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Phase 2 Open-Label Extension Of Donidalorsen In Patients With Hereditary Angioedema: A Week 196 Analysis

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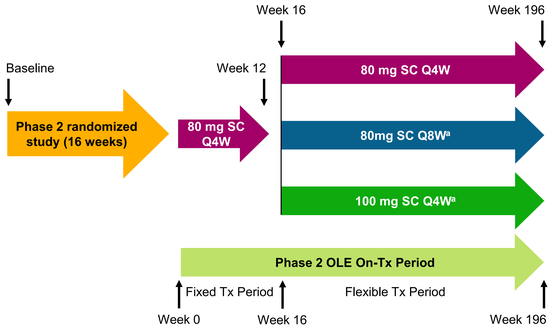
INTRODUCTION

- Hereditary angioedema (HAE) is a rare disease characterized by unpredictable bouts of swelling that may be disabling and potentially life-threatening[1–3]
- In patients with HAE, pathogenic variants of the *SERPING1* gene result in C1 inhibitor (C1INH) protein dysfunction or dysregulation that destabilizes the kallikrein-kinin system[4,5]
- Donidalorsen is an investigational RNA-targeted antisense oligonucleotide that specifically reduces plasma prekallikrein production in the liver[4,6]
- Reduced plasma prekallikrein concentration stabilizes the kallikrein-kinin system in patients with HAE, leading to decreased HAE attacks and improved disease control[2]
- A phase 2 randomized study (NCT04030598) reported a 90% reduction in HAE attacks in patients treated with donidalorsen[2]
- Here, we report the safety and efficacy of donidalorsen in an interim analysis from March 2024 of the open-label extension (OLE; NCT04307381) of the phase 2 randomized study of patients with HAE-C1INH-Type1 or HAE-C1INH-Type2 treated with donidalorsen for up to 196 weeks

METHODS

- Patients ≥18 years of age who completed the phase 2 randomized study through Week 16 were eligible to enroll in the OLE
- The OLE on-treatment period was made up of fixed and flexible treatment periods (**Figure 1**)
  - During the fixed treatment period (Weeks 0–12), all patients received donidalorsen 80 mg subcutaneously (SC) once every 4 weeks (Q4W)
  - In the flexible treatment period (Weeks 16–196), patients could switch their dosing regimen to 80 mg once every 8 weeks (Q8W) if they were attack-free for ≥12 weeks after entering the OLE study
  - Patients who experienced HAE attacks in the first 12 weeks of the OLE could be switched to 100 mg Q4W dosing
- Endpoints summarize data from the on-treatment period up to the March 2024 data cut compared with baseline from the phase 2 study (NCT04030598)
- Angioedema Quality of Life (AE-QoL) questionnaire scores and prekallikrein concentrations are reported from from the prespecified Week-156 time point

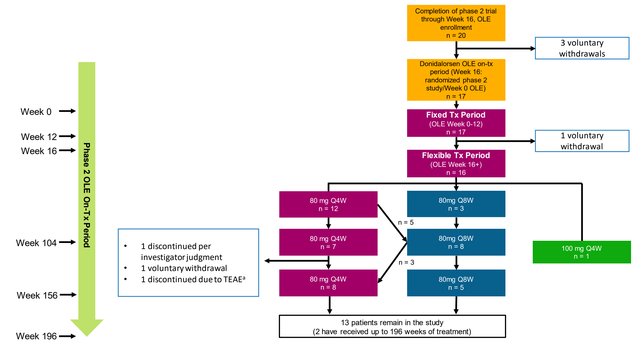
Figure 1. Study Design



[a]Switch dosing regimen per the principal investigator.
Weeks 0–16 in the phase 2 study 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; the Week 197 data cut reported here represents 196 weeks of donidalorsen treatment.
OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously; Tx, treatment.

RESULTS

Figure 2. Patient Disposition



Weeks 0–16 in the phase 2 study 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; the Week 197 data cut reported here represents 196 weeks of donidalorsen treatment.
[a]Patient received donidalorsen 100 mg Q4W.
OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; Tx, treatment.

- A total of 17 patients enrolled in the OLE study, and 13 (76%) have remained in the study for ≥3 years
- Of these, 8 patients have received donidalorsen Q8W

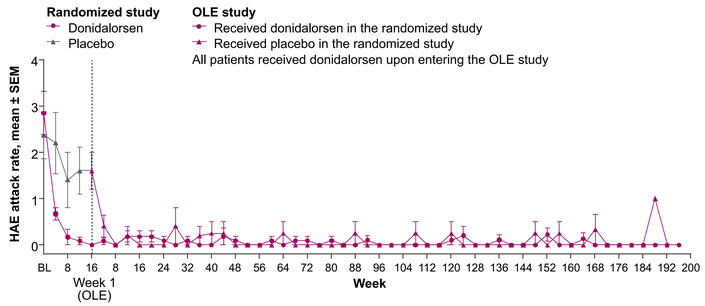
Table 1. Overview of Treatment-Emergent Adverse Events

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

[a]TEAE is defined as any adverse event starting or worsening on or after the first dose of donidalorsen.
COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

- There was 1 patient who discontinued due to a treatment-emergent adverse event (TEAE)
- Overall, 12 patients reported only mild or moderate TEAEs
  - Of these, 7 (41%) patients experienced mild or moderate TEAEs that were related to the study drug; there were no severe study-drug–related TEAEs reported
- There were no serious adverse events reported during the study
- The most common TEAEs reported were COVID-19 (n = 8), urinary tract infection (n = 4), and headache (n = 4)
- There were no clinically significant changes in electrocardiograms or clinically significant changes in any laboratory parameters, including liver function tests, platelets, or renal function

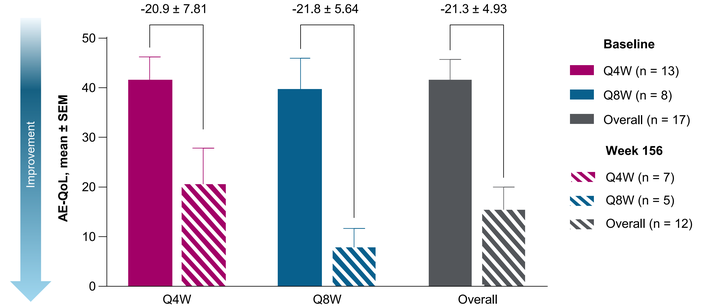
Figure 3. Summary of HAE Attack Rates



HAE, hereditary angioedema; OLE, open-label extension; SEM, standard error of the mean.

- Among all patients, the HAE attack rate during the on-treatment period decreased by 96% from baseline
- Mean (standard error of the mean; SEM) HAE attack rates were reduced from 2.70 (0.36) attacks/month at baseline to 0.06 (0.02) attacks/month overall
- For patients treated with donidalorsen Q8W (n = 8), the mean (SEM) HAE attack rate was reduced by 83%, from 2.20 (0.30) attacks/month at baseline to 0.30 (0.20) attacks/month during the flexible dosing period
- The mean (SEM) longest attack-free duration was 762 (99.64) days

Figure 4. Mean Total AE-QoL Questionnaire Scores at Week 156



AE-QoL, Angioedema Quality of Life; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- For all patients with available data at Week 156 (n = 12), the mean (SEM) AE-QoL total score decreased by 21.3 (4.93) points from baseline
- In patients with data at Week 156 who received donidalorsen Q8W (n = 5), the mean (SEM) AE-QoL total score was reduced by 21.8 (5.64) points from baseline

Changes in plasma prekallikrein

- For all patients at Week 156 (n = 13), the mean (SEM) plasma prekallikrein concentration was reduced by 51%, from 97.2 (4.8) mg/L at baseline to 46.7 (6.2) mg/L
- In patients who received donidalorsen Q8W (n = 5), the mean (SEM) prekallikrein concentration was reduced by 42%, from 102.9 (8.6) mg/L at baseline to 57.2 (10.6) mg/L at Week 156

CONCLUSIONS

Safety and Tolerability

- In this OLE over 196 weeks, donidalorsen demonstrated an acceptable safety profile and resulted in no safety signals

Efficacy

- In this OLE over 196 weeks, donidalorsen resulted in a sustained reduction in HAE attack rate for up to 196 weeks of treatment

Quality of Life

- Donidalorsen Q4W or Q8W resulted in a clinically meaningful improvement in QoL from baseline at Week 156

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DISCLOSURES

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