National Institute for Health and Care Excellence

Health Technology Evaluation

Donidalorsen for preventing recurrent attacks of hereditary angioedema in people 12 years and over ID6457
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Otsuka Pharmaceuticals	Otsuka believes that the evaluation of donidalorsen by NICE for the prevention of hereditary angioedema (HAE) attacks is appropriate due to the current unmet need for convenient, well-tolerated, long-term prophylaxis (LTP) options that demonstrate efficacy in reducing the frequency of HAE attacks. Donidalorsen has a novel ribonucleic acid (RNA)-targeted mechanism of action, which inhibits plasma prekallikrein production, thereby preventing the subsequent chain of events leading to an HAE attack.[1,2] Donidalorsen is administered subcutaneously via an auto-injector pen, offering patients a convenient mode of administration. Furthermore, the once-monthly dosing schedule of donidalorsen, with the flexibility to move to once-every-two-month dosing, provides a less frequent treatment schedule compared to other LTPs. Therefore, donidalorsen may offer greater convenience to patients.[3–6] Otsuka agrees that donidalorsen should be evaluated through the single technology appraisal (STA) route.	Comments noted. The committee will consider unmet need during the development of the appraisal. No action required.

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	BSACI/ BSI-CIPN/RCPath	The evaluation is appropriate as there are still unmet needs in the management of patients with hereditary angioedema. The proposed evaluation route is appropriate.	Comments noted. The committee will consider unmet need during the development of the appraisal. No action required.
	Genetic Alliance UK	In preparation for this response, Genetic Alliance UK reached out to Hereditary Angioedema UK (HAE UK), a member of Genetic Alliance UK, but were unable to discuss the scope in the time frame for this consultation. For this reason, we defer to HAE UK's expertise in this area and have responded to questions where possible. To our knowledge, donidalorsen is unlikely to meet the criteria for appraisal via HST pathway. While HAE is a rare condition, it is not classified as ultra-rare in the context of HST eligibility. Therefore, the routing of donidalorsen via the STA pathway appears appropriate.	Comments noted, no action required.
	NHSE	Appropriate for this purpose	Comment noted, no action required.
Wording	Otsuka Pharmaceuticals	Donidalorsen is anticipated to be indicated for use as an LTP. LTP is a treatment strategy used for the routine prevention of recurrent HAE attacks (i.e., when a patient has experienced more than one attack. Donidalorsen has not been investigated for use as a short-term prophylaxis (STP). Considering Otsuka's understanding of the anticipated indication and market authorisation for donidalorsen, Otsuka requests that the remit to read as: 'To appraise the clinical and cost effectiveness of donidalorsen within its marketing authorisation for preventing recurrent hereditary angioedema attacks.'	Comments noted. The draft remit has been updated to include 'recurrent'.

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		This proposed remit is in line with the final scope for garadacimab, and the final NICE recommendations of lanadelumab (TA606) and berotralstat (TA738), all of which are potentially relevant comparators to donidalorsen.[7–9]	
	BSACI/ BSI-CIPN/RCPath	The wording of the remit is appropriate.	Comment noted, no action required.
	NHSE	The wording is appropriate but within scope is a comparison with Androgens and Tranexamic acid and it is suggested these are removed since they are a) no longer advised b) removed from similar recent evaluations.	Comment noted, no action required to the draft remit. The scope has been updated by removing 'attenuated androgens' and 'antifibrinolytics' from the list of comparators.
Timing Issues	Otsuka Pharmaceuticals	The significant burden of HAE, including the constant risk of mortality and morbidity, and limitations in the current standard of care, means there is a pressing need for a convenient, well-tolerated treatment option.[10] The goals of treatment in HAE are to achieve complete control of the disease and to normalise patients' lives. This can currently only be achieved by LTP, i.e., the regular use of medication that reduces the burden of the disease by preventing attacks.[11] Despite advances in LTP for HAE, there remains a need for improvement in outcomes for patients, including reducing overall attack frequency and the frequency of moderate/severe attacks, and more convenient treatment options to address patient dissatisfaction with current therapies.[12]	Comments noted. NICE aims to publish guidance as soon as possible after the company receives the marketing authorisation and introduces the technology in the UK. NICE has scheduled this topic into its work programme. The committee will consider unmet need

