Positive Phase 3 Data Positions Donidalorsen as a Potential Preferred Treatment for HAE

May 31, 2024

Nasdaq: IONS

Forward-Looking Statements

This presentation 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 but not limited to those related to our commercial products and the medicines in our pipeline, and particularly 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 our Form 10-K for the year ended December 31, 2023 and most resent Form 10-Q, which are on file with the SEC. Copies of these and other documents are available at www.ionispharma.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

Agenda

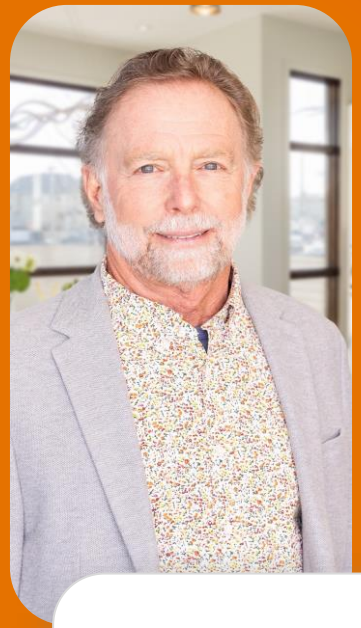
Topic	Speaker
Delivering Next-level Value to Patients & All Stakeholders	**Brett Monia, Ph.D.** *Chief Executive Officer*
Donidalorsen: A Potential Advance in Prophylactic Treatment for HAE	**Eugene Schneider, M.D.** *Chief Clinical Development Officer*
Phase 3 OASIS-HAE Study Results **Phase 3 OASISplus: OLE and Switch Study Results**	**Marc Riedl, M.D., M.S.** *Clinical Director, US HAEA Angioedema Center, Clinical Service Chief, Division of Allergy & Immunology, University of California, San Diego*
Donidalorsen: Poised to Advance HAE Treatment	**Eugene Schneider, M.D.** *Chief Clinical Development Officer*
Delivering Donidalorsen to People with HAE	**Kyle Jenne** *Chief Global Product Strategy Officer*
Concluding Remarks	**Brett Monia, Ph.D.** *Chief Executive Officer*
Q&A	

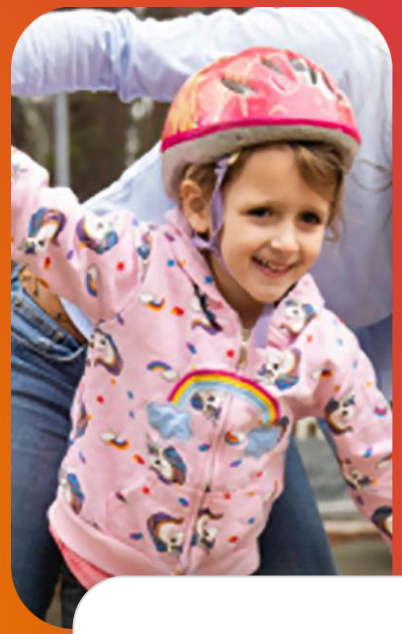
Delivering Next-level Value to Patients & All Stakeholders

Brett Monia, Ph.D.
Chief Executive Officer

Next-Level Value for Patients & All Stakeholders

Scientific and Clinical Innovation / Financial Responsibility






Prioritizing and Expanding the Ionis Wholly Owned Pipeline

Delivering Ionis Medicines Directly to Patients

Leading Technology

Realizing the Promise of our Innovative Medicines[1]

First Ionis-Branded Medicine[2]

WAINUA (eplontersen) 45 mg injection for subcutaneous use

Launched in ATTRv-Polyneuropathy January 2024

Ongoing fully enrolled Phase 3 study for ATTR Cardiomyopathy[3]

Co-developing and commercializing in the U.S. with AstraZeneca

First Ionis Independent Launches[1,4]

Olezarsen

Launch in FCS expected by YE:2024[4]

Pivotal sHTG program on track

Blockbuster opportunity[5]

Donidalorsen

Launch in HAE expected in 2025[4]

Efficient commercial organization

Establishing global access

Next Wave of Wholly Owned Medicines

Leading Neurology Pipeline

Proven track record of delivering first-in-class disease modifying medicines

ION582

Angelman Syndrome data planned in July[1]

7 wholly owned medicines in clinical development by YE:2024

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. WAINUA: www.wainua.com 3. Data planned for ATTR-CM as early as 2025. 4. Assuming approval. 5. In aggregate.

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Donidalorsen: A Potential Advance in Prophylactic Treatment of HAE

Eugene Schneider, M.D.
Chief Clinical Development Officer

Donidalorsen: Positioned to Advance the Prophylactic Treatment Paradigm for People with HAE[1]

Robust Data Set

Phase 2 Study

Phase 2, 2-year OLE

Phase 3 OASIS-HAE

OASISplus: OLE + Switch

Reduced HAE Attacks

Significant and **sustained reductions in HAE attacks**

High levels of disease control

Improved Quality-of-Life Measures

Significant and **clinically meaningful improvements** in **quality-of-life** measures

Additional Benefit with Longer Use

Treatment over time continued to **improve**:

HAE attack rates

Quality-of-Life Measures

and resulted in:

High levels of disease control

Switch Data

HAE attack rates decreased

Improved quality-of-life measures and **disease control**

Demonstrated **strong donidalorsen preference**

Useful data to **inform potential switching**

Favorable Safety and Tolerability

Favorable safety and **tolerability profile**

Administration Profile

Simplicity of **monthly** or **every two-month self-administration** via an **auto-injector**

1. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data.

Donidalorsen: Positioned to Advance the Prophylactic Treatment Paradigm for People with HAE[1]

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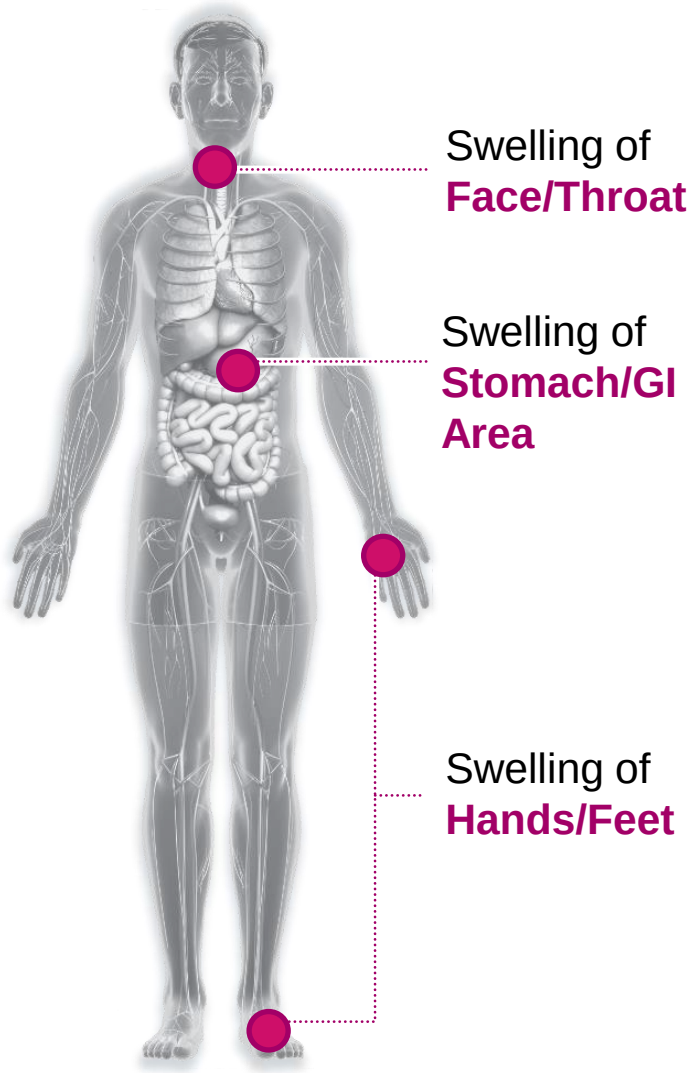
Hereditary Angioedema (HAE) Disease Overview[1-6]

A rare, chronic and potentially life-threatening **genetic disease** that can impact multiple family members

—

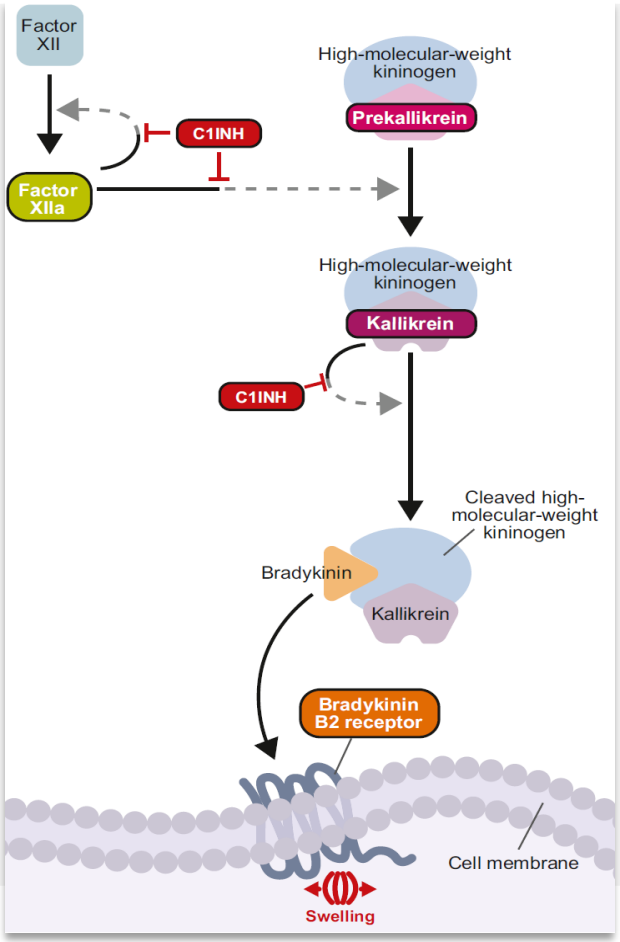
Patients experience recurring, unpredictable, severe and potentially fatal **swelling attacks**, commonly affecting the hands, feet, stomach, face and throat



1. Busse, P.J. and Christiansen, S.C., 2020 NEJM ; 2. Busse 2020 J Allergy Clin Immunol Pract; 3. HAEI; 4. HAEA; 5. Banerji, A. et al., 2020 Ann Allergy Asthma Immunol; 6. Banerji, A. et. al. 2015 Allergy & Asthma.

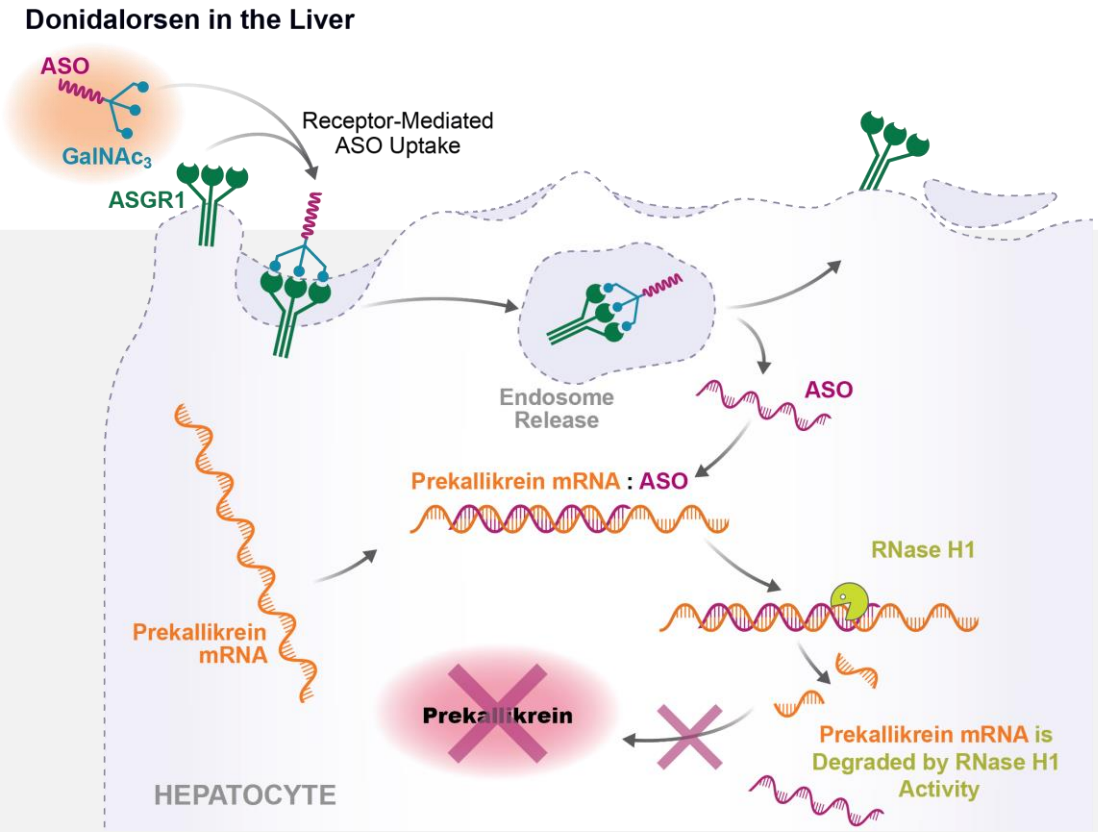
Donidalorsen: A First-in-Class RNA-Targeted Investigational Medicine[1]

HAE Disease Pathway



Inadequate C1 esterase inhibitor (C1-INH) activity causes aberrant activation of the kinin-kallikrein system

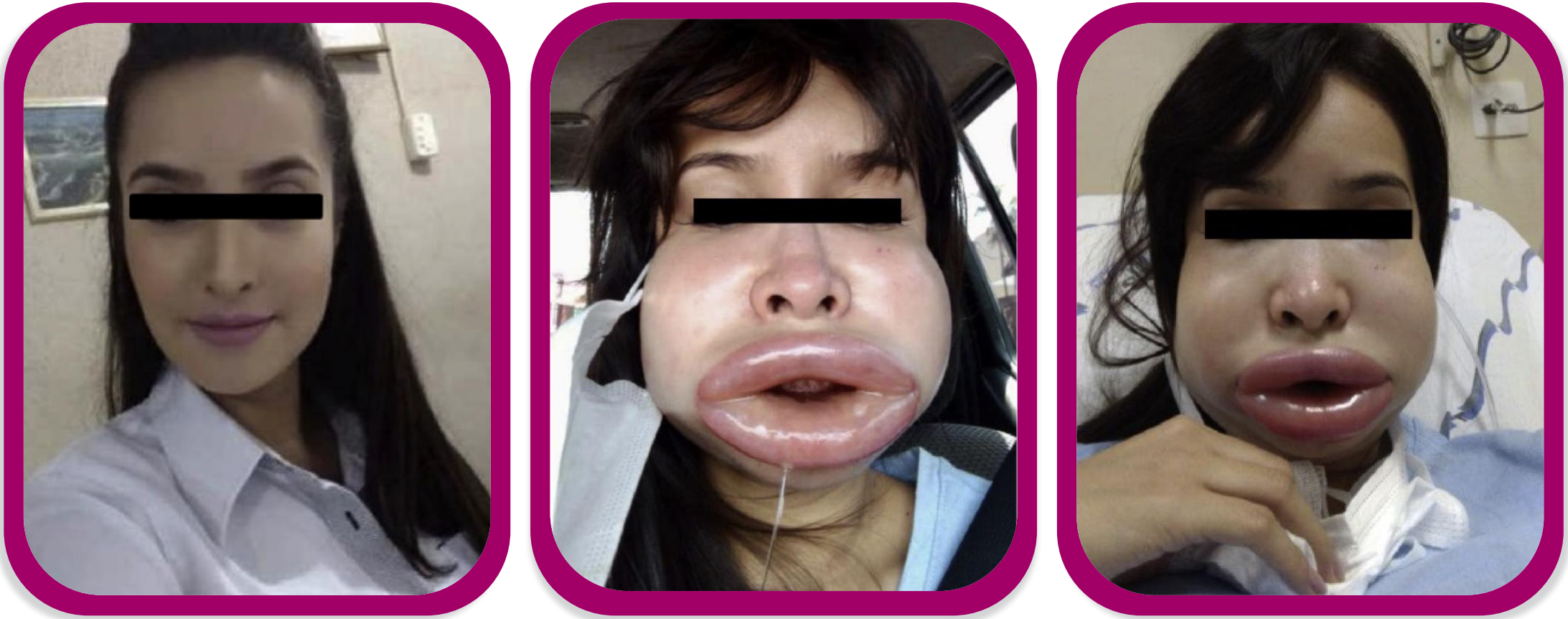
- Plasma prekallikrein **(PKK)** is produced in the liver and is the **precursor of kallikrein**
- **Uncontrolled kallikrein** activation leads to **elevated bradykinin** levels and **HAE symptoms** mediated through BK2 receptor activation



Donidalorsen is designed to specifically degrade PKK mRNA in the liver, interrupting the pathway that leads to HAE attacks

1. First figure based on Riedl MA, et al. *J Allergy Clin Immunol Pract*. 2024. In Press. This work is licensed under CC-BY 4.0. https://creativecommons.org/licenses/by/4.0/deed.en; second figure adapted from Crooke ST, et al. *Nucleic Acid Thera*. 2019;29:16-32

HAE Attacks are Unpredictable, Debilitating and can be Fatal[1]



Images from Arruda LK,et al. J Aller Clin Immun 2021. https://doi.org/10.1016/j.jaci.2021.05.023.

1. Busse, P.J. and Christiansen, S.C., 2020 NEJM.

HAE: Prevalence, Disease Onset and Diagnosis[1-7]

>20K

People in the US and Europe with HAE[1]

Estimated incidence of 1:50,000

Age of HAE onset varies[3,4]

~50% of people experience an attack **before the age of 10**

Most experienced their first attack **before the age of 18**

HAE attacks have been reported in children **as young as 1 year old**

Challenging Diagnosis

People with HAE experience an average of **5 years to diagnosis**

Diagnostic tests[7]

Common: Blood tests (C1-INH quantitative, C1-INH functional, C4)

Uncommon: SERPING1 gene testing (blood, saliva or buccal)

Normal C1-INH: no approved diagnostic test

25% of people diagnosed **do not** have a family history of HAE

1. Busse, P.J. and Christiansen, S.C., 2020 NEJM ; 2. Busse 2020 J Allergy Clin Immunol Pract; 3. HAEI; 4. Sandra C. Christiansen MD , Joyce Wilmot MS , Anthony J. Castaldo MPA , Bruce L. Zuraw MD, For the US HAEA Medical Advisory Board members, The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities, Annals of Allergy, Asthma Immunology (2023)
5. Banerji, A. et al., 2020 Ann Allergy Asthma Immunol; 6. Banerji, A. et. al. 2015 Allergy & Asthma. 7. HAEI (https://haei.org/hae/faq/ accessed May 2024).

Attacks Can Significantly Impact People with HAE[1,2]

Attack Impact on People with HAE

87%	have gone to the ER
67%	have been hospitalized
16%	have been intubated (ICU admission)
16%	have had inappropriate abdominal surgery

Attacks may last from 1–5 days, if untreated

Attacks can **interfere** with patients' **daily activities,** including attending work or school

Unpredictable attacks can **reduce quality of life**

"I have been **intubated** three times. The very first time they had to **resuscitate me** because they had trouble getting the tube down. I stayed in the **ICU** for **three days**…"

1. Sandra C. Christiansen MD , Joyce Wilmot MS , Anthony J. Castaldo MPA , Bruce L. Zuraw MD , For the US HAEA Medical Advisory Board members, The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities, Annals of Allergy, Asthma Immunology (2023) 2. HAEI (https://haei.org/hae/faq/ accessed May 2024).

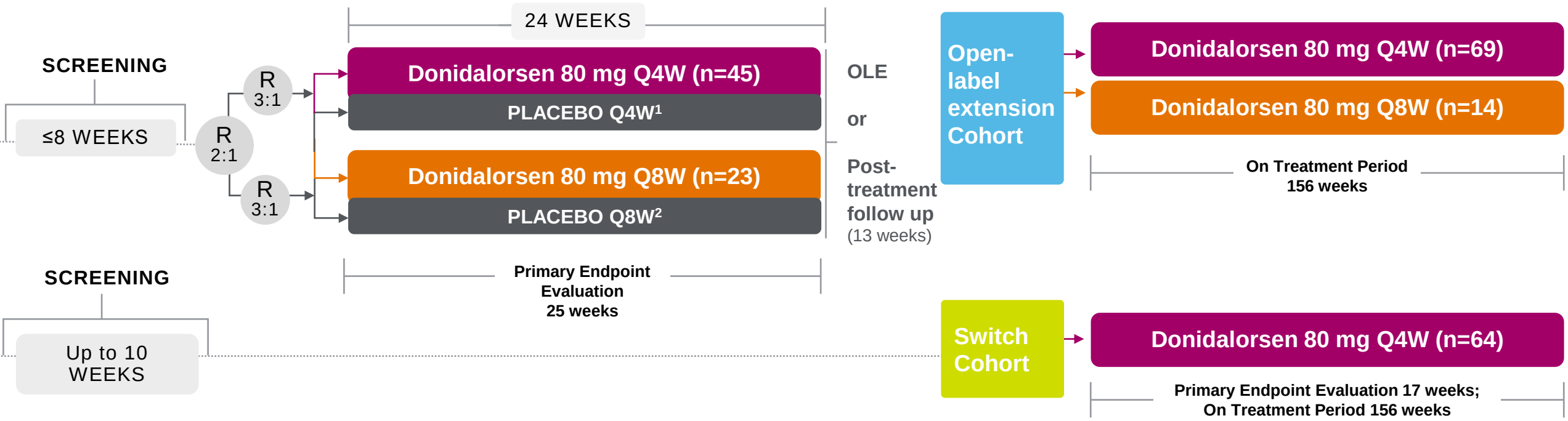
Comprehensive Donidalorsen Phase 3 Program Designed to Provide Robust Data

OASIS

Phase 3, global, randomized, double-blind, **placebo-controlled** study in patients aged ≥12 years with HAE-C1INH-Type1 or HAE-C1IND-Type2[1]

OASIS plus

Phase 3, multicenter, **open-label study** in patients with HAE consisting of two cohorts: **OLE cohort** of patients from OASIS-HAE and **Switch cohort**[3]



1. OASIS-HAE: Patients with HAE were screened for up 8 weeks and randomized to Q4W or Q8W dosing in a 2:1 ratio (Q4W:Q8W). Within each dosing schedule, patients were again randomized to donidalorsen 80 mg SC or placebo SC in a 3:1 ratio (donidalorsen:placebo). Patients that had at least five HAE attacks per month for 8 consecutive months after Week 5 were given the opportunity to terminate from the treatment period and enroll into an open-label extension study. All patients were followed for up to 13 weeks after completion of the study, or early termination. NCT05139810 2.Pooled placebo n=22. 3. NCT05392114, refer to slide 37 and 44 for further details on the OASISplus study.

Donidalorsen: Robust Data Supports Potential Preferred Treatment for HAE Prophylaxis[1]

OASIS

- Substantial reductions in HAE attack rates + favorable safety and tolerability
- Improved QoL measures
- High levels of disease control
- U.S. and EU Orphan drug designations

OASIS plus

- OLE cohort demonstrated that long-term treatment continued to improve HAE attack rates and QoL measures
- Positive results from Switch cohort in patients previously treated with other prophylactic therapies showed:
  - Improved HAE attack rates, QoL measures and disease control
  - Strong preference for donidalorsen
  - Useful data to inform potential switching

Phase 2 & Phase 2 OLE

- Positive Phase 2 data published in *New England Journal of Medicine*
- Positive 1 and 2-year OLE data reinforce donidalorsen's compelling profile
- 3-year OLE data planned for H2:2024

U.S. and EU filings on track this year; Prepared to launch in 2025

1. Timing expectations based on current assumptions and subject to change.

Phase 3 OASIS-HAE Study Results

Marc Riedl, M.D., M.S.
Clinical Director, US HAEA Angioedema Center and Clinical Service Chief,
Division of Allergy & Immunology, University of California, San Diego

Disclosures

Marc Riedl, M.D., M.S. reports advisory board/lecturing fees paid to his institution by:

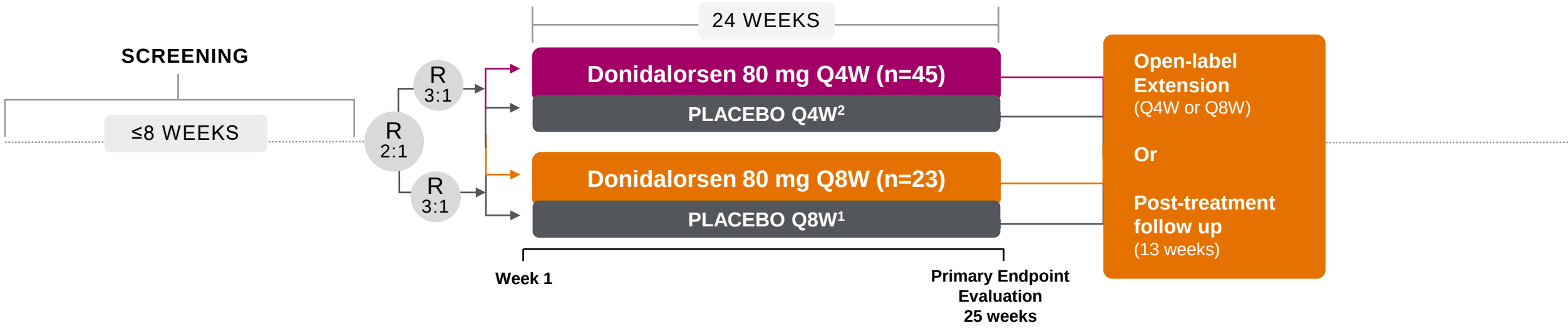
- Research support: Biocryst, Biomarin, CSL Behring, Ionis, Kalvista, Pharvaris, Takeda
- Consulting: Astria, Biocryst, Biomarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, Kalvista, Pfizer, Pharming, Pharvaris, Sanofi-Regeneron, Takeda

Donidalorsen is an investigational drug in late-stage development

Funding: Ionis Pharmaceuticals

Phase 3 OASIS-HAE Study in Patients with HAE[1]

DESIGN	**A global, randomized, double-blind, placebo-controlled study** of monthly and every two-month subcutaneous injections of **donidalorsen or placebo** in patients aged ≥12 years with HAE-C1INH-Type1 or HAE-C1INH-Type2
PRIMARY ENDPOINT	**Time-normalized HAE attack rate over Weeks 1 to 25**



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Phase 3 OASIS-HAE Study: Secondary and Other Endpoints

Key Secondary Endpoint	**Time-normalized HAE attack rate over Weeks 5 to 25**
Other Secondary Endpoints[1]	• HAE attacks requiring acute therapy • Moderate to severe HAE attacks • Percentage of attack-free patients • Clinical response (≥70% reduction from baseline in HAE attack rate) from Week 5 to Week 25 • Mean change from baseline in AE-QoL questionnaire total score at Week 25[2] • Percentage of patients who are well-controlled on the AECT (score ≥10 points)[3] at Week 25
Exploratory Endpoints	• Incidence of emergency room visits (Weeks 1 to 25) • Plasma PKK concentration
Safety Endpoints	• Incidence and severity of adverse events

1. The subset of trial endpoints included in this presentation are listed. 2. Angioedema Quality of Life (AE-QoL). 3. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050–2057.e4.; Angioedema Control Test (AECT).

Patient Disposition[1]

	Donidalorsen Q4W	Donidalorsen Q8W	Placebo
Patients randomized	46	23	22
Full analysis set (dosed)	45	23	22
Early termination[1]	**2 (4%)**	**2 (9%)**	**4 (18%)**
Lack of efficacy	1	1	3
Voluntary withdrawal	1	0	0
Adverse event	0	1	0
Pregnancy	0	0	1
Completed treatment	**44 (96%)**	**21 (91%)**	**18 (82%)**

91% of randomized patients completed the study treatment

94% of eligible patients in OASIS-HAE entered the OASISplus open-label extension study[2]

1. Early terminators with at least 5 HAE attacks/month for 2 consecutive months after Week 5 were enrolled directly in to the open-label extension OASISplus study per protocol (safety valve). 2. OASISplus: NCT05392114, Patients were eligible for enrollment in the OASISplus open-label extension study if they completed the OASIS-HAE study or were allowed to exit the OASIS-HAE study per protocol with an acceptable safety and tolerability profile.

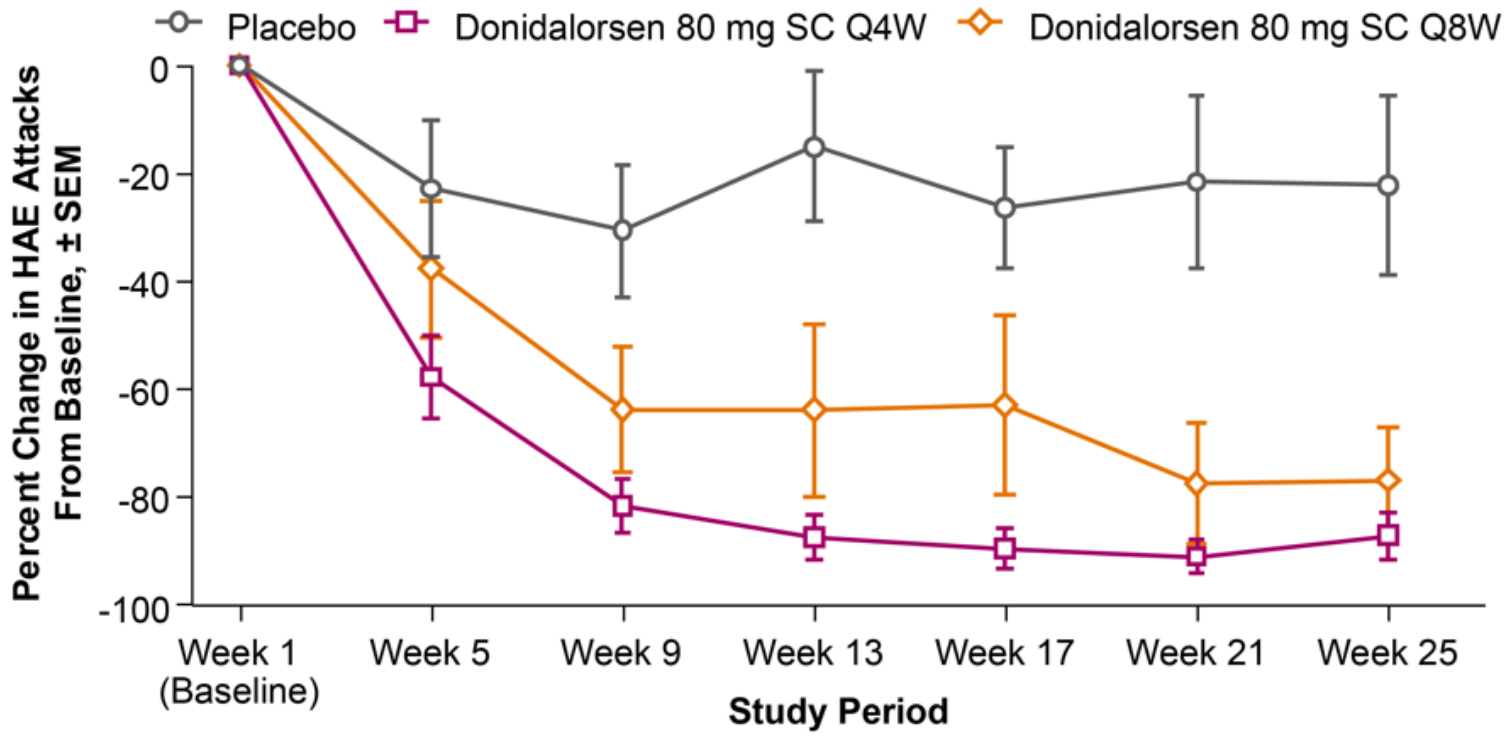
Baseline Characteristics

	Donidalorsen Q4W n = 45	Donidalorsen Q8W n = 23	Placebo n = 22
Age, years, n (%)			
12–17	4 (9)	3 (13)	0
≥18	41 (91)	20 (87)	22 (100)
Sex, n (%)			
Male	17 (38)	11 (48)	14 (64)
Female	28 (62)	12 (52)	8 (36)
Race, n (%)			
White	42 (93)	22 (96)	18 (82)
Multiple or other	3 (7)	1 (4)	4 (18)
Hereditary angioedema, n (%)			
HAE-C1INH-Type1	42 (93)	22 (96)	20 (91)
HAE-C1INH-Type2	3 (7)	1 (4)	2 (9)
Number of HAE attacks in last 12 months, mean ± SD[1,2]	**45.7 ± 43.04**	**33.3 ± 21.95**	**29.1 ± 21.13**
Number of HAE attacks during run-in period,[2] mean ± SD[1,2]	**3.61 ± 2.24**	**3.18 ± 2.15**	**2.90 ± 1.66**

HAE attack rate was lower in the placebo group compared to donidalorsen groups in the 12 months before study start (including run-in period)

1. Standard deviation (SD). 2. The number of HAE attacks in the last 12 months refers to the time before screening visit. The run-in period HAE attack rate for each patient is calculated as the number of investigator-confirmed HAE attacks that occurred during the run-in period divided by the number of days the patient contributed to the run-in period and then multiplied by 28 days.

Donidalorsen Treatment Resulted in Substantial and Sustained Reduction in HAE Attacks[1]



- **Q4W significantly reduced** mean **HAE attack rates[2]:**
  - **87%** compared to placebo over weeks 5 to 25 ($p<0.001$)
  - **81%** compared to placebo over weeks 1 to 25 ($p<0.001$)
- Donidalorsen **Q8W** had a **similar effect** as **Q4W** dosing over time

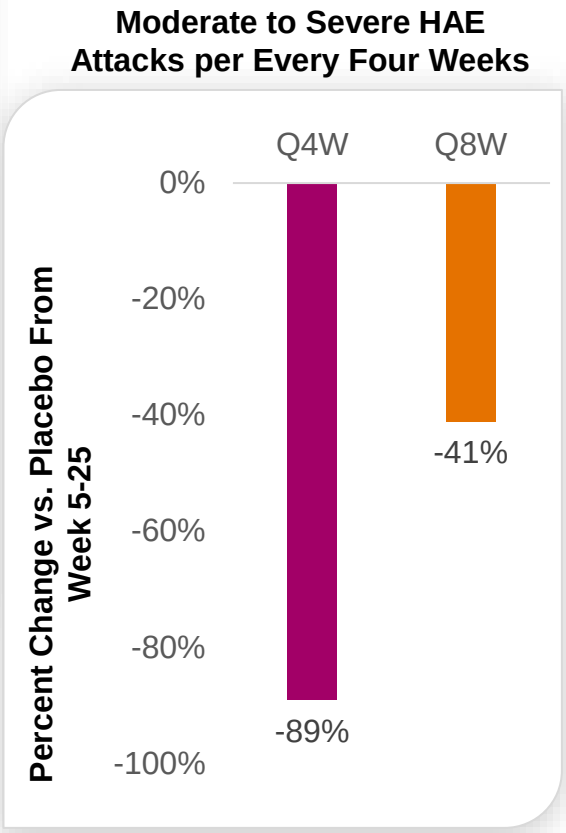
1. Standard error of the mean (SEM). 2. Least-squares mean (LSM) difference HAE attack rate.

Additional Improvements Over Weeks 5 to 25 with Donidalorsen Treatment[1]

Reduced Moderate to Severe Attacks per month by

89% for Q4W (p<0.001)

41% for Q8W



1. Percent change compared to pooled placebo from weeks 5 to 25.

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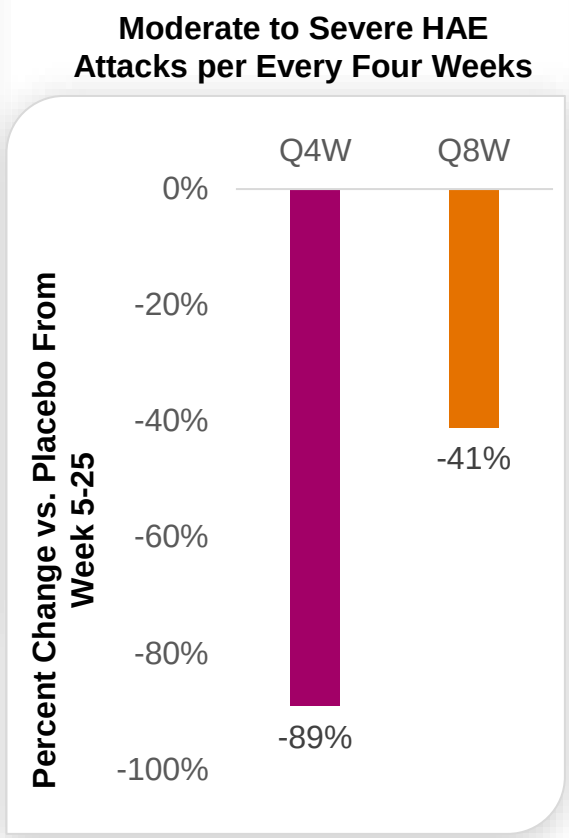
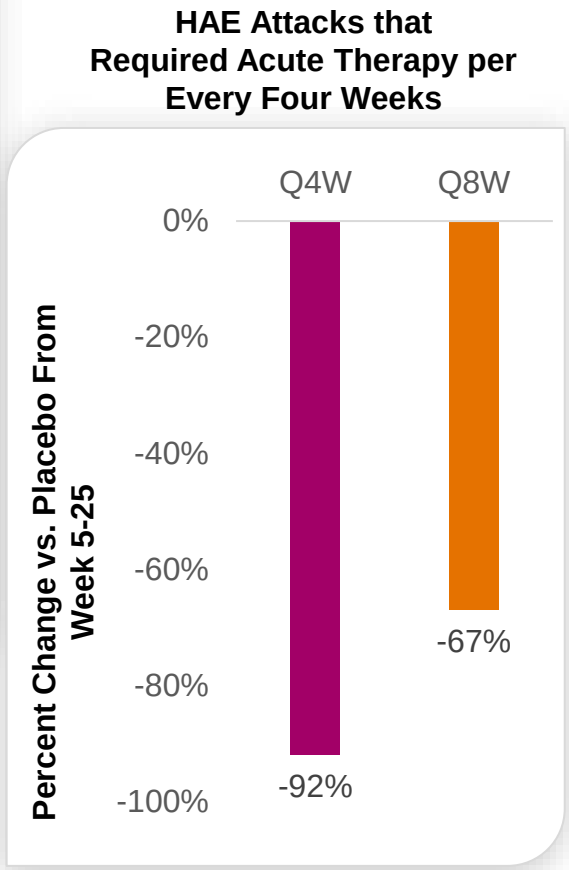


Reduced HAE Attacks that Require Acute Therapy

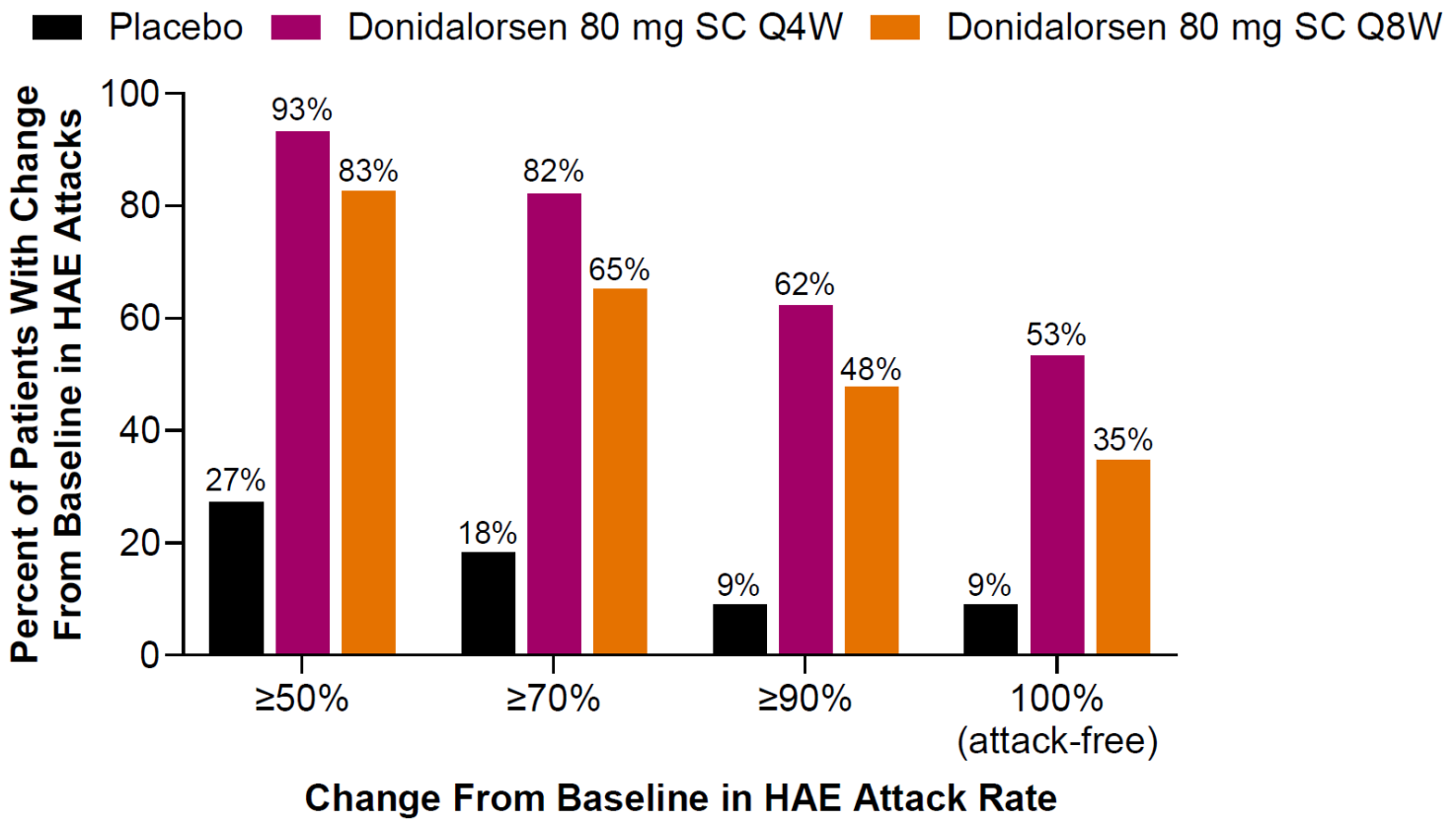
92% for Q4W (p<0.001)

67% for Q8W (p=0.004)



1. Percent change compared to placebo from weeks 5 to 25.

Nearly All Donidalorsen Patients Achieved Substantial Reduction in HAE Attacks[1]



Substantially higher percentage of patients in both **donidalorsen** groups had a **≥70% reduction[2]** from baseline in **HAE attack rate** compared to placebo over Weeks 5 to 25

- **Q4W:** p<0.001
- **Q8W:** p=0.004

1. Percentage of patients who achieved a threshold reduction in time-normalized investigator-confirmed HAE attack rate between Week 5 and Week 25. 2. Secondary endpoint: Clinical response (≥70% reduction from baseline in HAE attack rate) from Week 5 to Week 25.

Donidalorsen Treatment Resulted in Clinically Significant Improvement in Quality-of-Life Measures[1]

Angioedema Quality of Life Questionnaire (AE-QoL):

An improvement of **6 points** or more is considered **clinically meaningful**[2]

Donidalorsen treatment resulted in:

Q4W

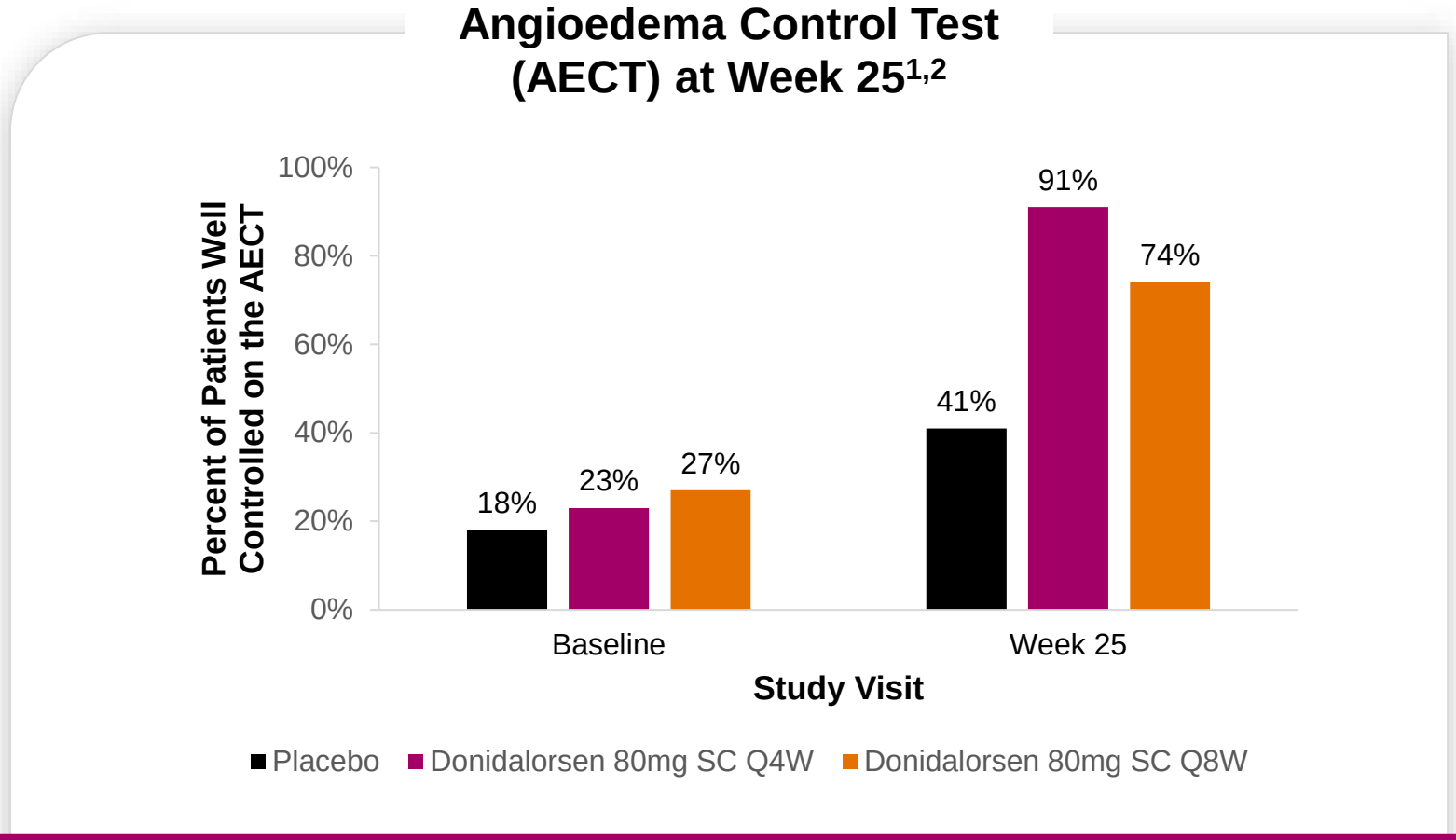
Least-squares mean change of 25 points compared to 6 points for placebo **(p<0.001)**, with numerical improvements observed across all domains

Q8W

Least-squares mean change of 20 points (p=0.010), with numerical improvements observed across all domains

1. LSM change at week 25 compared to baseline. 2.Weller K et al. *Allergy*. 2016;71(8):1203–9.

High Levels of Disease Control Reinforces Donidalorsen's Profile



91% and 74% of donidalorsen patients on Q4W and Q8W, respectively were *well controlled*

1. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4; well controlled is defined as an AECT score ≥10. 2. Missing values at week 25 were imputed by using last observation carried forward (LOCF).

>90% Reduction in ER Visits with Q4W and Q8W Dosing[1]

	Donidalorsen Q4W n = 45	Donidalorsen Q8W n = 23	Placebo n = 22
All-cause ER visits, LS mean rate (95% CI)	0.02 (0.004–0.087)	0.02 (0.003–0.162)	0.26 (0.145–0.479)
Percent reduction vs placebo (95% CI)	**93%** (63.2–98.6)	**92%** (33.0–98.9)	–
ER visits due to HAE attacks, LS mean rate (95% CI)	0.01 (0.001–0.100)	0.01 (0.001–0.216)	0.22 (0.104–0.446)
Percent reduction vs placebo (95% CI)	**95%** (47.9–99.5)	**93%** (-10.6–99.6)	–

92% to 95% Fewer ER visits (all-cause and HAE attack-specific) for donidalorsen patients over 25 weeks

1. Compared to baseline.

Favorable Safety and Tolerability Profile

- No serious TEAEs in donidalorsen groups
- TEAEs higher in placebo group
  - Injection-site reactions were the most common donidalorsen-related TEAEs; all were mild

	Donidalorsen Q4W n = 45	Donidalorsen Q8W n = 23	Placebo n = 22
Any TEAE,[1] n (%)	33 (73%)	14 (61%)	18 (82%)
Related to study drug[2]	19 (42%)	4 (17%)	6 (27%)
Leading to study drug discontinuation	0	1 (4%)[4]	0
Any serious TEAE, n (%)	0	0	1 (5%)
Related to study drug	0	0	0
TEAEs potentially related to study drug (≥5% of patients)[2]			
Injection site reactions, n (%)	9 (20%)	1 (4%)	0
Headache	3 (7%)	0	3 (14%)

1. A treatment-emergent adverse event (TEAE) is defined as any adverse event starting or getting worse on or after the first dose of the study drug. 2. Related is defined as "Related," "Possible," or missing relationship to study drug (donidalorsen or placebo). 4. One patient discontinued treatment in the Q8W group who was non-compliant with the study protocol and had an ALT elevation that did not meet the stopping rule per protocol. Patient was previously on danazol for more than 15 years, which was discontinued the day of screening.

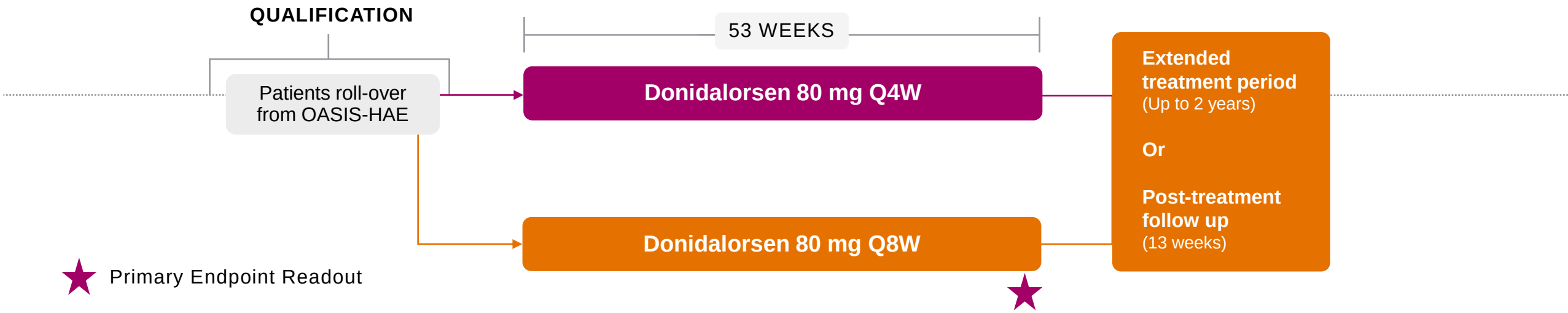
Phase 3 OASIS-HAE Results: Clinically Meaningful Benefit with Donidalorsen Treatment in Patients with HAE

- Donidalorsen Q4W met all primary and secondary endpoints with 87% HAE attack rate reduction for weeks 5 to 25
- Donidalorsen Q8W had a similar effect as Q4W dosing over time
- Donidalorsen improved quality-of-life measures and resulted in high levels of disease control
- Donidalorsen decreased ER visits
- Donidalorsen had a favorable safety and tolerability profile

Phase 3 OLE and Switch Study Results

Donidalorsen Phase 3 OLE Study

DESIGN	**Open label extension study** of every 4 weeks or every 8 weeks subcutaneous injections **of donidalorsen** in patients aged ≥12 years, with HAE-C1INH-Type1 or HAE-C1INH-Type2
PRIMARY OUTCOME	Incidence and severity of **treatment-emergent adverse events (TEAEs)**
SECONDARY OUTCOME	**Long-term efficacy** and effects of treatment on the number of HAE attacks and QoL



94% of eligible patients in OASIS-HAE entered the OASISplus OLE study

1. NCT05392114. Placebo patients from OASIS-HAE received 80 mg SC Q4W in the OLE. Patients who were not attack free for ≥8 weeks (Weeks 17–25 in OASIS-HAE) received donidalorsen 80 mg SC Q4W.

OLE: Patient Disposition and Study Treatment Exposure[1]

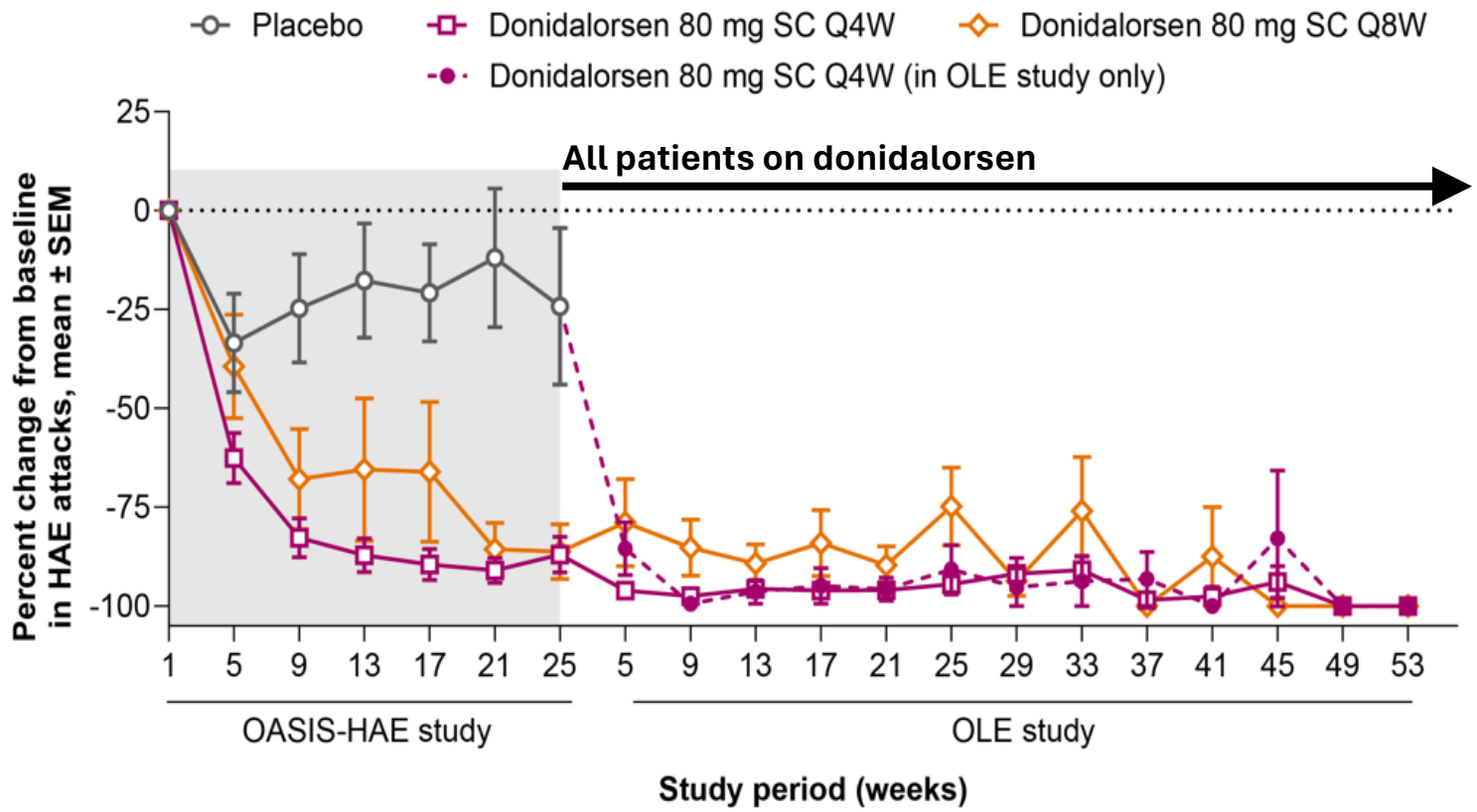
	Donidalorsen Q4W[2]	Donidalorsen Q8W	Total
Patients dosed, n	69	14	83
Completed 1 year of follow-up, n (%)	5 (7)	2 (14)	7 (8)
Patients still ongoing, n (%)	**67 (97%)**	**14 (100%)**	**81 (98%)**
Early termination, n (%)			
Voluntary withdrawal	1 (1)	0	1 (1)
Family planning	1 (1)	0	1 (1)

98% of OLE Patients Remain in the Study[1]

Treatment Duration up to >18 months[1,3]

1. As of February 28, 2024. 2. Q4W incudes all placebo patients (n=19) and six patients from the Q8W group from OASIS-HAE, in addition to those on Q4W in OASIS-HAE. 3. Includes 25 weeks of treatment in OASIS-HAE.

OLE: Further Reduction in HAE Attacks with Extended Donidalorsen Treatment[1,2]



Placebo, n =	19	19	19	19	18	17	16	19	19	19	19	16	15	13	10	6	5	5	4	2
Donidalorsen 80 mg Q4W, n =	44	44	44	44	44	43	43	44	44	43	43	36	30	26	24	18	11	8	4	3
Donidalorsen 80 mg Q8W, n =	20	20	20	20	20	20	19	20	20	20	20	16	14	13	12	8	4	3	2	2

- **Q4W substantially reduced** mean **HAE attack rates:**
  - **93% improvement** from baseline at the start of OASIS-HAE[3]
- **Q8W** had a **similar effect** as **Q4W** dosing
  - **92% improvement** from baseline at the start of OASIS-HAE in HAE attack rates[3]

1. OASIS-HAE primary endpoint evaluation at 25 weeks, after which patients rolled over into the OASISplus OLE study. 2. Patients previously on placebo in OASIS-HAE transitioned to Q4W dosing. 3. Change in time-normalized mean HAE attacks per month.

OLE: Extended Treatment Resulted in Further Improved QoL Measures and High Levels of Disease Control[1]

Donidalorsen Q4W

- 28-point mean improvement in AE-QoL score[2]
- 42/46 (91%) patients reported well-controlled disease[3]

Donidalorsen Q8W

- 24-point mean improvement in AE-QoL score[2]
- 9/9 (100%) patients reported well-controlled disease[3]

1. Data cutoff of February 28, 2024, assessed at week 25. 2. AE-QoL: an improvement of 6 points or more is considered clinically meaningful, Weller K et al. *Allergy*. 2016;71(8):1203–9. Change from baseline in the Phase 3 OASIS-HAE study before entering the OLE. 3. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4; well controlled is defined as an AECT score ≥10.

OLE: Continued Favorable Safety and Tolerability Profile[1]

- There were no serious TEAEs related to the study drug
- Most TEAEs were mild in severity
- No patients discontinued due to TEAEs

	Donidalorsen Q4W (n = 69)	Donidalorsen Q8W (n = 14)	Total (N = 83)
Any TEAE n (%)	56 (81)	10 (71)	66 (80)
Related to study drug	16 (23)	2 (14)	18 (22)
Leading to discontinuation	0	0	0
Any serious TEAE, n (%)	4 (6)	0	4 (5)
Related to study drug	0	0	0
Severity of TEAEs related to study drug, n (%)			
Mild	14 (20)	2 (14)	16 (19)
Moderate	2 (3)	0	2 (2)
Severe	0	0	0

1. As of data cutoff date, through week 53 for some patients.

Prospective Switch Study Results

Donidalorsen Phase 3 OASISplus: Switch Study

- Patients continued use of prior HAE prophylactic therapy during the screening period
- A stable dose of androgens and tranexamic acid were allowed during the treatment period

Previous Prophylactic Therapy	% of Patients	Schedule
Lanadelumab	49%	The last dose of lanadelumab was administered 14 days **prior** to first dose of donidalorsen
Berotralstat	17%	Continued taking berotralstat for 14 days **after** the first dose of donidalorsen
C1-INH	34%	Continued taking C1-INH for 14 days **after** the first dose of donidalorsen

Switch Study Design

Design

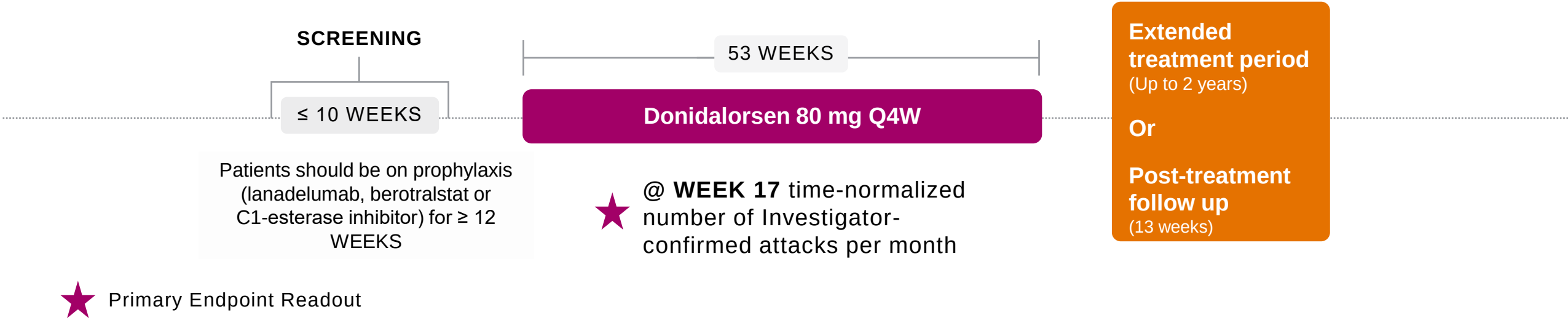
An Open Label study of Q4W dosing of **donidalorsen in patients** aged ≥12 years, with HAE-C1INH-Type1 or HAE-C1INH-Type2 on stable dose of **prophylactic treatment** (lanadelumab, berotralstat or C1-INH) for ≥12 weeks **prior** to the **screening** period

Objectives

- Demonstrate how to switch to donidalorsen without loss of control or adverse events
- Evaluate the long-term efficacy and effects of donidalorsen
- Evaluate patient preference

Methods

- HAE attack rates
- Quality-of-life assessments
- Disease control assessment
- Preference survey
  - All patient-related outcomes were administered independently by site personnel



Patients should be on prophylaxis (lanadelumab, berotralstat or C1-esterase inhibitor) for ≥ 12 WEEKS

★ @ **WEEK 17** time-normalized number of Investigator-confirmed attacks per month

★ Primary Endpoint Readout

1. NCT05392114.

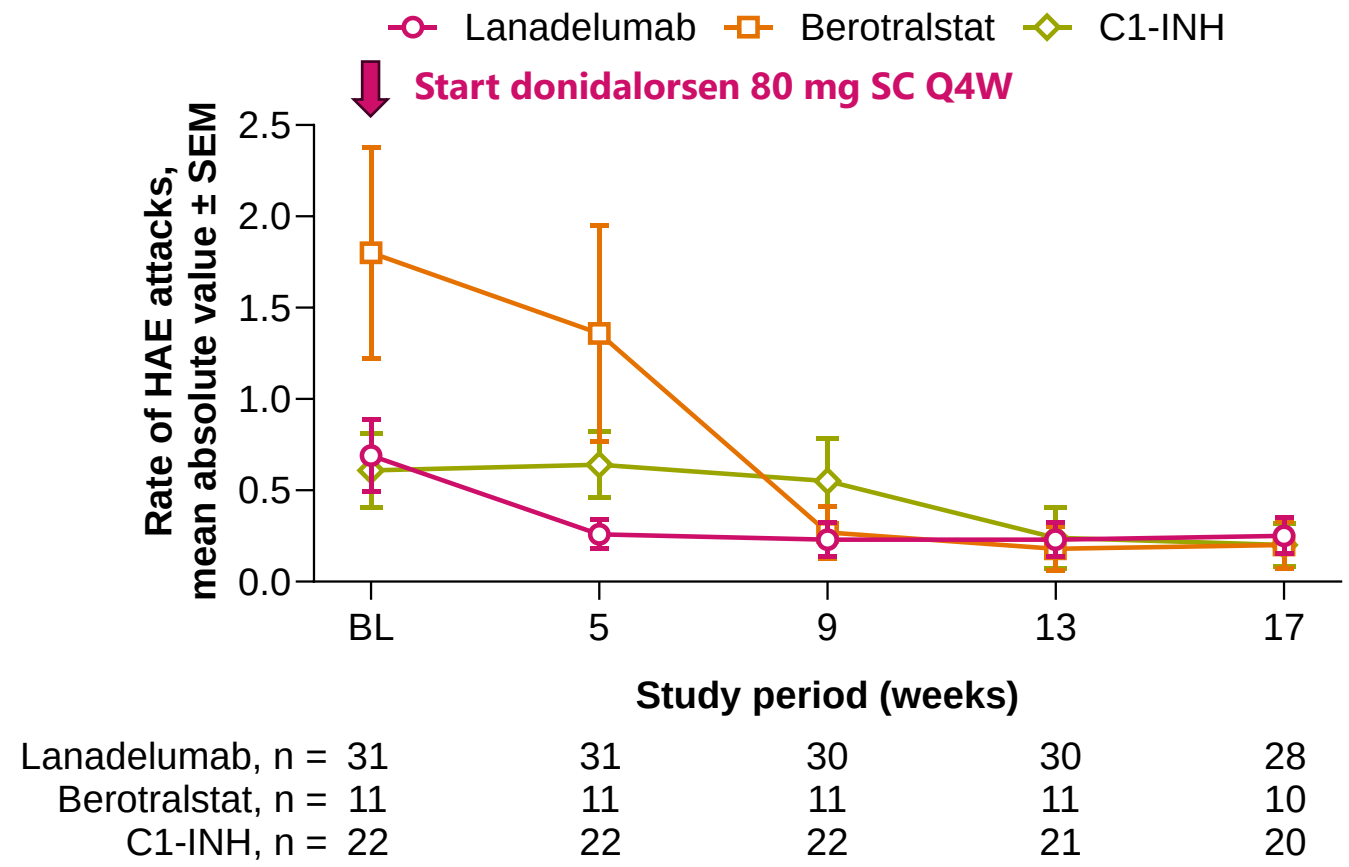
Switch: Patient Disposition and Study Treatment Exposure

	Lanadelumab	Berotralstat	C1-INH	Total
Patients enrolled, n	**32**	**11**	**22**	**65**
Patients dosed, n	**31**	**11**	**22**	**64**
Completed Week 17 of treatment, n (%)	**28 (88)**	**10 (91)**	**20 (91)**	**58 (89)**
Early termination, n (%)				
Lack of efficacy	3 (9)	0	1 (5)	4 (6)
Serious adverse event	1 (3)	0	0	1 (2)
Lost to follow-up	1 (3)	0	0	1 (2)
Voluntary withdrawal	0	0	1 (5)	1 (2)
Other (not dosed)	1 (3)	0	0	1 (2)

88% of Switch Patients Remain in the Study with a Mean Treatment Duration of ~ 8 Months[1]

1. As of February 28, 2024.

Switch: HAE Attack Rate Improved For All Patients Compared to Baseline for Previous Prophylactic Treatments[1,2]

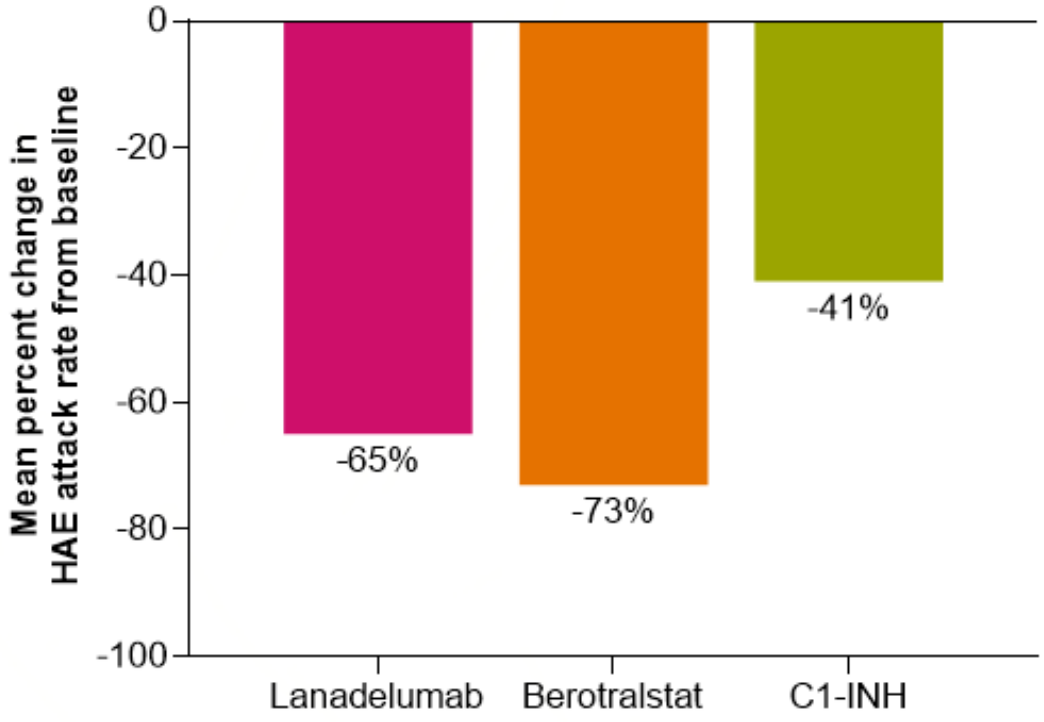


62% Total Mean Reduction in HAE Attack Rate from Baseline

1. Baseline attack rate during the screening period for the Switch study. 2. As of February 28, 2024.

Donidalorsen Substantially Reduced HAE Attack Rates After Switching[1-3]

% Reduction in HAE Attack Rate[4]

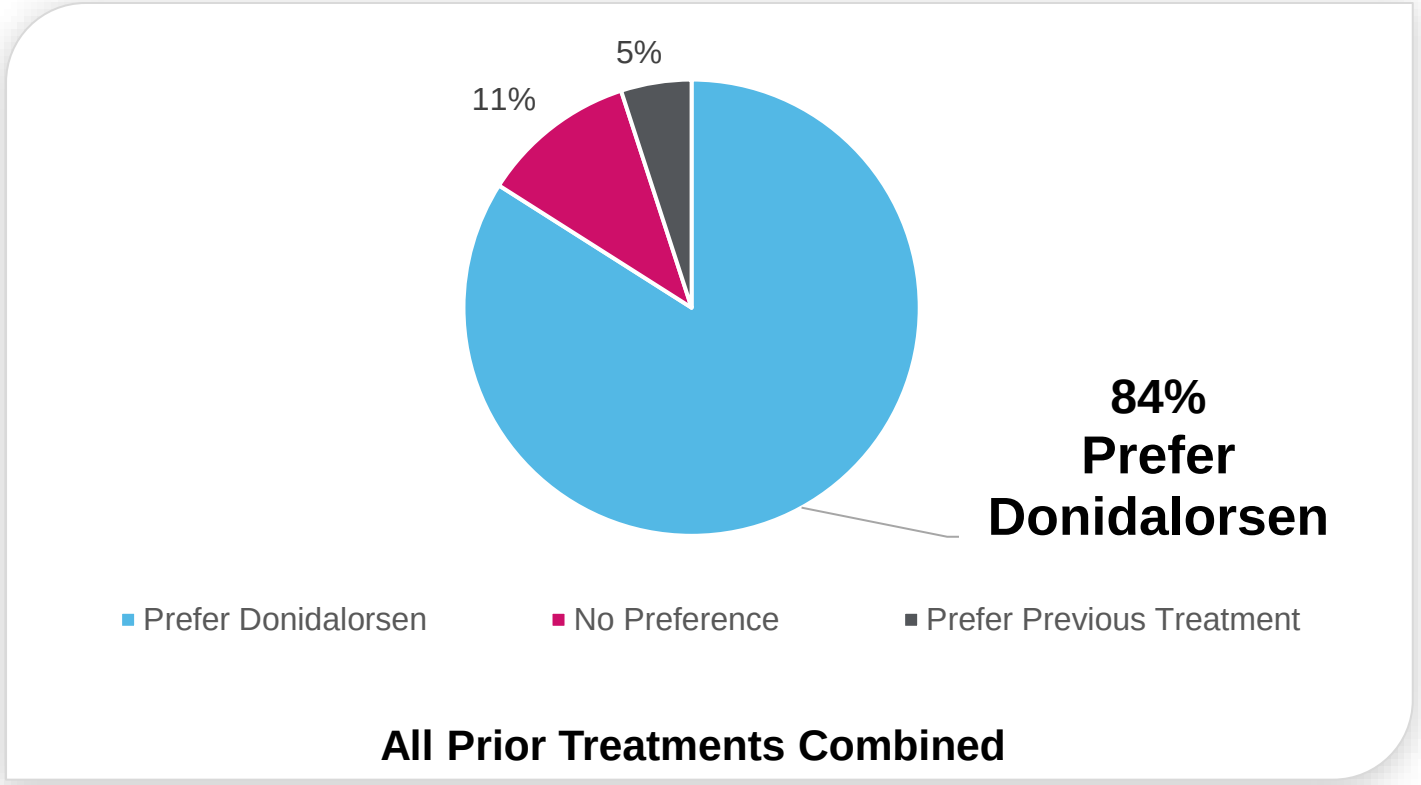


n =	31	11	22
Baseline, mean ± SD =	0.69 ± 1.09	1.80 ± 1.92	0.61 ± 0.96
Donidalorsen Q4W, mean ± SD =	0.24 ± 0.33	0.48 ± 0.53	0.36 ± 0.69

1. As of February 28, 2024 for Weeks 1-17. 2. Mean (SD). 3. Baseline HAE attack rate during the screening period for the Switch study. 4. Time-normalized number of HAE attacks per month (Weeks 1–17).

>80% of Switch Patients Preferred Donidalorsen Treatment[1,2]

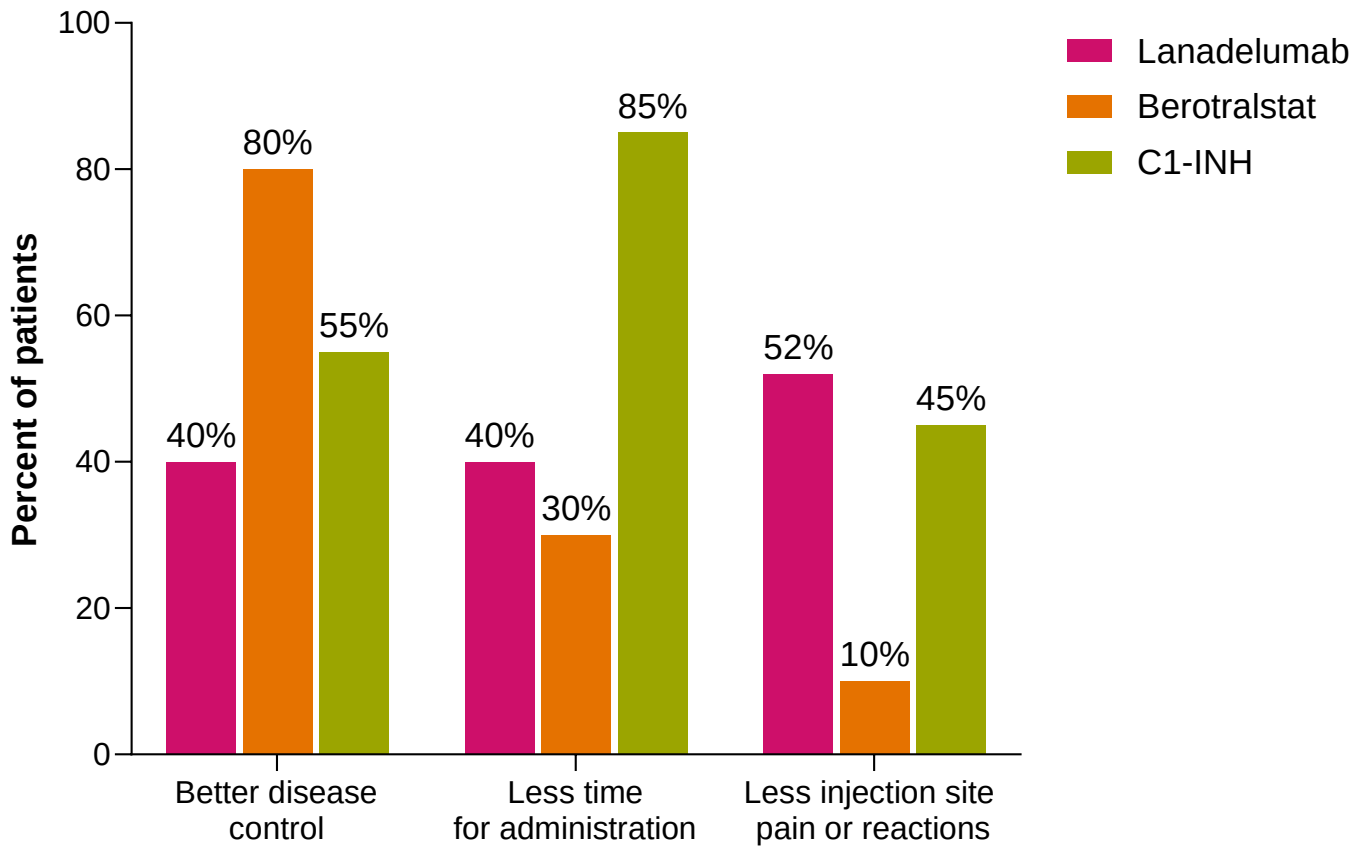
Data generated from independently administered survey



	Lanadelumab (n=25)	Berotralstat (n=10)	C1-INH (n=20)	Total (n=55)
% of Patients who Preferred Donidalorsen	72%	90%	95%	84%

1. As of February 28, 2024. 2. Assessed at Week 17.

Donidalorsen Preference Reasons Address Patient Needs[1,2]



1. As of February 28, 2024. 2. Assessed at week 17. Patients were permitted to indicate multiple reasons for preference.

Switch Results Reinforced with Continued Improvement in QoL Measures; ≥90% of Patients Well-Controlled at Week 17[1]

AE-QoL Mean Improvement from Baseline with Donidalorsen Treatment

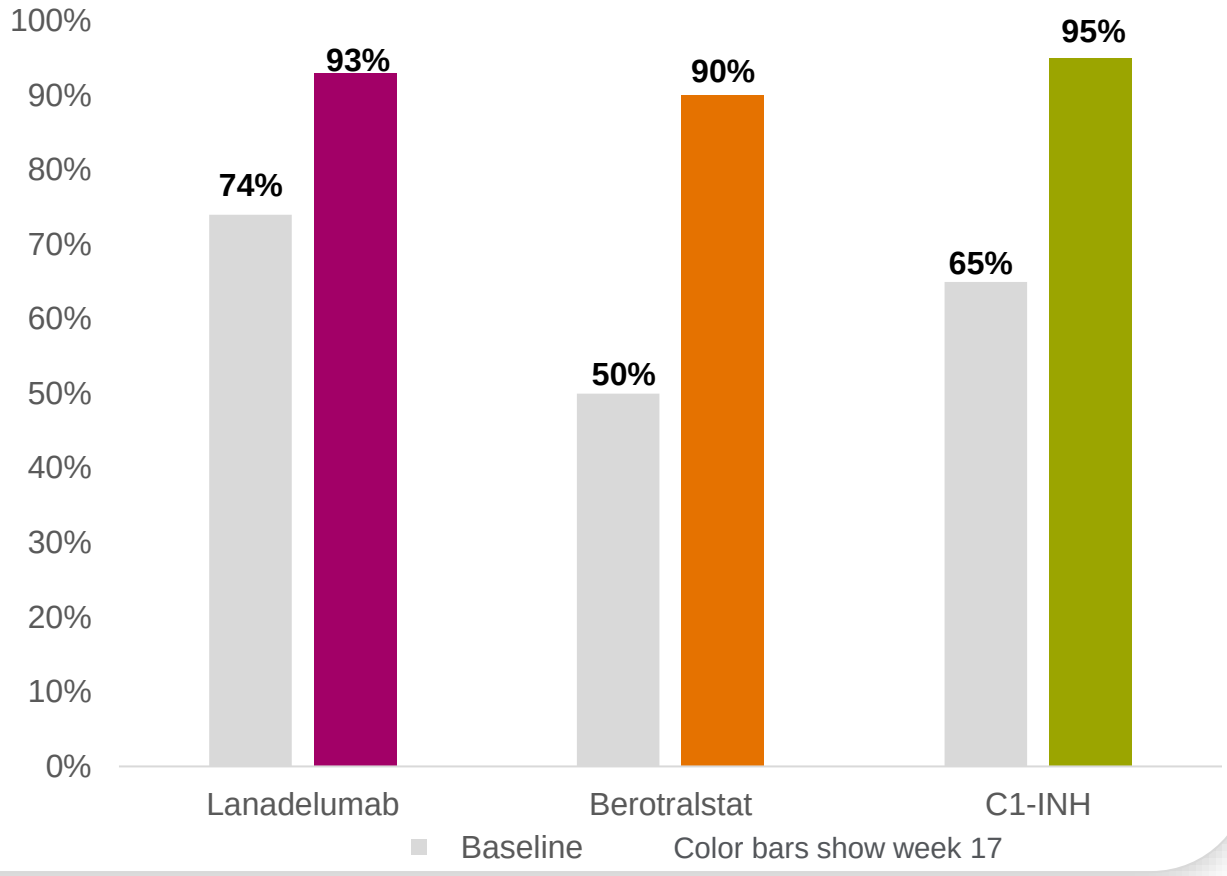
Lanadelumab:
8-point improvement

Berotralstat:
17-point improvement

C1-INH:
10-point improvement

An improvement of 6 points or more on AE-QoL is considered clinically meaningful[2]

AECT: Well-Controlled Patients Increased with Donidalorsen Treatment[3]



1. As of February 28, 2024. 2. Weller K et al. *Allergy*. 2016;71(8):1203–9. 3. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4; well controlled is defined as an AECT score ≥10.

Switch: Favorable Safety and Tolerability Profile[1]

- No serious TEAEs[2] related to the study drug
- Most TEAEs were mild
- One TEAE that was <u>not</u> related to study drug led to discontinuation[3]

	Donidalorsen Q4W (n = 64)
Any TEAE, n (%)	50 (78)
Related to study drug	21 (33)
Leading to discontinuation	1 (2)
Any serious TEAE, n (%)	1 (2)
Related to study drug	0
Severity of TEAE related to study drug, n (%)	
Mild	15 (23)
Moderate	5 (8)
Severe	1 (2)[4]

1. As of February 28, 2024. 2. A treatment-emergent adverse event (TEAE) is defined as any adverse event starting or getting worse on or after the first dose of the study drug. 3. One patient experienced two serious TEAEs - renal disorder and cardiac failure - which were not considered related to the study drug. Patient discontinued from study per investigator judgement. 4. One patient reported a headache assessed by the PI as possibly related, was non-serious, resolved and there was no action taken with the study drug.

Robust Positive Data from Phase 3 OASISplus: OLE and Switch

- Long-term donidalorsen treatment resulted in continued patient improvement on all measures
- All patients had further reductions in HAE attack rate with donidalorsen treatment after switching
- Donidalorsen improved quality-of-life measures and resulted in high levels of disease control
- Strong preference for donidalorsen reported in switch patients
- Donidalorsen had a favorable safety and tolerability profile

Donidalorsen: Poised to Advance HAE Treatment

Eugene Schneider, M.D.
Chief Clinical Development Officer

Switch Study Results[1]

Demonstrate **Meaningful Improvements** with **Donidalorsen**

≥90%	Patients Well-Controlled at Week 17[2]
>60%	Further Reduction in HAE Attack Rate for All Patients[3]
>80%	Patients Preferred Donidalorsen Treatment

1. As of February 28, 2024, assessed at week 17. 2. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4; well controlled is defined as an AECT score ≥10. 3. Compared to Baseline for Previous Prophylactic Treatments.

Compelling Data Position Donidalorsen to Advance the HAE Prophylactic Treatment Paradigm[1,2]

HAE is a severe, rare, genetic disease

New prophylactic treatments are needed

Donidalorsen robust data demonstrated**:**

- **Substantial** and **sustained** reduction in HAE attacks
- **Improvement** in **QoL** measures and **≥90% were well-controlled[2]**
- **Extended dosing** to monthly and every two-months with simple self-administered **autoinjector**
- **All patients had a reduction in HAE attack rates after switching to donidalorsen[3]** and **>80% preference** over **other prophylactic treatments**
- **Favorable safety and tolerability profile**

1. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data as of February 28, 2024. 2. In Q4W dose in OASIS-HAE, Q4W and Q8W in OLE and in switch. Weller K, et al. *J Allergy Clin Immunol Pract.* 2020;8(6):2050-7.e4; well controlled is defined as an AECT score ≥10. 3. Compared to baseline.

Delivering Donidalorsen to People with HAE

Kyle Jenne
Chief Global Product Strategy Officer

HAE Landscape Dynamics Underscore Donidalorsen Potential[1,2]

Well Defined Population with **>20K People with HAE** in U.S. & EU

Growing Global Market

New Treatment Options Needed

People with HAE Have Shown **Willingness to Switch**

Concentrated Prescriber Base in the US

Efficient Commercial Model

1. Market data on file. 2. Lumry et al. "Hereditary Angioedema: The Economics of Treatment of an Orphan Disease. Front. Med., 16 February 2018 Sec. Hematology Volume 5 – 2018.

New Treatment Options for HAE Still Needed[1]

Patient reported data collected by the US HAEA across

>500 participants

showed:

57% of those surveyed reported **using a prophylactic medication in the past 12 months**

34% of those surveyed reported **> 2 attacks per month**

1. Sandra C. Christiansen MD , Joyce Wilmot MS , Anthony J. Castaldo MPA , Bruce L. Zuraw MD , For the US Hereditary Angioedema Association (HAEA) Medical Advisory Board members, The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities, Annals of Allergy, Asthma Immunology (2023).

Donidalorsen Treatment Resulted in ≥90% of Patients Being Well-Controlled Across All Phase 3 Studies[1,2]

>90%
of Patients Well-Controlled In OASIS-HAE

Q4W dosing at Week 25

>90%
of Patients Well-Controlled In OASISplus OLE

Q4W: 91%; Q8W: 100%
at Week 25 of OLE[3]

≥90%
of Patients Well-Controlled In OASISplus Switch[3]

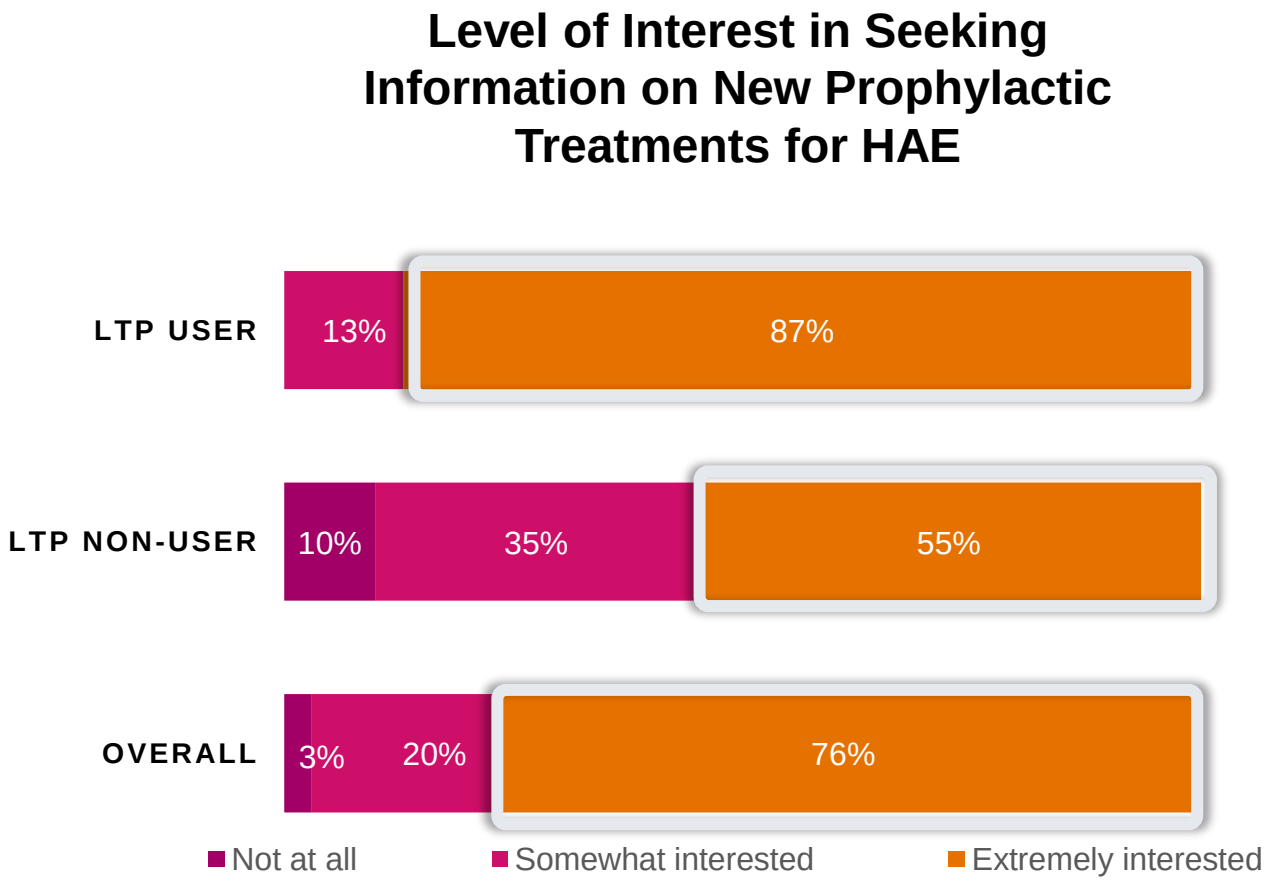
Prior treatments:
93%: lanadelumab
90%: berotralstat; 95%: C1-INH
at Week 17

1. Weller K, et al. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-7.e4; well controlled is defined as an AECT score ≥10. 2. Based on data generated from Phase 3 and Phase 3 OLE + Switch data. 3. As of the data cutoff date of February 28, 2024.

People with HAE Demonstrate Interest in New Treatments[1,2]

3 out of 4 People with HAE

are **Interested** in Seeing Information on **New** Prophylactic **Treatments**[1]

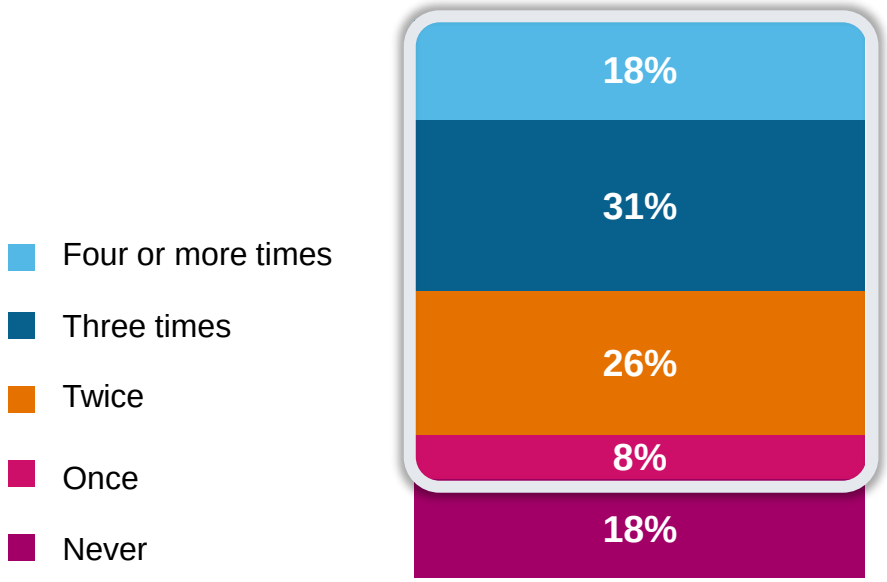


1. Ionis primary qualitative market research, 2024; n=39 LTP User, n=20 LTP non-user. 2. LTP= long-term prophylactic.

Donidalorsen Profile Positioned to Meet Need; Consistent with Patients' Reasons for Switching[1,2]

4 out of 5 People with HAE Have **Switched Treatments**[2]

Patient Lifetime Switching History[1]



Patient Switching Driven By[1]:

- Improved efficacy (fewer attacks)
- Less severe attacks
- Improved convenience

Donidalorsen[2]:

- Strong efficacy across robust development program
- 92%-95% Fewer ER visits[3]
- Monthly or every two-month self-administration via an autoinjector

1. Ionis primary qualitative market research, 2022; n=36. 2. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 3. From Phase 3 data, compared to baseline

Efficient and Targeted Approach to Reach People with HAE and HCPs

Lauren & Lindsey
Sisters Living with HAE

Concentrated Prescriber Base

Majority of People with HAE in the US are Treated by Allergists

~1,000 Allergist/Immunologists Manage >70% of HAE Patients[1]

Efficient Field Team

Planning for <100 Person Customer-Facing Team

Field Sales Reps Focused on Top Allergist & Immunologist Prescribers

Patient Education Managers Supporting Donidalorsen Patients

Direct-to-Patient Engagement

Dedicated High-Touch Patient Services

Continued Engagement and Adherence Through Integrated Omnichannel Solutions

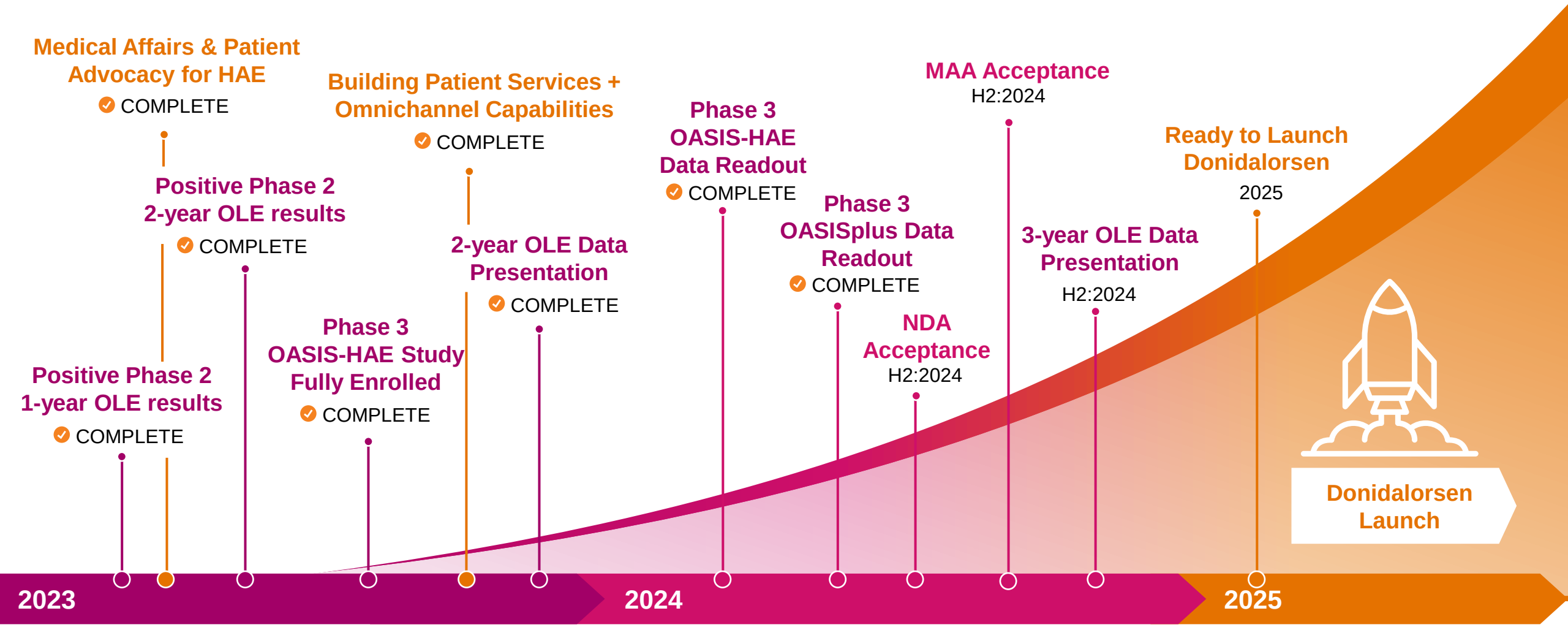
1. Ionis secondary market research (2021).

Donidalorsen: A Potential Preferred Choice for People with HAE[1,2]

- Potential First-in-Class RNA-Targeted Medicine
- Substantial and Sustained Attack Rate Reduction with Long-Term Durability and Disease Control
- Unique Data Showing Strong Preference and to Inform Potential Switching
- Favorable safety and tolerability profile
- Simplicity of a monthly or every two-month self-administration with an autoinjector

1.Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 2. Assuming approval.

Next Steps to Bring Donidalorsen to People with HAE[1,2]



1. Timing expectations based on current assumptions and subject to change 2. Assuming approval.

Concluding Remarks

Brett Monia, Ph.D.
Chief Executive Officer

Key Value-Driving Events Planned For 2024[1]

Phase 3 Clinical Data Events

Donidalorsen
- OASIS-HAE topline data
- OASIS-HAE full data
- OASISplus OLE + Switch data

Olezarsen
- Balance study full data, FCS
- CORE & CORE2 studies fully enrolled, SHTG

Phase 2 Clinical Data Events

Donidalorsen
3-year OLE, HAE

IONIS-FB-L$_{Rx}$
Geographic Atrophy

IgA nephropathy (OLE)

ION224
- MASH (NASH)

ION582
- Angelman syndrome

ION541
ALS

Regulatory Actions

Eplontersen
OUS approval decisions, ATTRv-PN
- OUS filings, ATTRv-PN

Olezarsen
NDA acceptance, FCS[2]

FDA approval decision, FCS[3]

EU acceptance, FCS

Donidalorsen
NDA acceptance, HAE

QALSODY
- EMA approval decision, SOD1-ALS

New Product Launches

WAINUA
- ATTRv-PN[4]

Olezarsen
FCS[3]

QALSODY
EU, SOD1-ALS

1. Timing expectations are based on current assumptions and are subject to change, timing of partnered program catalysts based on partners' most recent publicly available disclosures. Green checkmarks indicate positive outcome. Red checkmarks indicate program is not moving forward. 2. NDA submission completed. 3. Assuming priority review. 4. WAINUA: www.wainua.com

Well-Positioned to Build on Momentum by Executing on Strategic Priorities

01

Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas (neurology and cardiology)

02

Integrated Commercial Capabilities in Place

Steady cadence of new potentially **transformational medicines** to the **market**

03

Leading Technology

Advancing technology to **expand existing franchises and address new therapeutic areas**

04

Effective Financial Strategy Poised for Growth

Multi-billion-dollar revenue opportunity to enable future **positive cash flow**

Jackson,
Angelman Syndrome Patient

Driving Next-Level Value for Patients and All Ionis Stakeholders

Q&A

Brett Monia, Ph.D.
Chief Executive Officer

Eugene Schneider, M.D.
Chief Clinical Development Officer

Kyle Jenne
Chief Global Product Strategy Officer

Jonathan Birchall
Chief Commercial Officer

Thought Leader Here Today

Marc Riedl, M.D., M.S.

Professor of Medicine
Clinical Director –
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Clinical Service Chief –
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