



Ionis presents positive results from OASIS-HAE and OASISplus studies of investigational medicine donidalorsen in patients with hereditary angioedema

May 31, 2024

- Donidalorsen delivered significant and sustained reductions in HAE attacks, with high levels of disease control and improvement in quality of life measures with monthly or every two-month dosing; continued attack rate reduction over time
- In first-of-its-kind prospective analysis, patients switching from prior prophylactic treatment to donidalorsen experienced further reductions in mean monthly HAE attack rates from baseline
- Donidalorsen demonstrated a favorable safety and tolerability profile across all cohorts
- Data to be presented today at EAACI Congress 2024 and published in *The New England Journal of Medicine*
- Ionis to host webcast on Friday, May 31 at 8:00am ET

CARLSBAD, Calif., May 31, 2024 -- [Ionis Pharmaceuticals, Inc.](#) (Nasdaq: IONS) today announced positive results from the Phase 3 OASIS-HAE and OASISplus studies of donidalorsen in patients with hereditary angioedema (HAE) demonstrating significant and sustained reduction in mean monthly HAE attack rates and continued attack rate improvement of >90% with one year of treatment for both monthly or every two-month dosing. Patients who switched to donidalorsen from prior prophylactic treatment also showed 62% further reduction in mean monthly HAE attack rates from baseline, and 84% of patients who switched reported a preference for donidalorsen. Donidalorsen had a favorable safety and tolerability profile across both studies, including when self-administered via an auto-injector. Results will be presented in three late-breaking oral presentations at the 2024 European Academy of Allergy and Clinical Immunology (EAACI) Annual Congress in Valencia, Spain and published in [The New England Journal of Medicine](#).¹ Based on these data, Ionis is pursuing regulatory approval of donidalorsen as a potential treatment for HAE.

HAE is a rare and potentially life-threatening genetic condition that involves recurrent attacks of severe swelling (angioedema) in various parts of the body, including the hands, feet, genitals, stomach, face and/or throat. Donidalorsen is an investigational RNA-targeted prophylactic medicine designed to reduce the production of prekallikrein (PKK), interrupting the pathway that leads to HAE attacks.

"We're delighted by the results from the OASIS clinical program, which we believe position donidalorsen to advance the prophylactic treatment paradigm for people living with HAE. Despite currently available therapies, people living with HAE still face significant disease burden and new prophylactic treatments are needed," said Brett Monia, Ph.D., chief executive officer of Ionis. "These data underscore the potential of donidalorsen to continually improve HAE attack rates and quality of life over time, positioning donidalorsen as an attractive potential treatment option. In our prospective switch cohort, patients switched to donidalorsen from another prophylactic without increased breakthrough attacks and achieved greater disease control. In fact, a majority of patients who switched reported a preference for donidalorsen. We thank the patients, families and clinicians who participated in these important studies. Based on these results, Ionis will pursue regulatory approval for donidalorsen, and we look forward to launching it as part of our growing independent commercial pipeline, if approved."

OASIS-HAE Study Results

In the Phase 3 OASIS-HAE study, patients with HAE were treated with donidalorsen (80 mg) via subcutaneous injection every four weeks (Q4W) (n=45) or every eight weeks (Q8W) (n=23), or placebo (n=22), over 24 weeks.

- The study met its primary endpoint, demonstrating 81% lower monthly HAE attack rate with donidalorsen Q4W compared to placebo over weeks one to 25 ($p<0.001$), and 55% reduction with Q8W ($p=0.004$).
- In weeks five to 25, donidalorsen Q4W significantly reduced mean monthly HAE attack rates by 87% ($p<0.001$) compared to placebo, a key secondary endpoint.
 - In the same time frame, treatment with donidalorsen Q4W reduced severe to moderate attacks per month by 89% ($p<0.001$).
 - Donidalorsen Q4W also reduced HAE attacks that require acute therapy by 92% ($p<0.001$).
- At week 25, 91% of donidalorsen Q4W patients were well-controlled as measured by the Angioedema Control Test (AECT).
 - Donidalorsen resulted in clinically significant improvement in quality of life as measured by the Angioedema Quality of Life Questionnaire (AE-QoL).
- Donidalorsen Q8W had a similar benefit as Q4W dosing over time on attack rate reduction and quality of life measures.
- Donidalorsen was well-tolerated, with no serious treatment emergent adverse events (TEAEs) related to donidalorsen. Most adverse events (AEs) were mild or moderate in severity, and injection site reactions were the most common AE. One patient in the donidalorsen Q8W group discontinued based on investigator recommendation due to patient noncompliance

and a TEAE.

OASISplus Study Results – Open-Label Extension and Switch

The OASISplus study included an open-label extension (OLE) cohort and a first-of-its-kind prospective cohort to assess patients switching from both newer oral and injectable long-term prophylactic treatments to donidalorsen.

Open-Label Extension Cohort

Following completion of the placebo-controlled treatment period in OASIS-HAE, 94% of eligible patients enrolled in the OLE cohort. Participants continued to receive treatment with donidalorsen via subcutaneous injection dosed every four weeks (n=69) or every eight weeks (n=14). As of the February 28, 2024 data cut:

- Attack rates continued to improve over time, resulting in 93% and 92% improvement from baseline measured at the start of OASIS-HAE across Q4W and Q8W, respectively.
- Extended treatment resulted in further improved quality of life measures and high levels of disease control.
 - At week 25, 91% (Q4W) and 100% (Q8W) of patients reported well-controlled disease as measured by the AECT.
 - AE-QoL scores improved by 28 points (Q4W) and 24 points (Q8W) at week 25 compared to baseline in OASIS-HAE. An improvement of 6 points is considered clinically meaningful.
- Safety results were consistent with findings from OASIS-HAE, with no serious safety concerns and no patient discontinuations.

Switch Cohort

The OASISplus switch cohort evaluated the safety and efficacy of long-term dosing of donidalorsen every four weeks in patients (n=64) who were previously treated with another prophylactic HAE medication (lanadelumab, berotralstat or C1-esterase inhibitor) for at least 12 weeks prior to entering the study. Patients followed a pre-defined specific protocol to transition from their prior therapy to donidalorsen. Results from a pre-defined endpoint of 17 weeks indicate:

- Patients switched to donidalorsen from prior prophylactic treatment without an increase in breakthrough attacks.
- Patients experienced a 62% further improvement in mean monthly HAE attack rate compared to baseline for previous prophylactic treatment.
- 84% of patients who switched reported a preference for donidalorsen over their previous treatment, citing better disease control, less time to administer, and less injection site pain or reactions.²
- Quality of life measures also showed continued improvement, with 93% of patients reporting well-controlled disease compared to 67% at baseline with prior prophylactic treatment. Results also demonstrated ≥8-point improvement in AE-QoL scores.
- Safety results were consistent with findings from OASIS-HAE, with no serious safety concerns. One patient discontinued due to TEAE not related to donidalorsen.

“People living with HAE are facing a lifelong battle, and I see that impact firsthand in my practice. It’s critical for treatment options to have lasting, durable efficacy,” said Marc Riedl, M.D., M.S. clinical director, U.S. HAEA Angioedema Center; clinical service chief, Division of Allergy & Immunology, University of California, San Diego. “The OASISplus study demonstrated patients are able to change therapy to donidalorsen without the risk of increased breakthrough HAE attacks while continuing to improve in measures of quality of life and disease control.”

“The comprehensive OASIS clinical program demonstrates how donidalorsen can potentially address key concerns patients may experience with currently available treatment options,” said Kenneth Newman, M.D., senior vice president of clinical development at Ionis. “Donidalorsen significantly reduced HAE attack rates, and with the simplicity of monthly or every two-month self-administration via autoinjector, we believe that donidalorsen has a unique profile that may address the needs of people with HAE.”

Ionis plans to file a New Drug Application this year with the U.S. Food and Drug Administration (FDA), marking progress toward the goal of launching our second wholly owned medicine. Otsuka Pharmaceutical Co., Ltd., which has exclusive rights to commercialize donidalorsen in Europe, is also preparing to submit a Marketing Authorization Application to the European Medicines Agency this year.

All presentations can be found on Ionis' [website](#) after today's presentations at 10:45am ET.

Webcast

Ionis will hold a webcast today at 8:00am ET to discuss this update. Interested parties may access the webcast [here](#). A webcast replay will be available for a limited time.

About the OASIS-HAE Study

The global, multicenter, randomized, double-blind, placebo-controlled Phase 3 OASIS-HAE study ([NCT05139810](#)) enrolled 91 participants, age 12 and above, with HAE-1 and HAE-2 hereditary angioedema. Participants were randomized in a 2:1 ratio to receive donidalorsen (80mg) or placebo via subcutaneous injection once every four weeks for 24 weeks or donidalorsen (80mg) or

placebo via subcutaneous injection once every eight weeks for 24 weeks. Within each cohort, participants were randomized in a 3:1 ratio to receive donidalorsen or matching-placebo. The primary endpoint was the time-normalized number of investigator-confirmed HAE attacks from week one to week 25 compared to placebo. Following completion of the treatment period, 94% of eligible patients entered the Phase 3 OASISplus open-label extension study.

About the OASISplus Study

The Phase 3 OASISplus open-label extension (OLE) study is a 53-week global, multicenter study of subcutaneous injections of donidalorsen administered every four weeks (80mg) and every eight weeks (80mg) in patients completing the OASIS-HAE study. These are patients aged 12 and above, with HAE-1 and HAE-2 hereditary angioedema. The study is designed to evaluate the safety and efficacy of extended dosing of donidalorsen following completion of the Phase 3 OASIS-HAE study. The OASISplus switch cohort is evaluating the safety and efficacy of long-term dosing of donidalorsen every four weeks in patients who were previously treated with another prophylactic HAE medication. Additional information about OASISplus ([NCT04307381](https://clinicaltrials.gov/ct2/show/study/NCT04307381)) may be found at [ClinicalTrials.gov](https://clinicaltrials.gov).

About Hereditary Angioedema (HAE)

HAE is a rare and potentially life-threatening genetic condition that involves recurrent attacks of severe swelling (angioedema) in various parts of the body, including the hands, feet, genitals, stomach, face and/or throat.^{3,4,5,6,7} HAE is estimated to affect more than 20,000 patients in the U.S. and Europe.⁸ In the U.S., doctors frequently use prophylactic treatment approaches to prevent and reduce the severity of HAE attacks in patients.

About Donidalorsen

Donidalorsen is an investigational **L**igand-**C**onjugated **A**ntisense (LICA) medicine designed to target prekallikrein (PKK), which plays an important role in activating inflammatory mediators associated with acute attacks of hereditary angioedema (HAE). By reducing the production of PKK, donidalorsen could be an effective prophylactic approach to preventing HAE attacks.

About Ionis Pharmaceuticals, Inc.

For three decades, Ionis has invented medicines that bring better futures to people with serious diseases. Ionis currently has five marketed medicines and a leading pipeline in neurology, cardiology, and other areas of high patient need. As the pioneer in RNA-targeted medicines, Ionis continues to drive innovation in RNA therapies in addition to advancing new approaches in gene editing. A deep understanding of disease biology and industry-leading technology propels our work, coupled with a passion and urgency to deliver life-changing advances for patients.

To learn more about Ionis, visit ionispharma.com and follow us on [X](#) (Twitter) and [LinkedIn](#).

Ionis Forward-looking Statements

This press release includes forward-looking statements regarding Ionis' business, financial guidance and the therapeutic and commercial potential of our commercial medicines, donidalorsen, additional medicines in development and technologies. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties including those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on Form 10-K for the year ended December 31, 2023, and most recent Form 10-Q, which are on file with the Securities and Exchange Commission. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our" and "us" all refer to Ionis Pharmaceuticals and its subsidiaries.

Ionis Pharmaceuticals® is a registered trademark of Ionis Pharmaceuticals, Inc.

Ionis Investor Contact:

D. Wade Walke, Ph.D.
info@ionisph.com 760-603-2331

Ionis Media Contact:

Hayley Soffer
CorporateCommunications@ionisph.com 760-603-4679

1. Reidl M, et Efficacy and Safety of Donidalorsen for Hereditary Angioedema. *New England Journal of Medicine*. 2024; 10.1056/NEJMoa2402478
2. Patients selected a reason for switching from a predefined list of reasons.
3. Manning ME. *Dermatol Ther (Heidelb)*. 2021; 11:1829-1838.
4. Valerieva A, et al. *Balkan Med J*. 2021;8:89-103.
5. Santacroce R, et al. *J Clin Med*. 2021;10:2023.
6. Pines JM, et al. *J Emerg Med*. 2021;60:35-43.X
7. Maurer M, et al. *World Allergy Organ J*. 2022;15:100627.
8. Weller K, et al. *Allergy*. 2016;71(8): 1203-1209.