



Clinical trial results:

Phase III, single-arm, open-label, international, multi-centre study to evaluate the efficacy and safety of lomitapide in paediatric patients with Homozygous Familial Hypercholesterolaemia (HoFH) on stable lipid-lowering therapy

Summary

EudraCT number	2019-002278-30
Trial protocol	DE IT
Global end of trial date	06 June 2024

Results information

Result version number	v1 (current)
This version publication date	21 December 2024
First version publication date	21 December 2024

Trial information

Trial identification

Sponsor protocol code	APH-19
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04681170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amryt Pharmaceuticals DAC
Sponsor organisation address	45 Mespil Road, Dublin 4, Ireland,
Public contact	Head of Clinical Operations, Amryt Pharmaceuticals DAC, 353 15180200, janet.boylan@amrytpharma.com
Scientific contact	Head of Clinical Operations, Amryt Pharmaceuticals DAC, 353 15180200, janet.boylan@amrytpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001124-PIP01-10
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2024
Global end of trial reached?	Yes
Global end of trial date	06 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lomitapide as defined by the percent change in low-density lipoprotein cholesterol (LDL-C) at the maximum tolerated dose (MTD) at Week 24±3 days (W24) compared to baseline when added to stable lipid-lowering therapy (LLT, including lipoprotein apheresis [LA] where applicable) in paediatric patients (5 to ≤17 years of age) 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 and with Good Clinical Practice (GCP) guidelines as denoted in the International Conference on Harmonization (ICH) E6 requirements. 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 record 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 subject identities were kept confidential. Each subject was assigned a unique subject number, which in turn was used in the electronic case report form (eCRF) instead of the subject's name.

Background therapy:

All subjects were required to complete a Run in Period of a minimum of 6 weeks. During the Run in period, subjects were stabilised on their current LLT (including LA, if applicable). Each subject was to remain on their stable LLT regimen (including LA, if applicable) during the 24 week Efficacy Phase. After 24 weeks, adjustments to background LLT (including LA, if applicable) were allowed for optimal standard of care at the discretion of the Investigator.

Evidence for comparator:

Not applicable

Actual start date of recruitment	14 December 2020
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	Saudi Arabia: 15
Country: Number of subjects enrolled	Tunisia: 7
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	46
EEA total number of subjects	21

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)	21
Adolescents (12-17 years)	25
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and female subjects aged 5 to ≤ 17 years with HoFH were enrolled in the trial at 12 study centres in various countries (3 in Germany, 1 in Israel, 2 in Italy, 2 in Saudi Arabia, 3 in Spain and 1 in Tunisia). The first patient first visit was 14 Dec 2020 and the last patient last visit was 06 Jun 2024.

Pre-assignment

Screening details:

Subjects underwent assessments to determine eligibility at the Initial Screening Visit (up to 12 weeks prior to Day 0).

A total of 46 subjects were enrolled in this study. Of these, 3 subjects were 'Run in' failures and did not complete the Run in Period.). Therefore, a total of 43 (93.5%) subjects entered the Efficacy Phase at Visit 4.

Period 1

Period 1 title	Pre-run in
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All patients from all age groups
Arm description: -	
Arm type	Main arm - screening phase - no IMP administrated
Investigational medicinal product name	Lomitapide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

In the screening phase no IMP has been administered.

Number of subjects in period 1	All patients from all age groups
Started	46
Completed	46

Period 2

Period 2 title	Stratified enrolment & run-in
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All age groups
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	All age groups
Started	46
Completed	43
Not completed	3
Consent withdrawn by subject	1
Death due to a non-treatment emergent AE	1
Protocol deviation	1

Period 3

Period 3 title	Open label efficacy phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	5-10 years

Arm description: -

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

Dosage and administration details:

Lomitapide capsules were provided in 4 dose strengths of 2 mg, 5 mg, 10 mg, and 20 mg and were administered orally once daily.

After stabilization of each subject on his/her current MTD of LLT (including LA, if applicable) during the 6 week Run in Period, treatment with lomitapide was started as add on therapy on Day 0 of the Efficacy Phase.

The dose was initiated at the recommended starting dose for the subject's age and escalated to the maximum dose applicable to their age as shown below based upon safety and tolerability in addition to LDL C values:

- 5-10 years old subjects: Starting dose 2 mg/day; MTD 20 mg/day

Arm title	11-17 years
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Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lomitapide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lomitapide capsules were provided in 4 dose strengths of 2 mg, 5 mg, 10 mg, and 20 mg and were administered orally once daily.

