



Clinical trial results:

A Phase 3 Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients With Hereditary Angioedema (HAE)

Summary

EudraCT number	2021-002571-19
Trial protocol	FR IT ES NL DE BE BG DK PL
Global end of trial date	08 November 2023

Results information

Result version number	v1 (current)
This version publication date	22 December 2024
First version publication date	22 December 2024

Trial information

Trial identification

Sponsor protocol code	ISIS721744-CS5
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05139810
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-003112-PIP01-21
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	08 November 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of donidalorsen in subjects with Hereditary Angioedema (HAE) and effect of donidalorsen on the quality and pattern of HAE attacks and their impact on quality of life (QoL).

Protection of trial subjects:

Each subject, or legally acceptable representative, signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Türkiye: 20
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Belgium: 1
Worldwide total number of subjects	90
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
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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)	7
Adults (18-64 years)	81
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 39 investigative sites from 03 December 2021 to 09 November 2023.

Pre-assignment

Screening details:

A total of 91 subjects were enrolled and randomized in study. Out of 91, 1 subject randomized to Cohort A, withdrew consent prior to receiving study drug. As pre-specified in protocol/statistical analysis plan, for purposes of analysis data for placebo subjects, from Cohort A and Cohort B was pooled for comparison to donidalorsen treated subjects.

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, Carer, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pooled Placebo

Arm description:

Subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) received placebo subcutaneously (SC) either every 4 weeks (Week 1, 5, 9, 13,17, and 21) or 8 weeks (Week 1, 9, and 17).

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

Dosage and administration details:

Placebo was administered SC either every 4 weeks or 8 weeks.

Arm title	Cohort A: Donidalorsen 80 mg
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Arm description:

Subjects with HAE-1/HAE-2 received donidalorsen, 80 mg, SC, every 4 weeks at Weeks 1, 5, 9, 13, 17, and 21.

Arm type	Experimental
Investigational medicinal product name	Donidalorsen 80 mg
Investigational medicinal product code	ISIS 721744
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Donidalorsen, 80 mg, administered SC, every 4 weeks.

Arm title	Cohort B: Donidalorsen 80 mg
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Arm description:

Subjects with HAE-1/HAE-2 received donidalorsen, 80 mg, SC, every 8 weeks at Weeks 1, 9, and 17.

Arm type	Experimental
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Investigational medicinal product name	Donidalorsen 80 mg
Investigational medicinal product code	ISIS 721744
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Donidalorsen, 80 mg, administered SC, every 8 weeks.

Number of subjects in period 1	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg
Started	22	45	23
Completed	0	1	3
Not completed	22	44	20
Roll Over to CS7	19	44	20
Voluntary Withdrawal	2	-	-
Pregnancy	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Pooled Placebo
Reporting group description: Subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) received placebo subcutaneously (SC) either every 4 weeks (Week 1, 5, 9, 13,17, and 21) or 8 weeks (Week 1, 9, and 17).	
Reporting group title	Cohort A: Donidalorsen 80 mg
Reporting group description: Subjects with HAE-1/HAE-2 received donidalorsen, 80 mg, SC, every 4 weeks at Weeks 1, 5, 9, 13, 17, and 21.	
Reporting group title	Cohort B: Donidalorsen 80 mg
Reporting group description: Subjects with HAE-1/HAE-2 received donidalorsen, 80 mg, SC, every 8 weeks at Weeks 1, 9, and 17.	

