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Safety, Tolerability and Efficacy of Microsomal Triglyceride Protein (MTP) Inhibitor

This study has been completed.

Sponsor:
Aegerion Pharmaceuticals, Inc.

Collaborators:
University of Pennsylvania
Doris Duke Charitable Foundation

Information provided by (Responsible Party):
Aegerion Pharmaceuticals, Inc.

ClinicalTrials.gov Identifier:
NCT01556906

First received: March 7, 2012
Last updated: April 4, 2013
Last verified: April 2013
History of Changes

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Purpose

The primary objective of this study is to evaluate the safety and tolerability of 4 doses of lomitapide (AEGR-733; BMS-201038) given as an initial low dose and then escalated through an additional 3 dose levels over a 16-week period.

The secondary objectives of this study included the evaluation of the pharmacodynamics of lomitapide based on:

- Percent change in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides, and very low density lipoprotein cholesterol (VLDL-C) concentrations at the end of each 4-week dosing period compared to the Baseline value of each parameter at the end of the previous dose phase(s).
- Changes in other plasma lipoproteins: apolipoproteins (apo B, apo AI, apo AII, apo CIII, apo E) and lipoprotein a [Lp(a)].

Condition	Intervention	Phase
Homozygous Familial Hypercholesterolemia	Drug: Lomitapide	Phase 2

Study Type: Interventional
Study Design: Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase II Open Label, Dose-Escalation Study to Determine the Safety, Tolerability and Efficacy of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor BMS-201038 in Patients With Homozygous Familial Hypercholeterolemia

Resource links provided by NLM:

Genetics Home Reference related topics: Chanarin-Dorfman syndrome cholesteryl ester storage disease hypercholesterolemia

MedlinePlus related topics: Cholesterol

Drug Information available for: Lomitapide

Genetic and Rare Diseases Information Center resources: Hyperlipoproteinemia Type 2 Sphingolipidosis

U.S. FDA Resources

Further study details as provided by Aegerion Pharmaceuticals, Inc.:

Primary Outcome Measures:

- LDL-C [Time Frame: Up to 16 weeks of treatment comapred to Baseline] [Designated as safety issue: No]

Percent change in LDL-C compared to Baseline.

Secondary Outcome Measures:

- Absolute Change From Baseline in Alanine Aminotransferase (ALT) [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute change from Baseline in ALT

- Absolute Change From Baseline in Aspartate Aminotransferase (AST) [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute change from Baseline in AST

- Absolute Change From Baseline in Total Bilirubin [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute change from Baseline in total bilirubin

- Absolute Change From Baseline in Hepatic Fat Percent [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute change from Baseline in hepatic fat percent

- Absolute Change From Baseline in Forced Expiratory Volume During 1 Second (FEV1) [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute change from Baseline in FEV1

- Absolute Change From Baseline in Carbon Monoxide Lung Diffusing Capacity (DLCO)(a Pulmonary Function Test) [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute change from Baseline in DLCO

- Absolute Change From Baseline in Vitamin A [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute change from Baseline in vitamin A

- Absolute Change From Baseline in Vitamin E [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute change from Baseline in vitamin E

- Absolute Change From Baseline in Vitamin D [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute Change From Baseline in Vitamin D

- Absolute Change From Baseline in Ratio of Vitamin E to Total Lipids [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute Change From Baseline in ratio of vitamin E to total lipids

- Absolute Change From Baseline in Alpha Linoleic Acid (ALA) [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute Change From Baseline in ALA

- Absolute Change From Baseline in Eicosapentaenoic Acid (EPA) [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute Change From Baseline in EPA

- Absolute Change From Baseline in Docosahexaenoic Acid (DHA) [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute Change From Baseline in DHA

- Absolute Change From Baseline in Linoleic Acid (LA) [Time Frame: Baseline and 16 weeks of treatment] [Designated as safety issue: Yes]

  Absolute Change From Baseline in LA

Enrollment: 6
Study Start Date: June 2003

Study Completion Date: February 2004
Primary Completion Date: February 2004 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Lomitapide This is an open label trial where all patients receive lomitapide (AEGR733/BMS-201038)at escalating doses	Drug: Lomitapide Oral administration with escalating doses administered once daily Other Names: • AEGR-733 • BMS-201038

Detailed Description:

This is a single center, open-label, Phase 2 clinical trial designed to evaluate the safety, tolerability, and pharmacodynamics of lomitapide in the treatment of patients with homozygous familial hypercholesterolemia (HoFH).

Patients are required to stop all lipid-lowering therapies, including apheresis, within 4 weeks prior to the Baseline visit and throughout the study. Patients are placed on a rigorous low-fat diet (<10% of energy from total dietary fat) at the Screening assessment; dietary counseling by a registered dietitian will be initiated at Screening and will continue at each subsequent study visit.

Patients initially receive 0.03 mg/kg of lomitapide orally every day for 4 weeks. Intra-patient dose escalation to 0.1 mg/kg, 0.3 mg/kg/day and 1.0 mg/kg/day occur every 4 weeks if specific protocol-defined stopping rules related to Grade 3 or 4 toxicities or serious adverse events (SAEs) do not apply.

The study includes 15 study visits over 22 weeks: a Screening visit (Visit 1) conducted within 2 weeks prior to dosing, a Baseline visit (Visit 2) conducted on Day 1 prior to the first dose, 12 visits conducted during the treatment period (Visits 3 through 14), and a Follow-up visit (Visit 15) conducted approximately 4 weeks after the last dose of lomitapide.

Screening and Baseline procedures include medical and medication history, physical examination, vital signs, 12-lead electrocardiogram (ECG), pulmonary function tests (PFTs), safety laboratory tests, fat soluble vitamin levels and a fatty acid profile. Nuclear magnetic resonance spectroscopy (NMRS) of the liver will be conducted at Baseline, at the end of each dosing period, and at the follow up visit to assess hepatic fat content. Baseline efficacy assessment includes a fasting lipid profile (TC, LDL-C [directly measured], VLDL-C, high density lipoprotein-cholesterol [HDL-C], triglycerides, and apolipoproteins [apo B, apo AI, apo AII, apo CIII, apo E] and Lp(a)).

Safety and lipid profile assessments are repeated during the treatment period and at the Follow-up visit conducted 28 days after the last dose of lomitapide.

Eligibility

Ages Eligible for Study: 13 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

1. Males and females ≥13 years of age
2. Clinical diagnosis of HoFH AND one of the following (a, b, or c):
   - Documented functional mutation in both LDL receptor alleles, OR
   - Skin fibroblast LDL receptor activity <20% of normal, OR
   - TC >500 mg/dL AND triglycerides < 300 mg/dL AND both parents with documented TC >250 mg/dL
3. Body weight ≥40 kg
4. Negative screening pregnancy test if female of child-bearing potential
5. Subjects must be willing and able to comply with all study-related procedures
6. Subjects must be willing and able to go off all lipid-lowering medications, dietary supplements (psyllium preparations) and LDL apheresis within 4 weeks prior to the Baseline visit until the end of the study.

Exclusion Criteria:

1. Uncontrolled hypertension defined as: systolic blood pressure >180 mmHg, diastolic blood pressure >95 mmHg
2. History of chronic renal insufficiency (serum creatinine >2.5 mg/dL)
3. History of liver disease or abnormal LFTs at screening (>3x upper limit of normal [ULN])
4. Any major surgical procedure occurring < 3 months prior to the screening visit
5. Cardiac insufficiency defined by the New York Heart Association classification as functional Class III or Class IV
6. History of a non-skin malignancy within the previous 5 years
7. History of alcohol or drug abuse

8. Participation in an investigational drug study within 6 weeks prior to the screening visit
9. Serious or unstable medical or psychological conditions that, in the opinion of the Investigator, would compromise the patient's safety or successful participation in the study.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01556906

Locations

United States, Pennsylvania

University of Pennsylvania
Philadelphia, Pennsylvania, United States, 19104

Sponsors and Collaborators

Aegerion Pharmaceuticals, Inc.

University of Pennsylvania

Doris Duke Charitable Foundation

Investigators

Principal Investigator: Dan J Rader, MD University of Pennsylvania

More Information

Publications:

Cuchel M, Bloedon LT, Szapary PO, Kolansky DM, Wolfe ML, Sarkis A, Millar JS, Ikewaki K, Siegelman ES, Gregg RE, Rader DJ. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007 Jan 11;356(2):148-56.

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Additional relevant MeSH terms:

Hypercholesterolemia	Hyperlipoproteinemias
Hyperlipoproteinemia Type II	Lipid Metabolism Disorders
Dyslipidemias	Lipid Metabolism, Inborn Errors
Genetic Diseases, Inborn	Metabolic Diseases
Hyperlipidemias	Metabolism, Inborn Errors

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