After stabilization of each subject on his/her current MTD of LLT (including LA, if applicable) during the 6 week Run in Period, treatment with lomitapide was started as add on therapy on Day 0 of the Efficacy Phase.

The dose was initiated at the recommended starting dose for the subject's age and escalated to the maximum dose applicable to their age as shown below based upon safety and tolerability in addition to LDL C values:

- 11-15 years old subjects: Starting dose 2 mg/day; MTD 40 mg/day
- 16-17 years old subjects: Starting dose 5 mg/day; MTD 60 mg/day

Arm title	All age groups
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lomitapide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Lomitapide capsules were provided in 4 dose strengths of 2 mg, 5 mg, 10 mg, and 20 mg and were administered orally once daily.

After stabilization of each subject on his/her current MTD of LLT (including LA, if applicable) during the 6 week Run in Period, treatment with lomitapide was started as add on therapy on Day 0 of the Efficacy Phase.

The dose was initiated at the recommended starting dose for the subject's age and escalated to the maximum dose applicable to their age as shown below based upon safety and tolerability in addition to LDL C values:

- 5-10 years old subjects: Starting dose 2 mg/day; MTD 20 mg/day
- 11-15 years old subjects: Starting dose 2 mg/day; MTD 40 mg/day
- 16-17 years old subjects: Starting dose 5 mg/day; MTD 60 mg/day

Number of subjects in period 3	5-10 years	11-17 years	All age groups
Started	20	23	43
Completed	20	21	41
Not completed	0	2	2
Adverse event, non-fatal	-	2	2

Period 4

Period 4 title	Open label safety phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	All age groups

Arm description: -

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

Dosage and administration details:

Each subject was to continue to receive their MTD of lomitapide achieved during the Efficacy Phase (unless criteria were met for reducing or increasing the dose) for an additional 80±1 weeks in the Safety Phase (for a total treatment period of 2 years).

Arm title	5-10 years
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Arm description: -

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

Dosage and administration details:

Each subject was to continue to receive their MTD of lomitapide achieved during the Efficacy Phase (unless criteria were met for reducing or increasing the dose) for an additional 80±1 weeks in the Safety Phase (for a total treatment period of 2 years).

Arm title	11-17 years
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Arm description: -

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

Dosage and administration details:

Each subject was to continue to receive their MTD of lomitapide achieved during the Efficacy Phase (unless criteria were met for reducing or increasing the dose) for an additional 80±1 weeks in the Safety Phase (for a total treatment period of 2 years).

Number of subjects in period 4	All age groups	5-10 years	11-17 years
Started	41	20	21
Completed	39	20	19
Not completed	2	0	2
Consent withdrawn by subject	1	-	1
AEs and none compliance	1	-	1

Baseline characteristics

Reporting groups

Reporting group title

Pre-run in

Reporting group description: -

Reporting group values	Pre-run in	Total	
Number of subjects	46	46	
Age categorical			
Units: Subjects			
5-10 years	21	21	
11-17 years	25	25	
Gender categorical			
Units: Subjects			
Female	25	25	
Male	21	21	

End points

End points reporting groups

Reporting group title	All patients from all age groups
Reporting group description: -	
Reporting group title	All age groups
Reporting group description: -	
Reporting group title	5-10 years
Reporting group description: -	
Reporting group title	11-17 years
Reporting group description: -	
Reporting group title	All age groups
Reporting group description: -	
Reporting group title	All age groups
Reporting group description: -	
Reporting group title	5-10 years
Reporting group description: -	
Reporting group title	11-17 years
Reporting group description: -	

Primary: LDL-C at Baseline and Week 24/LOCF

End point title	LDL-C at Baseline and Week 24/LOCF ^[1]
End point description:	
End point type	Primary
End point timeframe:	
Percent change from Baseline in LDL-C at Week 24±3 days.	

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: This was a single-arm study, no comparative group can be assigned; the comparison made is done only between baseline and Week 24. Analysis was made using the one-sample t-test to test the null hypothesis that the percentage change from Baseline was equal to zero against the alternative hypothesis that the percentage change from Baseline was not equal to zero.

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline	435.791 (± 189.4620)			
Week 24/LOCF	175.404 (± 89.8979)			
Change from Baseline	-260.386 (± 192.1284)			
Percent Change from Baseline	-53.910 (± 25.8287)			

Attachments (see zip file)	Waterfall Plot of Percentage Change from Baseline/Waterfall.
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in non-HDL-C from Baseline at Week 24/LOCF

End point title	Percent Change in non-HDL-C from Baseline at Week 24/LOCF
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End point description:

Analysis was made using the one-sample t-test to test the null hypothesis that the percentage change from Baseline was equal to zero against the alternative hypothesis that the percentage change from Baseline was not equal to zero.

End point type	Secondary
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End point timeframe:

Percent change from Baseline at Week 24±3 days for the lipid parameter non-HDL-C

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mg/dL				
arithmetic mean (standard deviation)				
Observed Value	183.632 (± 92.0566)			
Change from Baseline	-270.493 (± 194.7326)			
Percent Change from Baseline	-54.185 (± 25.0256)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in TC from Baseline at Week 24/LOCF

End point title	Percent Change in TC from Baseline at Week 24/LOCF
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End point description:

Analysis was made using the one-sample t-test to test the null hypothesis that the percentage change from Baseline was equal to zero against the alternative hypothesis that the percentage change from Baseline was not equal to zero.

End point type	Secondary
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End point timeframe:

Percent change from Baseline at Week 24±3 days for the lipid parameter TC

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mg/dL				
arithmetic mean (standard deviation)				
Observed Value	216.866 ($\pm$ 94.1528)			
Change from Baseline	-268.668 ($\pm$ 194.2576)			
Percent Change from Baseline	-50.176 ($\pm$ 24.5397)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in VLDL-C from Baseline at Week 24/LOCF

End point title	Percent Change in VLDL-C from Baseline at Week 24/LOCF
End point description:	
Analysis was made using the one-sample t-test to test the null hypothesis that the percentage change from Baseline was equal to zero against the alternative hypothesis that the percentage change from Baseline was not equal to zero.	
End point type	Secondary
End point timeframe:	
Percent change from Baseline at Week 24 $\pm$ 3 days for the lipid parameter VLDL-C	

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mg/dL				
arithmetic mean (standard deviation)				
Observed Value	8.344 ($\pm$ 4.7206)			
Change from Baseline	-9.981 ($\pm$ 8.1272)			
Percent Change from Baseline	-49.678 ($\pm$ 31.6126)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Apo B from Baseline at Week 24/LOCF

End point title	Percent Change in Apo B from Baseline at Week 24/LOCF
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End point description:

Analysis was made using the one-sample t-test to test the null hypothesis that the percentage change from Baseline was equal to zero against the alternative hypothesis that the percentage change from Baseline was not equal to zero.

End point type	Secondary
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End point timeframe:

Percent change from Baseline at Week 24±3 days for the lipid parameter Apo B

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mg/dL				
arithmetic mean (standard deviation)				
Observed Value	131.3 (± 62.59)			
Change from Baseline	-185.3 (± 130.66)			
Percent Change from Baseline	-53.1 (± 24.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Triglycerides from Baseline at Week 24/LOCF

End point title	Percent Change in Triglycerides from Baseline at Week 24/LOCF
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End point description:

Analysis was made using the one-sample t-test to test the null hypothesis that the percentage change from Baseline was equal to zero against the alternative hypothesis that the percentage change from Baseline was not equal to zero.

End point type	Secondary
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End point timeframe:

Percent change from Baseline at Week 24±3 days for the lipid parameter Triglycerides

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mg/dL				
arithmetic mean (standard deviation)				
Observed Value	42.068 (± 23.1235)			
Change from Baseline	-49.828 (± 40.4354)			

Percent Change from Baseline	-49.28 ($\pm$ 31.7290)			
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Lipid Parameter Lp(a) from Baseline at Week 24/LOCF

End point title	Percent Change in Lipid Parameter Lp(a) from Baseline at Week 24/LOCF
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End point description:

Analysis was made using the one-sample t-test to test the null hypothesis that the percentage change from Baseline was equal to zero against the alternative hypothesis that the percentage change from Baseline was not equal to zero.

End point type	Secondary
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End point timeframe:

Percent change from Baseline at Week 24 $\pm$ 3 days for the lipid parameter Lp(a)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: nmol/L				
arithmetic mean (standard deviation)				
Observed Value	82.493 ($\pm$ 75.5080)			
Change from Baseline	-47.383 ($\pm$ 59.2811)			
Percent Change from Baseline	-26.757 ($\pm$ 32.5675)			

Attachments (see zip file)	Change in Lp(a) (mg/dL vs. nmol/L)/Lp(a).pdf
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in LDL-C from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in LDL-C from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

From Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	-1.962 ($\pm$ 20.7168)			
Week 8	-6.798 ($\pm$ 19.1524)			
Week 12	-16.638 ($\pm$ 23.1978)			
Week 16	-36.458 ($\pm$ 17.9894)			
Week 20	-50.730 ($\pm$ 24.8321)			
Week 24	-54.602 ($\pm$ 26.4557)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in LDL-C from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in LDL-C from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Secondary
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End point timeframe:

From Baseline at All Other Time Points to Week 104 (refer also to the above-listed results covering the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-55.518 ($\pm$ 28.5714)			
Week 32	-52.126 ($\pm$ 28.7496)			

Week 36	-39.823 (± 32.6612)			
Week 40	-49.427 (± 29.5830)			
Week 44	-44.312 (± 30.3775)			
Week 48	-45.315 (± 29.6526)			
Week 52	-44.583 (± 32.8128)			
Week 56	-45.994 (± 34.3631)			
Week 68	-40.831 (± 37.3821)			
Week 80	-42.319 (± 34.9400)			
Week 92	-37.199 (± 39.6625)			
Week 104	-40.159 (± 30.5026)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in non-HDL-C from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in non-HDL-C from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in non-HDL-C from Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	-1.765 (± 21.1682)			
Week 8	-6.745 (± 18.6776)			
Week 12	-16.497 (± 22.9850)			
Week 16	-36.610 (± 17.4339)			

Week 20	-50.928 ($\pm$ 24.3958)			
Week 24	-55.033 ($\pm$ 25.4297)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in non-HDL-C from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in non-HDL-C from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in non-HDL-C from Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-55.984 ($\pm$ 27.5559)			
Week 32	-52.629 ($\pm$ 27.8748)			
Week 36	-40.574 ($\pm$ 31.4293)			
Week 40	-50.013 ($\pm$ 28.4878)			
Week 44	-44.702 ($\pm$ 29.8885)			
Week 48	-46.770 ($\pm$ 29.3974)			
Week 52	-45.222 ($\pm$ 31.9577)			
Week 56	-46.558 ($\pm$ 33.4734)			
Week 68	-41.576 ($\pm$ 36.0854)			
Week 80	-42.388 ($\pm$ 34.3439)			
Week 92	-37.755 ($\pm$ 38.4243)			
Week 104	-40.511 ($\pm$ 30.1102)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in TC from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in TC from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in TC from Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	-2.057 (± 19.3772)			
Week 8	-6.970 (± 17.6904)			
Week 12	-15.961 (± 21.4313)			
Week 16	-33.976 (± 15.7159)			
Week 20	-48.177 (± 23.2987)			
Week 24	-50.922 (± 24.9738)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in TC from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in TC from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in TC from Baseline at All Other Time Points to Week 104 (refer also to the above-listed results covering the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-51.998 (± 26.9668)			
Week 32	-48.945 (± 26.2375)			
Week 36	-40.643 (± 30.5125)			
Week 40	-45.402 (± 27.5358)			
Week 44	-41.443 (± 28.3745)			
Week 48	-44.164 (± 27.6987)			
Week 52	-42.764 (± 30.6617)			
Week 56	-43.234 (± 31.3599)			
Week 68	-39.672 (± 33.2025)			
Week 80	-40.291 (± 31.9119)			
Week 92	-34.946 (± 35.8485)			
Week 104	-36.017 (± 32.2354)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in VLDL-C from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in VLDL-C from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in VLDL-C from Baseline at All Other Time Points to Week 104 (refer also to the below-

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	9.770 ($\pm$ 42.2029)			
Week 8	2.857 ($\pm$ 34.5887)			
Week 12	-7.405 ($\pm$ 48.8428)			
Week 16	-34.706 ($\pm$ 31.6590)			
Week 20	-49.068 ($\pm$ 25.6958)			
Week 24	-53.050 ($\pm$ 27.2118)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in VLDL-C from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in VLDL-C from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in VLDL-C from Baseline at All Other Time Points to Week 104 (refer also to the above-listed results covering the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-55.394 ($\pm$ 25.0601)			
Week 32	-47.899 ($\pm$ 55.7396)			

