Poster #R091

Phase 2 Open-Label Extension Study Of Donidalorsen In Patients With Hereditary Angioedema: A 4-Year Analysis

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Background

- Hereditary angioedema (HAE) is a rare disease characterized by recurrent, potentially life-threatening attacks of tissue swelling[1,2]
- HAE is most often caused by C1 inhibitor (C1INH) deficiency (HAE-C1INH-Type1) or dysfunction (HAE-C1INH-Type2)[3]

Figure 1. Donidalorsen Mechanism of Action

Figure created using BioRender (https://www.biorender.com).
ASO, antisense oligonucleotide; mRNA, messenger RNA; PKK, prekallikrein; RNase H1, ribonuclease H1.

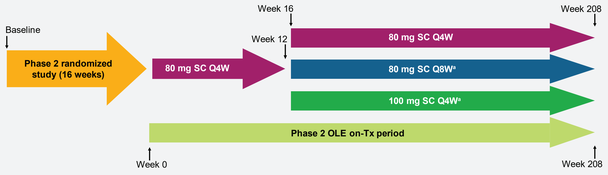
- Donidalorsen is an RNA-targeted antisense oligonucleotide that specifically and reversibly reduces plasma prekallikrein (PKK) production in the liver[4]
- Donidalorsen is indicated for prophylaxis to prevent attacks of HAE in adult and pediatric patients 12 years of age and older[5]
- Reduction of prekallikrein concentration stabilizes the kallikrein-kinin system in patients with HAE[6]
- In a phase 2 randomized clinical trial (NCT04030598), donidalorsen administered subcutaneously (SC) once every 4 weeks (Q4W) led to a 90% reduction in monthly HAE attack rate vs placebo[6]

Study Design

Patients and Trial Design

- Safety and efficacy results from an open-label extension (OLE; NCT04307381) of the phase 2 randomized study in patients with HAE-C1INH-Type1 or HAE-C1INH-Type2 are reported
- Patients were ≥18 years of age and completed the phase 2 study

Figure 2. Trial Design



[a]Switch in dosing regimen per the principal investigator.
Weeks 0–16 were termed Weeks 1–17 in previous publications. Time points have been adjusted to start at Week 0 to align with the 4-week dosing schedule.
OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously; Tx, treatment.

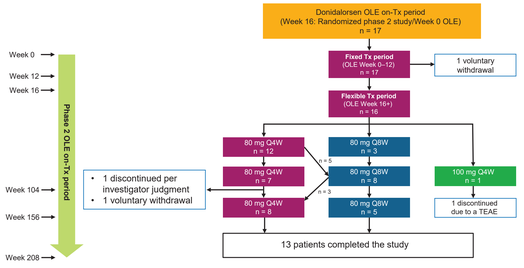
- The fixed treatment period was from Weeks 0 to 12
  - All patients received donidalorsen 80 mg SC Q4W
- The flexible treatment period was from Weeks 16 to 208
  - Patients could switch to 80 mg SC once every 8 weeks (Q8W) if they were attack-free for ≥12 weeks
- Patients who experienced HAE attacks in the prior 12 weeks could switch to 100 mg SC Q4W

Outcomes

- Primary endpoint: Incidence and severity of treatment-emergent adverse events (TEAEs)
- Secondary endpoints:
  - Monthly time-normalized HAE attack rate
  - Angioedema Quality of Life Questionnaire (AE-QoL) score at the prespecified Week 156 time point
    - AE-QoL is scored from 0 to 100 points[7]
  - Plasma PKK concentrations
- Endpoints summarize data using descriptive statistics

Results

Figure 3. Patient Disposition



OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event; Tx, treatment.

- Of the 17 patients enrolled in the OLE study, 13 patients completed the full 4 years of study treatment and 4 discontinued
- The median treatment exposure period for enrolled patients was 3.99 years
- Of the 13 patients who completed the study, 8 patients received donidalorsen Q8W during the flexible period

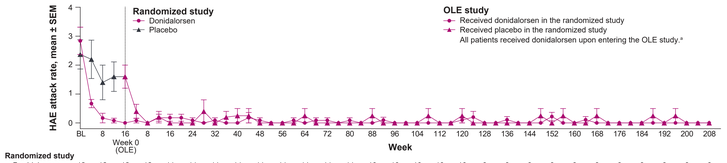
Table 1. Overview of TEAEs

n (%)	Total (N = 17)
Any TEAE[a]	15 (88)
Related to study drug[b]	7 (41)
Leading to discontinuation	1 (6)
Severity of TEAE[a]	
Mild	2 (12)
Moderate	10 (59)
Severe	3 (18)
Any serious TEAE[a]	0
Most common TEAEs (≥15% of patients)	
COVID-19	8 (47)
Influenza	5 (29)
Abdominal pain	4 (24)
Headache	4 (24)
Urinary tract infection	4 (24)
Arthralgia	3 (18)
Back pain	3 (18)
Cough	3 (18)
Gastroenteritis viral	3 (18)
Injection-site discoloration	3 (18)
Nasopharyngitis	3 (18)
Nausea	3 (18)

[a]Defined as any adverse event starting or getting worse on or after the first dose of the study drug in the open-label extension.
[b]Defined as related, possible, or missing relationship to the study drug.
COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

- Fifteen patients experienced a TEAE, and of these, 12 (80%) reported mild or moderate TEAEs
- There were no serious TEAEs and no severe TEAEs related to the study drug
- The most common TEAEs (≥15% of patients) were COVID-19 (n = 8), influenza (n = 5), and abdominal pain, headache, and urinary tract infection (n = 4 each)
- The most common TEAE related to the study drug was injection-site discoloration (n = 3)

Figure 4. Summary of HAE Attack Rates From Baseline to Week 208

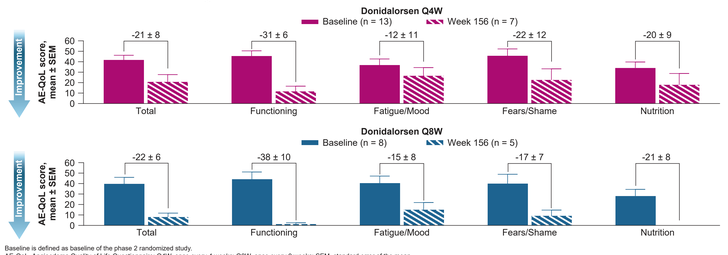


Randomized study																															
Donidalorsen, n =	12	12	12	11	11	11	11	11	11	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	8
Placebo, n =	5	5	5	5	5	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	3

BL was defined as the 56-day run-in period of the phase 2 randomized study.
[a]Data are pooled across patients in all dosing groups during the flexible dosing period (donidalorsen: 80 mg Q4W, 80 mg Q8W, or 100 mg Q4W).
BL, baseline; HAE, hereditary angioedema; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- Mean (SD) HAE attack rates decreased from baseline by 97% in the Q4W group to 0.04 (0.07) attacks/month and by 83% in the Q8W group to 0.30 (0.57) attacks/month
- The median longest attack-free duration was 990 days; 71% of patients were attack-free for >1 year

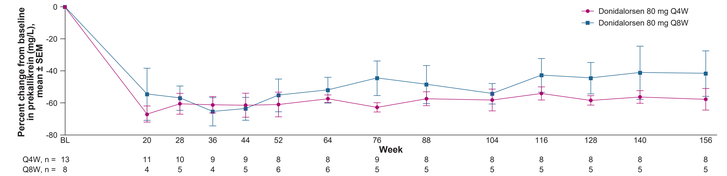
Figure 5. AE-QoL Scores at Baseline and Week 156



Baseline is defined as baseline of the phase 2 randomized study.
AE-QoL, Angioedema Quality of Life Questionnaire; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- The mean AE-QoL total score decreased by 21 points in patients receiving donidalorsen Q4W and by 22 points in patients receiving donidalorsen Q8W from baseline to the prespecified Week 156 time point
  - Among 12 patients with data at both baseline and Week 156, 10 (83%) achieved a clinically meaningful ≥6-point improvement in AE-QoL total score[8]
- Patients receiving donidalorsen Q4W or Q8W reported improvements in all AE-QoL domains

Figure 6. Trough Plasma Prekallikrein Concentrations Through Week 156



BL		20	28	36	44	52	64	76	88	104	116	128	140	156
Q4W, n =	13	11	10	9	9	8	8	9	8	8	8	8	8	8
Q8W, n =	8	4	5	4	5	6	6	5	5	5	5	5	5	5

Baseline is defined as the baseline of the phase 2 randomized study.
BL, baseline; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- Mean trough PKK concentrations among the 13 patients with data available at Week 156 decreased from baseline by 58% in the donidalorsen Q4W group and 42% in the donidalorsen Q8W group

Conclusions

- Overall, donidalorsen treatment for up to 4 years was well tolerated with an acceptable safety profile
- Donidalorsen treatment provided lasting reductions in HAE attack rates, PKK concentrations, and improvements in AE-QoL scores

Randomized, Placebo-Controlled Phase 2 Study

N = 20
HAE Type:
HAE-C1INH-Type1
HAE-C1INH-Type2

Open-Label Extension Cohort

N = 17

Study Treatment

Donidalorsen 80 mg or placebo Q4W for 16 weeks

Study Treatment

Fixed treatment period: Donidalorsen 80 mg Q4W
Flexible treatment period: Donidalorsen Q4W 80 or 100 mg, or Q8W 80 mg

Long-Term Safety

- **76% of patients completed the study**
- 71% **Mild-to-moderate TEAEs**
- **No serious TEAEs related to donidalorsen**

Efficacy

Q4W	Q8W	
97%	83%	**Reduced monthly HAE attack rates to Week 208**
21	22	**Improvement in mean AE-QoL total score**
58%	42%	**Reduced mean trough PKK concentration**
2.7 years		**Median longest attack-free interval**

AE-QoL, Angioedema Quality of Life Questionnaire; PKK, prekallikrein; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

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