



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of AKCEAAPOCIIIILRx Administered Subcutaneously to Patients With Familial Chylomicronemia Syndrome (FCS)

Summary

EudraCT number	2020-002536-67
Trial protocol	DE SE NO FR PT SK HU NL ES IT
Global end of trial date	17 October 2023

Results information

Result version number	v1 (current)
This version publication date	03 November 2024
First version publication date	03 November 2024

Trial information

Trial identification

Sponsor protocol code	ISIS 678354-CS3
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04568434
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc
Sponsor organisation address	2855 Gazelle Court, Carlsbad, CA, United States, 92010
Public contact	Ionis Clinical Trial Information, Ionis Pharmaceuticals, Inc, +1 760-603-2346 , globalregulatoryaffairs@ionis.com
Scientific contact	Ionis Clinical Trial Information, Ionis Pharmaceuticals, Inc, +1 760-603-2346 , globalregulatoryaffairs@ionis.com

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	17 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to evaluate the efficacy of olezarsen as compared to placebo on the percent change in fasting triglycerides (TG) from baseline.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 November 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	Canada: 10
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	66
EEA total number of subjects	35

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)	60
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at investigative sites in the United States, Canada, France, Italy, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden and the United Kingdom from 18 November 2020 to 17 October 2023.

Pre-assignment

Screening details:

Participants with familial chylomicronemia syndrome were enrolled and randomized to receive either olezarsen (50 milligrams [mg] or 80 mg) or olezarsen-matching placebo for a 53-week treatment period. Participants completing treatment had an option to enroll in the Open-label Extension (OLE) Study ISIS 678354-CS13 (NCT05130450).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received olezarsen-matching placebo, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Olezarsen-matching placebo was administered by SC injection.

Arm title	Olezarsen 50 mg
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Arm description:

Subjects received olezarsen 50 mg, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.

Arm type	Experimental
Investigational medicinal product name	Olezarsen
Investigational medicinal product code	ISIS 678354
Other name	AKCEAAPOCIILRx
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Olezarsen was administered by SC injection.

Arm title	Olezarsen 80 mg
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Arm description:

Subjects received olezarsen 80 mg, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.

Arm type	Experimental
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Investigational medicinal product name	Olezarsen
Investigational medicinal product code	ISIS 678354
Other name	AKCEAAPOCIIIILRx
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Olezarsen was administered by SC injection.

Number of subjects in period 1	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
Started	23	21	22
Completed This Study, Entered OLE Study	22	19	19
Completed	22	19	19
Not completed	1	2	3
Adverse event, non-fatal	-	-	2
Adverse Events (AE) or Serious Adverse Event (SAE)	-	1	-
voluntary withdrawal	-	1	1
Reason not Specified	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received olezarsen-matching placebo, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.	
Reporting group title	Olezarsen 50 mg
Reporting group description:	
Subjects received olezarsen 50 mg, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.	
Reporting group title	Olezarsen 80 mg
Reporting group description:	
Subjects received olezarsen 80 mg, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.	

Reporting group values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
Number of subjects	23	21	22
Age Categorical			
Units: Subjects			

Age continuous			
Full Analysis Set (FAS) included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.			
Units: years			
arithmetic mean	44.0	43.2	47.7
standard deviation	± 14.67	± 12.11	± 13.30
Gender categorical			
Units: Subjects			
Male	11	6	11
Female	12	15	11
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	3	1
Not Hispanic or Latino	20	18	21
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
White	22	17	17
Asian	0	3	3
Native Hawaiian or Other Pacific Islander	0	1	0
Other	1	0	2
Fasting Triglycerides (TG)			
Units: milligrams per deciliter (mg/dL)			
arithmetic mean	2595.7	2683.8	2613.1
standard deviation	± 1255.72	± 1235.06	± 1498.96

Reporting group values	Total		
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Number of subjects	66		
Age Categorical			
Units: Subjects			
Age continuous			
Full Analysis Set (FAS) included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Male	28		
Female	38		
Ethnicity			
Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	59		
Unknown or Not Reported	0		
Race			
Units: Subjects			
White	56		
Asian	6		
Native Hawaiian or Other Pacific Islander	1		
Other	3		
Fasting Triglycerides (TG)			
Units: milligrams per deciliter (mg/dL)			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Pooled Olezarsen
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received 50 mg or 80 mg olezarsen, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.

Reporting group values	Pooled Olezarsen		
Number of subjects	43		
Age Categorical			
Units: Subjects			

Age continuous			
Full Analysis Set (FAS) included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.			
Units: years			
arithmetic mean	45.5		
standard deviation	± 12.79		

Gender categorical Units: Subjects			
Male	17		
Female	26		
Ethnicity Units: Subjects			
Hispanic or Latino	4		
Not Hispanic or Latino	39		
Unknown or Not Reported	0		
Race Units: Subjects			
White	34		
Asian	6		
Native Hawaiian or Other Pacific Islander	1		
Other	2		
Fasting Triglycerides (TG) Units: milligrams per deciliter (mg/dL) arithmetic mean standard deviation	2647.6 ± 1360.54		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects received olezarsen-matching placebo, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.	
Reporting group title	Olezarsen 50 mg
Reporting group description: Subjects received olezarsen 50 mg, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.	
Reporting group title	Olezarsen 80 mg
Reporting group description: Subjects received olezarsen 80 mg, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.	
Subject analysis set title	Pooled Olezarsen
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received 50 mg or 80 mg olezarsen, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.	

Primary: Percent Change From Baseline in Fasting TG at Month 6

End point title	Percent Change From Baseline in Fasting TG at Month 6
End point description: FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.	
End point type	Primary
End point timeframe: Baseline, Month 6	

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	22	
Units: percent change				
least squares mean (confidence interval 95%)	11.52 (-5.321 to 28.356)	-10.85 (-27.797 to 6.095)	-31.99 (-49.031 to -14.940)	

Statistical analyses

Statistical analysis title	Percent Change From Baseline at Month 6
Comparison groups	Olezarsen 80 mg v Placebo

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009 ^[1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-43.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69.085
upper limit	-17.921

Notes:

[1] - Nominally significant. ANCOVA model included effects of treatment (olezarsen 80 mg, olezarsen 50 mg, or placebo): dependent variable, protocol specified 2 randomization stratification factors: fixed effects, log-transformed baseline TG: covariate.

Statistical analysis title	Percent Change From Baseline at Month 6
Comparison groups	Olezarsen 50 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0775 ^[2]
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	-22.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.2
upper limit	2.463

Notes:

[2] - Analysis of covariance (ANCOVA) model included effects of treatment (olezarsen 80 mg, olezarsen 50 mg, or placebo): dependent variable, protocol specified 2 randomization stratification factors: fixed effects, log-transformed baseline TG: covariate.

Secondary: Percent Change From Baseline in Fasting TG at Month 12

End point title	Percent Change From Baseline in Fasting TG at Month 12
End point description:	
FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.	
End point type	Secondary
End point timeframe:	
Baseline, Month 12	

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	22	
Units: percent change				
least squares mean (confidence interval 95%)	20.89 (1.016 to 40.764)	-22.92 (-42.505 to -3.336)	-38.50 (-58.187 to -18.815)	

Statistical analyses

Statistical analysis title	Percent Change From Baseline at Month 12
Comparison groups	Olezarsen 50 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0044 ^[3]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-43.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-73.928
upper limit	-13.692

Notes:

[3] - Nominally significant. ANCOVA model included percent change from baseline in fasting TG at Month 12: dependent variable, treatment group, protocol specified 2 randomization stratification factors: fixed effects, log-transformed baseline TG: covariate.

Statistical analysis title	Percent Change From Baseline at Month 12
Comparison groups	Olezarsen 80 mg v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 ^[4]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-59.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-90.663
upper limit	-28.119

Notes:

[4] - Nominally significant. ANCOVA model included percent change from baseline in fasting TG at Month 12: dependent variable, treatment group, protocol specified 2 randomization stratification factors: fixed effects, log-transformed baseline TG: covariate

Secondary: Percent Change From Baseline in Fasting Apolipoprotein C-III (apoC-III) at Months 6 and 12

End point title	Percent Change From Baseline in Fasting Apolipoprotein C-III
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End point description:

FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.

End point type Secondary

End point timeframe:

Baseline, Months 6 and 12

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	22	
Units: percent change				
least squares mean (confidence interval 95%)				
Month 6	7.57 (-5.229 to 20.359)	-57.91 (-71.193 to -44.631)	-66.13 (-79.437 to -52.823)	
Month 12	17.08 (2.149 to 32.009)	-59.98 (-75.163 to -44.795)	-64.20 (-79.408 to -48.984)	

Statistical analyses

Statistical analysis title	Percent Change from Baseline at Month 6
Comparison groups	Olezarsen 50 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-65.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.634
upper limit	-48.32

Notes:

[5] - Nominally significant. ANCOVA model included percent change from baseline in fasting TG at Month 12: dependent variable, treatment group, protocol specified 2 randomization stratification factors: fixed effects, log-transformed baseline TG: covariate

Statistical analysis title	Percent Change from Baseline at Month 12
Comparison groups	Olezarsen 80 mg v Placebo

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-81.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-104.656
upper limit	-57.894

Notes:

[6] - Nominally significant. ANCOVA model included percent change from baseline in fasting TG at Month 12: dependent variable, treatment group, protocol specified 2 randomization stratification factors: fixed effects, log-transformed baseline TG: covariate

Statistical analysis title	Percent Change from Baseline at Month 12
Comparison groups	Olezarsen 50 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[7]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-77.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-98.938
upper limit	-55.177

Notes:

