Poster #R092

Long-Term Efficacy And Safety Of Donidalorsen Taken Once Every 8 Weeks: 2-Year Results From OASISplus

Aleena Banerji[1], Mar Guilarte[2], Danny M Cohn[3], Laura Bordone[4], Kenneth B Newman[4], Sabrina Treadwell[4], Tao Lin[4], James Ruggles[4], Catherine A Schnabel[4], Timothy Craig[5,6]

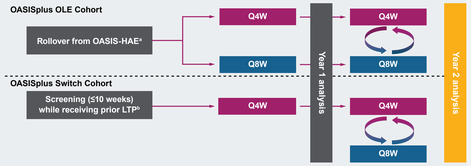
[1]Division of Allergy and Clinical Immunology, Department of Medicine, Mass General Brigham, Harvard Medical School, Boston, MA, USA; [2]Department of Allergy, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain; [3]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; [4]Ionis, Carlsbad, CA, USA; [5]Departments of Medicine, Pediatrics, Obstetrics and Gynecology, Maternal-Fetal Medicine, and Biomedical Sciences, The Pennsylvania State University, Hershey, PA, USA; [6]Vinmec International Hospital, Times City, Hanoi, Vietnam

Introduction

- Hereditary angioedema (HAE) is a rare disease characterized by painful and potentially life-threatening attacks of tissue swelling[1]
- Donidalorsen is a prekallikrein (PKK) messenger RNA–targeted antisense oligonucleotide approved for prophylaxis to prevent HAE attacks in adults and adolescents ≥12 years of age[2]
- In the pivotal phase 3 OASIS-HAE study (NCT05139810), donidalorsen administered subcutaneously once every 4 weeks (Q4W) and once every 8 weeks (Q8W) demonstrated significant reductions in mean HAE attack rate by 81% (P <0.001) and 55% (P = 0.004) over Weeks 0 to 24 and by 87% (P <0.001) and 60% (P = 0.004) over Weeks 4 to 24, respectively; acceptable safety; and improvements in quality of life and disease control over Weeks 0 to 24[3]
- In the phase 3 OASISplus study (NCT05392114), the reduction in HAE attack rate (94%) and acceptable safety observed in OASIS-HAE were sustained in the open-label extension (OLE) cohort during 1 year of treatment[4]
- In a separate prospective cohort of OASISplus, patients who switched from a prior long-term prophylactic treatment (LTP) to donidalorsen without washout via a predefined algorithm experienced similar reductions in HAE attack rates (lanadelumab, 64%; berotralstat, 83%; C1 inhibitor, 51%) and improvements in quality of life and disease control from OASISplus baseline on prior LTP (Switch cohort)[5]
- Here, we present a post hoc analysis of the safety and efficacy of donidalorsen in patients who received Q8W dosing at any point in the OLE and Switch cohorts over 2 years of treatment

Study Design

Figure 1. OASISplus Study Design

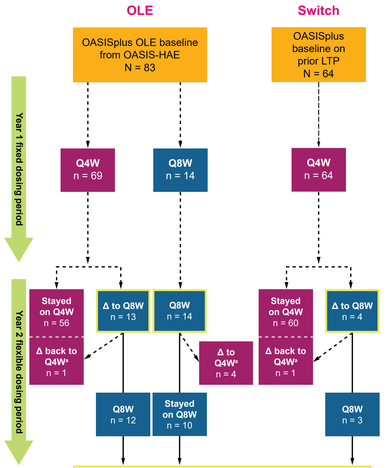


[a]Patients who were not attack free for ≥8 weeks (Weeks 16–24 in OASIS-HAE) received donidalorsen 80 mg SC Q4W.
[b]Prior LTPs were lanadelumab, C1INH, and berotralstat.
C1INH, C1 inhibitor; LTP, long-term prophylactic treatment; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SC, subcutaneously.

- Eligible patients were ≥12 years of age with HAE
- In the OLE cohort, patients from OASIS-HAE rolled over to OASISplus and continued the same dosing frequency, unless not attack free for the last 8 weeks of OASIS-HAE, in which case they received donidalorsen Q4W in OASISplus
  - Baseline in the OLE cohort is defined as the OASIS-HAE run-in period
- In the Switch cohort, patients on stable doses of LTPs switched to donidalorsen Q4W without washout via a predefined algorithm
  - Baseline in the Switch cohort is defined as the OASISplus run-in period
- After Year 1, patients could change between Q4W and Q8W dosing with the option to change back to their original dosing
- This post hoc analysis included the following 3 patient subgroups:
  - OLE patients who initiated OASISplus with Q8W dosing and continued on Q8W dosing through Year 2 (OLE index Q8W)
  - OLE patients who changed from Q4W dosing in Year 1 to Q8W dosing in Year 2 (OLE Q4W to Q8W)
  - Switch patients who changed from Q4W dosing in Year 1 to Q8W dosing in Year 2 (Switch Q4W to Q8W)
- Endpoints assessed in this post hoc analysis were as follows:
  - Incidence of treatment-emergent adverse events (TEAEs)
  - Time-normalized rate of investigator-confirmed HAE attacks per month over 2 years
  - Percent change in plasma PKK concentration from baseline
  - Angioedema Quality of Life Questionnaire (AE-QoL) total score at baseline, Year 1, and Year 2

Results

Figure 2. Dose Changes to Q8W Over 2 Years



[a]In patients who changed to or back to Q4W, data from their time on Q8W dosing are included in the post hoc analysis.
Δ, change; LTP, long-term prophylactic treatment; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- Fourteen OLE patients received donidalorsen Q8W at the beginning of OASISplus, and 13 joined these patients from the Q4W group after Year 1 (OLE Q4W to Q8W)
  - Four patients in the OLE index Q8W group changed to Q4W dosing after Year 1
- In the Switch cohort, 4 patients changed from Q4W to Q8W dosing after Year 1, and of these, 1 patient changed back to Q4W dosing

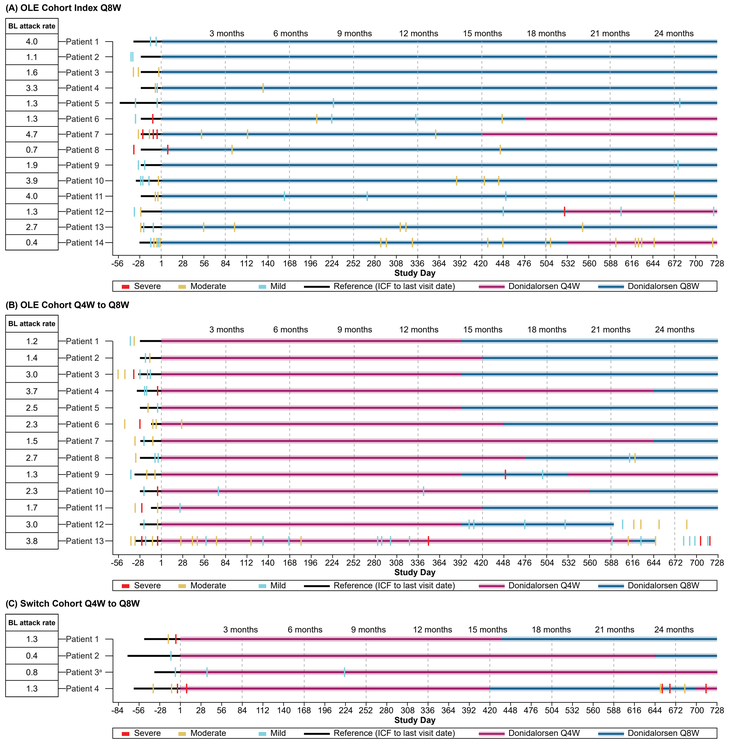
Table 1. Baseline Demographics of Patients Who Received Q8W Dosing

	OLE Cohort		Switch Cohort Q4W to Q8W (n = 4)
	Index Q8W (n = 14)	Q4W to Q8W (n = 13)	
Age, years, mean ± SD	30 ± 9	33 ± 10	54 ± 5
Sex, n (%)			
Male	9 (64)	6 (46)	1 (25)
Female	5 (36)	7 (54)	3 (75)
Race n (%)			
White	14 (100)	11 (85)	4 (100)
American Indian or Alaska Native	0	1 (8)	0
Asian	0	1 (8)	0

OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SD, standard deviation.

- Most patients included in this analysis were White with a mean age ranging from 30 to 54 years

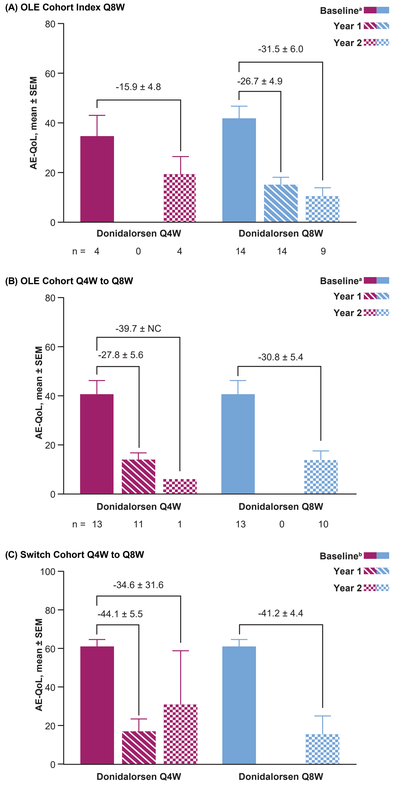
Figure 3. Illustration of Dosing Transitions Over 2 Years



The baseline attack rate represents the monthly HAE attack rate in the run-in period of the OASIS-HAE study for the OLE cohort and the run-in period of the OASISplus study in the Switch cohort.
[a]Patient changed to Q8W dosing during the follow-up period on Day 763.
HAE, hereditary angioedema; BL, baseline; ICF, informed consent form; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks.

- Overall reductions in HAE attack rate from OASIS-HAE baseline were 95% (Q4W, 92%; Q8W, 94%) in the OLE index Q8W cohort (n = 14) over 2 years and 97% (Q4W, 97%; Q8W, 92%) in the OLE cohort that changed from Q4W to Q8W dosing (n = 13) during Year 2
- In the Switch cohort, for patients who changed from Q4W to Q8W dosing (n = 4), the reduction in HAE attack rate was 91% (Q4W, 95%; Q8W, 86%) from OASISplus baseline on prior LTP through Year 2
- Only 2 patients who changed to Q8W dosing changed back to their original Q4W dosing
- PKK concentrations decreased by 55% (Q4W, 75%; Q8W, 47%) in the OLE index Q8W group and by 52% (Q4W, 87%; Q8W, 47%) in the OLE Q4W to Q8W group from OASIS-HAE baseline, and by 62% (Q4W, 72%; Q8W, 52%) in the Switch Q4W to Q8W group from OASISplus baseline on prior LTP to Year 2

Figure 4. Change in AE-QoL Total Score



[a]Baseline in the OLE cohort is defined as the last measurement on or before Day 1 of the OASIS-HAE study.
[b]Baseline in the Switch cohort is defined as the last measurement on or before Day 1 of the OASISplus study.
AE-QoL, Angioedema Quality of Life Questionnaire; NC, not calculated; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SEM, standard error of the mean.

- Clinically meaningful improvement in mean AE-QoL total score (≥6 points)[6] was reported in all 3 subgroups: 26.7 points in OLE cohort index Q8W patients, 31.6 points in OLE cohort Q4W to Q8W patients, and 37.9 points in Switch cohort Q4W to Q8W patients

Table 2. Summary of TEAEs in Patients Who Received Q8W Dosing

n (%)	OLE Cohort		Switch Cohort Q4W to Q8W (n = 4)
	Index Q8W (n = 14)	Q4W to Q8W (n = 13)	
Any TEAE	12 (86)	13 (100)	3 (75)
Related to study drug	3 (21)	6 (46)	2 (50)
Leading to discontinuation	0	1 (8)	0
Any serious TEAE	1 (7)[a]	2 (15)[b]	0
Most common TEAEs (>10% of total patients)			
Nasopharyngitis	5 (36)	3 (23)	3 (75)
Headache	3 (21)	4 (31)	0
Upper respiratory tract infection	0	5 (38)	0
Back pain	2 (14)	3 (23)	0
Diarrhea	1 (7)	3 (23)	0
Injection-site discoloration	1 (7)	2 (15)	1 (25)
Nausea	2 (14)	2 (15)	0
Pyrexia	2 (14)	2 (15)	0
Viral infection	1 (7)	3 (23)	0
ALT increased	2 (14)	1 (8)	0
Ear pain	1 (7)	2 (15)	0
Viral gastroenteritis	1 (7)	2 (15)	0
Vomiting	2 (14)	1 (8)	0

[a]Patient experienced a benign uterine leiomyoma.
[b]Serious TEAEs were miscarriage and benign uterine leiomyoma.
ALT, alanine aminotransferase; OLE, open-label extension; Q4W, once every 4 weeks; Q8W, once every 8 weeks; TEAE, treatment-emergent adverse event.

- Most TEAEs were mild to moderate in severity
- The serious TEAEs were not related to the study drug

Conclusions

- Patients who changed from Q4W to Q8W dosing after Year 1 had comparable reductions in mean HAE attack rate (OLE Q4W to Q8W, 97%; Switch Q4W to Q8W, 91%) with those who were indexed to donidalorsen Q8W and received treatment for 2 years (95%)
- Reductions in mean PKK concentrations were maintained over 2 years and during the changes in dosing
- Changes in mean AE-QoL total score indicated clinically meaningful improvements in the Q8W group
- Patients who received Q8W dosing had acceptable safety with few serious TEAEs not related to treatment, and most TEAEs were mild to moderate in severity

REFERENCES

1. Watt M, et al. *Orphanet J Rare Dis.* 2026;21(1):55.
2. Dawnzera (donidalorsen). *Full Prescribing Information.* Carlsbad, CA: Ionis Pharmaceuticals, Inc.; 2025.
3. Riedl MA, et al. *N Engl J Med.* 2024;391(1):21-31.
4. Lumry WR, et al. *J Asthma Allergy.* 2026;19:592079.
5. Riedl MA, et al. *Allergy.* 2026;81(8):2833-42.
6. Weller K, et al. *Allergy.* 2016;71(8):1203-9.

ACKNOWLEDGMENTS

We thank the study participants and their families and the team of investigators, research coordinators, and study staff. We also thank Lauren Elfman, PharmD, of Ionis, for editorial review. Medical writing and editorial assistance were provided by Sophia Nies, PharmD, of Red Nucleus, and funded by Ionis Pharmaceuticals, Inc. The study was funded by Ionis Pharmaceuticals, Inc.

DISCLOSURES

AB reports grants from Astria, Intellia, and Ionis; and being on advisory boards for ADARx, Astria, BioCryst, CSL Behring, Intellia, Ionis, KalVista, Pharvaris, and Takeda. **MG** has served as a speaker or advisor and/or received research funding from BioCryst, BioMarin Pharmaceutical, Blueprint Medicines, CSL Behring, KalVista, Novartis, Pharvaris, and Takeda. **DMC** has received speaker or consultancy fees from ADARx, Amgen, Astria, BioCryst, CSL Behring, Intellia, Ionis, KalVista, Otsuka, Pharvaris, and Takeda. **LB, KBN, ST, TL, JR,** and **CAS** are employees of Ionis. **TC** has received research support from ADARx, Argo, Astria, BioMarin Pharmaceutical, CSL Behring, Intellia, Ionis, KalVista, Pharvaris, and Takeda; consulted for ADARx, Astria, BioMarin Pharmaceutical, CSL Behring, Grifols, Intellia, Ionis, KalVista, Pharvaris, and Takeda; and provided speaker presentations for Astria, CSL Behring, Grifols, Ionis, KalVista, and Takeda.