



## Clinical trial results:

### A Phase III Study of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor AEGR-733 in Patients with Homozygous Familial Hypercholesterolemia on Current Lipid-lowering Therapy

#### Summary

EudraCT number	2008-007058-36
Trial protocol	IT
Global end of trial date	13 October 2011

#### Results information

Result version number	v1 (current)
This version publication date	22 April 2018
First version publication date	22 April 2018

#### Trial information

##### Trial identification

Sponsor protocol code	AEGR-733-005
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00730236
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Aegerion Pharmaceuticals, Inc.
Sponsor organisation address	One Main Street, Suite 800, Cambridge, United States, 02142
Public contact	Agnieszka Jurecka, MD, PhD, Aegerion Pharmaceuticals, +1 857-242-5140, agnieszka.jurecka@aegerion.com
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Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 October 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 October 2011
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of lomitapide as defined by percent change from Baseline in LDL-C at the maximum tolerated dose after 26 weeks of treatment in combination with other lipid-lowering therapy in patients with HoFH.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, with Good Clinical Practice-International Conference on Harmonisation guidelines (GCP-ICH Consolidated Guideline) and with Directive 2001/20/EC. These practices included: IRB/IEC procedures, informed consent, protocol adherence, administrative documents, drug supply accountability, data collection, patient records (source documents), adverse event (AE) recording and reporting, inspection and audit preparation, and records retention. The Investigator was made aware that regulatory authorities and representatives of the Sponsor could inspect the documents and patient records at any time. All patient identities were kept confidential. Each patient was assigned a unique patient number, which in turn was used on the case report form (CRF) instead of the patient's name.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	South Africa: 11
Worldwide total number of subjects	29
EEA total number of subjects	6

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	29
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was performed from 18 Dec 2007 to 13 Oct 2011. A total of 11 medical clinics participated in the study.

### Pre-assignment

Screening details:

6-week Run-in Phase. Following screening, patients entered a 6-week Run-in Phase to stabilize their regimen of current lipid-lowering therapy(ies) and to be placed on a low-fat diet containing <20% energy from fat.

### Period 1

Period 1 title	Efficacy Phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Lomitapide escalated
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Arm description:

Lomitapide escalated with an initial oral dose of 5 mg/day for 2 weeks and then escalated at 4 week intervals to 60 mg/day. In rare situations (1 patient) who met strict safety and efficacy criteria could have their dose escalated to 80 mg/day.

Arm type	Experimental
Investigational medicinal product name	Lomitapide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

During the 26-week Efficacy Phase (Weeks 0 to 26), lomitapide capsules were administered orally once daily to all patients who met study entry criteria. The dose was initiated at 5 mg/day for 2 weeks; the dose of lomitapide was then escalated to 10 mg/day for 4 weeks and subsequently to 20, 40, and 60 mg/day at 4-week intervals unless specific stopping rules applied. In rare situations, patients who met strict safety and efficacy criteria could have their dose escalated to 80 mg.

Number of subjects in period 1	Lomitapide escalated
Started	29
Completed	23
Not completed	6
Consent withdrawn by subject	3
Adverse event, non-fatal	2
Non-compliance or lack of cooperation	1

**Period 2**

Period 2 title	Safety Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	Lomitapide escalated
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## Arm description:

Lomitapide escalated with an initial oral dose of 5 mg/day for 2 weeks and then escalated at 4 week intervals to 60 mg/day. In rare situations (1 patient) who met strict safety and efficacy criteria could have their dose escalated to 80 mg/day.

Arm type	Experimental
Investigational medicinal product name	Lomitapide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

## Dosage and administration details:

Following completion of the 26-week Efficacy Phase, patients entered the 52-week Safety Phase (Weeks 26 through 78) during which they received the maximum tolerated dose of lomitapide defined during the Efficacy Phase. Lomitapide capsules were administered orally once daily to all patients. During the Safety Phase, study drug dosage could be decreased if specific dose modification rules applied, but could not be increased above the highest dose administered during the Efficacy Phase.

<b>Number of subjects in period 2</b>	Lomitapide escalated
Started	23
Completed	23

## Baseline characteristics

### Reporting groups

Reporting group title	Efficacy Phase
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Reporting group description: -

Reporting group values	Efficacy Phase	Total	
Number of subjects	29	29	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	30.7		
standard deviation	± 10.64	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	16	16	
Race			
Units: Subjects			
Caucasian	25	25	
Asian	2	2	
African American	1	1	
Other	1	1	
Weight			
Units: kg			
arithmetic mean	73.5		
standard deviation	± 18.10	-	
BMI			
Units: 1 kg / m2			
arithmetic mean	25.8		
standard deviation	± 5.43	-	

## End points

### End points reporting groups

Reporting group title	Lomitapide escalated
Reporting group description: Lomitapide escalated with an initial oral dose of 5 mg/day for 2 weeks and then escalated at 4 week intervals to 60 mg/day. In rare situations (1 patient) who met strict safety and efficacy criteria could have their dose escalated to 80 mg/day.	
Reporting group title	Lomitapide escalated
Reporting group description: Lomitapide escalated with an initial oral dose of 5 mg/day for 2 weeks and then escalated at 4 week intervals to 60 mg/day. In rare situations (1 patient) who met strict safety and efficacy criteria could have their dose escalated to 80 mg/day.	