Reporting group values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg
Number of subjects	22	45	23
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	35.4 ± 11.03	39.6 ± 15.23	34.1 ± 13.22
Gender categorical Units: Subjects			
Male	14	17	11
Female	8	28	12
Race Units: Subjects			
American Indian or Alaskan Native	2	0	1
Asian	0	1	0
Black or African American	1	1	0
White	18	42	22
Multiple	1	0	0
Other	0	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	21	43	20

Reporting group values	Total		
Number of subjects	90		
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Male	42		
Female	48		
Race Units: Subjects			
American Indian or Alaskan Native	3		
Asian	1		
Black or African American	2		
White	82		
Multiple	1		
Other	1		
Ethnicity Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	84		

End points

End points reporting groups

Reporting group title	Pooled Placebo
Reporting group description: Subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) received placebo subcutaneously (SC) either every 4 weeks (Week 1, 5, 9, 13,17, and 21) or 8 weeks (Week 1, 9, and 17).	
Reporting group title	Cohort A: Donidalorsen 80 mg
Reporting group description: Subjects with HAE-1/HAE-2 received donidalorsen, 80 mg, SC, every 4 weeks at Weeks 1, 5, 9, 13, 17, and 21.	
Reporting group title	Cohort B: Donidalorsen 80 mg
Reporting group description: Subjects with HAE-1/HAE-2 received donidalorsen, 80 mg, SC, every 8 weeks at Weeks 1, 9, and 17.	

Primary: Time-Normalized Investigator-Confirmed (IC) HAE Attack Rate (Per Month) From Week 1 to Week 25

End point title	Time-Normalized Investigator-Confirmed (IC) HAE Attack Rate (Per Month) From Week 1 to Week 25
End point description: The time-adjusted HAE attack rate was calculated as number of IC HAE attacks occurring from Week 1 to Week 25, divided by the number of days the subject contributed to the period multiplied by 28 days. An HAE attack was defined as an event with signs or symptoms consistent with an attack in at least 1 of the locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). The full analysis set (FAS) included all randomized subjects who received at least 1 dose of the study drug (donidalorsen or placebo). As given in protocol/SAP, data for placebo subjects from Cohort A and Cohort B was pooled for comparison to donidalorsen treated subjects.	
End point type	Primary
End point timeframe: Week 1 to Week 25	

End point values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	45	23	
Units: HAE attacks per month				
least squares mean (confidence interval 95%)	2.26 (1.657 to 3.085)	0.44 (0.265 to 0.727)	1.02 (0.651 to 1.594)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The Poisson regression model includes treatment groups, baseline (the run-in period HAE attack rate),

the treatment-by-baseline interaction as a covariate, and the logarithm of time in every-4-week that each subject was observed from Week 1 to Week 25 used as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson regression model to account for potential over dispersion.

Model adjusted rate ratio from Poisson regression model.

Comparison groups	Pooled Placebo v Cohort A: Donidalorsen 80 mg
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson regression model
Parameter estimate	IC HAE attack rate ratio
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.107
upper limit	0.351

Statistical analysis title

Statistical analysis 2

Statistical analysis description:

The Poisson regression model includes treatment groups, baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time in every-4-week that each subject

was observed from Week 1 to Week 25 used as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson regression model to account for potential overdispersion.

Model adjusted rate ratio from Poisson regression model.

Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Poisson regression model
Parameter estimate	IC HAE attack rate ratio
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.261
upper limit	0.777

Secondary: Percentage of IC HAE Attack-Free Subjects From Week 5 to Week 25

End point title	Percentage of IC HAE Attack-Free Subjects From Week 5 to Week 25
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End point description:

An HAE attack was defined as an event with signs or symptoms consistent with an attack in at least 1 of the locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking,

difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). Percentages are rounded off to the nearest decimal. The FAS included all randomized subjects who received at least 1 dose of the study drug (donidalorsen or placebo). As given in protocol/SAP, data for placebo subjects from Cohort A and Cohort B was pooled for comparison to donidalorsen treated subjects.

End point type	Secondary
End point timeframe:	
Week 5 to Week 25	

End point values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	45	23	
Units: Percentage of subjects				
number (not applicable)	9.1	53.3	34.8	

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24 ^[1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	22.85

Notes:

[1] - p-value was calculated based on logistic regression with baseline and the treatment-by-baseline interaction as a covariate.

