lipid-modifying therapy.

Secondary Efficacy:
* To assess percent change from baseline to Week 12 in low-density lipoprotein cholesterol (LDL C)

Tertiary Efficacy:
* To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid-lowering therapy
* To assess high-density lipoprotein cholesterol (HDL C), non-HDL C, total cholesterol (TC), and triglycerides (TG) values at Week 12, 24, and 52
* To assess apolipoprotein B (apoB) and high-sensitivity C reactive protein (hs CRP) values at Week 12, 24, and 52

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, study evaluating the long-term safety and tolerability of ETC 1002 in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies (eg, ezetimibe, fibrates [except gemfibrozil]). A patient*s maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient*s self-reported history of lipid-modifying therapy. However, patients who are currently taking simvastatin at average daily doses that are greater than 40 mg per day, or who are currently taking a PCSK9 inhibitor (alirocumab or evolocumab), or have taken a PCSK9 inhibitor within the past 4 weeks of Week -2 (Visit S1) will be excluded from enrolling in this study. PCSK9 inhibitors may be initiated as adjunctive therapy at Week 24 if the LDL C threshold criteria have been met as described in the protocol.

Screening (Visit S1) will occur approximately 2 weeks prior to Day 1 (Visit T1). Patients on maximally tolerated lipid-lowering therapy, as determined by the investigator, will be stratified based on the patient*s CV risk and baseline statin dose. There will be no cap placed on randomization into any particular stratum. Approximately 1950 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either ETC 1002 180 mg (n = 1300), or placebo (n = 650) once daily for 52 weeks. Randomized patients will continue in the study until they have completed Week 52 (Visit T7). Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), Week 12 (Visit T4), Week 24 (Visit T5), Week 36 (Visit T6), and Week 52 (Visit T7). Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule and procedures.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety data from this and other ongoing studies of ETC 1002.

Intervention

Approximately 1950 eligible patients will be randomized 2:1 on Day 1 to receive either ETC 1002 180 mg (n = 1300), or placebo (n = 650) once daily for 52 weeks. Randomized patients will continue in the study until they have completed Week 52. ETC 1002/placebo are film-coated tablets which will be taken by mouth once daily, with or without food.

Study burden and risks

To date, the nonclinical and clinical data indicate that ETC 1002 has a

favorable risk-benefit profile. The ability of ETC 1002 to achieve clinically meaningful LDL C-lowering responses while demonstrating a favorable tolerability profile in a variety of patient populations supports continued development of ETC 1002, an oral ACL inhibitor, in Phase 3 studies.

Please refer to the most recent IB for additional information regarding previous human experience.

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. Age *18 years or legal age of majority based on regional law, whichever is greater at Week -2 (Visit S1)
2. Men and non-pregnant, nonlactating women. Women must be either:

* Naturally postmenopausal or;
* Women of childbearing potential must be willing to use 1 acceptable method of birth control.
3. Fasting LDL-C at Week -2 (Visit S1) *70 mg/dL (1.8 mmol/L)
4. Have high cardiovascular risk that is defined as either:
* Diagnosis of HeFH
OR
* Have ASCVD (with established CHD or CHD risk equivalents) i.e. with:
*Acute myocardial infarction (MI)
*Silent MI
*Unstable angina
*Coronary revascularization procedure (e.g, percutaneous coronary intervention or coronary artery bypass graft surgery)
*Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)
Documented CHD risk equivalents (includes one or more of the following criteria):
*peripheral arterial disease
*previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. CT or MRI must have been performed to rule out hemorrhage and non-ischemic neurological disease
*Patients with Type 2 diabetes mellitus (T2DM) are allowed in this study, however for this study T2DM is not considered a CHD risk equivalent.
5. Be on maximally tolerated lipid-modifying therapy, including a maximally tolerated statin either alone or in combination with other lipid-lowering therapies, at a stable doses for at least 4 weeks prior to screening (6 weeks for fibrates, however, gemfibrozil is not allowed). Regimens other than daily dosing, including those at very low doses, are acceptable.
A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipidmodifying therapy.;For the complete list of inclusion and exclusion criteria, please refer to Section 7 of the protocol.

Exclusion criteria

1. Total fasting triglyceride *500 mg/dL (5.6 mmol/L) at Wk -2 /vS1;2. Renal dysfunction or nephritic syndrome or a history of nephritis, including eGFR (using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL / min/ 1.73m2 at Wk -2 /vS1
Note: At discretion of the investigator, the screening period may be extended up to 2 weeks for a single repeat eGFR. For those patients who have a repeat eGFR the repeat value will be used to determine eligibility.
Note: Also excluded are renally impaired patients receiving an average daily dose of simvastatin 40 mg with eGFR below <45 mL/min/1.73 m2.;3. Body mass index (BMI) *50 kg/m2;4. Concomitant use of simvastatin at average daily doses greater than 40 mg.;5.Concomitant use of a PCSK inhibitor (Praluent® [alirocumab] or Repatha®

[evolocumab]) at Week 2 (Visit S1) or prior use of a PCSK9 inhibitor within the past 4 weeks of Week 2 (Visit S1) will be excluded from this study.;6. Recent (within 3 months prior to the screening visit [Wk -2 /vS1] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack, endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the Investigator to be stable for the previous 3 months.;7.Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) *160 mmHg and diastolic blood pressure (DBP) *100 mmHg after sitting quietly for 5 minutes. ;8. Hemoglobin A1C (HbA1C) *10% at Wk -2 /vS1;9. Uncontrolled hypothyroidism, including thyroid-stimulating hormone >1.5 × the upper limit of normal (ULN) at Wk -2 /vS1. Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization are allowed.;10. Liver disease or dysfunction, including:
* Positive serology for hepatitis B surface antigen and/or hepatitis C antibodies at Wk -2 /vS1 or
* Alanine aminotransferase , aspartate aminotransferase *2 × ULN, and/or total bilirubin *1.2 × ULN at Wk -2 /vS1.;11. Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that may affect drug absorption;12. Hematologic or coagulation disorders or a hemoglobin (Hgb) level <10.0 g/dL (100 g/L) at Week 2 (Visit S1);13. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Patients with a history of non-metastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed);14. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK *3 × ULN prior to randomization.;15. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner can be enrolled after evaluation by the Investigator.;16. Blood donation, blood transfusion for any reason, participation in a clinical study with multiple blood draws, major trauma, or surgery with or without blood loss within 30 days prior to randomization;17. Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever is longer;18. Prior participation in a previous ETC-1002 clinical study. Prior participation in a clinical study with ETC-1002 is defined as having been enrolled in an ETC-1002 study.;19. Use of any of the following drugs within 3 months prior to screening or a plan to use these drugs during the study;
* New or planned dose changes of systemic corticosteroids
* Requirement for mipomersen or lomitapide or apheresis therapy;20. Planned initiation of the following drugs during the clinical trial or changes to the following drugs prior to randomization:
* Hormone replacement (6 weeks prior to randomization)
* Thyroid replacement (6 weeks prior to randomization)
* Diabetes medications (4 weeks prior to randomization)
* Obesity medication (3 months prior to randomization);21. An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-

Investigator, or Sponsor.;For the complete list of inclusion and exclusion criteria, please refer to Section 7 of the protocol.

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):	21-07-2016
Enrollment:	162
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ETC-1002
Generic name:	NA

Ethics review

Approved WMO

Date:	09-03-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	14-06-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-09-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-02-2017
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Not approved Date:	09-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	14-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2015-004136-36-NL
ClinicalTrials.gov	NCT02666664
CCMO	NL54734.100.15