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		Currently commissioned treatments are associated with a number of limitations, including: • Only a small proportion of patients experience a sufficient number of attacks (≥2 per week) to be considered eligible for lanadelumab and C1-INH.[13–15] In a 2019 survey across 37 UK centres, just 8% of patients with HAE were treated with C1-INHs.[13] • Dosing regimens may be inconvenient and burdensome, leading to adherence issues. Lanadelumab requires administration every two weeks and intravenous (IV) C1-INH requires administration twice weekly.[3,14] Berotralstat requires daily administration and patients need to discontinue treatment if the number of attacks per month does not reduce by ≥50% after three months of treatment initiation.[4,9] In the APeX-2 trial, this accounted for 42% of patients treated with berotralstat that failed to achieve a ≥50% reduction in attacks.[16] • Side effects and tolerability issues which may further contribute to adherence issues, particularly berotralstat which is associated with gastrointestinal (GI) tolerability concerns.[4,9] In the current commissioning landscape for HAE, patients who do not benefit from or tolerate berotralstat and are not eligible for lanadelumab or C1-INHs are left with no licensed treatment options.[7, 9,14] Donidalorsen has the potential to address the unmet need and limitations of current treatment options. The clinical benefits of donidalorsen were comprehensively evaluated through a 25-week randomised controlled trial (OASIS-HAE) and long-term, open label extension (OASISplus), demonstrating a reduction in attack frequency of donidalorsen once monthly and once every two month dosing compared to placebo.[17–19]	during the development of the appraisal. No action required
	NHSE	Non-urgent	Comment noted, no action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Otsuka Pharmaceuticals	Otsuka broadly agrees with the background information provided. Otsuka would like to expand on the burden of living with HAE for patients and their families/carers, specifically the impact the unpredictability of attacks has on patients' mental health and normal daily living, as well as the impact of long diagnosis delays patients typically experience.[10,20–22] The unpredictable and frequent nature of recurrent HAE attacks mean people with HAE continue to experience persistent fear, anxiety, and depression between attacks.[20,21] Patients have to make significant changes to their lifestyles to avoid potential triggers and compromising situations, which impacts normal daily activities such as driving, exercising, work, school, and socialising, exacerbating emotional distress.[21] The HAEBOIS-Europe study found that 56% of patients reported missing time from school or work during their most recent attack.[23] The inconvenient administration associated with current treatments only adds to this burden, significantly disrupting patients' normal daily living. Therefore, there is a significant unmet need for new, alternative therapies with more convenient dosing and administration. Caregivers and families of people with HAE also experience significant emotional and psychological distress. The unpredictability of attacks means that they suffer from feelings of fear and anxiety between attacks and need to be prepared for support and care during severe attacks".[22] The ongoing psychological burden, exacerbated by the unpredictability of attacks, can also lead to feelings of isolation and helplessness for families and caregivers.[24] People with HAE can often go long periods before they receive a diagnosis with HAE, following misdiagnoses or patients' symptoms going undetected due to misunderstanding of symptoms and general lack of disease awareness.[10] The long wait that patients experience can delay the start of their treatment and significantly impact quality-of-life.[10] A UK study of 376	Comments noted. The background section of the scope provides a brief overview of the disease. The scope has been updated with the wording describing the approaches for managing HAE. It has also specifically been updated to include 'Avoidance of trigger factors is not usually sufficient to control HAE attacks as they often occur randomly without any triggers.' Additionally, the appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical

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		patients recorded average diagnostic delays of 10 and 18 years for people with Type 1 and Type 2 HAE, respectively.[25] Otsuka also suggest the following amendments to the background section to improve the accuracy and completeness: • The draft scope states that '*there are 3 approaches to managing HAE: avoidance of factors that trigger HAE (e.g. minor trauma, hormone replacement therapy), preventive (prophylactic) treatments and acute treatments*.' Otsuka would like to note that while patients try to avoid known triggers (such as stress, medication, and minor trauma), "*often a specific trigger cannot be identified*".[26] For clarity and accuracy, Otsuka suggest this section is amended to: "there are 2 treatment strategies for managing HAE: preventive (LTP, or STP ahead of known triggers) and acute (on-demand therapy)." This ensures that the management strategies mentioned in the draft scope reflect the current management of HAE in clinical practice. • The draft scope states that C1 esterase inhibitor (C1-INHs) "*such as Cinryze, Ruconest or Berinert can be used*" as LTP. While Otsuka agrees that some C1-INHs are used as LTP, Ruconest is neither licensed, nor commissioned by NHS England, for use as an LTP, and it is predominantly used for on-demand treatment in clinical practice.[7, 14,27,28] Otsuka therefore suggest removing Ruconest from the disease background section. This has been established in previous technology appraisals for lanadelumab and berotralstat (TA606 and TA738).[7,9] Otsuka note that anti-fibrinolytics, such as tranexamic acid, are not licensed as an LTP and it is not commonly used because of concerns about limited efficacy, as highlighted in TA606 and TA738 and noted in the latest NHS England HAE treatment algorithm.[7, 9,29] Otsuka therefore suggest removing	and cost-effectiveness evidence and current clinical practice. The scope has been updated by removing 'attenuated androgens' and 'antifibrinolytics' from the list of comparators. Finally, the appraisal committee will consider unmet need during the development of the appraisal.

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		anti-fibrinolytics from the background section (see below for further information regarding inclusion of appropriate comparators).	
	BioCryst Pharmaceuticals	The Background section should include refence to the recently adopted NHSE HAE treatment algorithm, "*Commissioned treatment options for patients with Hereditary Angioedema* *secondary to C1 esterase inhibitor deficiency (HAE-C1-INH)*" (hereditary-amd-acquired-angioedema-algorithms.pdf), which is informed by the latest NICE technology appraisals and NHS England clinical commissioning policies. This algorithm was published on Feb 10, 2025	Comments noted. The background section of the scope provides a brief overview of the disease.
	BSACI/ BSI-CIPN/RCPath	Background information is generally complete. The disability caused by HAE attacks can also affect work and schooling/educational attainment. It should be noted that avoidance of trigger factors is not usually sufficient to control hereditary angioedema attacks as attacks often occur randomly without any triggers, and that this can have a significant psychological burden. It should also be pointed out that attenuated androgens and anti-fibrinolytics are not considered first-line where there are other approved medications for prophylaxis and should only be used as first-line if there are no other prophylaxis therapy options available. Attenuated androgens are associated with androgenic side effects, and there is little evidence for the efficacy of anti-fibrinolytics.	Comments noted. The background section of the scope provides a brief overview of the disease. The scope has been updated by removing 'attenuated androgens' and 'antifibrinolytics' from the list of comparators.
	NHSE	Fibrinolytics and androgens should be removed as they are not licensed, there are no RCTs and not in any guidelines for 1st or second line therapy	Comment noted. The background section of the scope provides a brief overview of the disease. The scope has

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			been updated by removing ‘attenuated androgens’ and ‘antifibrinolytics’ from the list of comparators.
Population	Otsuka Pharmaceuticals	Otsuka agree that the population described in the draft scope is appropriate.	Comment noted, no action required.
	BSACI/ BSI-CIPN/RCPath	The population needs to specify which types of hereditary angioedema are included	Comment noted. The population in the scope is intended to be broad to cover the final marketing authorisation. The draft remit has been updated to include ‘recurrent’.
	Genetic Alliance UK	To our knowledge, yes population is defined appropriately.	Comment noted, no action required.
	NHSE	Yes – although the definition of HAE3 is poor and a non-preferred term	Comment noted, no action required.
Subgroups	Otsuka Pharmaceuticals	Donidalorsen is not anticipated to be clinically more effective in any subgroup. This aligns with previous technology appraisals for lanadelumab and berotralstat for treatment of HAE where clinical data and expert opinion indicated that there are no treatment effect modifiers for response to LTP in people with HAE.[7,9]	Comments noted, no action required.

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Comparators	Otsuka Pharmaceuticals	Otsuka agrees that LTPs are the only appropriate comparator for donidalorsen, in line with its anticipated marketing authorisation. However, Otsuka requests that the following amendments to ensure the comparators are an accurate representation of current commissioning policies, NICE recommendations and established clinical practice, per Sections 2.2.12–13 and Sections 6.2.2–3 of the NICE manual:[30] • Remove Ruconest • Remove androgens • Remove antifibrinolytics • Specify the use of Berinert IV and not Berinert subcutaneous (SC), as the SC formulation is not routinely commissioned in the NHS **Ruconest** Otsuka requests to remove Ruconest from the C1-INH comparator because currently, ruconest is predominantly used as an on-demand therapy for the treatment of acute attacks and is not considered to be an appropriate comparator for donidalorsen. The marketing authorisation of Ruconest states that: "*Ruconest is indicated for treatment of acute angioedema attacks in adults, adolescents, and children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency*".[28] Furthermore, Ruconest is neither recommended by NICE nor commissioned by NHS England for use as an LTP.[14,27,28] The NHS commissioning policy for C1-INH treatment specifically discusses plasma derived C1-INHs, in contrast to Ruconest which is a recombinant treatment.[14,28] This has been established in previous technology appraisals for lanadelumab and berotralstat (TA606 and TA738).[7,9] **Androgens**	Comments noted. The list of comparators is intended to be broad. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice. The scope has been updated by removing 'attenuated androgens' and 'antifibrinolytics' from the list of comparators.

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		Otsuka requests to remove androgens as a comparator because they are not licensed as LTP, nor are they recommended by NICE for the long-term prevention of HAE attacks. Off-label use of androgens (such as danazol) was historically considered standard of care for long-term prophylaxis in HAE.[31] Since then, the availability of licensed and commissioned treatments in England has improved, and as such androgens are no longer considered a treatment option when patients are initiated on an LTP, or require an alternative LTP. An algorithm of commissioned treatment options for the management of HAE, published by NHS England, states "*Some adult patients are treated with androgens as oral prophylactic treatment. However, evidence is limited and accessing treatment is difficult so this is not recommended as first line for patients newly starting on prophylaxis. Where existing patients are established on androgen therapy, this may continue if considered clinically appropriate; if established patients do cease treatment with androgen therapy then review the need for any prophylaxis. An individualised assessment to withdrawal of androgens and commencing new prophylaxis should be taken. If a historical attack frequency is documented, it can be used as the basis for selecting other prophylaxis treatment options."*[29] Additionally, in TA738 (berotralstat) clinical expert feedback stated that people under the age of 18 should not be treated with androgens; patients aged 12 years and above are included in the anticipated licence of donidalorsen.[9] Androgens are also associated with adverse androgenic and anabolic effects, drug interactions, and contraindications.[9] Furthermore, danazol has been discontinued in the UK and current treatment directives state to not start new patients on androgens.[29,32,33] **Anti-fibrinolytics**	

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		Otsuka requests to remove anti-fibrinolytics as a comparator as they are not licensed as an LTP, nor are they recommended by NICE for the long-term prevention of HAE. Similar to androgens, off-label use of anti-fibrinolytics, such as tranexamic acid, was historically considered standard of care for long-term prophylaxis in HAE.[31] Since then, the availability of licensed and commissioned treatments in England has improved, while anti-fibrinolytics are not indicated as LTPs for patients with HAE. Specifically, the marketing authorisation for tranexamic acid indicates its use for "*short term use"* for patients with HAE.[34] Additionally, international World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI) guidelines do not recommend antifibrinolytics, such as tranexamic acid, as LTP due to the limited efficacy data available.[11] **Berinert** Otsuka requests that only Berinert IV is included in the draft scope, to ensure clarity and accuracy. Berinert is available via two different routes of administration, SC and IV. Berinert IV is licensed for the treatment and pre-procedure prevention of acute episodes but not as an LTP. Berinert IV was accepted as an appropriate comparator in TA606 (lanadelumab) as clinicians confirmed it is prescribed as an LTP outside its marketing authorisation.[6,35] Berinert IV is used off-label as an LTP for patients who experience ≥2 attacks per week who have either failed or have a contraindication for oral prophylaxis.[6,14] The committee in TA606 agreed that Berinert SC is not a comparator LTP, as no plasma-derived C1-INH SC therapies are approved in the UK for LTP.[7] Furthermore, the NHS England commissioning policy for plasma derived C1-INH only discusses the use of IV plasma derived C1-INH treatments for HAE indicating the SC delivery method is not used within the NHS England.[14]	