### Primary: Percent Change From Baseline in Low-density Lipoprotein Cholesterol (LDL-C)

End point title	Percent Change From Baseline in Low-density Lipoprotein Cholesterol (LDL-C) <sup>[1]</sup>
End point description: Percent change from Baseline in LDL-C	
End point type	Primary
End point timeframe: Baseline and Week 26	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The hypothesis of no mean percent change (and mean change) from baseline will be tested using a paired t-test (or Wilcoxon Signed Rank test, if the data are not normally distributed) at each visit.

End point values	Lomitapide escalated			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percent change				
arithmetic mean (standard deviation)	-40.1 (± 31.25)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Total Cholesterol (TC)

End point title	Percent Change From Baseline in Total Cholesterol (TC)
End point description: Percent change from Baseline in TC	
End point type	Secondary
End point timeframe: Baseline and Week 26	

End point values	Lomitapide escalated			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percent change				
arithmetic mean (standard deviation)	-36.4 (± 28.2)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline for Apolipoprotein B (Apo B)

End point title	Percent Change From Baseline for Apolipoprotein B (Apo B)
End point description:	Percent change from Baseline for Apo B
End point type	Secondary
End point timeframe:	Baseline and Week 26

End point values	Lomitapide escalated			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percent change				
arithmetic mean (standard deviation)	-39.4 (± 30.01)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Triglycerides

End point title	Percent Change From Baseline in Triglycerides
End point description:	Percent change from Baseline in triglycerides
End point type	Secondary
End point timeframe:	Baseline and Week 26



End point values	Lomitapide escalated			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percent change				
arithmetic mean (standard deviation)	-29.0 (± 55.72)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in Non-HDL-C

End point title	Percent Change From Baseline in Non-HDL-C
End point description:	Percent change from Baseline in non-HDL-C
End point type	Secondary
End point timeframe:	Baseline and Week 26

End point values	Lomitapide escalated			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: percent change				
arithmetic mean (standard deviation)	-40.0 (± 29.66)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent change from Baseline in very-low density lipoprotein (VLDL-C)

End point title	Percent change from Baseline in very-low density lipoprotein (VLDL-C)
End point description:	Percent change from Baseline in VLDL-C
End point type	Secondary
End point timeframe:	Baseline and Week 26

End point values	Lomitapide escalated			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Percent change				
arithmetic mean (standard deviation)	-28.6 (± 57.45)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent change in low-density lipoprotein-A (Lp(a))

End point title	Percent change in low-density lipoprotein-A (Lp(a))
End point description: Percent change from Baseline in Lp(a)	
End point type	Secondary
End point timeframe: Baseline and Week 26	

End point values	Lomitapide escalated			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Percent change				
arithmetic mean (standard deviation)	-11.0 (± 34.04)			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Week -2 to Week 78

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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### Reporting groups

Reporting group title	Safety Population
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Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 29 (10.34%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery arteriosclerosis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0		
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Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Safety Population		
Total subjects affected by non-serious adverse events subjects affected / exposed	27 / 29 (93.10%)		
Vascular disorders Hot flush subjects affected / exposed occurrences (all)  Hypertension subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2  2 / 29 (6.90%) 2		
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)	7 / 29 (24.14%) 8  5 / 29 (17.24%) 5  3 / 29 (10.34%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Epistaxis subjects affected / exposed occurrences (all)  Nasal congestion	2 / 29 (6.90%) 2  2 / 29 (6.90%) 3		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pharyngolarygeal Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 29 (10.34%)</p> <p>3</p> <p>4 / 29 (13.79%)</p> <p>5</p>		
<p>Psychiatric disorders</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>3</p> <p>2 / 29 (6.90%)</p> <p>2</p>		
<p>Investigations</p> <p>Alanine aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Aspartate aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Transaminases increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>5 / 29 (17.24%)</p> <p>7</p> <p>2 / 29 (6.90%)</p> <p>2</p> <p>2 / 29 (6.90%)</p> <p>3</p> <p>7 / 29 (24.14%)</p> <p>7</p>		
<p>Injury, poisoning and procedural complications</p> <p>Laceration</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Limb injury</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thermal burn</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 29 (6.90%)</p> <p>2</p> <p>2 / 29 (6.90%)</p> <p>2</p> <p>2 / 29 (6.90%)</p> <p>2</p>		
Cardiac disorders			

Angina pectoris subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Palpitations subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 6		
Headache subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3		
Paraesthesia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Lymphadenopathy subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	6 / 29 (20.69%) 6		
Abdominal distension subjects affected / exposed occurrences (all)	6 / 29 (20.69%) 14		
Abdominal pain subjects affected / exposed occurrences (all)	8 / 29 (27.59%) 13		

Abdominal pain upper			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	15		
Defaecation urgency			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	23 / 29 (79.31%)		
occurrences (all)	86		
Dyspepsia			
subjects affected / exposed	11 / 29 (37.93%)		
occurrences (all)	14		
Eructation			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	6 / 29 (20.69%)		
occurrences (all)	10		
Gastritis			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	5		
Gingivitis			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	19 / 29 (65.52%)		
occurrences (all)	53		
Rectal tenesmus			
subjects affected / exposed	3 / 29 (10.34%)		
occurrences (all)	4		

Vomiting subjects affected / exposed occurrences (all)	10 / 29 (34.48%) 33		
Stomach Discomfort subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 5		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Back pain subjects affected / exposed occurrences (all)	4 / 29 (13.79%) 4		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Myalgia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Pain in extremity subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3		
Gastroenteritis subjects affected / exposed occurrences (all)	4 / 29 (13.79%) 4		
Influenza subjects affected / exposed occurrences (all)	6 / 29 (20.69%) 6		



Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 29 (17.24%) 13		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2		

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported