Health Technology Briefing
April 2024

Donidalorsen for the prophylactic treatment of hereditary angioedema

Company/Developer	Otsuka Pharmaceuticals (U.K.) Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28092	NICE ID: Not available	UKPS ID: 674370

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Donidalorsen is in clinical development for the preventive treatment of patients with hereditary angioedema (HAE). HAE is a rare inherited disorder characterised by recurrent episodes of the accumulation of fluids outside of the blood vessels, blocking the normal flow of blood or lymphatic fluid and causing rapid swelling of tissues in the hands, feet, limbs, face, intestinal tract, or airway causing discomfort and pain (angioedema). HAE may be life-threatening when the swelling occurs in the throat as it can obstruct the airways and impede breathing. HAE has no known cure, and the goal of treatment is to minimise the burden of illness on patients and enable them to lead normal lives.

Donidalorsen works by binding to and inactivating the production of the protein (prekallikrein) that causes angioedema, thereby reducing the frequency of HAE attacks. Early studies of donidalorsen have shown that it helped to reduce the frequency of HAE attacks, with no serious side effects. As donidalorsen is administered subcutaneously just once per month, it makes it easier to use for routine prevention of HAE attacks. If licensed, donidalorsen will offer an additional prophylactic treatment option for adults and adolescents with HAE.

Proposed Indication

Prophylactic treatment of hereditary angioedema (HAE) in patients 12 years and over.[1-3]

Technology

Description

Donidalorsen (ISIS 721744, IONIS-PKK-LRx) is a 2′-O-methoxyethyl–modified antisense oligonucleotide conjugated to a triantennary N-acetylgalactosamine (GalNAc3) moiety. Donidalorsen was designed to inhibit the production of plasma prekallikrein through ribonuclease (RNase) H1-mediated degradation of plasma prekallikrein messenger RNA (mRNA), thereby decreasing the production of prekallikrein protein, which plays a key role in the activation of inflammatory mediators associated with acute attacks of HAE. The $GalNAc_3$ conjugation to the antisense molecule facilitates uptake into hepatic parenchymal cells, the main site of plasma prekallikrein production.[3,4]

Donidalorsen is in clinical development for the prophylactic treatment of HAE by reducing the frequency of attacks and the disease burden in patients aged 12 years and older. In the phase III clinical trial (NCT05392114, EudraCT-2022-000757-93), donidalorsen is administered as a subcutaneous (SC) injection monthly for up to 157 weeks.[2]

Key Innovation

Donidalorsen is a new medicinal product that is an RNA-based therapy, classified as antisense oligonucleotide (ASO) with inherent advantages. These include no risk of intersectional mutagenesis, transient effects, ease of development and manufacture, and cost effectiveness.[5]

The $GalNAc_3$ conjugation strategy used with donidalorsen increases potency up to 30 times that observed with unconjugated antisense oligonucleotides. This finding supports the use of lower doses and less frequent administration (once per month), with consequent reductions in systemic exposure, and a potential good safety profile.[3,6] Selective inhibition of plasma prekallikrein production is postulated to reduce the frequency of HAE attacks and the burden of disease.[3]

If licensed, donidalorsen will offer an additional prophylactic treatment option for adolescent and adult patients with HAE.

Regulatory & Development Status

Donidalorsen does not currently have marketing authorisation in the EU/UK for any indication.

Donidalorsan has the following regulatory designation;

- Orphan drug designation from the United States FDA in 2023 for HAE[7]

Donidalorsen is not in phase II/III clinical trials for any other indication.

Patient Group

Disease Area and Clinical Need

HAE is an autosomal dominant disease caused by mutations to the *SERPING1* gene that lead to deficient or dysfunctional C1 inhibitor (C1-INH). C1-INH is the major inhibitor for several complement proteases and a deficient or dysfunctional C1-INH is thought to lead to defective vascular permeability that is dependent on bradykinin. HAE is characterised by recurrent episodes of nonpruritic, nonpitting oedema and swelling involving the extremities, trunk, gastrointestinal tract, genitalia, face, tongue, or larynx.[8,9] Episodes affecting the abdomen or oropharynx can be associated with significant morbidity and mortality, and, HAE also presents substantial physical, emotional, and economic burden.[10] Bradykinin is the predominant mediator of enhanced vascular permeability in hereditary-angioedema attacks.[11] HAE attacks can be provoked by a variety of triggers including physical injury, trauma, infections, psychological stress, and certain medication, and are often preceded by prodromal symptoms (early warning symptoms preceding a swelling) like pain, an itch, feeling of anxiety, skin rash or flushing.[12-14]

HAE is estimated to affect 1 in 50,000 individuals globally,[15] with a minimum prevalence of 1 in 59,000 (HAE-1/2) in the United Kingdom.[16]As at March 2012, there were approximately 600-900 patients with HAE on active treatment, 500 patients under investigation (not on treatment).[17] The population likely to be eligible to receive donidalorsen could not be estimated from available published sources, but the number of adults in England and Wales with HAE can be estimated based on 2021 UK mid-year population estimates of 47,263,713, using the prevalence of 1 in 59,000, to include a minimum of about 800 adults.[18]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends the following treatment options for patients with HAE:

- Lanadelumab for preventing recurrent attacks of HAE in people aged 12 and older, if having 2 or more clinically significant attacks per week over 8 weeks despite oral preventive therapy, or oral therapy is contraindicated or not tolerated.[19]
- Berotralstat for preventing recurrent attacks of HAE in people 12 years and older, if having at least 2 attacks per month and if it is stopped when the number of attacks does not reduce by at least 50% after 3 months.[20]

Clinical Trial Information

Trial	NCT05392114, EudraCT-2022-000757-93; An open-label, long-term safety and efficacy study of donidalorsen in the prophylactic treatment of Hereditary Angioedema (HAE) **Phase III** – Recruiting **Location(s)**: UK, 8 EU countries, US, Canada and others **Primary completion date**: December 2026
Trial Design	Open-label, single-group assignment
Population	N= 144 (estimated); subjects with HAE-1 (Type 1) or HAE-2 (Type 2), aged 12 years and over

Intervention(s)	Donidalorsen by SC injection for up to 157 weeks.
Comparator(s)	None
Outcome(s)	**Primary outcome:** Percentage of Participants with at Least One Treatment-emergent Adverse Event (TEAE), Graded by Severity [Time Frame: Up to approximately 70 weeks, plus 104 weeks for Group 1; up to approximately 76 weeks, plus 104 weeks for Group 2] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**OASIS-HAE, NCT05139810, EudraCT2021-002571-19**; A phase 3 double-blind, placebo-controlled study to evaluate the efficacy and safety of ISIS 721744 in patients with HAE **Phase III –** Completed **Location(s):** UK, 9 EU countries, US, Canada and others **Study completion date:** November 2023
Trial Design	Randomised, double-blind, placebo-controlled
Population	N= 91 (actual); subjects with documented diagnosis of HAE-1 (Type 1) or HAE-2 (Type 2); aged 12 years and over
Intervention(s)	Donidalorsen by SC injection for up to 25 weeks
Comparator(s)	Matched placebo by SC injection for up to 25 weeks
Outcome(s)	**Primary outcome:** Time-normalized number of investigator-confirmed HAE attacks (per month) from week 1 to week 25 [Time Frame: week 1 to week 25] See trial record for full list of other outcomes
Results (efficacy)	The trial met its primary endpoint of reduction in rate of angioedema attacks in patients treated with donidalorsen (80mg) via subcutaneous injection dosed every 4 weeks (Q4W) ($p<0.001$) or every 8 weeks (Q8W) ($p=0.004$), compared to placebo.[21]
Results (safety)	There were no serious adverse events in the patients treated with donidalorsen.[21]

Clinical Trial Information		
Trial	NCT04030598, EudraCT 2019-001044-22; A randomised, double-blind, placebo-controlled, phase 2a	NCT04307381, EudraCT2020-000197-14; An open-label extension study of ISIS 721744 in patients with HAE

	study to assess the clinical efficacy of ISIS 721744, a second-generation ligand-conjugated antisense inhibitor of prekallikrein, in patients with Hereditary Angioedema **Phase II -** Completed **Location(s):** 1 EU country and US **Study completion date:** March 2021	**Phase II -** Active, not recruiting **Location(s):** 1 EU country and US **Primary completion date:** April 2025
Trial Design	Randomised, parallel assignment, triple masked	Single group assignment, open label
Population	N=23 (actual); subjects with documented diagnosis of HAE-1/HAE-2 (for inclusion in Part A) or hereditary angioedema with normal C1-inhibitor (HAE-nC1-INH) (for inclusion in Part B); aged 18 years and over	N= 20 (actual); subjects with satisfactory completion of index study (ISIS 721744-CS2) through week 17 with an acceptable safety and tolerability profile; aged 18 years and over
Intervention(s)	Donidalorsen 80mg, administered SC, every 4 weeks at weeks 1, 5, 9, and 13.	Donidalorsen administered SC for up to 53 weeks, then in the extended treatment period for an additional 156 weeks.
Comparator(s)	Matched placebo	None
Outcome(s)	**Primary outcome**: Time-normalized number of HAE attacks (per month) from week 1 to week 17 [Time Frame: week 1 to week 17] See trial record for full list of other outcomes	**Primary outcome:** Percentage of participants with at least one Treatment-emergent Adverse Event (TEAE), graded by severity [Time Frame: up to week 221] See trial record for full list of other outcomes
Results (efficacy)	The mean monthly rate of investigator-confirmed angioedema attacks was 0.23 (95% confidence interval [CI], 0.08 to 0.39) among patients receiving donidalorsen and 2.21 (95% CI, 0.58 to 3.85) among	Mean monthly HAE attack rate was 96% lower than the study run-in baseline rate (mean, 0.06/month; 95% confidence interval [CI], 0.02–0.10; median, 0.04 on-treatment vs. mean, 2.70/month; 95% CI, 1.94–3.46; median, 2.29 at baseline). Mean monthly attack rate for Q8W

	patients receiving placebo (mean difference, −90%; 95% CI, −96 to −76; P<0.001)[3]	dosing (*n* = 8) was 0.29 (range, 0.0–1.7; 95% CI, −0.21 to 0.79; median, 0.00). Mean plasma prekallikrein and D-dimer concentrations decreased, and Angioedema Quality of Life Questionnaire total score improved from baseline to week 105 with donidalorsen.[22]
Results (safety)	The incidence of mild-to-moderate adverse events was 71% among patients receiving donidalorsen and 83% among those receiving placebo.[3]	No serious TEAEs or TEAEs leading to treatment discontinuation were reported.[22]

Estimated Cost

The cost of donidalorsen is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over (GID-TA11452). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over (GID-TA11334). Expected date of issue to be confirmed.
- NICE technology appraisal. Berotralstat for preventing recurrent attacks of hereditary angioedema (TA738). October 2021.
- NICE technology appraisal. Lanadelumab for preventing recurrent attacks of hereditary angioedema (TA606). October 2019.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Plasma derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II. 16045/P. July 2016.
- NHS England. 2013/14 NHS Standard Contract for Medical Genetics (All Ages). E01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Immunology (all ages). B09/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Allergy Services (all ages). B09/S/b

Other Guidance

- Maurer M et al. The international World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guideline for the management of hereditary angioedema. 2021.[15]

- Cicardi M et al. Evidence-based recommendations for the therapeutic management of angioedema owing to C1 inhibitor deficiency; a consensus report of Hereditary Angioedema International Working Group.2012.[23]
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Additional Information

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