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		Therefore, as per section 2.2.13 of the NICE manual, Berinert IV should be considered as the only relevant method of administration, in line with clinical practice use within NHS England.[30] Berinert SC should not be considered a relevant comparator in this evaluation as it is not routinely commissioned in the prevention of HAE attacks within NHS England. In summary, Otsuka consider lanadelumab, berotralstat, garadacimab (subject to NICE recommendation) and plasma derived C1-INH inhibitors (specifically Berinert IV and Cinryze) are the only relevant comparators for this appraisal.	
	Takeda	In line with our public response to the draft remit and scope for garadacimab for preventing recurrent attacks of hereditary angioedema in people 12 years and over [ID6394], we are pleased to see and agree with the inclusion of attenuated androgens as an appropriate comparator given their continued routine use as long-term prophylaxis in the UK. To demonstrate androgens current usage, a recent interim analysis from 2024 of a Takeda UK sponsored real world evidence study showed that 28.9% (11/38) of an adult HAE population in the UK using long-term prophylaxis were taking androgens and 26.3% (10/38) were taking tranexamic acid, making androgens the most widely used long-term prophylactic agent in the UK in this dataset (n = 85).[1] Further, Yong et al reports on data from 2019, where 55% of patients taking long-term prophylaxis took androgens alone and 6% took androgens and tranexamic acid combined.[2] Additionally, the continued use of androgens as long-term prophylaxis has been acknowledged the new HAE treatment algorithm published by the NHS	Comments noted. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice. The scope has been updated by removing ‘attenuated androgens’ and ‘antifibrinolytics’

		England (February 2025).[3] Despite not recommending androgens as a first line prophylactic treatment, it has been recognised that some patients are still receiving androgens and may continue to do so if clinically appropriate: '*Some adult patients are treated with androgens as oral prophylactic treatment…Where existing patients are established on androgen therapy, this may continue if considered clinically appropriate.*'[3] Therefore, given this supportive evidence demonstrating that patients with HAE are still receiving androgens as long-term prophylaxis, we agree with NICE that attenuated androgens should be considered as an appropriate comparator for the appraisal of donidalorsen [ID6457]. As a final comment, while we agree with all listed comparators, we suggest that NICE includes "in line with NHS England's commissioning policy"[4] that is referenced against lanadelumab, to the pre-mentioned "C1-esterase inhibitors" in the first bullet point of the draft comparators. This clarification is important to ensure consistent application of the policy across all relevant treatments, providing clear and comprehensive guidance for their use prophylactically. 1. BSACI 2024 Yong et al, Patient Characteristics, Treatment Patterns and Clinical Outcomes of Hereditary Angioedema Patients Self-administering Icatibant using Homecare in the UK: An Interim Analysis of a Real-World Study. Poster presentation Poster A014 2. Yong, P.F.K. et al. (2023) 'A national survey of hereditary angioedema and acquired C1 inhibitor deficiency in the United Kingdom', The Journal of Allergy and Clinical Immunology: In Practice, 11(8), pp. 2476–2483. 3. NHS England algorithm for commissioned treatment options for hereditary angioedema, February 2025. Available at: hereditary-amd-acquired-angioedema-algorithms-v2.pdf.	from the list of comparators based on the responses received by other commentators during the scope consultation, including healthcare professional groups and NHS England.

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		NHS Clinical commissioning: plasma derived C1-esterase inhibitor for prophylactic treatment of HAE (2016).https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/16045_FINAL.pdf (last accessed 23/05/2025)	
	BSACI/ BSI-CIPN/RCPath	All relevant comparators are listed. It should be noted that attenuated androgens and anti-fibrinolytics are not considered first-line where there are other approved medications for prophylaxis and should only be used as first-line if there are no other prophylaxis therapy options available. Additionally, published international guidelines do not recommend anti-fibrinolytics as the evidence quality is insufficient to demonstrate effectiveness in hereditary angioedema.	Comments noted. The list of comparators is intended to be broad. The appraisal committee will discuss the most appropriate comparator(s) during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, the clinical and cost-effectiveness evidence and current clinical practice. The scope has been updated by removing 'attenuated androgens' and 'antifibrinolytics' from the list of comparators.

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	NHSE	See above fibrinolytics and androgens to be removed. Other comparators are appropriate.	Comment noted. The scope has been updated by removing 'attenuated androgens' and 'antifibrinolytics' from the list of comparators.
Outcomes	Otsuka Pharmaceuticals	Otsuka broadly agree that the outcomes listed in the draft scope are appropriate and generally aligned with those assessed in the key trials. However, Otsuka requests the following endpoints to be removed, as per section 2.1.2 in the NICE manual: • Attack free period • Time to first attack 'Attack free period' and 'time to first attack' were not included as the primary or secondary outcome measures in the pivotal Phase III trial (OASIS-HAE) of donidalorsen.[17,36] Furthermore, 'attack free period' and 'time to first attack' are not considered principal outcome measures for the cost-effectiveness analysis, and Otsuka do not anticipate that these endpoints will inform the analysis.	Comments noted. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list. No action required.
	BSACI/ BSI-CIPN/RCPath	Outcomes are appropriate. Carer disutility should be considered as well if possible.	Comments noted. Carer disutility will be captured by "Health-related quality of life (for patients and carers)." No action required.

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	Genetic Alliance UK	To our knowledge, this is appropriate.	Comment noted, no action required.
	NHSE	Yes	Comment noted, no action required.
Equality	Otsuka Pharmaceuticals	Otsuka do not believe that the draft remit or scope will exclude people protected by equality legislation.	Comment noted, no action required.
	BSACI/ BSI-CIPN/RCPath	No specific changes to suggest here.	Comment noted.
	Genetic Alliance UK	We are not aware of any protected group being specifically excluded by the draft scope. Both males and females and all ethnicities, are affected by HAE and would be eligible for donidalorsen if they meet clinical criteria. The scope aligns with the licensed age (≥12 years), so younger children are not included. Pregnant or breastfeeding women (protected under sex/pregnancy status) were not studied in the trials; but it is possible that management in pregnancy needs specialist review. People with disabilities (e.g. cognitive or mobility impairments) should not be excluded from treatment. In fact, home injection support services already exist (e.g. community nurses) and can help patients who cannot self-inject. Importantly, NHS policy specifies that 'all patients with HAE should be under the care of specialised immunology centres', which advances equality by ensuring every patient (of any background) has access to expert care. Overall, offering donidalorsen is expected to benefit any disadvantaged HAE patients (for example, women who cannot use androgen therapy), rather than exacerbate inequalities.	Comments noted, no action required.
	NHSE	No concerns	Comment noted.

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Other considerations	BSACI/ BSI-CIPN/RCPath	No other additional issues.	Comment noted.
Questions for consultation	Otsuka Pharmaceuticals	**Where do you consider donidalorsen will fit into the existing care pathway for the prevention of hereditary angioedema attacks?** The proposed positioning of donidalorsen is for routine prevention of recurrent HAE attacks in patients aged 12 years and older. This effectively positions donidalorsen in line with the current standard of care for the routine prevention of HAE attacks: • Berotralstat: for those with ≥2 HAE attacks per month, • Lanadelumab and C1-esterase inhibitors: for those with ≥2 attacks per week. **Would donidalorsen be used to prevent recurrent attacks or to treat acute attacks of hereditary angioedema?** Donidalorsen will only be used to prevent recurrent attacks. Donidalorsen has not been investigated for use an on-demand therapy for the treatment of acute attacks and is anticipated to be indicated as an LTP. **Please select from the following, will donidalorsen be:** **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.**	Comments noted. During the appraisal, it will be discussed if all benefits of donidalorsen were captured in the cost-effectiveness analyses. No action required.

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		Donidalorsen will be prescribed in secondary care with routine follow-up in secondary care. **Are there any subgroups of people in whom donidalorsen is expected to be more clinically effective and cost effective or other groups that should be examined separately?** As described above, donidalorsen is not anticipated to be clinically more effective in any subgroup. **Would donidalorsen be a candidate for managed access?** Otsuka does not believe that donidalorsen is a candidate for managed access. **Do you consider that the use of donidalorsen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Donidalorsen has the potential to significantly alleviate the burden of HAE attacks and the psychological impacts associated with their unpredictability for patients and caregivers by reducing the frequency of attacks. The appraisal will use QALYs to quantify the estimated impact of HAE attacks on patients' HRQoL. The true impact of HAE on normal daily living, absenteeism, and mental health of patients cannot be fully captured by the QALY calculation. This also applies to caregivers, as the burden associated with HAE can contribute to absenteeism and impaired mental welfare for families and carers, which cannot be fully captured within the caregiver disutility. These factors should be taken into consideration in addition to cost-effectiveness estimates when evaluating the benefits of donidalorsen.	

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	BioCryst Pharmaceuticals	Please consider including the additional questions below: 1. Which HAE patients would be the most appropriate candidates for treatment with donidalorsen in the context of the other treatments that are currently available? 2. What is the frequency of administration of donidalorsen for LTP maintenance expected to be in the real-world setting to ensure adequate disease control? Given that RNA interference is a novel mode of action for the long-term prophylaxis of HAE, are there anticipated costs associated with long-term safety surveillance of patients treated with donidalorsen?	Comment noted, no action required.
	BSACI/ BSI-CIPN/RCPath	Donidalorsen would fit into existing care pathways in the same place as other licensed prophylactic therapies for hereditary angioedema. Donidalorsen would be used to prevent recurrent attacks. It is not intended to be used for the treatment of acute attacks. Donidalorsen should be prescribed in secondary care with routine follow up in secondary care. Comparators and subsequent treatments would almost always be in a secondary setting as well. Not aware of any specific subgroups where donidalorsen would be expected to be more or less clinically effective. Patients with a greater number of attacks would be expected to gain greater benefit. Donidalorsen could be considered for managed access.	Comments noted, no action required.
	Genetic Alliance UK	Please note, we defer to stakeholders with more expertise in this area, however we've tried to provide some response we hope will support the NICE review team.	Comments noted. During the appraisal, it will be discussed if all benefits of donidalorsen were captured in the

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		Where do you consider donidalorsen will fit into the existing care pathway for the prevention of hereditary angioedema attacks? To our understanding, care for HAE is delivered in specialist immunology/allergy centres (per NHS service specifications) rather than in general practice. We would expect donidalorsen to be prescribed and monitored by these specialist teams as part of routine preventive care, similarly to lanadelumab or berotralstat. **Would donidalorsen be used to prevent recurrent attacks or to treat acute attacks of hereditary angioedema?** Donidalorsen is intended for preventing recurrent HAE attacks, not for treating acute attacks. The Phase III OASIS-HAE trial showed a large reduction in attack rates with regular donidalorsen dosing (81% lower attack rate with 4-weekly dosing vs placebo). The authors concluded this supports its use as a prophylactic therapy. Like lanadelumab and berotralstat (which are licensed for prevention), donidalorsen is given on a schedule to prevent attacks, while standard on-demand treatments (icatibant or C1-INH concentrate) would still be used for any breakthrough attacks. *Riedl MA, et al. 2025. Patient-Reported Outcomes in the Phase III OASIS-HAE Study of Donidalorsen for Hereditary Angioedema. Allergy. doi: 10.1111/all.16563* **Please select from the following, will donidalorsen be: C. Prescribed in secondary care with routine follow-up in secondary care** Patients are usually trained to self-inject or receive infusions at home, but prescribing and ongoing monitoring are handled by the specialist service (options A or B would not be appropriate, since primary care does not initiate or supervise these high-cost, specialist HAE treatments). **Are there any subgroups of people in whom donidalorsen is expected to**	cost-effectiveness analyses. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		be more clinically effective and cost effective or other groups that should be examined separately? As far as we are aware, there is no known race/ethnic disparity in prevalence, although awareness of HAE may be lower in minority groups. However, gender appears to matter clinically for people with HAE. Women may experience hormone-driven flares and one study found women report significantly higher HAE-related psychological distress. Recurrent, unpredictable attacks can also be disabling. Many people with the condition qualify as having a chronic disability under the Equality Act due to frequent incapacitating episodes. Consideration may also be needed for the impact of living with HAE on mental health (e.g. anxiety, PTSD from near-misses) which may amount to disability. Access to donidalorsen should not be harder for patients with co-morbid mental health issues or learning disabilities. *Hews-Girard J, Goodyear M. 2021. Psychosocial burden of type 1 and 2 hereditary angioedema: a single-center Canadian cohort study. Allergy Asthma Clin Immunol 17, 61 (2021). https://doi.org/10.1186/s13223-021-00563-0* **Would donidalorsen be a candidate for managed access?** Given HAE is a rare condition and donidalorsen is a novel therapy, a managed access agreement might be appropriate. This could allow earlier patient access under agreed monitoring while additional data (on long-term safety, effectiveness and resource use in UK practice) are collected. For example, collecting registry data on attack rates, QALYs and hospitalisations in patients on donidalorsen could reduce uncertainty. Many patients with life-impacting HAE would welcome early access, and a managed access scheme (with clear stopping rules if it fails to work) could provide that while ensuring the NHS can gather real-world evidence.	

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		Do you consider that the use of donidalorsen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Donidalorsen may improve aspects of patient well-being that generic QALY measures might under-capture. In trials, patients on donidalorsen reported much less anxiety/fear about attacks and better daily function. For instance, 88% of patients on 4-week dosing had a clinically meaningful quality-of-life improvement (≥6 points) versus only 45% on placebo. We also just wanted to emphasise that HAE is often unpredictable and can cause considerable distress among patients because the symptoms and episodes can be painful and disfiguring. At times, they can even be life-threatening. For these reasons, The Angioedema Control Test has been found to be a useful patient-reported outcome measure (PROM) that reflects a meaningful improvement of disease control and attack free days to people living with recurrent angioedema. *Weller K, et al. 2020. Validation of the Angioedema Control Test (AECT)-A Patient-Reported Outcome Instrument for Assessing Angioedema Control. J Allergy Clin Immunol Pract;8(6):2050-2057.e4. doi: 10.1016/j.jaip.2020.02.038.* *Fijen LM, et al. Sensitivity to change and minimal clinically important difference of the angioedema control test. 2023. Clin Transl Allergy;13(9):e12295. doi: 10.1002/clt2.12295.* **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** We defer to HAE UK's expertise in this area as a member of Genetic Alliance UK.	

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	NHSE	Where do you consider donidalorsen will fit into the existing care pathway for the prevention of hereditary angioedema attacks? **Donidalorsen would be used to prevent recurrent attacks of hereditary angioedema.** Please select from the following, will donidalorsen be: **C. Prescribed in secondary care with routine follow-up in secondary care** For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. **Existing approved/commissioned prophylaxis (berotralstat and lanadelumab) and forthcoming agents (e.g. garadacimab, if recommended by NICE) are all prescribed and followed up in Secondary care only.** Are there any subgroups of people in whom donidalorsen is expected to be more clinically effective and cost effective or other groups that should be examined separately? **Patients who are non-responsive to current prophylaxis may benefit more from this intervention, especially those managed on C1E prophylaxis only as this is high cost already and may have homecare/hospital infusion costs associated or be at higher dose subcutaneously (where available) and so this may be a more cost-effective option. Others may benefit in a cost-effective manner depending on the cost of this intervention. Those subgroups are likely to be too small to study separately.**	Comments noted, no action required.

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		Would donidalorsen be a candidate for managed access? **May be helpful if the cost benefit is not clear or the overall NHS cost implication is not clear.** Do you consider that the use of donidalorsen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **Unlikely since fewer visits and treatments, as an e.g. 8 weekly therapy, are likely to be captured in QALY scoring.** Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. **N/A** NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which donidalorsen will be licensed; **No** • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by	

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		making it more difficult in practice for a specific group to access the technology; **No** • could have any adverse impact on people with a particular disability or disabilities. **No**	
Additional comments on the draft scope	Otsuka Pharmaceuticals	In the draft scope, the following appraisal in development is listed as a related NICE recommendation: • Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over (2025) NICE technology appraisal guidance ID6284. Publication expected December 2025. As donidalorsen is anticipated to be indicated as an LTP, used for the prevention of recurrent HAE attacks, Otsuka believe that the sebetralstat appraisal is not relevant as it related to the on-demand treatment of acute HAE attacks. Thus, Otsuka requests that this is removed from the related NICE recommendations section. Additionally, Otsuka note that the draft scope does not contain a related national policy section. As donidalorsen is anticipated to be authorised for use as a prophylactic therapy, Otsuka requests that the following NHS England commissioning policy is included in the draft scope: NHS England (2016) Clinical Commissioning Policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II	Comments noted. 'Sebetralstat for treating acute attacks of hereditary angioedema in people aged 12 and over' has been removed from the draft scope. Please note that the Related National Policy section is no longer included in NICE scopes.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Hereditary Angioedema UK