[7] - Nominally significant. ANCOVA model included percent change from baseline in fasting TG at Month 12: dependent variable, treatment group, protocol specified 2 randomization stratification factors: fixed effects, log-transformed baseline TG: covariate

Statistical analysis title	Percent Change from Baseline at Month 6
Comparison groups	Olezarsen 80 mg v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[8]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-73.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-94.553
upper limit	-52.837

Notes:

[8] - Nominally significant. ANCOVA model included percent change from baseline in fasting TG at Month 12: dependent variable, treatment group, protocol specified 2 randomization stratification factors: fixed effects, log-transformed baseline TG: covariate

Secondary: Percentage of Subjects With $\geq 40\%$ Reduction in Fasting TG at Month 6

End point title	Percentage of Subjects With $\geq 40\%$ Reduction in Fasting TG at Month 6
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End point description:

Percentages are rounded off to the nearest single decimal place. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.

End point type	Secondary
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End point timeframe:

Month 6

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	22	
Units: percentage of subjects				
number (not applicable)	4.3	33.3	40.9	

Statistical analyses

Statistical analysis title	Percent Change from Baseline at Month 6
Comparison groups	Placebo v Olezarsen 50 mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.186 ^[9]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-33.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.612
upper limit	16.041

Notes:

[9] - ANCOVA model included percent change from baseline in fasting apoB-48 to Month 6: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline apoB-48: covariate.

Statistical analysis title	Percent Change from Baseline at Month 6
Comparison groups	Placebo v Olezarsen 80 mg

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.0019 ^[11]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-83.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-136.949
upper limit	-30.982

Notes:

[10] - ANCOVA model included percent change from baseline in fasting apoB-48 to Month 6: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline apoB-48: covariate.

[11] - Nominally significant as described in SAP.

Statistical analysis title	Percent Change from Baseline at Month 12
Comparison groups	Placebo v Olezarsen 50 mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4219 ^[12]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-32.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-113.254
upper limit	47.459

Notes:

[12] - ANCOVA model included percent change from baseline in fasting apoB-48 to Month 12: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline apoB-48: covariate.

Statistical analysis title	Percent Change from Baseline at Month 12
Comparison groups	Placebo v Olezarsen 80 mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056 ^[13]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-75.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-153.195
upper limit	1.927

Notes:

[13] - ANCOVA model included percent change from baseline in fasting apoB-48 to Month 12: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline apoB-48: covariate.

Secondary: Percent Change From Baseline in Fasting Apolipoprotein B-48 (apoB-48) at Months 6 and 12

End point title	Percent Change From Baseline in Fasting Apolipoprotein B-48 (apoB-48) at Months 6 and 12
End point description: FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.	
End point type	Secondary
End point timeframe: Baseline, Months 6 and 12	

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	22	
Units: percent change				
least squares mean (confidence interval 95%)				
Month 6	24.50 (-9.972 to 58.973)	-8.78 (-42.976 to 25.406)	-59.46 (-93.164 to 25.765)	
Month 12	-3.52 (-53.159 to 46.124)	-36.41 (-77.689 to 4.860)	-79.15 (-118.442 to -39.861)	

Statistical analyses

Statistical analysis title	Percent Change from Baseline at Month 6
Statistical analysis description: ANCOVA model included percent change from baseline in fasting apoB-48 to Month 6: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline apoB-48: covariate.	
Comparison groups	Olezarsen 50 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.186
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-33.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-82.612
upper limit	16.041

Statistical analysis title	Percent Change from Baseline at Month 12
Statistical analysis description: ANCOVA model included percent change from baseline in fasting apoB-48 to Month 12: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline apoB-48: covariate.	
Comparison groups	Olezarsen 80 mg v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.056
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-75.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-153.195
upper limit	1.927

Statistical analysis title	Percent Change from Baseline at Month 12
Statistical analysis description: ANCOVA model included percent change from baseline in fasting apoB-48 to Month 12: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline apoB-48: covariate.	
Comparison groups	Olezarsen 50 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4219
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-32.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-113.254
upper limit	47.459

Statistical analysis title	Percent Change from Baseline at Month 6
Statistical analysis description: ANCOVA model included percent change from baseline in fasting apoB-48 to Month 6: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline apoB-48: covariate.	
Comparison groups	Olezarsen 80 mg v Placebo

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-83.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-136.949
upper limit	-30.982

Secondary: Percent Change From Baseline in Fasting Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) at Months 6 and 12

End point title	Percent Change From Baseline in Fasting Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) at Months 6 and 12
End point description: FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.	
End point type	Secondary
End point timeframe: Baseline, Months 6 and 12	

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	22	
Units: percent change				
least squares mean (confidence interval 95%)				
Month 6	5.33 (-5.345 to 16.014)	-12.35 (-23.541 to -1.163)	-18.86 (-29.952 to -7.774)	
Month 12	12.01 (-2.480 to 26.494)	-17.84 (-32.128 to -3.545)	-27.69 (-41.722 to -13.664)	

Statistical analyses

Statistical analysis title	Percent Change from Baseline Month 6
Comparison groups	Olezarsen 50 mg v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority ^[14]
P-value	= 0.0401 ^[15]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-17.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.571
upper limit	-0.801

Notes:

[14] - ANCOVA model included percent change from baseline in fasting non-HDL-C to Month 6: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline non-HDL-C: covariate.

[15] - Nominally significant as described in SAP.

Statistical analysis title	Percent Change from Baseline at Month 12
Comparison groups	Olezarsen 80 mg v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority ^[16]
P-value	= 0.0009 ^[17]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-39.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-63.108
upper limit	-16.292

Notes:

[16] - ANCOVA model included percent change from baseline in fasting non-HDL-C to Month 12: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline non-HDL-C: covariate.

[17] - Nominally significant as described in SAP.

Statistical analysis title	Percent Change from Baseline at Month 12
Comparison groups	Olezarsen 50 mg v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority ^[18]
P-value	= 0.0134 ^[19]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-29.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.49
upper limit	-6.198

Notes:

[18] - ANCOVA model included percent change from baseline in fasting non-HDL-C to Month 12: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline non-HDL-C: covariate.

[19] - Nominally significant as described in SAP.

Statistical analysis title	Percent Change from Baseline Month 6
Comparison groups	Olezarsen 80 mg v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority ^[20]
P-value	= 0.0036 ^[21]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-24.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.484
upper limit	-7.911

Notes:

[20] - ANCOVA model included percent change from baseline in fasting non-HDL-C to Month 6: dependent variable, treatment group, protocol prespecified randomization stratification factors: fixed effects & log-transformed baseline non-HDL-C: covariate.

[21] - Nominally significant as described in SAP.

Secondary: Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Subject-Years During the Treatment Period (Week 1 Through Week 53) in Subjects With Prior History of Pancreatitis

End point title	Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Subject-Years During the Treatment Period (Week 1 Through Week 53) in Subjects With Prior History of Pancreatitis ^[22]
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End point description:

All AEs & SAEs that consistently occurred during study with an event of acute pancreatitis were adjudicated by a blinded independent committee according to Atlanta classification of acute pancreatitis as outlined in the Acute Pancreatitis Adjudication Committee (PAC) Charter. These events were categorized: documented pancreatitis, probable pancreatitis, possible pancreatitis, unable to adjudicate, no diagnosis of acute pancreatitis. Adjudicated event rate represents average number of events per 100 subject-years during treatment period. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo. 'Subjects analyzed' indicates the number of subjects with a history of pancreatitis within 10 years prior to screening. As prespecified in the protocol, data for this endpoint was collected and reported in a pooled manner for olezarsen (combined Olezarsen 50 mg + Olezarsen 80 mg).

End point type	Secondary
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End point timeframe:

During the treatment period Week 1 through Week 53

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analysed only in subjects who received Placebo and Pooled Olezarsen.

End point values	Placebo	Pooled Olezarsen		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	32		
Units: events per 100 subject-years				
arithmetic mean (confidence interval 95%)	66.22 (30.490 to 143.817)	6.73 (1.612 to 28.087)		

Statistical analyses

Statistical analysis title	Adjudicated Acute Pancreatitis Mean Event Rate
Statistical analysis description:	
Regression model: treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week 1to53:offset variable.	
Comparison groups	Placebo v Pooled Olezarsen
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	= 0.0052 ^[24]
Method	Negative Binomial Regression Model
Parameter estimate	Mean Rate Ratio
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.506

Notes:

[23] - Regression model: treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week 1 to 53:offset variable.

[24] - Nominally significant as described in SAP.

Secondary: Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Subject-Years During the Treatment Period (Week 1 Through Week 53)

End point title	Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Subject-Years During the Treatment Period (Week 1 Through Week 53) ^[25]
End point description:	
All AEs & SAEs that consistently occurred during study with an event of acute pancreatitis were adjudicated by a blinded independent committee according to Atlanta classification of acute pancreatitis as outlined in the PAC Charter. These events were categorized as documented pancreatitis, probable pancreatitis, possible pancreatitis, unable to adjudicate, and no diagnosis of acute pancreatitis. Adjudicated event rate represents average number of events per 100 subjects-years during treatment period. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo. As prespecified in the protocol, data for this endpoint was collected and reported in a pooled manner for olezarsen (combined Olezarsen 50 mg + Olezarsen 80 mg).	
End point type	Secondary
End point timeframe:	
During the treatment period Week 1 through Week 53	

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analysed only in subjects who received Placebo and Pooled Olezarsen.

End point values	Placebo	Pooled Olezarsen		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	23	43		
Units: events per 100 subject-years				
arithmetic mean (confidence interval 95%)	36.31 (14.700 to 89.685)	4.37 (0.942 to 20.298)		

Statistical analyses

Statistical analysis title	Adjudicated Acute Pancreatitis Mean Event Rate
Comparison groups	Placebo v Pooled Olezarsen
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority ^[26]
P-value	= 0.0144 ^[27]
Method	Negative Binomial Regression Model
Parameter estimate	Mean Rate Ratio
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.656

Notes:

[26] - Regression model: treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week 1to53:offset variable.

[27] - Nominally significant as described in SAP.

Secondary: Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Subject-Years During Week 13 Through Week 53 in Subjects With Prior History of Pancreatitis

End point title	Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Subject-Years During Week 13 Through Week 53 in Subjects With Prior History of Pancreatitis ^[28]
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End point description:

All AEs & SAEs that consistently occurred during study with an event of acute pancreatitis were adjudicated by a blinded independent committee according to Atlanta classification of acute pancreatitis as outlined in the PAC Charter. These events were categorized as documented pancreatitis, probable pancreatitis, possible pancreatitis, unable to adjudicate, and no diagnosis of acute pancreatitis. Adjudicated event rate represents average number of events per 100 subject-years during specified duration. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo. 'Subjects analyzed' indicates number of subjects with a history of pancreatitis within 10 years prior to screening. As prespecified in the protocol, data for this endpoint was collected and reported in a pooled manner for olezarsen (combined Olezarsen 50 mg + Olezarsen 80 mg).

End point type	Secondary
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End point timeframe:

Week 13 through Week 53

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analysed only in subjects who received Placebo and Pooled Olezarsen.

End point values	Placebo	Pooled Olezarsen		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15	32		
Units: events per 100 subject-years				
arithmetic mean (confidence interval 95%)	57.89 (24.469 to 136.972)	8.17 (1.952 to 34.177)		

Statistical analyses

Statistical analysis title	Adjudicated Acute Pancreatitis Mean Event Rate
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Statistical analysis description:

Regression model: treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week13to53:offset variable.

Comparison groups	Placebo v Pooled Olezarsen
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority ^[29]
P-value	= 0.0174 ^[30]
Method	Negative Binomial Regression Model
Parameter estimate	Mean Rate Ratio
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.709

Notes:

[29] - Regression model: treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week 13 to 53:offset variable.

[30] - Nominally significant as described in SAP.

Secondary: Adjudicated Acute Pancreatitis Mean Event Rate Per 100-Subject Years During Week 13 to Week 53

End point title	Adjudicated Acute Pancreatitis Mean Event Rate Per 100-Subject Years During Week 13 to Week 53 ^[31]
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End point description:

All AEs & SAEs that consistently occurred during study with an event of acute pancreatitis were adjudicated by a blinded independent committee according to Atlanta classification of acute pancreatitis as outlined in the PAC Charter. These events were categorized as documented pancreatitis, probable pancreatitis, possible pancreatitis, unable to adjudicate, and no diagnosis of acute pancreatitis. Adjudicated event rate represents average number of events per 100 subject-years during treatment period. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo. As prespecified in the protocol, data for this endpoint was collected and reported in a pooled manner for olezarsen (combined Olezarsen 50 mg + Olezarsen 80 mg)

End point type	Secondary
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End point timeframe:

Week 13 through Week 53

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analysed only in subjects who received Placebo and Pooled Olezarsen.

End point values	Placebo	Pooled Olezarsen		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	23	43		
Units: events per 100-subject years				
arithmetic mean (confidence interval 95%)	33.43 (13.250 to 84.321)	5.42 (1.229 to 23.897)		

Statistical analyses

Statistical analysis title	Adjudicated Acute Pancreatitis Mean Event Rate
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Statistical analysis description:

Regression model :treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week13to53:offset variable.

Comparison groups	Placebo v Pooled Olezarsen
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority ^[32]
P-value	= 0.0314 ^[33]
Method	Negative Binomial Regression Model
Parameter estimate	Mean Rate Ratio
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.85

Notes:

[32] - Regression model: treatment group & previous treatment (volanesorsen): factors adjudicated acute pancreatitis events in 5 years prior enrollment: covariate. Logarithm of time in year that each participant was observed from Week 13 to 53:offset variable.

[33] - Nominally significant as described in SAP.

Secondary: Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Subject-Years During Treatment Period in Subjects With ≥ 2 Events in 5 Years Prior to Enrollment

End point title	Adjudicated Acute Pancreatitis Mean Event Rate Per 100 Subject-Years During Treatment Period in Subjects With ≥ 2 Events in 5 Years Prior to Enrollment ^[34]
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End point description:

All AEs & SAEs that consistently occurred during study with an event of acute pancreatitis were adjudicated by a blinded independent committee according to Atlanta classification of acute pancreatitis as outlined in the PAC Charter. These events were categorized as documented pancreatitis, probable pancreatitis, possible pancreatitis, unable to adjudicate, and no diagnosis of acute pancreatitis. Adjudicated event rate represents average number of events per 100 subject-years during treatment period. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose

of olezarsen or placebo. 'Subjects analyzed' indicates the number of subjects with ≥ 2 adjudicated acute pancreatitis events in 5 years prior to enrollment. As prespecified in the protocol, data for this endpoint was collected and reported in a pooled manner for olezarsen (combined Olezarsen 50 mg + Olezarsen 80 mg).

End point type	Secondary
End point timeframe:	
During the treatment period Week 1 through Week 53	

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analysed only in subjects who received Placebo and Pooled Olezarsen.

End point values	Placebo	Pooled Olezarsen		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	12		
Units: events per 100 subject-years				
arithmetic mean (confidence interval 95%)	118.59 (61.226 to 229.698)	16.59 (4.051 to 67.948)		

Statistical analyses

Statistical analysis title	Adjudicated Acute Pancreatitis Mean Event Rate
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Statistical analysis description:

Regression model:treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week 1 to 53:offset variable.

Comparison groups	Placebo v Pooled Olezarsen
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	= 0.0137 ^[36]
Method	Negative Binomial Regression Model
Parameter estimate	Mean Rate Ratio
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.669

Notes:

[35] - Regression model:treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week 1 to 53: offset variable.

[36] - Nominally significant as described in SAP.

Secondary: Percentage of Subjects With $\geq 70\%$ Reduction in Fasting TG at Month 6

End point title	Percentage of Subjects With $\geq 70\%$ Reduction in Fasting TG at Month 6
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End point description:

Percentages are rounded off to the nearest single decimal place. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.

End point type	Secondary
End point timeframe:	
Month 6	

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	21	22	
Units: percentage of subjects				
number (not applicable)	0	4.8	9.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Fasting TG $\leq$ 880 mg/dL at Month 6

End point title	Percentage of Subjects With Fasting TG $\leq$ 880 mg/dL at Month 6
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End point description:

Percentages are rounded off to the nearest single decimal place. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo. 'Subjects analyzed' indicates the number of subjects with data available for analyses.

End point type	Secondary
End point timeframe:	
Month 6	

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	20	21	
Units: percentage of subjects				
number (not applicable)	0	10.0	14.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Fasting TG $\leq$ 500 mg/dL at Month 6

End point title	Percentage of Subjects With Fasting TG $\leq$ 500 mg/dL at Month 6
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End point description:

Percentages are rounded off to the nearest single decimal place. FAS included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo. Subjects analyzed

indicates the number of subjects with data available for the analyses.

End point type	Secondary
End point timeframe:	
Month 6	

End point values	Placebo	Olezarsen 50 mg	Olezarsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	21	22	
Units: percentage of subjects				
number (not applicable)	0	0	13.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjudicated Acute Pancreatitis Mean Event Rate Per 100-Subject Years From Week 13 to Week 53 in Subjects With ≥ 2 Events in 5 Years Prior to Enrollment

End point title	Adjudicated Acute Pancreatitis Mean Event Rate Per 100-Subject Years From Week 13 to Week 53 in Subjects With ≥ 2 Events in 5 Years Prior to Enrollment ^[37]
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End point description:

All AEs & SAEs that consistently occurred during study with an event of acute pancreatitis were adjudicated by a blinded independent committee according to Atlanta classification of acute pancreatitis as outlined in the PAC Charter. These events were categorized as documented pancreatitis, probable pancreatitis, possible pancreatitis, unable to adjudicate, and no diagnosis of acute pancreatitis. Adjudicated event rate represents average number of events per 100 subject-years during the specified duration. FAS: all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo. 'Subjects analyzed' indicates the number of subjects with ≥ 2 adjudicated acute pancreatitis events in 5 years prior to enrollment. As prespecified in the protocol, data for this endpoint was collected and reported in a pooled manner for olezarsen (combined Olezarsen 50 mg + Olezarsen 80 mg).

End point type	Secondary
End point timeframe:	
Week 13 through Week 53	

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was analysed only in subjects who received Placebo and Pooled Olezarsen.

End point values	Placebo	Pooled Olezarsen		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	12		
Units: events per 100-subject years				
arithmetic mean (confidence interval 95%)	106.91 (50.204 to 227.682)	21.36 (5.233 to 87.219)		

Statistical analyses

Statistical analysis title	Adjudicated Acute Pancreatitis Mean Event Rate
Statistical analysis description: Regression model:treatment group & previous treatment (volanesorsen):factors adjudicated acute pancreatitis events in 5 years prior enrollment:covariate. Logarithm of time in year that each participant was observed from Week 13to53:offset variable.	
Comparison groups	Placebo v Pooled Olezarsen
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048 ^[38]
Method	Negative Binomial Regression Model
Parameter estimate	Mean Rate Ratio
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.986

Notes:

[38] - Nominally significant as described in SAP.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to end of the follow-up (up to Week 66)

Adverse event reporting additional description:

Safety analysis set included all subjects that were randomly assigned to treatment and received at least 1 dose of olezarsen or placebo.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects received olezarsen-matching placebo, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.

Reporting group title	Olezarsen 80 mg
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Reporting group description:

Subjects received olezarsen 80 mg, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.

Reporting group title	Olezarsen 50 mg
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Reporting group description:

Subjects received olezarsen 50 mg, once every 4 weeks by SC injection, during Weeks 1 to 49 of the 53-week treatment period.

Serious adverse events	Placebo	Olezarsen 80 mg	Olezarsen 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 23 (39.13%)	3 / 22 (13.64%)	4 / 21 (19.05%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 23 (0.00%)	0 / 22 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 23 (0.00%)	0 / 22 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	4 / 23 (17.39%)	1 / 22 (4.55%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric varices			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric varices haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	3 / 23 (13.04%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis necrotising			
subjects affected / exposed	2 / 23 (8.70%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis bacterial			
subjects affected / exposed	0 / 23 (0.00%)	0 / 22 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatogenous diabetes			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Olezarsen 80 mg	Olezarsen 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 23 (82.61%)	18 / 22 (81.82%)	17 / 21 (80.95%)
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 23 (4.35%)	3 / 22 (13.64%)	1 / 21 (4.76%)
occurrences (all)	1	3	1
Injury, poisoning and procedural complications			
Skin laceration			
subjects affected / exposed	2 / 23 (8.70%)	1 / 22 (4.55%)	1 / 21 (4.76%)
occurrences (all)	2	1	1
Arthropod bite			
subjects affected / exposed	0 / 23 (0.00%)	0 / 22 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 23 (13.04%)	1 / 22 (4.55%)	4 / 21 (19.05%)
occurrences (all)	4	3	7
Migraine			
subjects affected / exposed	2 / 23 (8.70%)	0 / 22 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 23 (4.35%)	2 / 22 (9.09%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	1 / 23 (4.35%)	2 / 22 (9.09%)	1 / 21 (4.76%)
occurrences (all)	1	2	3
Injection site pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	2 / 21 (9.52%)
occurrences (all)	0	3	6
Fatigue			
subjects affected / exposed	4 / 23 (17.39%)	1 / 22 (4.55%)	1 / 21 (4.76%)
occurrences (all)	4	1	3
Gastrointestinal disorders			

Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	2 / 22 (9.09%) 2	2 / 21 (9.52%) 2
Abdominal pain subjects affected / exposed occurrences (all)	8 / 23 (34.78%) 14	4 / 22 (18.18%) 5	3 / 21 (14.29%) 5
Abdominal distension subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 22 (9.09%) 2	0 / 21 (0.00%) 0
Dental caries subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	6 / 23 (26.09%) 12	2 / 22 (9.09%) 2	1 / 21 (4.76%) 1
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 22 (9.09%) 2	1 / 21 (4.76%) 1
Nausea subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 22 (4.55%) 1	2 / 21 (9.52%) 4
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 22 (9.09%) 2	2 / 21 (9.52%) 2
Epistaxis subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	2 / 21 (9.52%) 2
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 22 (0.00%) 0	3 / 21 (14.29%) 6
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	3 / 21 (14.29%) 3
Back pain subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	1 / 22 (4.55%) 1	0 / 21 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	3 / 22 (13.64%) 4	2 / 21 (9.52%) 2
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	3 / 21 (14.29%) 4
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	0 / 22 (0.00%) 0	2 / 21 (9.52%) 2
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2	1 / 22 (4.55%) 1	2 / 21 (9.52%) 2
Influenza subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	1 / 22 (4.55%) 1	3 / 21 (14.29%) 3
Cellulitis subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 22 (0.00%) 0	0 / 21 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	8 / 23 (34.78%) 8	3 / 22 (13.64%) 3	6 / 21 (28.57%) 6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2020	Added 50 mg every 4 weeks dosing cohort, with target enrollment of 30 subjects in each cohort. Each cohort was randomized 2:1 to receive olezarsen or matching placebo every 4 weeks. Updated Study Design and Treatment Schema to include 2 study cohorts (Cohorts A and B). Updated secondary objectives to specify the analysis time points for each objective. Added secondary endpoints for percentage change from Baseline in fasting TG at 12 months and for proportion of subjects who achieve $\geq 70\%$ reduction in fasting TG from Baseline.
29 October 2020	Updated dosing for Cohort A to continue on 50 mg every 4 weeks or placebo up to Month 12 instead of up-titration to 80 mg every 4 weeks at Month 6. Added Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form v2.0 Cognitive Function 4a as optional evaluation. Updated Exclusion Criterion 3 to allow up to 2 retests at Screening and Qualification for patients with platelet counts $< 100,000$ per cubic millimeter (mm^3). Removed exclusion criterion related to history of oligonucleotide associated platelet count $< 75,000/\text{mm}^3$ (Exclusion Criterion 6 in original Study Protocol). Simplified Inclusion Criterion 7 by cross-referencing section on patient-reported outcomes (PROs). Added language for lab alerts to clarify safety monitoring criteria. Clarified confirmation window, criteria to restart treatment for patients with low platelet count. Updated stopping rules for liver chemistry elevations to note that ALT and AST levels were to be $\leq 3 \times \text{ULN}$ before treatment can be restarted in patients meeting liver stopping rules. An FCS Symptoms Two Week Recall questionnaire was added at Screening to obtain symptom data prior to randomization into the study.
21 December 2020	Clarified Exclusion Criterion 11 does not apply to vaccines (both mRNA and Viral Vector). Added sections on Additional Risks During the COVID-19 Pandemic and Allowances in the Circumstance of a Public Health Emergency. Added section on monitoring for LDL-C elevations. Added RDW and MPV to hematology laboratory analytes.
11 March 2021	Updated Exclusion Criterion 3e (and corresponding renal function safety monitoring criteria) to UPCR of ≥ 0.5 mg/mg or UACR of ≥ 300 mg/g. Added COVID-19 infection not resolved by Study Day 1 to Exclusion Criterion 6. Updated safety monitoring for renal function including UACR (> 300 mg/g, or $> 50\%$ Baseline whichever was greater) and UPCR levels (> 0.500 mg/mg, or $> 50\%$ Baseline whichever was greater). Updated LDL-C thresholds in monitoring criteria (and added conditional to > 100 mg/dL criterion to include either T2DM or CAD with Baseline LDL-C > 100 mg/dL). Added Day 15 ADA and PK sample collections, ADA sample collections on Follow-up Day 4 and 8, and Day 169 PK sample collection at $2\text{h} \pm 15$ min post-dose.
16 April 2021	Updated Exclusion Criterion 11 to allow a 4-month washout for treatment with a single dose of an oligonucleotide plus a "booster" (i.e., second) dose and to clarify this exclusion does not apply to any vaccine. Clarified conditions under which local repeat testing for hematology samples may be conducted. Clarified that site of injection for study drug should not be the same as injection site for COVID-19 vaccine. Clarified that Day 15 PK sample was collected Anytime rather than Pre-dose.

25 October 2021	Added ER visit to the definition of history on pancreatitis for Inclusion Criterion 5. Increased enrollment cap for patients without a recorded history of pancreatitis. Change/Rationale for Amendments. Removed GLP agonists from Exclusion Criteria 10b and 12b. Changed washout period for oligonucleotides in Exclusion Criterion 11 to 4 months prior to Screening, or 5 half-lives, whichever is longer. Clarified that race and ethnicity data were to be included in demographic information collected at screening. Clarified that the collection period of pancreatitis medical history was within 10 years prior to Screening with independent adjudication of information collected about events within 5 years prior to Screening. Clarified treatment of redacted documents during database lock. Clarified landmark visits in appendices.
26 October 2022	Added secondary endpoints for adjudicated pancreatitis event rates from Weeks 13 to 53. Clarified blinding to lipid data in study design. Added allowance for COVID-19 antiviral treatments under EUA outside of trial. Added true abstinence for males as acceptable method of contraception in the inclusion criteria and prevention of pregnancy sections. Adjusted contraceptive requirement period from 30 weeks to 17 weeks post-final dose based on updated PK modeling, fertility/early embryonic development study data. Provided additional guidance on highly effective contraception. Changed platelet count monitoring from weekly to every 2 weeks with platelet count $\geq 100,000/\text{mm}^3$ to $< 140,000/\text{mm}^3$. Added language to note that patients who experience persistent or increasing constitutional symptoms should be tested for ADA. Added language to clarify safety monitoring for hypersensitivity reactions (symptoms, procedures). Clarified that spontaneous abortion/miscarriage is an SAE. Added 2 new secondary endpoints for adjudicated acute pancreatitis event rate to be measured from Week 13 to 53, and with ≥ 2 events of adjudicated acute pancreatitis in 5 years prior to enrollment. Added language clarifying that urine collection should not be performed during menstruation.
19 June 2023	Added secondary endpoints measuring percent change in apoC-III and non-HDL-C, and updated the order of the study objectives. Clarified symptoms of hypersensitivity reactions and applicable lab assessments for monitoring. Updated AESI definitions to include pre-treatment to avoid a hypersensitivity reaction. Removed requirement for at least 1 post-Baseline TG assessment from Full Analysis Set definition. Updated secondary endpoint testing sequence. Clarified that sensitivity analysis in Per Protocol Set would occur for primary analysis, and secondary endpoints would be assessed in the Full Analysis Set alone.
02 August 2023	Added secondary endpoints for adjudicated acute pancreatitis event rates during Treatment Period (Weeks 1 to 53) and from Weeks 13 to 53 in a subset of the Full Analysis Set with prior history of pancreatitis in 10 years prior to Screening. Revised secondary endpoints containing cutoff fasting TG $\leq 750 \text{ mg/dL}$ to cutoff of $\leq 880 \text{ mg/dL}$ (per inclusion criteria at screening).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported