



Clinical trial results:

A Randomized, Double Blind, Placebo Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second Generation Ligand Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

Summary

EudraCT number	2019-001044-22
Trial protocol	GB
Global end of trial date	01 March 2021

Results information

Result version number	v1 (current)
This version publication date	22 October 2022
First version publication date	22 October 2022

Trial information

Trial identification

Sponsor protocol code	ISIS721744-CS2
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04030598
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. , 1 760603-2387, ClinicalTrials@ionisph.com
Scientific contact	Ionis Clinical Trial Information , Ionis Pharmaceuticals, Inc. , 1 760603-2387, ClinicalTrials@ionisph.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	01 March 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	01 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of antisense inhibitor of prekallikrein donidalorsen (IONIS PKK-LRx) in subjects with hereditary angioedema (HAE) type 1 (HAE-1), HAE type 2 (HAE-2), or HAE with normal C1-inhibitor (C1-INH).

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	07 January 2020
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: 15
Country: Number of subjects enrolled	Netherlands: 8
Worldwide total number of subjects	23
EEA total number of subjects	8

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)	22
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 7 investigative sites from 7 January 2020 to 1 March 2021.

Pre-assignment

Screening details:

Subjects with hereditary angioedema were enrolled in Part A and B. In Part A, 20 subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) were randomised in 2:1 ratio to receive donidalorsen/placebo for 13 weeks. In Part B, 3 subjects with HAE with normal C1-inhibitor (HAE-nC1-INH) received donidalorsen for 13 weeks after Part A.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: Placebo

Arm description:

Subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) received placebo subcutaneously (SC) every 4 weeks at Weeks 1, 5, 9, and 13.

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 administered (SC) every 4 weeks.

Arm title	Part 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, and 13.

Arm type	Experimental
Investigational medicinal product name	Donidalorsen 80 mg
Investigational medicinal product code	
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	Part B: Donidalorsen 80 mg
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Arm description:

Subjects with hereditary angioedema with normal C1-inhibitor (HAE-nC1-INH) received donidalorsen, 80 mg, SC, every 4 weeks at Weeks 1, 5, 9, and 13.

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

Dosage and administration details:

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

Number of subjects in period 1	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg
Started	6	14	3
Completed	6	13	3
Not completed	0	1	0
Voluntary Withdrawal	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Part A: Placebo
Reporting group description:	
Subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) received placebo subcutaneously (SC) every 4 weeks at Weeks 1, 5, 9, and 13.	
Reporting group title	Part 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, and 13.	
Reporting group title	Part B: Donidalorsen 80 mg
Reporting group description:	
Subjects with hereditary angioedema with normal C1-inhibitor (HAE-nC1-INH) received donidalorsen, 80 mg, SC, every 4 weeks at Weeks 1, 5, 9, and 13.	

Reporting group values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg
Number of subjects	6	14	3
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	40.0	37.8	34.0
full range (min-max)	22 to 56	21 to 66	25 to 40
Gender categorical Units: Subjects			
Female	4	9	3
Male	2	5	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	6	13	3
Unknown or Not Reported	0	0	0
Race Units: Subjects			
Black or African American	1	0	0
White	5	14	3

Reporting group values	Total		
Number of subjects	23		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years arithmetic mean full range (min-max)	-		
Gender categorical Units: Subjects			
Female	16		
Male	7		
Ethnicity Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	22		
Unknown or Not Reported	0		
Race Units: Subjects			
Black or African American	1		
White	22		

End points

End points reporting groups

Reporting group title	Part A: Placebo
Reporting group description: Subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) received placebo subcutaneously (SC) every 4 weeks at Weeks 1, 5, 9, and 13.	
Reporting group title	Part 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, and 13.	
Reporting group title	Part B: Donidalorsen 80 mg
Reporting group description: Subjects with hereditary angioedema with normal C1-inhibitor (HAE-nC1-INH) received donidalorsen, 80 mg, SC, every 4 weeks at Weeks 1, 5, 9, and 13.	

Primary: Time-normalised Number of HAE Attacks (Per Month) From Week 1 to Week 17

End point title	Time-normalised Number of HAE Attacks (Per Month) From Week 1 to Week 17
End point description: The Week 1 to end of on-treatment period HAE attack rate was calculated for each subject as number of HAE attacks occurring from Week 1 to 28 days after the last dose date 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 intent-to-treat (ITT) population included all enrolled or randomised subjects.	
End point type	Primary
End point timeframe: Week 1 to Week 17	

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	14	3	
Units: HAE attacks per month				
arithmetic mean (standard deviation)	2.21 (± 1.558)	0.23 (± 0.268)	1.52 (± 2.221)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.001
Method	Wald Chi-Square
Parameter estimate	Percentage Difference
Point estimate	-90
Confidence interval	
level	95 %
sides	2-sided
lower limit	-96
upper limit	-76

Notes:

[1] - The percentage difference in mean investigator-confirmed HAE attack rate between donidalorsen 80 mg and placebo was calculated as 100 percentage (%) × (mean rate ratio -1).

Secondary: Time-normalised Number of Investigator-confirmed HAE Attacks (Per Month) From Week 5 to Week 17

End point title	Time-normalised Number of Investigator-confirmed HAE Attacks (Per Month) From Week 5 to Week 17
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End point description:

The Week 5 to end of on-treatment period HAE attack rate was calculated for each subject as number of HAE attacks occurring from Week 5 to 28 days after the last dose date 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 diarrhoea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). ITT population included all enrolled or randomised subjects.

End point type	Secondary
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End point timeframe:

Week 5 to Week 17

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	14	3	
Units: HAE attacks per month				
arithmetic mean (standard deviation)	2.06 (± 1.574)	0.07 (± 0.267)	1.78 (± 2.795)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part A: Donidalorsen 80 mg v Part A: Placebo

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.003
Method	Wald Chi-Square
Parameter estimate	Percentage Difference
Point estimate	-97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100
upper limit	-69

Notes:

[2] - The percentage difference in mean investigator-confirmed HAE attack rate between donidalorsen 80 mg and placebo was calculated as 100 percentage (%) × (mean rate ratio - 1).

Secondary: Time-normalised Number of Moderate or Severe Investigator-confirmed HAE Attacks (Per Month) From Week 5 to Week 17

End point title	Time-normalised Number of Moderate or Severe Investigator-confirmed HAE Attacks (Per Month) From Week 5 to Week 17
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End point description:

Week 5 to end of on-treatment period HAE attack rate was calculated for each subject as number of moderate or severe HAE attacks occurring from Week 5 to 28 days after last dose date divided by number of days subject contributed to period multiplied by 28 days. HAE attack was defined as an event with signs/symptoms consistent with attack in at least 1 locations: peripheral angioedema (cutaneous swelling involving an extremity, face, neck, torso, genitourinary region), abdominal angioedema (abdominal pain, with or without abdominal distention, nausea, vomiting, or diarrhoea), laryngeal angioedema (stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx). HAE attack severity: Mild: transient or mild discomfort, Moderate: mild to moderate limitation in activity, some assistance needed, and Severe: marked limitation in activity, assistance required. ITT population included all enrolled or randomised subjects.

End point type	Secondary
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End point timeframe:

Week 5 to Week 17

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	14	3	
Units: HAE attacks per month				
arithmetic mean (standard deviation)	1.25 (± 1.208)	0.05 (± 0.178)	0.89 (± 1.540)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.004
Method	Wald Chi-Square
Parameter estimate	Percentage Difference
Point estimate	-96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-100
upper limit	-65

Notes:

[3] - The percentage difference in mean investigator-confirmed HAE attack rate between donidalorsen 80 mg and placebo was calculated as 100 percentage (%) × (mean rate ratio -1).

Secondary: Number of Subjects With Clinical Response by Week 17

End point title	Number of Subjects With Clinical Response by Week 17
End point description:	
Clinical response was defined as a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline in HAE attack rate from Week 5 to Week 17. HAE attack rate was calculated as number of investigator-confirmed HAE attacks occurring from Week 5 to 28 days after last dose administration, divided by the number of days the subject contributed to the period multiplied by 28 days. 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). ITT=all enrolled or randomised subjects. Subjects analysed=overall number of subjects with data available for analyses.	
End point type	Secondary
End point timeframe:	
Week 5 to Week 17	

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	13	3	
Units: subjects				
$\geq 50\%$ Reduction	2	13	2	
$\geq 70\%$ Reduction	1	12	2	
$\geq 90\%$ Reduction	0	12	1	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.004
Method	Fisher Exact
Parameter estimate	Risk Difference (RD)
Point estimate	66.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.5
upper limit	95.7

Notes:

[4] - For $\geq 50\%$ reduction from Baseline in the HAE attack rate.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.003
Method	Fisher Exact
Parameter estimate	Risk Difference (RD)
Point estimate	75.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	26.8
upper limit	96.5

Notes:

[5] - For $\geq 70\%$ reduction from Baseline in the HAE attack rate.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	< 0.001
Method	Fisher Exact
Parameter estimate	Risk Difference (RD)
Point estimate	92.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	48
upper limit	99.8

Notes:

[6] - For $\geq 90\%$ reduction from Baseline in the HAE attack rate.

Secondary: Number of Investigator-confirmed HAE Attacks Requiring Acute Therapy

From Week 5 to Week 17

End point title	Number of Investigator-confirmed HAE Attacks Requiring Acute Therapy From Week 5 to Week 17
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End point description:

The Week 5 to end of on-treatment period HAE attack rate was calculated for each subject as number of HAE attacks requiring acute therapy occurring from Week 5 to 28 days after the last dose date 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 diarrhoea), 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 medical intervention or hospitalization marked on the case report form (CRFs). ITT= all enrolled or randomised subjects.

End point type	Secondary
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End point timeframe:

Week 5 to Week 17

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	14	3	
Units: HAE attacks per month				
arithmetic mean (standard deviation)	1.40 (± 1.727)	0.07 (± 0.267)	0.89 (± 1.540)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.009
Method	Wald Chi-Square
Parameter estimate	Percentage Difference
Point estimate	-95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-99
upper limit	-52

Notes:

[7] - The percentage difference in mean investigator-confirmed HAE attack rate between donidalorsen 80 mg and placebo was calculated as 100 percentage (%) × (mean rate ratio -1).

Secondary: Percentage of Cleaved High Molecular Weight Kininogen (cHMWK) Levels at Weeks 9 and 17

End point title	Percentage of Cleaved High Molecular Weight Kininogen
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End point description:

High-molecular-weight kininogen (HMWK) is an abundant protein found in plasma and it has a critical role in acute attacks of HAE. During HAE attack plasma kallikrein cleaves HMWK producing cleaved HMWK (cHMWK) and bradykinin, the major biologic peptide that promotes the oedema, one of the characteristic traits of HAE. Percentage of cHMWK levels were assessed to evaluate pharmacodynamics of donidalorsen. ITT population included all enrolled or randomised subjects. n is number of subjects with data available for analysis at specified time point.

End point type	Secondary
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End point timeframe:

Weeks 9 and 17

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	14	3	
Units: percentage of cHMWK levels				
arithmetic mean (standard deviation)				
Week 9 (n=6, 14, 3)	5.62 (± 3.255)	2.07 (± 1.241)	1.03 (± 0.115)	
Week 17 (n=6, 13, 3)	7.00 (± 4.338)	2.35 (± 1.353)	2.13 (± 0.929)	

Statistical analyses

No statistical analyses for this end point

Secondary: Prekallikrein (PKK) Activity Levels at Weeks 9 and 17

End point title	Prekallikrein (PKK) Activity Levels at Weeks 9 and 17
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End point description:

Prekallikrein (PKK) has a critical role in acute attacks of HAE. During HAE attack PKK is activated to form plasma kallikrein. Plasma kallikrein cleaves HMWK producing cleaved HMWK (cHMWK) and bradykinin, the major biologic peptide that promotes the edema, one of the characteristic traits of HAE. Prekallikrein levels were measured to assess pharmacodynamics of donidalorsen. ITT population included all enrolled or randomised subjects. n is number of subjects with data available for analysis at specified timepoint.

End point type	Secondary
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End point timeframe:

Weeks 9 and 17

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	14	3	
Units: milligram per liter (mg/L)				
arithmetic mean (standard deviation)				
Week 9 (n=6, 14, 3)	95.467 (± 23.7193)	37.676 (± 14.5639)	25.630 (± 19.2671)	

Week 17 (n=6, 13, 2)	98.600 (\pm 34.5944)	37.795 (\pm 38.6618)	28.615 (\pm 22.8042)	
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Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Consumed On-demand Medication at Weeks 9 and 17

End point title	Number of Subjects Who Consumed On-demand Medication at Weeks 9 and 17
End point description: Treatment options for HAE included on-demand treatment of attacks and prophylaxis. On-demand medication options included supplementation of C1-INH (either plasma-derived or recombinant C1-INH concentrate) and inhibition of BK2 receptor activation (BK2-receptor antagonist). The number of subjects who used on-demand medication at Week 9 (Day 57) and at Week 17 (end of the on-treatment period) were reported. ITT population included all enrolled or randomised subjects.	
End point type	Secondary
End point timeframe: Weeks 9 and 17	

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	14	3	
Units: subjects				
Week 9	6	12	3	
Week 17	6	11	3	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 9	
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Risk Difference (RD)
Point estimate	-14.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.1
upper limit	33.9

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 17	
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.521
Method	Fisher exact
Parameter estimate	Risk Difference (RD)
Point estimate	-21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.9
upper limit	27.1

Secondary: Change From Baseline in Angioedema Quality of Life (AE-QoL) Questionnaire Total Score at Weeks 9 and 17

End point title	Change From Baseline in Angioedema Quality of Life (AE-QoL) Questionnaire Total Score at Weeks 9 and 17
End point description: AE-QoL was developed to measure health-related quality of life (HRQoL) impairment in subjects with recurrent angioedema. It is a self-administered questionnaire that can be completed in less than 5 minutes. It comprises 17 items across 4 domains: functioning, fatigue/mood, fears/shame, and food. Responses use a 5-point Likert scale ranging from '0 = never' to '4 = very often.' Per-subject scores for each domain were computed using the appropriate scoring algorithm applied to the question response scores for each domain. Per-subject total scores (including all 4 domains) were similarly computed using the question response scores for all 17 questions. Outputs from scoring algorithm were normalised on scale ranging from 0 (less adverse impact) to 100 (most adverse impact). Global total score ranges from 0 to 100, with higher scores indicating greater impairment. ITT=all enrolled or randomised subjects. n= number of subjects with data available at specified timepoints.	
End point type	Secondary
End point timeframe: Baseline, Weeks 9 and 17	

End point values	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	14	3	
Units: score on a scale				
arithmetic mean (standard deviation)				
Change from Baseline at Week 9 (n=6, 14, 3)	-5.51 (\pm 13.436)	-25.84 (\pm 14.558)	-33.58 (\pm 29.452)	
Change from Baseline at Week 17 (n=6, 13, 3)	-10.17 (\pm 5.331)	-24.32 (\pm 19.201)	-32.11 (\pm 17.652)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 9	
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mixed Effect Model Repeated Measure
Point estimate	-25.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.1
upper limit	-14.74

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 17	
Comparison groups	Part A: Placebo v Part A: Donidalorsen 80 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mixed Effect Model Repeated Measure
Point estimate	-20.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.7
upper limit	-8.68

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to end of the study (Up to Week 26)

Adverse event reporting additional description:

The safety population included all enrolled subjects who received at least 1 dose of study drug (donidalorsen or placebo).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Part A: Placebo
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Reporting group description:

Subjects with hereditary angioedema type I/type II (HAE-1/HAE-2) received placebo SC every 4 weeks at Weeks 1, 5, 9, and 13.

Reporting group title	Part 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, and 13.

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

Subjects with hereditary angioedema with normal C1-inhibitor (HAE-nC1-INH) received donidalorsen, 80 mg, SC, every 4 weeks at Weeks 1, 5, 9, and 13.

Serious adverse events	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Part A: Placebo	Part A: Donidalorsen 80 mg	Part B: Donidalorsen 80 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)	2 / 14 (14.29%)	3 / 3 (100.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 6 (33.33%)	2 / 14 (14.29%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Lethargy			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0	1 / 3 (33.33%) 2
General disorders and administration site conditions			
Application site rash			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Feeling hot			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 14 (7.14%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	3
Nasal congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 14 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0	1 / 3 (33.33%) 1
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0	1 / 3 (33.33%) 1
Infections and infestations Coronavirus infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0	1 / 3 (33.33%) 1
Fungal infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0	1 / 3 (33.33%) 1
Tooth abscess subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0	1 / 3 (33.33%) 2
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 14 (0.00%) 0	1 / 3 (33.33%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2019	The primary purpose of this amendment was to specify a minimal compliance level in the inclusion criteria for completion of the Angioedema Activity Score, during the screening period, as a requirement prior to randomization to treatment in Part A, or initiation of treatment in Part B, of the study. Broadened the exclusion criteria to include elevated partial thromboplastin time (PTT), history of coagulopathy or bleeding diathesis, and renal and hepatic diseases. Modified the exclusion criteria to allow for subjects who tested positive for hepatitis B or C enzyme but were non-reactive. Provided the definition of an HAE attack and delineated how discrete attacks would be counted. Designated adverse events of special interest (AESIs). In the Schedule of Procedures, added anti-drug antibody testing at Day 15 and Day 29 visits and removed the requirement for a physical examination from the day 15 visit.
29 January 2020	The primary purpose of this amendment was to update the established mutations in the plasminogen and angiopoietin genes from the legacy description to the Human Genome Variation Society description in the diagnostic report. The plasminogen gene was changed from c.9886A>G to 988A>G and the angiopoietin-1 gene from c.807G>T to 355G>T. Changed the duration of male and female contraceptive advice from at least 13 weeks to at least 24 weeks. This allowed for near-complete elimination of ISIS 721744 as 24 weeks encompassed approximately 5 half-lives of ISIS 721744 and 1 menstrual cycle (requested by the Medicines and Healthcare products Regulatory Agency (MHRA), to comply with Clinical Trial Facilitation Group guidance (Clinical Trial Facilitation Group 2014). Added language that subject who completed Study Visit Week 17 and met eligibility requirements could start the Treatment Period in the ISIS 721744-CS3 open label study (OLE) study any time after the Week 17 visit and discontinue participation in the CS2 Post-Treatment Evaluation Period at that time. Removed as secondary endpoints the time-normalised number of HAE attacks (per month) from Week 9 to Week 21 and the time-normalised number of moderate or severe HAE attacks (per month) from Week 9 to Week 21 because subject were allowed to rollover to the ISIS 721744-CS3 OLE study after the Week 17 visit. Removed the requirement that subject must fast before visits that required blood sampling because none of the laboratories required fasting and, therefore, fasting was an unnecessary burden for the subject.
05 May 2020	The primary purpose of this amendment was to adjust the length of time subjects must not have received lanadelumab prior to screening for ISIS 721744-CS2 from 6 months to 10 weeks (i.e., 5 times the ~14-day half-life for lanadelumab). To decrease the burden of site visits where feasible for subjects, added that Study Drug administration, assessments, and procedures may have been conducted by either a Home Healthcare professional (if available) or the Study Center, as arranged by the Study Center personnel, for visits as noted in the Schedule of Procedures. To decrease the burden of pharmacokinetic (PK) sampling for subjects, revised to only a subgroup of approximately 6 subjects (rather than all subjects) would have blood draws at pre-dose, 1, 2, 4, and 6 hours post-dose on Day 1 and Day 85. This, along with a pre-dose and a 2 hour post-dose blood collection on Day 1 and Day 85 in all subjects, would provide enough information to determine PK parameters.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported