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OHSU Drug Effectiveness Review Project Summary Report – Pharmaceutical Treatments for Hereditary Angioedema: Prevention and Acute Treatment of Attacks

Date of Review: April 2026

Date of Last Review: June 2021
Literature Search: Through 7/15/2025

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- Hereditary angioedema (HAE) is a disorder that can cause swelling in different places in the body. When swelling happens in the face and airway it can be life-threatening. This disorder is passed along by genes and often runs in families. This swelling, also called an attack, can last for several days and can be brought on by trauma, infection, stress, or some medicines in people who have the disorder.
- Medicines for hereditary angioedema either focus on making the swelling go away faster or preventing the swelling from happening at all. Medicines for this class can be given in a vein, an injection into the fat below the skin, or as an oral pill.
- The purpose of this review is to look at new published data comparing medicines for hereditary angioedema.
- There are no studies that compare one medicine to another. All medicines for hereditary angioedema have been studied compared to placebo (sugar pill).[1]
- The United States (US) Food and Drug Administration (FDA) approved three new medicines for hereditary angioedema in 2025. Donidalorsen (DAWNZERA) is for prevention of attacks in people who are at least 12 years old. It is an injection given into the fat below the skin every 4 weeks.[2] Garadacimab-GXII (ANDEMBRY) is used to prevent attacks in people 12 years and older and is given as a monthly injection into the fat below the skin.[3] Sebetralstat (EKTERLY) is given during attacks in people 12 years and older as an oral tablet.[4]
- Providers must send the Oregon Health Authority (OHA) information to document why they are prescribing medications before the Oregon Health Plan (OHP) will pay for the medicine. This process is called prior authorization (PA).

Research Questions:

1. What is the effectiveness of HAE medications for prevention and treatment of attacks?
2. What are the potential harms of HAE medications for prevention and treatment of attacks?
3. Do the listed interventions vary in their effectiveness or potential harms based on patient or disease characteristics (e.g., age, type of HAE)?
4. What are the clinical practice recommendations for medications for prevention and treatment of attacks?

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Conclusions:

- There is no direct comparative evidence available to determine efficacy and safety between agents.[1]
- There are 3 new agents which have been approved since last review of this class by the Pharmacy and Therapeutics committee in 2021.
    - Donidalorsen (DAWNZERA): indicated for prophylaxis of HAE attacks in patients 12 years and older as a subcutaneous (SC) injection every 4 weeks with consideration of every 8 weeks injection interval.[2] There is high certainty evidence that donidalorsen reduced the rate of attacks from approximately 2.25/month to 0.23-0.44/month and moderate certainty evidence of clinical response in 65%-82% of participants ($p<0.05$) when compared to placebo.[1]
    - Garadacimab-GXII (ANDEMBRY): indicated for prophylaxis of HAE attacks in patients 12 years and older as a monthly SC injection.[3] Compared to placebo, the monthly attack rate was reduced by 87% over 6 months ($p<0.01$) in the phase 3 trial with a 92-100% response rate from baseline based on moderate certainty evidence.[1] For attacks requiring an on-demand treatment there was a mean of 0.23 attacks on garadacimab compared to 1.86 attacks with placebo based on moderate certainty evidence .[1]
    - Sebetralstat (EKTERLY): indicated for acute HAE attacks in patients 12 years and older as an oral tablet.[4] There is low certainty evidence that compared to placebo, sebetralstat had quicker initial and sustained improvements in symptoms, including complete resolution of symptoms and less use of on demand rescue medications. [1]
- Two expanded indications have been granted since the previous class update:
    - Lanadelumab-flyo (TAKZYRO) use was approved in 2023 for patients aged 2 to less than 12 years for prevention of HAE attacks.
    - Berotralstat (ORLADEYO) use was approved in 2025 for patients aged 2 to less than 12 years for prevention of HAE attacks, and an oral pellet formulation is now available.
- The most recent guidelines were published in 2022 by World Allergy Association and European Academy of Allergy and Clinical Immunology (WAA/EAACI).[1] Guidelines were of fair quality.[1] Products recently approved by the Food and Drug Administration after guideline publication were not included in current recommendations. First-line recommendations include:[1]
    - Acute Treatment: Intravenous C1 esterase inhibitors, ecallantide, and icatibant.
    - Acute Treatment in children: C1 esterase inhibitors and icatibant
    - Prophylactic treatment: Plasma-derived C1-esterase inhibitors (intravenous or subcutaneous), lanadelumab, and berotralstat.
    - Prophylactic treatment in children: C1-esterase inhibitors
    - Acute and prophylactic treatment in pregnant people and those breastfeeding: C1-esterase inhibitors
- New randomized controlled trials (RCT) published since last review to support approval of new agents and one new RCT of lanadelumab are summarized in the DERP review. All comparisons were versus placebo and results support current policy for HAE management.

Recommendations:

- Update prior authorization criteria for inclusion of new agents.
- After review of costs in executive session, make generic icatibant preferred.

Summary of Prior Reviews and Current Policy

- Therapy for HAE can be divided into 2 types: acute and prophylactic treatment. There is no direct comparative evidence evaluating drugs for either prophylactic or acute treatment of HAE.

- Medications for HAE were last reviewed in June 2021 with a class update and new drug evaluation of berotralstat. The prior authorization criteria were updated to include berotralstat. No other changes were made based on clinical information or evaluation of medication costs in executive session.
- Prior authorization is required for all HAE medications, and certain C1 esterase inhibitors (BERINERT for acute attacks, HAEGARDA for prophylaxis) are preferred. Prior authorization does not apply to treatments administered during emergency department visits or hospitalization.

Methods:
The December 2025 systematic review on "Pharmaceutical Treatments for Hereditary Angioedema: Prevention and Acute Treatment of Attacks" by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. An additional literature search was conducted by Drug Use Research and Management (DURM) in OVID Medline through 2/28/26 to look for comparative evidence from end of DERP literature search date until the present. No direct comparative evidence was identified in that additional search.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Evidence is listed with certainty grading, where high certainty of evidence (CoE) equates to a high degree of confidence in the stated outcome (e.g., difference, or difference) between study groups. OHSU does not recommend or endorse any guidelines or recommendations developed by users of these reports.

Summary Findings:
There were 22 RCTs that met inclusion criteria reporting data in 51 publications with 9 reporting on interventions for acute attacks and 13 RCTs reporting on therapeutics for prevention.[1] Many of these studies were available during previous HAE class update. Additionally, one 2022 guideline of fair quality on the management of prevention of HAE attacks by WAA/EAACI was included.[1] **Appendix 2** includes names and routes of currently approved and marketed products for HAE.

<u>Guideline</u>
World Allergy Association and European Academy of Allergy and Clinical Immunology (WAA/EAACI) Guideline for the Management of Hereditary Angioedema (2021, published 2022)

This revision of the original 2017 guideline was graded as methodologically fair by DERP.[1] The formal GRADE assessments were not reported and the formal systematic review was not provided or cited and external peer review was not mentioned by the guideline committee.[1] Given the 2022 publication data, newer agents for HAE were not included in the recommendations.

The first-line medications for acute attacks are intravenous C1 esterase inhibitors (either plasma-derived or recombinant), icatibant, and ecallantide.[1] Notably, ecallantide must be administered in a health care setting due to risk of anaphylaxis and hypersensitivity reaction.[1]

Short-term prophylaxis prior to procedures (e.g., medical, surgical, or dental) is recommended to include intravenous (IV), plasma-derived, C1 esterase inhibitors administered as close as possible to the procedure.[1] Alternatively, a recombinant C1 esterase inhibitor may be used.[1]

First-line recommendations for long-term prophylaxis are plasma-derived C1 esterase inhibitors (IV or SC), lanadelumab, and berotralstat.[1] The plasma-derived C1 esterase inhibitors are considered equally effective.[1] Lanadelumab may be given SC every 2 weeks, with the option to extend to every 4-week dosing, while berotralstat is an oral product.

For acute attacks in children, C1 esterase inhibitors and icatibant are preferred. Recommended prophylaxis regimens include plasma-derived C1 esterase inhibitors for those under 12 years of age.[1] Ecallantide, lanadelumab, and berotralstat are not recommended for children due to insufficient safety data.[1] Of note, use of icatibant in people under 18 years is off-label in the United States (US), and berotralstat has been approved for use in those 2 years of age and older since publication of these guidelines. Additionally, for pregnant people and those breastfeeding, C1 esterase inhibitors are the preferred and safest therapy for acute attacks and prophylaxis.[1]

Randomized controlled trials

Most of the 22 RCTs included in the DERP report were published prior to previous DURM class updates and do not provide new information to inform policy. There were no direct comparative studies of agents in this class.[1]

Sebetralstat (EKTERLY) was approved by the FDA in 2025 for acute attacks in patients 12 years and older as an oral tablet.[4] Two RCTs, one with low risk of bias (RoB) (n=136, 3-way cross-over with 300 mg sebetralstat, 600 mg sebetralstat, and placebo), the other with moderate RoB (n=68, phase 2, cross-over design) found that versus placebo, sebetralstat had quicker initial and sustained improvements in symptoms, including complete resolution of symptoms (low certainty of evidence [CoE]) and less use of on demand rescue medications (low CoE).[1] In the phase 3 study, there was a significantly shorter median time to symptom relief in participants receiving 300 mg and 600 mg of sebetralstat (1.61 hours; interquartile range [IQR], 0.78 to 7.04 for 300 mg; and 1.79 hours; IQR, 1.02 to 3.79 for 600 mg) than placebo (6.72 hours; IQR, 1.34 to > 12; $P < 0.001$ for 300 mg and $P = 0.001$ for 600 mg, respectively).[1] It was unclear if sebetralstat was associated with a higher risk of adverse events (AE) with short term use (high CoE).[1] At least one AE was experienced by 37% of patients.[1] The most common AEs were headache, nausea, dyspepsia, fatigue, irregular menstruation, rash, dysgeusia, and abdominal pain.[1]

Two new trials were published on the efficacy of lanadelumab, approved for prevention of HAE attacks since the last class update. One was an observational study (n=20). The other was the CASPIAN Study, a 26-week RCT (n=77) that evaluated 300 mg SC every 2 weeks or placebo in patients 12 years or older with at least one HAE attack in the previous 4 weeks while on high-dose antihistamines and history of non-histaminergic angioedema and normal C1 inhibitor function.[1] Investigators-confirmed attacks were recorded during the study period. The model-based mean attack rate of 1.82 attacks/month for lanadelumab and 1.78 attacks/month for placebo did not show statistical significance between groups (rate ratio 1.02; $P= 0.90$). The 2 previously published RCTs did show a significant difference in this comparison. With 2 of 3 published RCTs showing statistical significance in attack rate reductions, there is low CoE in a reduction in rate of HAE attacks with lanadelumab.[1] There is an average of approximately 0.25 attacks/month pooled across the 3 studies.[1] Most participants receiving lanadelumab reported AEs (92%), with injection site pain (30%), arthralgia (14%), and headache (12%) being the most common.[1]

Donidalorsen (DAWNZERA) was approved by the FDA in 2025 for prophylaxis of attacks in patients 12 years and older as a SC injection every 4 weeks.[2] Dosing every 8 weeks may be considered for people who have stable symptoms without attacks.[2] Two RCTs, both rated as low RoB were included; a phase 2 trial (n=20) in adults and a phase 3 trial (N=91) in people age 12 years and older.[1] Compared to placebo, donidalorsen reduced the rate of attacks from approximately 2.25/month to 0.23-0.44/month (high CoE) and demonstrated clinical response in 65%-82% of participants ($p<0.05$) (moderate CoE).[1]

Additionally, there was an improvement in the Angioedema Quality of Life (Ae-QoL) score by 18.6 to 20.7 points (minimum clinically important difference is 6 points) (moderate CoE).[1] Adverse events were generally mild (high CoE) with no severe AEs.[1]

Garadacimab-gxii (ANDEMBRY) was approved by the FDA in 2025 for prophylaxis of attacks in patients 12 years and older as a SC injection monthly.[3] Two RCTs, both rated as having low RoB were included.[1] A phase 2 trial (n=32) with a duration of 12 weeks included 3 garadacimab doses (75 mg, 200 mg, or 600 mg).[1] The 600 mg dose was not found to provide additional clinical benefit.[1] A phase 3 RCT (n=65) was conducted using a 400 mg loading dose followed by 200 mg monthly dosing for 6 months in patients with type I or type II HAE.[1] Compared to placebo, the monthly attack rate was reduced by 87% ($p<0.01$) in the phase 3 RCT and 100% ($p<0.01$) in the phase 2 RCT (moderate CoE) with a 92-100% response rate from baseline (moderate CoE).[1] For attacks requiring an on-demand treatment there was a mean of 0.23 attacks on garadacimab compared to 1.86 attacks with placebo (moderate CoE).[1] The AEs were generally mild, and no severe AEs were reported (moderate CoE).[1]

Reference:

1. Lindsey W, Hartsell F, Bricken L, Trinidad K, Key C, Krehling K, Hepburn Z, Davis L, Grabowsky A. Pharmaceutical treatments for hereditary angioedema: prevention and acute treatment of attacks. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2025.
2. Dawnzera (donidalorsen) package insert. Carlsbad, CA. Ionis Pharmaceuticals. August 2025.
3. Andembry (garadacimab-gxii) package insert. King of Prussia, PA. CSL Behring LLC. June 2026.
4. Ekterly (sebetralstat). package insert. Cambridge, MA. KalVista Pharmaceuticals Inc. July 2025.

Appendix 1: Current Preferred Drug List*

Generic	Brand	Route	Form	PDL
C1 esterase inhibitor	BERINERT	INTRAVEN	KIT	Y
C1 esterase inhibitor	BERINERT	INTRAVEN	VIAL	Y
C1 esterase inhibitor	HAEGARDA	SUBCUT	VIAL	Y
C1 esterase inhibitor	CINRYZE	INTRAVEN	VIAL	N
C1 esterase inhibitor, recomb	RUCONEST	INTRAVEN	VIAL	N
berotralstat hydrochloride	ORLADEYO	ORAL	CAPSULE	N
sebetralstat	EKTERLY	ORAL	TABLET	N
donidalorsen sodium	DAWNZERA	SUBCUT	AUTO INJCT	N
icatibant acetate	FIRAZYR	SUBCUT	SYRINGE	N
icatibant acetate	ICATIBANT	SUBCUT	SYRINGE	N
icatibant acetate	SAJAZIR	SUBCUT	SYRINGE	N
lanadelumab-flyo	TAKHZYRO	SUBCUT	SYRINGE	N
ecallantide	KALBITOR	SUBCUT	VIAL	N
lanadelumab-flyo	TAKHZYRO	SUBCUT	VIAL	N

*Garadacimab-gxii (ANDEMBRY) subcutaneous injection not listed in First Data Bank as of 3/3/26.

Hereditary Angioedema

Goal(s):

- To promote safe and effective use of hereditary angioedema treatments.

Length of Authorization:

- Up to 12 months

Requires PA:

- All pharmacotherapy for hereditary angioedema (pharmacy and provider administered claims).

  NOTE: This policy does not apply to hereditary angioedema treatments administered during emergency department visits or hospitalization.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA Approved indications and dosing for hereditary angioedema treatments

Drug Name	Place in Therapy	FDA Indication(s)	Dose and Frequency
C1 esterase inhibitor (Berinert®)	Acute	Abdominal, facial, or laryngeal attacks	20 units/kg intravenously as a single dose
C1 esterase inhibitor, recombinant (Ruconest®)	Acute	Attacks in adults and adolescents. Efficacy has not been established in laryngeal attacks.	50 units/kg intravenously as a single dose; maximum dose: 4,200 units; may repeat once within 24 hours if attack continues
Ecallantide (Kalbitor®)	Acute	Attacks in patients ≥12 years of age	30 mg as a one-time dose (3 subcutaneous injections); may repeat once within 24 hours if attack continues
Icatibant (Firazyr®)	Acute	Attacks in adults ≥18 years of age	30 mg injection once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg
Sebetralstat (Ekterly®)	Acute	Attacks in patients ≥12 years of age	600mg (2 tablets) orally; may repeat a second 600 mg dose after 3 hours if response inadequate; maximum dose per 24 hours: 1200 mg
Berotralstat (Orladayo™)	Prophylaxis	HAE prophylaxis in patients ≥2 years of age	110 mg or 150 mg orally daily (capsules) 72, mg 96 mg, 108 mg, or 132 mg orally daily (weight based; pellets)

C1 esterase inhibitor (Cinryze®)	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	1,000 units intravenously every 3 to 4 days (twice weekly); doses up to 2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
C1 esterase inhibitor (Haegarda®)	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	60 units/kg subcutaneous every 3 to 4 days (twice weekly)
Donidalorsen (Dawnzera™)	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	80 mg subcutaneous injection every 4 weeks; may consider 8-week interval
Garadacimab-gxii (Andembry®)	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	400 mg loading dose (two subcutaneous injections); then 200 mg subcutaneously monthly
Lanadelumab-flyo (Takhzyro™)	Prophylaxis	HAE prophylaxis in patients ≥2 years of age	300 mg subcutaneous injection every 2 weeks (for ≥12 years) or 150 mg every 2 weeks (for 6-12 years); may consider dosing every 4 weeks for patients who are well-controlled for > 6 months; 150 mg every 4 weeks for 2-6 years of age

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of prophylactic therapy OR for treatment of a second acute attack previously approved through fee-for-service?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for an FDA approved indication and place in therapy according to **Table 1** and is there confirmed laboratory diagnosis of hereditary angioedema (e.g., low C4 levels and either low C1 inhibitor antigenic levels or low C1 inhibitor functional levels)?	**Yes**: Go to #4 Document labs	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Has the provider documented discussion with the patient of risks (including thrombotic events and/or anaphylaxis) versus benefits of therapy?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Notify provider of potential serious adverse effects of therapy. See notes below.
5. Is the request for a C1 esterase inhibitor or ecallantide?	**Yes:** Go to #6	**No:** Go to #7
6. Is the patient prescribed concurrent epinephrine, or do they have epinephrine on hand?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the medication intended to be administered by a non-healthcare professional (e.g., self-administered)?	**Yes:** Go to #8	**No:** Go to #9
8. Has the member received training on identification of an acute attack?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the request for treatment of an acute hereditary angioedema attack?	**Yes:** Go to #12 Document attack severity if available	**No:** Go to #10
10. Is the request for prophylactic use in a patient with a history of hereditary angioedema attacks?	**Yes:** Go to #11 Document baseline number of attacks in the last 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
11. Have potential triggering factors for angioedema including medications such as estrogens, progestins, or angiotensin converting enzyme inhibitors been assessed and discontinued when appropriate?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the requested medication a preferred product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Approve for the following recommended durations: Acute treatment: Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**) Prophylactic treatment: Approve for up to 6 months or length of therapy, whichever is less.	**No:** Go to # 13
13. Is there documentation of lack of benefit or contraindications to all preferred agents that have same place in therapy (e.g., acute or prophylaxis treatment), or of extenuating circumstances necessitating need of a nonpreferred product?	**Yes:** Approve for the following recommended durations: Acute treatment: Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**) Prophylactic treatment: Approve for up to 6 months or length of therapy, whichever is less.	**No:** Pass to RPh. Deny; medical appropriateness. Inform prescriber of covered alternatives in class.

Renewal Criteria		
1. Is the request for additional treatment for acute attacks?	**Yes:** Go to #2	**No:** Go to #5
2. Is there documented utilization and benefit of the initial approved dose?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**). Document attack severity if available	**No:** Go to #3
3. Does the patient currently already have at least one on-demand dose for an acute attack?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is there documentation from the prescriber that an on-demand dose is necessary and risks of therapy continue to outweigh the benefits?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**). Document attack severity if available	**No:** Pass to RPh. Deny; medical appropriateness.
5. Since initiation of therapy, has the number or severity of hereditary angioedema attacks decreased?	**Yes:** Go to #6 Document change in attack frequency or severity	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been attack free for at least 6 months?	**Yes:** Go to #7	**No:** Approve for up to 12 months.

Renewal Criteria		
7. Is there documentation from the prescriber that they have evaluated continued necessity of long-term prophylactic treatment at the current dose?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Notes on adverse effects of treatment:

Berotralstat

- Doses above 150 mg daily have been associated with QT prolongation. Dose adjustment is recommended for patients with moderate to severe hepatic impairment or with concomitant p-glycoprotein or BCRP inhibitors. Avoid use with p-glycoprotein inducers.

C1 esterase inhibitors

- In clinical trials of patients with moderate to severe hereditary angioedema attacks, use of C1 esterase inhibitors improved the duration of symptoms by an average 1-2 hours compared to placebo. Prophylactic use has only been evaluated in patients with more than 2 attacks per month.
- Hypersensitivity reactions have been observed with C1 esterase inhibitors. Due to the risk of anaphylaxis, it is recommended that all patients prescribed human derived C1 esterase inhibitors have epinephrine immediately available.
- Serious arterial and venous thrombotic events have been reported with use of C1 esterase inhibitors, particularly in patients with pre-existing risk factors for thromboembolism. The exact incidence of thrombosis with C1 esterase inhibitors is unclear. In patients using prophylactic therapy with Cinryze®, over an average of 2.6 years, 3% of patients experienced thrombosis.

Ecallantide

- The average improvement in symptoms compared to placebo at 4 hours after treatment of an acute attack was 0.4 points on a 0-3 point scale.
- Ecallantide has a box warning for anaphylaxis. In clinical trials, 3-4% of patients treated with ecallantide experienced anaphylaxis. Risks of treatment should be weighed against the benefits.

Icatibant

- In clinical trials of icatibant for acute attacks, time to 50% overall symptom improvement was 17.8 hours better than placebo (19 vs. 2 hours). A second study demonstrated no difference from placebo in time to symptom improvement. There are no data available on quality of life, daily activities, physical or mental functioning with use of icatibant.

Lanadelumab-flyo

- Prophylactic use has only been evaluated in patients with more than 1 moderate-severe attack per month. Hypersensitivity reactions were observed in 1% of patients treated with C1 esterase inhibitors. Elevated liver enzymes were also observed more frequently with lanadelumab compared to placebo (2% vs. 0%), and the long-term safety is unknown.