Week 36	-46.596 (± 25.9994)			
Week 40	-51.167 (± 26.7498)			
Week 44	-46.750 (± 33.3163)			
Week 48	-38.148 (± 50.6100)			
Week 52	-49.469 (± 30.0996)			
Week 56	-47.051 (± 32.7429)			
Week 68	-47.832 (± 30.6844)			
Week 80	-36.881 (± 44.5589)			
Week 92	-41.368 (± 31.7375)			
Week 104	-39.055 (± 40.2422)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in apo B from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in apo B from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in apo B from Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	0.2 (± 18.99)			
Week 8	-6.5 (± 19.25)			
Week 12	-15.5 (± 21.91)			
Week 16	-36.1 (± 16.70)			
Week 20	-51.6 (± 24.21)			
Week 24	-54.0 (± 25.02)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in apo B from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in apo B from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in apo B from Baseline at All Other Time Points to Week 104 (refer also to the above-listed results covering the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-56.2 (± 26.17)			
Week 32	-52.0 (± 28.64)			
Week 36	-43.9 (± 30.91)			
Week 40	-48.9 (± 29.11)			
Week 44	-46.1 (± 28.75)			
Week 48	-48.6 (± 29.03)			
Week 52	-47.7 (± 30.16)			
Week 56	-47.1 (± 33.06)			
Week 68	-44.8 (± 33.99)			
Week 80	-47.1 (± 30.58)			
Week 92	-41.8 (± 35.12)			
Week 104	-44.6 (± 30.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in triglycerides from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in triglycerides from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in triglycerides from Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	9.387 (± 41.7233)			
Week 8	2.649 (± 35.3115)			
Week 12	-7.258 (± 49.6990)			
Week 16	-34.970 (± 30.2259)			
Week 20	-48.989 (± 25.8872)			
Week 24	-52.878 (± 26.8475)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in triglycerides from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in triglycerides from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in triglycerides from Baseline at All Other Time Points to Week 104 (refer also to the above-listed results covering the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-55.639 (± 24.6317)			
Week 32	-48.697 (± 54.0396)			
Week 36	-46.823 (± 25.4762)			
Week 40	-51.612 (± 25.9533)			
Week 44	-47.065 (± 31.7596)			
Week 48	-39.769 (± 48.3307)			
Week 52	-49.415 (± 28.4096)			
Week 56	-47.707 (± 32.0150)			
Week 68	-48.471 (± 30.8061)			
Week 80	-38.312 (± 44.1074)			
Week 92	-41.549 (± 30.2027)			
Week 104	-39.739 (± 39.8597)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in LP(a) from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in LP(a) from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in LP(a) from Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: %				
arithmetic mean (standard deviation)				
Week 4	9.660 (± 63.5768)			
Week 8	1.508 (± 46.1156)			
Week 12	0.592 (± 32.5241)			
Week 16	-14.648 (± 26.3140)			
Week 20	-16.602 (± 47.9856)			
Week 24	-28.874 (± 33.5277)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in LP(a) from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in LP(a) from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
End point description:	
End point type	Secondary
End point timeframe:	
Percent Change in LP(a) from Baseline at All Other Time Points to Week 104 (refer also to the above-listed results covering the efficacy phase)	

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-32.628 (± 32.4047)			
Week 32	-20.594 (± 50.1160)			
Week 36	-25.278 (± 32.4201)			
Week 40	-28.257 (± 34.6849)			

Week 44	-30.124 (± 34.9943)			
Week 48	-17.905 (± 38.3429)			
Week 52	-25.635 (± 42.3832)			
Week 56	-22.366 (± 34.5809)			
Week 68	-20.634 (± 42.9257)			
Week 80	-22.659 (± 42.2271)			
Week 92	-22.235 (± 41.1508)			
Week 104	-29.064 (± 34.5930)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in TC/HDL-C ratio from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in TC/HDL-C ratio from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in TC/HDL-C ratio from Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	0.108 (± 27.5756)			
Week 8	-5.292 (± 29.1737)			
Week 12	-14.501 (± 27.7248)			
Week 16	-33.384 (± 25.8765)			
Week 20	-45.689 (± 27.0372)			
Week 24	-52.155 (± 25.1906)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in TC/HDL-C ratio from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in TC/HDL-C ratio from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in TC/HDL-C ratio from Baseline at All Other Time Points to Week 104 (refer also to the above-listed results covering the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-50.986 (± 31.0715)			
Week 32	-48.651 (± 35.4572)			
Week 36	-35.860 (± 35.4801)			
Week 40	-43.976 (± 36.8573)			
Week 44	-40.395 (± 38.1876)			
Week 48	-41.720 (± 36.2674)			
Week 52	-43.496 (± 38.2302)			
Week 56	-39.188 (± 55.5616)			
Week 68	-36.874 (± 41.9020)			
Week 80	-39.189 (± 37.9268)			
Week 92	-37.274 (± 41.0451)			
Week 104	-39.358 (± 34.3438)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in HDL-C ratio from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)