Statistical analysis title	Statistical analysis 1
Comparison groups	Pooled Placebo v Cohort A: Donidalorsen 80 mg
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 ^[2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.79

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.34
upper limit	59.36

Notes:

[2] - p-value was calculated based on logistic regression with baseline and the treatment-by-baseline interaction as a covariate.

Secondary: Time-Normalized IC HAE Attack Rate (Per Month) From Week 5 to Week 25

End point title	Time-Normalized IC HAE Attack Rate (Per Month) From Week 5 to Week 25
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End point description:

The time-adjusted HAE attack rate was calculated as number of IC HAE attacks occurring from Week 5 to Week 25, divided by the number of days the subject contributed to the period multiplied by 28 days. An HAE attack was defined as an event with signs or symptoms consistent with an attack in at least 1 of the locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). The FAS included all randomized subjects who received at least 1 dose of the study drug (donidalorsen or placebo). As given in protocol/SAP, data for placebo subjects from Cohort A and Cohort B was pooled for comparison to donidalorsen treated subjects.

End point type	Secondary
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End point timeframe:

Week 5 to Week 25

End point values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	45	23	
Units: HAE attacks per month				
least squares mean (confidence interval 95%)	2.25 (1.594 to 3.183)	0.30 (0.151 to 0.581)	0.90 (0.529 to 1.520)	

Statistical analyses

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

The Poisson regression model includes treatment groups, baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time in every-4-week that each subject was observed from Week 5 to Week 25 used as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson regression model to account for potential over dispersion.

Model adjusted rate ratio from Poisson regression model.

Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
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Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Poisson regression model
Parameter estimate	IC HAE attack rate ratio
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.212
upper limit	0.748

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The Poisson regression model includes treatment groups, baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time in every-4-week that each subject was observed from Week 5 to Week 25 used as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson regression model to account for potential over dispersion.

Model adjusted rate ratio from Poisson regression model.

Comparison groups	Pooled Placebo v Cohort A: Donidalorsen 80 mg
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson regression model
Parameter estimate	IC HAE attack rate ratio
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.062
upper limit	0.281

Secondary: Number of Subjects With a Clinical Response From Week 5 to Week 25

End point title	Number of Subjects With a Clinical Response From Week 5 to Week 25
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End point description:

Clinical response= $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline in HAE attack rate from Week 5 to Week 25. HAE attack rate between Week 5 and Week 25 for each subject is calculated as number of HAE attacks (occurring from Week 5 to week 25)/number of days subject contributed to period*28 days. An HAE attack- an event with signs or symptoms consistent with an attack in at least 1 of locations: peripheral angioedema (cutaneous swelling involving an extremity, face, neck, torso and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). Baseline= Run-in period which is period from screening to last day prior to Day 1. FAS. As per protocol/SAP, data for placebo subjects from Cohort A&B was pooled for comparison to donidalorsen treated subjects.

End point type	Secondary
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End point timeframe:

Week 5 to Week 25

End point values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	45	23	
Units: Subjects				
≥ 50% Reduction	6	42	19	
≥ 70% Reduction	4	37	15	
≥ 90% Reduction	2	28	11	

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

≥ 50% Reduction: The odds ratio and its 95% confidence interval were calculated based on a logistic regression with baseline (the time-normalized run-in period attack rate) and the treatment-by-baseline interaction as a covariate.

Comparison groups	Pooled Placebo v Cohort A: Donidalorsen 80 mg
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	310.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.63
upper limit	8279.94

Notes:

[3] - p-value was calculated based on logistic regression with baseline and the treatment-by-baseline interaction as a covariate.

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

≥ 50% Reduction: The odds ratio and its 95% confidence interval were calculated based on a logistic regression with baseline (the time-normalized run-in period attack rate) and the treatment-by-baseline interaction as a covariate.

Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
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Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	14.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.15
upper limit	69.41

Notes:

[4] - p-value was calculated based on logistic regression with baseline and the treatment-by-baseline interaction as a covariate.

Statistical analysis title	Statistical analysis 3
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Statistical analysis description:

≥ 70% Reduction: The odds ratio and its 95% confidence interval were calculated based on a logistic regression with baseline (the time-normalized run-in period attack rate) and the treatment-by-baseline interaction as a covariate.

Comparison groups	Pooled Placebo v Cohort A: Donidalorsen 80 mg
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	34.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.32
upper limit	164.87

Notes:

[5] - p-value was calculated based on logistic regression with baseline and the treatment-by-baseline interaction as a covariate.

Statistical analysis title	Statistical analysis 4
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Statistical analysis description:

≥ 70% Reduction: The odds ratio and its 95% confidence interval were calculated based on a logistic regression with baseline (the time-normalized run-in period attack rate) and the treatment-by-baseline interaction as a covariate.

Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.05
upper limit	41.09

Notes:

[6] - p-value was calculated based on logistic regression with baseline and the treatment-by-baseline interaction as a covariate.

Statistical analysis title	Statistical analysis 5
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Statistical analysis description:

≥ 90% Reduction: The odds ratio and its 95% confidence interval were calculated based on a logistic regression with baseline (the time-normalized run-in period attack rate) and the treatment-by-baseline interaction as a covariate.

Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	17.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.36
upper limit	86.42

Notes:

[7] - p-value was calculated based on logistic regression with baseline and the treatment-by-baseline interaction as a covariate.

Statistical analysis title	Statistical analysis 6
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Statistical analysis description:

≥ 90% Reduction: The odds ratio and its 95% confidence interval were calculated based on a logistic regression with baseline (the time-normalized run-in period attack rate) and the treatment-by-baseline interaction as a covariate.

Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014 ^[8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.56
upper limit	48.52

Notes:

[8] - p-value was calculated based on logistic regression with baseline and the treatment-by-baseline interaction as a covariate.

Secondary: Time-Normalized Moderate or Severe IC HAE Attack Rate (Per Month)

From Week 5 to Week 25

End point title	Time-Normalized Moderate or Severe IC HAE Attack Rate (Per Month) From Week 5 to Week 25
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End point description:

Time-adjusted HAE attack rate was calculated as number of IC moderate or severe HAE attacks occurring from Week 5 to Week 25, divided by the number of days the subject contributed to the period multiplied by 28 days. An HAE attack was defined as an event with signs or symptoms consistent with an attack in at least 1 of the locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of tongue, palate, uvula, or larynx). The FAS included all randomized subjects who received at least 1 dose of the study drug (donidalorsen or placebo). As given in protocol/SAP, data for placebo subjects from Cohort A and Cohort B was pooled for comparison to donidalorsen treated subjects.

End point type	Secondary
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End point timeframe:

Week 5 to Week 25

End point values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	45	23	
Units: HAE attacks per month				
least squares mean (confidence interval 95%)	1.15 (0.718 to 1.831)	0.12 (0.044 to 0.351)	0.68 (0.372 to 1.229)	

Statistical analyses

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

The Poisson regression model includes treatment groups, baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time in every-4-week that each subject was observed from Week 5 to Week 25 used as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson regression model to account for potential over dispersion. Model adjusted rate ratio from Poisson regression model.

Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.173
Method	Poisson regression model
Parameter estimate	IC HAE attack rate ratio
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.276
upper limit	1.26

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The Poisson regression model includes treatment groups, baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time in every-4-week that each subject

was observed from Week 5 to Week 25 used as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson

regression model to account for potential over dispersion.

Model adjusted rate ratio from Poisson regression model.

Comparison groups	Pooled Placebo v Cohort A: Donidalorsen 80 mg
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson regression model
Parameter estimate	IC HAE attack rate ratio
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.035
upper limit	0.339

Secondary: IC HAE Attack Rate Requiring Acute HAE Therapy From Week 5 to Week 25

End point title	IC HAE Attack Rate Requiring Acute HAE Therapy From Week 5 to Week 25
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End point description:

Time-adjusted HAE attack rate= number of investigator-confirmed HAE attacks requiring acute therapy occurring from Week 5 to Week 25, divided by number of days subject contributed to period multiplied by 28 days. HAE attack- event with signs or symptoms consistent with an attack in at least 1 of locations: peripheral angioedema (cutaneous swelling involving an extremity, the face, neck, torso, and/or genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx).). HAE attacks requiring acute therapy included those attacks with following concomitant medications c1 esterase inhibitors (human and recombinant), plasma kallikrein inhibitor (human), and bradykinin antagonist. FAS. As per protocol/SAP, data for placebo subjects from Cohort A and Cohort B was pooled.

End point type	Secondary
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End point timeframe:

Week 5 to Week 25

End point values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	45	23	
Units: HAE attacks per month				
least squares mean (confidence interval 95%)	1.80 (1.232 to 2.616)	0.15 (0.057 to 0.391)	0.59 (0.308 to 1.146)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

The Poisson regression model includes treatment groups, baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time in every-4-week that each subject was observed from Week 5 to Week 25 used as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson regression model to account for potential over dispersion.

Model adjusted rate ratio from Poisson regression model.

Comparison groups	Pooled Placebo v Cohort A: Donidalorsen 80 mg
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson regression model
Parameter estimate	IC HAE attack rate ratio
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.234

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

The Poisson regression model includes treatment groups, baseline (the run-in period HAE attack rate), the treatment-by-baseline interaction as a covariate, and the logarithm of time in every-4-week that each subject was observed from Week 5 to Week 25 used as an offset variable. Pearson chi-square scaling of standard errors was used in the Poisson regression model to account for potential over dispersion.

Model adjusted rate ratio from Poisson regression model.

Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Poisson regression model
Parameter estimate	IC HAE attack rate ratio
Point estimate	0.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.155
upper limit	0.706

Secondary: Change From Baseline in Angioedema Quality of Life (AE-QoL) Questionnaire Total Score at Week 25

End point title	Change From Baseline in Angioedema Quality of Life (AE-QoL) Questionnaire Total Score at Week 25
End point description:	
AE-QoL: validated tool to assess symptom-specific health-related QOL impairment in subjects suffering from recurrent angioedema. It is a self-administered questionnaire comprising 17 questions across 4 domains: functioning, fatigue/mood, fears/shame, and food. The responses are scored from 0 to 4 where, 0=never, 1=rarely, 2=occasionally, 3=often, 4=very often. The AE-QoL domain scores and total score were calculated by using the following formula: (Sum score of all completed items) / (maximum sum score of all possible items) × 100. Total scores ranges from 0 to 100, with higher scores indicating greater impairment. Negative change from baseline indicates improvement. Calculated domain and total scores were not raw scores but linear transformations to a 0 to 100 scale. Baseline= score on Study Day 1. FAS. Subjects analyzed= number of subjects with data available for analysis at specified time point. As per protocol/SAP, data for placebo subjects from Cohort A and Cohort B was pooled.	
End point type	Secondary
End point timeframe:	
Week 25	

End point values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	42	22	
Units: Score on a scale				
least squares mean (confidence interval 95%)	-6.19 (-13.737 to 1.353)	-24.76 (-29.860 to -19.652)	-19.85 (-26.960 to -12.734)	

Statistical analyses

Statistical analysis title	Statistical analysis 2
Comparison groups	Pooled Placebo v Cohort B: Donidalorsen 80 mg
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	MMRM
Parameter estimate	Treatment difference]
Point estimate	-13.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.024
upper limit	-3.286

Statistical analysis title	Statistical analysis 1
Comparison groups	Pooled Placebo v Cohort A: Donidalorsen 80 mg
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model with repeated measures(MMRM)
Parameter estimate	Treatment difference
Point estimate	-18.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.673
upper limit	-9.454

Secondary: Percentage of Subjects Who Are Well Controlled on the Angioedema Control Test (AECT) at Week 25

End point title	Percentage of Subjects Who Are Well Controlled on the Angioedema Control Test (AECT) at Week 25
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End point description:

AECT is a validated subject-reported outcome instrument to assess disease activity in subjects with recurrent angioedema. Questionnaire consists of 4 questions asking about the frequency and severity of angioedema experienced in last four weeks. Each question has 5 response choices with total score ranging from 0 to 16. AECT can be used to identify subjects with poorly controlled disease by working with a cutoff value of greater than or equal to 10 points. Subjects who score less than 10 points (0-9) in the AECT have poorly controlled disease whereas subjects with well-controlled disease score 10-16 points. Percentages are rounded off to the nearest decimal. FAS included all randomized subjects who received at least 1 dose of the study drug (donidalorsen or placebo). Subjects analyzed indicates the number of subjects with data available for analysis at the specified timepoint. As per protocol/SAP, data for placebo subjects from Cohort A and Cohort B was pooled.

End point type	Secondary
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End point timeframe:

Week 25

End point values	Pooled Placebo	Cohort A: Donidalorsen 80 mg	Cohort B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	42	22	
Units: Percentage of subjects				
number (not applicable)	47.1	92.9	77.3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 38

Adverse event reporting additional description:

The safety set included all randomized subjects who received at least 1 dose of the study drug (donidalorsen or placebo). As pre-specified in the protocol and statistical analysis plan, for purposes of analysis, data for placebo subjects from Cohort A and Cohort B was pooled for comparison to donidalorsen treated subjects.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	Pooled Placebo
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Reporting group description:

Subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) received placebo subcutaneously (SC) either every 4 weeks (Week 1, 5, 9, 13,17, and 21) or 8 weeks (Week 1, 9, and 17).

Reporting group title	Cohort B: Donidalorsen 80 mg
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Reporting group description:

Subjects with HAE-1/HAE-2 received donidalorsen, 80 mg, SC, every 8 weeks at Weeks 1, 9, and 17.

Reporting group title	Cohort A: Donidalorsen 80 mg
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Reporting group description:

Subjects with HAE-1/HAE-2 received donidalorsen, 80 mg, SC, every 4 weeks at Weeks 1, 5, 9, 13, 17, and 21.

Serious adverse events	Pooled Placebo	Cohort B: Donidalorsen 80 mg	Cohort A: Donidalorsen 80 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	0 / 45 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Limb Injury			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	0 / 45 (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	Pooled Placebo	Cohort B: Donidalorsen 80 mg	Cohort A: Donidalorsen 80 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 22 (68.18%)	23 / 23 (100.00%)	22 / 45 (48.89%)
Injury, poisoning and procedural complications			
Limb Injury			
subjects affected / exposed	3 / 22 (13.64%)	1 / 23 (4.35%)	0 / 45 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 22 (18.18%)	2 / 23 (8.70%)	7 / 45 (15.56%)
occurrences (all)	6	7	18
General disorders and administration site conditions			
Injection Site Discolouration			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	3 / 45 (6.67%)
occurrences (all)	0	1	9
Injection Site Pruritus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	9
Injection Site Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	8
Pyrexia			
subjects affected / exposed	1 / 22 (4.55%)	3 / 23 (13.04%)	0 / 45 (0.00%)
occurrences (all)	1	3	0
Injection Site Erythema			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	6 / 45 (13.33%)
occurrences (all)	0	1	14
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	3 / 45 (6.67%)
occurrences (all)	0	0	4
Abdominal Pain			
subjects affected / exposed	2 / 22 (9.09%)	0 / 23 (0.00%)	1 / 45 (2.22%)
occurrences (all)	2	0	1
Dyspepsia			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 23 (0.00%) 0	0 / 45 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 23 (8.70%) 2	0 / 45 (0.00%) 0
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 23 (4.35%) 1	3 / 45 (6.67%) 3
Infections and infestations Oral Herpes subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 23 (8.70%) 2	0 / 45 (0.00%) 0
Covid-19 subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	1 / 23 (4.35%) 1	1 / 45 (2.22%) 1
Gastroenteritis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	1 / 23 (4.35%) 1	1 / 45 (2.22%) 1
Sinusitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 23 (0.00%) 0	0 / 45 (0.00%) 0
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	3 / 23 (13.04%) 3	4 / 45 (8.89%) 4
Influenza subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	5 / 23 (21.74%) 5	4 / 45 (8.89%) 4
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 22 (22.73%) 5	3 / 23 (13.04%) 7	6 / 45 (13.33%) 9
Urinary Tract Infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 23 (8.70%) 2	4 / 45 (8.89%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2021	Secondary and exploratory objectives were summarized into more cohesive objectives because details were already provided in the endpoints. Added the inclusion and rationale for of a second dosing Cohort with a dose frequency of per 8 weeks (donidalorsen 80 mg once per 8 weeks). Additional subjects were added to the study with a new dosing cohort (donidalorsen 80 mg every 8 weeks). A clarification was added to the collection of HAE attack details that confirmed HAE attacks were based on symptoms and Investigator diagnosis, not on presence of symptoms alone. Safety stopping rules for platelet count and actions in subjects with confirmed low platelet count were updated to increase monitoring frequency for platelets for counts between 100,000 /mm ³ and 125,000/mm ³ and added requirement for Sponsor approval for continued dosing when platelets were $\geq 75,000/\text{mm}^3$ to $\leq 100,000/\text{mm}^3$. Added a safety monitoring plan. The definition of clinically relevant non-major bleeding events was updated to the most current version. Updated the Safety and PK population definitions to include randomized subjects. The primary efficacy analysis was updated to reflect that the primary analysis was to compare between the 80 mg donidalorsen-4 group versus placebo group. The recall period for the work productivity and impairment (WPAI) questionnaire was 7 days. Therefore, this assessment was completed by the subject weekly throughout the entire study rather than intermittently as specified in the original protocol. Added directions to follow if urine pregnancy test was positive in Schedule of Procedures. Electrocardiogram (ECG)-related assessment changes were added to the Schedule of Procedures including predose and 2 hours after dose. Updated Schedule of Procedures by adding a physical exam at every visit to examine for reactions due to study drug administration. Updated Schedule of Procedures and PK Sampling Schedule to reflect the new dosing groups.
01 October 2021	The time points for PK sampling were accidentally inverted in the original protocol. Study Drug administration did not occur at Week 25 and therefore, the time points for PK sampling at Weeks 21 and 25 were switched. Also added 2-hours post-dosing at Week 21 only for Cohort A and at Week 17 only for Cohort B. Added the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept. 2007 to indicate how Adverse Events (AE) were graded. Exclusion criteria's were updated.
12 July 2022	Added a clarification on how many attacks were required for a subject to be randomized i.e., ≥ 2 HAE attacks. Changed inclusion criteria 6 and 7 and contraception requirements to include the use of acceptable instead of highly effective contraceptive methods. Added a clarification to the exclusion criteria to exclude subjects with alcohol or drug abuse. Added a clarification to contraception requirements to note that the exclusion of combined estrogen and progesterone hormonal contraception was intended for oral hormonal therapy, and not for intrauterine or intravaginal estrogens. Updated the urine protein-creatinine ratio (UPCR) to a more accurate lab measure: UPCR > 1000 mg/g confirmed a quantitative total urine protein measurement of >1.0 g/24 hours. Added a clarification that the final analysis was to be performed before the follow-up period was completed. Deleted reference that dose reductions were allowed from the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported