CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	219407
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Reviewer Name(s)	Donella Fitzgerald, PharmD, DRM
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Acting Division Director	Laura Zendel, PharmD, DRM
Review Completion Date	August 15, 2025
Subject	Evaluation of Need for a REMS
[Established/Proper] Name	donidalorsen
Trade Name	Dawnzera
Name of Applicant	Ionis Pharmaceuticals, Inc.
Therapeutic Class	prekallikrein-directed antisense oligonucleotide
Dosage Form(s)	80 mg/0.8 mL solution in a single-dose autoinjector
Dosing Regimen	80 mg subcutaneously every 4 weeks or every 8 weeks

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Dawnzera (donidalorsen) is necessary to ensure the benefits outweigh its risks. Ionis Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) 219407 for donidalorsen with the proposed indication for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older. This application is under review in the Division of Pulmonology, Allergy and Critical Care (DPACC). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Donidalorsen, a new molecular entity,[a] is a prekallikrein-targeted *N*-acetyl galactosamine (GalNAc)-conjugated antisense oligonucleotide proposed for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older. The Applicant reports that donidalorsen selectively binds to prekallikrein (PKK) messenger RNA, consequently degrading it via ribonuclease H1 and preventing production of the PKK protein, leading to a reduction in the formation of bradykinin, an inflammatory peptide. Donidalorsen is proposed as an 80 mg/0.8 mL solution in a single dose autoinjector to be administered subcutaneously once monthly for chronic treatment.[b] Per the Applicant, a dosing interval of once every two months may be considered (b) (4)

Donidalorsen will likely primarily be used in the outpatient setting and administered by the patient or a caregiver. Donidalorsen was granted orphan drug designation on September 19, 2023 and is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219407 relevant to this review:

- 09/19/2023: Donidalorsen orphan drug designation granted for IND 142564 for the treatment of hereditary angioedema.
- 08/21/2024: NDA 219407 submission for prophylaxis to prevent attacks of hereditary angioedema in adult and pediatric patients 12 years of age and older received.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 01/30/2025: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no major safety concerns had been identified to date that require a risk mitigation strategy for donidalorsen.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Hereditary angioedema (HAE) is a rare and potentially life-threatening[c] autosomal dominant inherited disease of vascular permeability. The disease is caused by genetic mutations in the SERPING1 gene, leading to a deficiency or dysfunction of the C1-inhibitor (C1-INH) protein. The level and/or function of the C1-INH protein is used to classify HAE into two forms: HAE1 and HAE2. With HAE1 the C1-INH levels are low or absent and there is reduced functional activity; with HAE2 the C1-INH levels are normal (or near normal) but there is still significantly reduced functional activity.[1] Both types of HAE result in overproduction of the inflammatory peptide bradykinin, leading to vasodilation and swelling.[2] The clinical presentation for both HAE1 and HAE2 is the same. Patients present with unpredictable, recurrent, painful, and often debilitating swelling episodes referred to as attacks, which affect subcutaneous tissue (face, upper or lower extremities, genitals), abdominal organs (stomach, intestines, bladder), and the upper airway (larynx, tongue).[3] Untreated, swelling typically resolves within two to five days, however in some patients laryngeal angioedema may cause fatal asphyxiation.

Onset of HAE usually begins by age 20, most often by puberty.[4] The estimated prevalence in the US is 1:50,000 people, with reported ranges from 1:10,000 to 1:150,000 people.[5d] Variable clinical presentation can contribute to diagnostic delays, leading experts to believe that HAE may be significantly underdiagnosed.[6]

3.2. Description of Current Treatment Options

There is no cure for HAE, but there are several approved therapies for acute attacks and prophylaxis. On-demand therapies used for the acute treatment of HAE include: human plasma derived C1-esterase inhibitors (C1-INH) (Cinryze®, Berinert®), a recombinant human C1-INH (Ruconest®), a bradykinin B2 receptor antagonist, Firazyr® (icatibant), and the kallikrein inhibitor, Kalbitor[e] (ecallantidee).

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[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[e]Due to the risk of anaphylaxis, Kalbitor® was approved with a REMS consisting of a communication plan and

Prophylactic treatments include oral attenuated androgen (Danazol®), plasma-derived C1-INH replacement therapy (Cinryze®, Haegarda®), plasma kallikrein inhibitors (lanadelumab, berotralstat), and activated Factor XII inhibitor (garadacimab). None of the products approved to prevent HAE attacks were approved with a REMS, though Danazol® labeling includes a boxed warning for teratogenicity, thromboembolic events, liver injury, and pseudotumor cerebri. The other prophylactic treatment options have been associated with injection-site reactions, headache, nausea, rash, vomiting, fever, upper respiratory infection, myalgia, dizziness, and diarrhea.[7,8] Current oral treatment options are associated with gastrointestinal adverse events in some patients.[9] A table detailing the currently approved treatments to prevent HAE attacks is included in the Appendix of this review (Section 10.1). Unapproved therapies for HAE prophylaxis include the antifibrinolytics tranexamic and aminocaproic acids. Their usage has declined due to limited evidence of efficacy and the approval of newer and more effective HAE polylactic therapies.[10]

Although numerous approved prophylactic therapies exist for patients with HAE, breakthrough attacks are common. There is an unmet need for long-term prophylaxis from a new pharmacologic class that provides greater efficacy, safety, and tolerability, with an infrequent dosing regimen.[11]

4. Benefit Assessment

The pivotal trial (Study 721744-CS5 [OASIS], NCT05139810) supporting this application consisted of a single Phase 3 double-blind, placebo-controlled, randomized study evaluating donidalorsen 80 mg administered as a subcutaneous injection every 4 weeks (donidalorsen-4 group) or every 8 weeks (donidalorsen-8 group) in adult and pediatric (12 years of age and older) subjects with HAE over a 24-week treatment period. Subjects with HAE-1 or HAE-2 were randomly assigned in a 2:1 ratio to Cohort A (donidalorsen-4 group [45 subjects] or placebo) or Cohort B (donidalorsen-8 group [23 subjects] or placebo). Within each cohort, subjects were randomly assigned in a 3:1 ratio to receive donidalorsen or a matching volume of placebo. Data from subjects receiving placebo in Cohort A and Cohort B were pooled for analyses [22 subjects]. Subjects were required to discontinue other prophylactic HAE medications, except androgens and tranexamic acid, prior to entering the trial; all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks.[12]

The primary endpoint for the OASIS study was the time-normalized HAE attack rate per 4 weeks over a 24 week treatment period. Based on the study results DPACC concluded that the OASIS trial met its primary endpoint, demonstrating a statistically significant and clinically meaningful reduction in the number of HAE attacks per 4 weeks from baseline to Week 24 in the donidalorsen-4 group and the donidalorsen-8 group compared to pooled placebo.[13f] The results are outlined below in Table 1.[14]

timetable for submission of assessments on December 1, 2009. This REMS was eliminated on April 10, 2013 as the communication plan was complete and the REMS met its goals.

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Table 1: HAE Attack Rate (Attacks/4 Weeks) at Week 24 in OASIS-HAE			
	DAWNZERA 80 mg q4wks (N=45)	DAWNZERA 80 mg q8wks (N=23)	Placebo (N=22)
HAE Attack Rate per 4 Weeks from Week 0 to Week 24*			
LS mean (95% CI) attack rate	0.44 (0.27, 0.73)	1.02 (0.65, 1.59)	2.26 (1.66, 3.09)
% Reduction (95% CI) relative to placebo†	−81 (−89, −65)	−55 (−74, −22)	--
Wald chi-square p-value	<0.001	0.004	--

CI = confidence interval; HAE = hereditary angioedema; LS = least square; N = number of patients in the specific treatment group; q4wks = every 4 weeks; q8wks = every 8 weeks.

* Primary efficacy endpoint = comparison of the time-normalized number of investigator-confirmed HAE attacks per 4 weeks from Week 0 to Week 24 between the DAWNZERA 80 mg q4wks group and the placebo group.

† Calculated as the ratio of the model-based treatment period HAE attack rates (donidalorsen/placebo) minus 1 multiplied by 100.

While both dosing regimens demonstrated efficacy compared to placebo, donidalorsen-4 demonstrated greater efficacy than donidalorsen-8 across primary and secondary endpoints (proportion of subjects with a ≥50% reduction in attacks, number of attack-free subjects, moderate-to-severe HAE attacks, and HAE attacks requiring acute on-demand treatment). Per the DPACC, because both dosing intervals independently met the primary efficacy endpoint, both dosing options are being recommended for approval.[15] Based on the greater efficacy of the 80 mg every 4 week dosing regimen, however, the recommended starting dosage of donidalorsen is 80 mg administered subcutaneously every 4 weeks. A dosage of 80 mg every 8 weeks may be considered.[16]

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis consists of data from 171 subjects who completed the pivotal Phase 3 trial (OASIS). Supportive safety data from the ongoing open-label trials (ISIS 721744-CS3, NCT 04307381; ISIS 721744-CS7, EudraCT 2022-000757-93) is also included.

No deaths were reported in the Phase 3 pivotal trial (OASIS); however, one completed suicide was reported for a subject in the ISIS 721744-CS7 open-label trial (as of the safety update data cutoff date of June 27, 2024). The subject was a 48-year-old male with no known history of depression or anxiety who committed suicide on Study Day 239. The method of suicide is unknown as the Applicant reported that the family chose not to share additional details.[17] The event was assessed as not related to study drug by the investigator and Applicant.

No serious adverse events (SAEs) were reported in subjects receiving donidalorsen in the Phase 3 pivotal trial, but one subject (4.5%, 1/22) in the pooled placebo group experienced a serious limb injury. There was one subject (0.6%, 1/177) in the ISIS 721744-CS7 open-label trial who experienced a SAE of hypersensitivity on Study Day 816 (classified as anaphylaxis). Given the fulfillment of Sampson's

criteria[g], the temporal relationship to donidalorsen, and the lack of an alternative diagnosis, DPACC attributes the anaphylaxis to donidalorsen treatment.[18]

5.1. Hypersensitivity Reactions, including Anaphylaxis

Hypersensitivity reactions are a known, labeled adverse event for antisense oligonucleotides.[19] Hypersensitivity reactions, including anaphylaxis, were observed in the donidalorsen clinical development program. In addition to the anaphylaxis case previously discussed in Section 5, there were five non-serious hypersensitivity reactions that occurred in three patients (2%, 3/177) who received donidalorsen in the clinical trials (ISIS 721744-CS2 Phase 2a, ISIS 721744-CS3 Open-label Extension, ISIS 721744-CS5 Phase 3, and ISIS 721744-CS7 Open-Label Extension). Patient symptoms included generalized rash, dyspnea, chest pain and peri-oral swelling. Two of the six AEs of hypersensitivity reactions led to permanent treatment discontinuation in 2 (1%) patients. The risk of hypersensitivity, including anaphylaxis, will be included in the Warnings and Precautions (Section 5.1) of the donidalorsen label. The Patient Counseling Information in the label (Section 17) advises prescribers to instruct patients to immediately discontinue donidalorsen and seek medical attention if they experience signs and symptoms of serious hypersensitivity reaction.

6. Expected Postmarket Use

As donidalorsen is proposed for prophylactic use, it is expected to be used primarily in an outpatient setting. It is proposed as a subcutaneous injection that may be self-administered by the patient or administered by a caregiver. It is likely to be prescribed by allergists and clinical immunologists who have experience treating patients with HAE. Per the Prescribing Information, healthcare providers are to counsel patients at the point of care regarding the risk of hypersensitivity reactions with donidalorsen treatment. It is expected that HAE patients would be able to identify the signs and symptoms of a hypersensitivity reaction and seek medical attention. Additional resources for patients include Patient Information and Instructions for Use.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for donidalorsen beyond routine pharmacovigilance and labeling. Draft labeling includes Patient Information and Instructions for Use to be dispensed with every prescription.

[g] Sampson HA, Munoz-Furlong A, Campbell RL et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7.

8. Discussion of Need for a REMS

The review team recommends approval of donidalorsen on the basis of the efficacy and safety information currently available.

HAE is a rare and potentially life-threatening autosomal dominant inherited disease of vascular permeability that is characterized by unpredictable, recurrent and painful episodes of angioedema affecting subcutaneous tissue in the upper respiratory and gastrointestinal tracts. There is no cure for HAE, but multiple pharmacologic agents are used for acute attacks and prophylactic treatment. There are differences in administration, efficacy, safety, and tolerability across products. DPACC determined that an unmet need for safe and effective treatments remains, especially for agents from different pharmacologic classes.

Efficacy for donidalorsen was based on the results from a single, adequate and well-controlled trial by meeting the primary endpoint of the time-normalized HAE attack rate per 4 weeks over a 24 week treatment period with donidalorsen 80 mg versus placebo. The serious adverse event observed with donidalorsen use was anaphylaxis. Because donidalorsen is an antisense oligonucleotide, the risk of hypersensitivity, including anaphylaxis, was expected. Like other agents approved for HAE prophylaxis, such as lanadelumab and the C1-INHs, donidalorsen labeling will include a Warning and Precaution for hypersensitivity reactions. Prescribers are advised to inform patients to discontinue therapy if a hypersensitivity reaction occurs. Patients should be able to identify symptoms of hypersensitivity and contact their prescriber or seek emergency help if necessary. Per the review division, risk management beyond standard pharmacovigilance is unnecessary for safe use of donidalorsen. Based on the information currently available, this reviewer agrees that risk mitigation beyond labeling is not necessary at this time.

9. Conclusions & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of donidalorsen treatment outweigh the risks. Prescribers are knowledgeable about the hypersensitivity safety concern with antisense oligonucleotides, such as donidalorsen. And the symptoms of hypersensitivity and anaphylaxis can be identified by patients who can seek immediate medical assistance if needed. Should DPACC have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. Summary of FDA Approved Treatments for HAE prophylaxis

Product Trade Name (Generic) **Year of Approval**	**Indication**	**Dosing/Administration**	**Important Safety and Tolerability Issues**	**Risk Management Approaches/Boxed Warning, Medication Guide**
Danazol 1976	Prevention of HAE attacks of angioedema of all types; Treatment of endometriosis	Starting dose: 200 mg orally 2-3 times daily. Continuing dose may be titrated down by <50% every 1-3 months. Dosage may be increased up to 200 mg daily in event of attack.	- Androgenic and anabolic adverse effects - Teratogenicity - Thromboembolic events - Liver injury -Pseudotumor cerebri	Boxed Warning, Contraindication, Warnings and Precautions
Cinryze (C1-esterase inhibitor [human]) 2008	Routine prophylaxis against HAE attacks in adults, adolescents, and pediatric patients ≥ 6 years of age	500-1000 IU infused intravenously every 3 or 4 days	- Hypersensitivity reactions - Thromboembolic events - Risk of transmitting infectious agents	Warnings and Precautions
Haegarda (C1-esterase inhibitor [human])	Routine prophylaxis to prevent HAE attacks in adolescent and adult patients	60 IU per kg body weight subcutaneously twice weekly (every 3-4 days)	- Hypersensitivity reactions - Thromboembolic events - Risk of transmitting infectious agents	Warnings and Precautions
Takhzyro (lanadelumab) 2018	Prophylaxis to prevent HAE attacks in adults and pediatric patients ≥ 2 years of age	150-300 mg subcutaneous injection every 2-4 weeks	Hypersensitivity reactions	Warnings and Precautions
Orladeyo (berotralstat) 2020	Prophylaxis to prevent HAE attacks in adults and pediatric patients ≥ 12 years of age	150 mg orally once daily	QT prolongation	Warnings and Precautions

Andembry (garadacimab) 2025	Prophylaxis to prevent attacks of HAE in adult and pediatric patients aged ≥ 12 years	Loading dose: 400 mg subcutaneously Maintenance: 200 mg subcutaneously once monthly	No major safety concerns	

10.2. References

[1] Zuraw B, Bork K. Hereditary angioedema with normal C1 inhibitor. In: Saini S, Feldweg A, eds. *UptoDate*. Waltham, MA

[2] Zuraw B, Bork K. Hereditary angioedema with normal C1 inhibitor. In: Saini S, Feldweg A, eds. *UptoDate*. Waltham, MA

[3] Peterson RS, Bordone L, Riedel MA, et al. A phase 2 open-label extension study of prekallikrein inhibition with donidalorsen for hereditary angioedema. Allergy. 2024;79(3):724-734.

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[13] Division of Pulmonology, Allery and Critical Care. Draft Integrated Assessment of Marketing Application for donidalorsen NDA 219407. August 1, 2025.

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[15] Division of Pulmonology, Allery and Critical Care. Draft Integrated Assessment of Marketing Application for donidalorsen NDA 219407. August 1, 2025.

[16] Division of Pulmonology, Allery and Critical Care. Draft Integrated Assessment of Marketing Application for donidalorsen NDA 219407. August 1, 2025.

[17] Ionis Pharmaceuticals, Inc. 120 Day Safety Update for donidalorsen, NDA 219407. December 19, 2024.

[18] Division of Pulmonology, Allery and Critical Care. Draft Integrated Assessment of Marketing Application for donidalorsen NDA 219407. August 1, 2025.

[19] Division of Pulmonology, Allery and Critical Care. Draft Integrated Assessment of Marketing Application for donidalorsen NDA 219407. August 1, 2025.

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