End point title	Percent Change in HDL-C ratio from Baseline at All Other Time Points to Week 104 (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in HDL-C ratio from Baseline at All Other Time Points to Week 104 (refer also to the below-listed results covering the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	1.428 (± 19.6280)			
Week 8	4.482 (± 26.0635)			
Week 12	4.912 (± 29.1215)			
Week 16	8.059 (± 31.4604)			
Week 20	6.186 (± 33.3664)			
Week 24	11.412 (± 33.0044)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in HDL-C ratio from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)

End point title	Percent Change in HDL-C ratio from Baseline at All Other Time Points to Week 104 (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Secondary
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End point timeframe:

Percent Change in HDL-C ratio from Baseline at All Other Time Points to Week 104 (refer also to the above-listed results covering the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	11.154 (± 36.3133)			
Week 32	15.137 (± 33.9304)			
Week 36	8.537 (± 30.2218)			
Week 40	10.043 (± 35.0097)			
Week 44	12.765 (± 33.2136)			
Week 48	13.602 (± 37.5732)			
Week 52	18.032 (± 35.1079)			
Week 56	11.528 (± 29.1750)			
Week 68	9.557 (± 30.6616)			
Week 80	11.606 (± 30.8242)			
Week 92	17.320 (± 33.0024)			
Week 104	16.109 (± 37.2987)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LLT from Week 28 through Week 104

End point title	Change in LLT from Week 28 through Week 104
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End point description:

End point type	Secondary
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End point timeframe:

Week 28 through Week 104

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Number of patients				
Reduction due to low LDL-C	2			
Discontinuation due to lomitapide increase	1			
Discontinuation due to other reason	2			
Increase due to high LDL-C	3			
Increase due to other reason	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in LA from Week 28 through Week 104

End point title	Change in LA from Week 28 through Week 104
End point description:	
End point type	Secondary
End point timeframe:	
Week 28 through Week 104	

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Number of patients				
Reduction due to AE	1			
Reduction due to low LDL-C	3			
Reduction due to other reason	4			
Discontinuation due to low LDL-C	1			
Discontinuation due to other reason	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Achieving EAS Recommended Target (2013) of LDL-C at any timepoint between Baseline and Week 24

End point title	Percentage of Patients Achieving EAS Recommended Target
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(2013) of LDL-C at any timepoint between Baseline and Week 24

End point description:

End point type Secondary

End point timeframe:

Anytime up to Week 24

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Percentage of patients				
<135 mg/dL - anytime up to Week 24	42			
<115 mg/dL - anytime up to Week 24	37			
<110 mg/dL - anytime up to Week 24	33			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Achieving EAS Recommended Target (2013) of LDL-C at any time in the study

End point title Percentage of Patients Achieving EAS Recommended Target (2013) of LDL-C at any time in the study

End point description:

End point type Secondary

End point timeframe:

Anytime in the study

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of patients				
<135 mg/dL - anytime up to week 104	54			
<115 mg/dL - anytime up to week 104	57			
<110 mg/dL - anytime up to week 104	44			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent change of BMI (efficacy phase results from Baseline to Week 24)

End point title	Percent change of BMI (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 104 (refer also to the data presented in the table below for the safety phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: %				
arithmetic mean (standard deviation)				
Week 4	-1.06 (± 3.466)			
Week 8	-1.32 (± 3.954)			
Week 12	-2.36 (± 4.768)			
Week 16	-2.96 (± 5.288)			
Week 20	-4.21 (± 5.708)			
Week 24	-5.04 (± 5.997)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent change of BMI (safety phase results from Week 28 to Week 104)

End point title	Percent change of BMI (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 104 (refer also to the data presented in the table above for the efficacy phase)

End point values	All age groups			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: %				
arithmetic mean (standard deviation)				
Week 28	-4.13 (± 6.427)			
Week 32	-3.60 (± 7.145)			
Week 36	-3.92 (± 7.949)			
Week 40	-3.78 (± 8.293)			
Week 44	-3.71 (± 10.406)			
Week 48	-3.92 (± 10.420)			
Week 52	-3.21 (± 10.738)			
Week 56	-2.90 (± 11.520)			
Week 68	-3.00 (± 12.103)			
Week 80	-1.90 (± 12.665)			
Week 92	-1.00 (± 14.108)			
Week 104	-0.11 (± 13.718)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lipid Accumulation in the Liver Over Time - NMR (efficacy phase results from Baseline to Week 24)

End point title	Lipid Accumulation in the Liver Over Time - NMR (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Other pre-specified
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End point timeframe:

From Baseline to Week 104/EoT. Please refer also to the data below for data from the safety phase.

End point values	5-10 years	11-17 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	19		
Units: Number of patients				
Baseline - ≤10% liver fat	2	16		
Baseline - >10% and ≤20% liver fat	0	1		

Baseline - >20% liver fat	0	0		
Week 24 - ≤10% liver fat	1	12		
Week 24 - >10% and ≤20% liver fat	1	2		
Week 24 - >20% liver fat	0	1		
Week 24 - No result	2	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lipid Accumulation in the Liver Over Time - NMR (safety phase results from Week 28 to Week 104)

End point title	Lipid Accumulation in the Liver Over Time - NMR (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Other pre-specified
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End point timeframe:

From Baseline to Week 104/EoT. Please refer also to the data above for data from the efficacy phase.

End point values	5-10 years	11-17 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	19		
Units: Number of patients				
Week 56 - ≤10% liver fat	0	9		
Week 56 - >10% and ≤20% liver fat	1	4		
Week 56 - >20% liver fat	0	0		
Week 56 - No result	2	5		
Week 104/EoT - ≤10% liver fat	3	11		
Week 104/EoT - >10% and ≤20% liver fat	1	4		
Week 104/EoT - >20% liver fat	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lipid Accumulation in the Liver Over Time - Ultrasound (efficacy phase results from Baseline to Week 24)

End point title	Lipid Accumulation in the Liver Over Time - Ultrasound (efficacy phase results from Baseline to Week 24)
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End point description:

End point type	Other pre-specified
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End point timeframe:

From Baseline to Week 104/EoT. Please refer also to the data below for data from the safety phase.

End point values	5-10 years	11-17 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	2		
Units: Number of patients				
Baseline - $\leq 10\%$ liver fat	17	2		
Baseline - $> 10\%$ and $\leq 20\%$ liver fat	0	0		
Baseline - $> 20\%$ liver fat	0	0		
Week 24 - $\leq 10\%$ liver fat	15	2		
Week 24 - $> 10\%$ and $\leq 20\%$ liver fat	0	0		
Week 24 - $> 20\%$ liver fat	0	0		
Week 24 - No result	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lipid Accumulation in the Liver Over Time - Ultrasound (safety phase results from Week 28 to Week 104)

End point title	Lipid Accumulation in the Liver Over Time - Ultrasound (safety phase results from Week 28 to Week 104)
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End point description:

End point type	Other pre-specified
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End point timeframe:

From Baseline to Week 104/EoT. Please refer also to the data above for data from the efficacy phase.

End point values	5-10 years	11-17 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	2		
Units: Number of patients				
Week 56 - $\leq 10\%$ liver fat	15	2		
Week 56 - $> 10\%$ and $\leq 20\%$ liver fat	1	0		
Week 56 - $> 20\%$ liver fat	0	0		
Week 56 - No result	0	0		
Week 104/EoT - $\leq 10\%$ liver fat	15	0		
Week 104/EoT - $> 10\%$ and $\leq 20\%$ liver	0	1		
Week 104/EoT - $> 20\%$ liver fat	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were monitored throughout the study from the time of informed consent through Week 108.

Adverse event reporting additional description:

Safety variables included evaluations of AEs, laboratory test results (including assessment of bone health), vital signs, ECGs, pulmonary function tests, and imaging of the liver. In addition, available standard of care echocardiography results were reviewed.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients from all age groups from the time of informed consent through Week 108.

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 43 (25.58%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shunt occlusion			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Aortic valve disease mixed			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Vascular device occlusion			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Tendon disorder			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Vascular device infection			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 43 (97.67%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 43 (39.53%)		
occurrences (all)	28		
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 43 (34.88%)		
occurrences (all)	28		

Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	6 / 43 (13.95%) 6		
C-reactive protein increased subjects affected / exposed occurrences (all)	6 / 43 (13.95%) 8		
ECG signs of ventricular hypertrophy subjects affected / exposed occurrences (all)	5 / 43 (11.63%) 5		
Transaminases increased subjects affected / exposed occurrences (all)	5 / 43 (11.63%) 7		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 8		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	14 / 43 (32.56%) 21		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	8 / 43 (18.60%) 12		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	22 / 43 (51.16%) 44		
Abdominal pain subjects affected / exposed occurrences (all)	19 / 43 (44.19%) 59		
Vomiting subjects affected / exposed occurrences (all)	12 / 43 (27.91%) 26		
Abdominal pain upper			

subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	9		
Nausea			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	6		
Flatulence			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	9		
Oropharyngeal pain			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	6		
Xanthoma			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	12		
Nasopharyngitis			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	6		
Gastroenteritis			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Pharyngitis			

subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed occurrences (all)	6 / 43 (13.95%) 8		
Vitamin D deficiency			
subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 4		
Abnormal loss of weight			
subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 August 2019	Amendment 1.0: - Inconsistencies between the timing of assessments in the study flowchart and the visit descriptions corrected. - Assessment of bone health as a secondary objective clarified. - Genetic testing procedure clarified. - Description of palatability assessments included.
04 December 2019	Amendment 2.0 (first version of protocol approved in Germany): - Change of exclusion criterion 12 to avoid overlapping toxicities. - Amendment of exclusion criterion 14 to exclude breastfeeding subjects from the study. - Change of subject discontinuation criteria to obligatory permanently discontinue treatment in subjects meeting Hy's law case criteria or showing any comparable signs of liver toxicity, irrespective of origin. - Implementation of recruitment stop and individual benefit risk assessment for further administration of study medication in case a subject must discontinue treatment due to Hy's law or comparable signs of liver toxicity.
14 February 2020	Amendment 3.0 (Amendment 1.0 in Germany): - Long-term extension phase of study added instead of named patient supply of lomitapide. - Permission to down-titrate to intermediate doses at Investigator's discretion added. - Central laboratory measurements of fat-soluble vitamin levels and EFAs added. - Central genetic testing added and clarified that genetic testing was to be strongly encouraged but not mandated. - Exploratory sub-study (Liposcale® Test) using aliquots of PK samples added. - Screening laboratory tests for HBsAg and hepatitis C antibody deleted. - Inconsistencies between study flowchart and visit schedule for serum lipase corrected. - Address for SAE reporting updated. - Inconsistencies in safety follow-up and safety reporting details corrected. - Parameters to be measured during pulmonary function tests clarified. - Procedure for weighing subjects clarified. - Study design figure simplified. - Updated to allow local sourcing of dietary supplements. - List of participating countries revised.
04 September 2020	Amendment 4.0: - Inconsistencies in safety follow-up and safety reporting details corrected in Amendment 3.0 reverted (at request of BfArM, Germany). - Use of MRI or ultrasound for measurement of lipid accumulation in the liver clarified. - Rationale for dose selection updated. - Assessment of vital signs at every visit and inclusion of ECGs every 3 to 6 months added. - Collection of standard-of-care echocardiography data/results when available added. - Contraceptive measures section updated. - Re-screening process clarified. - Measurement of 'Holman Index' i.e., ratio of eicosatrienoic acid to arachidonic acid removed. - Sponsor address updated.

21 September 2020	Amendment 4.1: - Inconsistency in flowchart footnotes corrected.
17 November 2020	Amendment 4.2 (implemented in Germany only): - Re-screening details updated (at request of BfArM, Germany).
05 May 2022	Amendment 5.0: - Inconsistencies between objectives and endpoints corrected. - Updated to allow dose increase after Week 24. - Statistical methods clarified: - Clarified methodology of primary efficacy analysis and added timing of the primary efficacy analysis and final analysis. - Specified the use of 2-side significance level at 5% for primary and secondary efficacy parameters. - Updated definition of study population to clarify that safety analysis set included subjects with least one dose of the study medication, FAS included subjects with at least one post-Baseline measurement of LDL-C and completers analysis set included subjects not discontinued at the end of efficacy phase. - Analysis of primary efficacy endpoint was updated to specify the use of one sample t test to test the primary efficacy endpoint, clarified that imputation of missing data using LOCF only applies to Efficacy Phase and when a Baseline value is not missing, added sensitivity analyses using a MMRM, supplementary analyses based on per-protocol and completers analysis sets and subgroup analyses. - Addition of visit windows to handle time window violations for lipid data analyses. - Addition of exploratory and palatability endpoints. - Use of PER Registry for subjects who became pregnant during the study removed.
09 February 2023	Amendment 6.0: - Updated to remove reference to long-term extension study and include options to enter an EAP for subjects <18 years of age or to transition to commercial product for subjects ≥18 years of age. - References to EMA SmPC updated to Lojuxta® SPC in lieu of an Investigator's Brochure. - Updated to remove PK analysis of lomitapide metabolites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Lp(a) analysis was analysed locally as central analysis was only available from January 2022.

Notes: