National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Berotralstat for preventing acute attacks of hereditary angioedema

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	BioCryst Pharmaceuticals	It is appropriate to refer BCX7353 (Orladeyo) to NICE for appraisal however it should be recognised that the Single Technology Appraisal (STA) does not adequately account for orphan medicines such as Orladeyo and rare conditions like hereditary angioedema (HAE).	Comment noted. No action needed.
	HAE UK	Yes, it is entirely appropriate this product is considered at this time when the only other possible oral prophylaxis for HAE (which is in any case not licenced for HAE) has discontinued production in the UK. The only way to source any similar product is via more unlicenced products from EU and USA with no guarantee of being able to procure it.	Comment noted. No action needed.
	Takeda	Yes this topic is appropriate to be referred to NICE for appraisal.	Comment noted. No action needed.
	UK Primary Immunodeficiency Network	Yes, it would be appropriate to refer this topic to NICE for appraisal. There are limitations with current oral preventative treatment in HAE. Danazol is currently undergoing supply issues (and it is not clear whether there will definitely be a secure supply in the future) and is unlicensed. Tranexamic acid is relatively ineffective.	Comment noted. No action needed.

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Wording	BioCryst Pharmaceuticals	The wording of the remit accurately reflects the anticipated marketing authorisation for use of Orladeyo within clinical practice.	Comment noted. No action needed.
	HAE UK	As an oral product, can it truly be compared to injectables ie C1-INH and lanadelumab? It should be considered as the currently only licenced form of oral prophylaxis for hereditary angioedema	Thank you for your comment. The appraisal committee will discuss the most appropriate comparator during the development of this appraisal. This will depend on the final marketing authorisation, the current treatment pathway, clinical and cost effectiveness evidence and current clinical practice. The committee will also consider the quality of life benefits of each treatment. No action needed.
	UK Primary Immunodeficiency Network	Yes, it does.	Comment noted. No action needed.
Timing Issues	BioCryst Pharmaceuticals	People are constantly at risk of mortality and morbidity from this condition. Orladeyo can ameliorate these risks and there is therefore an urgent need to evaluate this drug so that it can be made available to meet patient needs as soon as it is licensed.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from

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		UK clinicians and patients have identified a significant unmet need within the HAE population. It is estimated approximately 1000 patients suffer with HAE in the UK, with a national audit in 2014 showing that 37% of patients were receiving some form of long-term oral prophylactic treatment, such as androgens or anti-fibrinolytics.[1] In this same investigation it was shown that only 8% of HAE patients experience a sufficient number of attacks to be eligible for regular C1-inhibitor injections or lanadelumab.[1] For those ineligible patients, attenuated androgens such as danazol were the most frequently prescribed long-term prophylactic treatment, despite not being licensed for this indication.[1] Androgens are often discontinued due to lack of efficacy or tolerability, with significantly increased rates of adverse events associated with prolonged treatment, meaning that many patients are left without a safe or effective long-term prophylactic treatment option.[2] Due to the increased risk of detrimental health implications there are extensive monitoring requirements for all patients prescribed long-term androgen therapy. It is recommended by the Hereditary Angioedema International Working Group that patients receiving long-term androgen prophylaxis should be monitored as follows: blood pressure, weight, signs of virilization, LFTs, a-fetoprotein, urinalysis, complete blood cell count, and lipid profile every 6 months and abdominal ultrasonography annually.[3] These regular monitoring requirements would mean there is continued strain on the healthcare system, however the suggested monitoring protocol is not always adhered to, leaving many patients at risk of potentially serious complications that go undetected. The introduction of Orladeyo into the treatment paradigm would provide the option of a licensed, targeted, orally administered prophylaxis therapy with an acceptable safety profile to many patients who do not currently have access to long-term preventative treatment.	the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.

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	HAE UK	Bearing in mind the large number of hereditary angioedema patients on attenuated androgens which are currently very difficult to procure in UK, this is an urgent need	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	UK Primary Immunodeficiency Network	It would be helpful to have the appraisal done soon as there are limited oral options for prophylactic treatment in HAE, and there are supply issues with danazol which is the most widely used oral prophylactic.	Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.

Comment 2: the draft scope

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Background information	BioCryst Pharmaceuticals	The company fully acknowledge that the correct treatment strategies used in UK clinical practice have been identified within the background information but would like to expand on this information to highlight the current unmet need within the treatment paradigm. As has been correctly identified in the draft scope, attenuated androgens such as danazol are not licensed for this indication. They are also often discontinued due to lack of clinical efficacy or safety concerns.[2] In addition, long term use of these drugs is known to cause hepatotoxicity with some cases of hepatocellular adenoma and carcinoma having been reported with long term use. Regular and close monitoring of patients is therefore required.[3] Long-term preventative strategies involve the use of repeated injections of C1-inhibitors and/or lanadelumab but these treatments are only reimbursed for patients experiencing two or more attacks per week for eight weeks prior to assessment, and thus are not widely prescribed.[4] It must also be mentioned that injectable therapies are not suitable for all patients, with many patients suffering from complications such as inability to locate a vein or anxiety issues of receiving puncture wounds with needles. The anti-fibrinolytic, tranexamic acid, is indicated for short-term prophylaxis of hereditary angioedema, and is started several days before planned procedures which may trigger an acute attack of hereditary angioedema.[5] Further, due to clinical efficacy concerns, tranexamic acid has been removed from treatment guidelines as a long-term prophylaxis treatment.[6] As such, tranexamic acid is indicated and recommended for use for a different aspect of the treatment pathway than is intended for Orladeyo, and should not be considered a relevant comparator. Collectively this highlights that a large proportion of patients have no access to licensed long-term prophylactic therapies, and therefore have to rely on	Thank you for your comments. The background section has been amended and now also includes acute therapy options in the treatment pathway.

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		avoiding triggers and the use of frequent injectable on-demand treatment options following attack onset.	
	HAE UK	yes	Comment noted. No action needed.
	Takeda	The wording in respect to TA606 is incomplete and should read '…and the lowest dosing frequency of lanadelumab is used when the condition is in a stable, attack-free phase.'	Thank you for your comment, the scope has been updated.
	UK Primary Immunodeficiency Network	The information is accurate and complete	Comment noted. No action needed.
The technology/ intervention	BioCryst Pharmaceuticals	Within the draft scope it is stated "the brand name is not known". The brand name of BCX7353 is 'Orladeyo'. The generic name is berotralstat	Thank you for your comment, the scope has been updated. This change has also been made to the appraisal title.
	HAE UK	Unable to comment	Comment noted. No action needed.
	UK Primary Immunodeficiency Network	The description of the technology is accurate, although the clinical trial has reported on its outcomes.	Comment noted. No action needed.
Population	BioCryst Pharmaceuticals	The company feel the current definition of the population accurately reflects the intended population.	Thank you for your comment. The population in the scope is intended to be broad

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		As discussed in the background above, it has also been identified that there are a significant number of patients who have no current prophylactic options. These are: • Patients aged 12 years and older with hereditary angioedema, [redacted]	to cover the final marketing authorisation. The committee will consider the current treatment pathway and unmet need during the development of the appraisal. No action needed.
	HAE UK	There is a substantial number of patients who do not have sufficiently regular attacks to qualify for either of the injectable prophylaxis treatments but are managed on a combination of (unlicenced) oral prophylaxis with some undesirable features and ad hoc use of acute medication in the form of Icatibant or C1-INH. Because of the unavailability of the currently used oral product, these patients are becoming increasingly dependent on having to use ad hoc acute medication to manage attacks rather than preventing them in the first place	Thank you for your comment. The committee will consider the current treatment pathway and unmet need during the development of the appraisal. The population is intended to be broad to reflect the final marketing authorisation. No action needed.
	Takeda	Population should be amended to refer to those with hereditary angioedema Type 1 or Type 2 In accordance with the NHS England Commissioning Policy for prophylactic treatment of HAE, the population should experience two or more clinically significant attacks per week over a period of least 56 days to be eligible for preventative treatment (unless contraindicated to oral prophylaxis). The requirement for a confirmed number of attacks should therefore be considered when defining the appropriate population.	Thank you for your comment. The population in the scope is intended to be broad to cover the final marketing authorisation. No action needed.

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	UK Primary Immunodeficiency Network	The population is appropriately defined	Comment noted. No action needed.
Comparators	BioCryst Pharmaceuticals	The wording for comparators states that Orladeyo may be compared with 'C1-esterase inhibitors, attenuated androgens and anti-fibrinolytics' and 'lanadelumab for people eligible for C1-esterase inhibitor treatment in line with NHS England's treatment pathway'. Although it is fully acknowledged that all potential competitor treatments for HAE prophylaxis have been included, there are many patients who remain without a suitable option for prophylaxis as stated in the background and population sections above. Orladeyo aims to provide a prophylactic option for these patients, specifically: Patients aged 12 years and older with hereditary angioedema who are [redacted] For these reasons, Orladeyo should be compared with the current standard of care, which involves avoidance of triggers and administration of on-demand rescue therapies following the onset of attacks. According to the anticipated place of Orladeyo in the treatment pathway, the company propose the appropriate comparator is as follows: • Standard of care: this involves a strategy of avoiding triggers and the administration of acute therapies that mitigate the symptoms associated with an attack. The acute therapies include 'Berinert', 'Cinryze', 'Firazyr' and 'Ruconest'. These therapies can be used at the point of onset of an attack and can be used in conjunction with Orladeyo. Thus, it is suggested the appraisal will compare the	Thank you for your comment. Acute therapies are not considered direct comparators since they are used in both arms. The list of comparators is intended to be broad to cover the final marketing authorisation. The appraisal committee will discuss the most appropriate comparator 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. No action needed.

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		current standard of care against the use of Orladeyo alongside the current standard of care. The rationale that the proposed comparators are not relevant are as follows: • Attenuated androgens are not licensed as a prophylactic treatment for the prevention of acute attacks for patients with HAE. Androgen use as a prophylactic treatment in the prevention of attacks due to HAE is often discontinued due to lack of sustained response or undesired side effects.[2] Thus, in this appraisal it is deemed that eligible patients will have already been considered for and advised against, or discontinued androgen use as part of their treatment strategy. As such, androgens are not direct comparators to Orladeyo in the UK clinical setting. • The current guidelines stipulate that patients qualify for prophylaxis with IV C1-esterase inhibitors when experiencing at least 2 clinically significant attacks per week. The company acknowledges the use of repeat injections of C1- esterase inhibitors in the prevention of attacks for these patients however in clinical practice the eligibility criteria means that the majority of patients are ineligible for treatment (i.e. those patients who experience less than 2 attacks per week or are not able or appropriate for long term IV therapy). For these reasons, it is proposed that C1- esterase inhibitors are not direct comparators for Orladeyo in a clinical setting. • Patients are eligible to receive lanadelumab as a prophylactic treatment for HAE if they fulfil the eligibility criteria to receive C1-inhibitors. Due to the same reasons mentioned in the previous point it is considered that lanadelumab is not a direct comparator for Orladeyo in a clinical setting. • Anti-fibrinolytics such as tranexamic acid are indicated for the short-term prevention of acute attacks due to HAE, but are not indicated for long-term prophylaxis.[5] There is very little evidence over the clinical effectiveness of tranexamic acid resulting in it no longer	

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		appearing on the guidelines as a long-term prophylactic therapy for HAE patients.[6,8] Due to its indication as a short term preventative treatment and lack of evidence for clinical effectiveness the company concludes that tranexamic acid is not a relevant comparator to Orladeyo. • Considering the above information, the company suggest that standard of care (on-demand therapy) is the appropriate comparator for Orladeyo.	
	HAE UK	Can an oral product be compared with injectable?	Thank you for your comment. The appraisal committee will discuss the most appropriate comparator 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 committee will also consider the quality of life benefits of each treatment. No action needed.
	Takeda	Comparison to C1-esterase inhibitors should include both plasma-derived (Berinert and Cinryze) and recombinant (conestat alfa) products. Although only Cinryze has a licence for prophylaxis, conestat alfa is increasingly used	Thank you for your comment. The comparators section

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		for prophylactic treatment in clinical practice. Furthermore, NHS England issued guidance in February 2020 advocating that new patients who require ongoing prophylactic treatment are treated with non-plasma derived products (conestat alfa and lanadelumab). We suggest updating the reference to the NHS England commissioning policy so that it is clear it is referring to the policy for prophylactic treatment of HAE Type I and II. The eligibility criteria for treatment in the policy apply to both C1-esterase inhibitors and lanadelumab.	has been updated to clarify that the relevant NHS England commissioning policy is for preventative C1 - esterase inhibitors.
	UK Primary Immunodeficiency Network	Yes, these are the standard treatments used in the NHS. The oral treatments have limitations as described above.	Comment noted. No action needed.
Outcomes	BioCryst Pharmaceuticals	All of the outcomes listed are appropriate and there is reason to believe two additional outcome measures are also appropriate in conveying the clinical benefit associated with Orladeyo. It is proposed that both attack location and attack duration play a significant role in the conveying of the key clinical benefits associated with Orladeyo. For this reason, we propose that two further outcomes should be considered: • Location of attack (specifically differentiating between Laryngeal, Abdominal and Limb/Peripheral attacks) • Duration of attacks Clinical decision-making on acute therapies and resource use associated with attacks in differing locations varies significantly thus justifying its inclusion as an outcome measure. Similarly, quality of life implications associated with attacks apply over the timeframe in which the attack takes place, meaning that attack duration has a meaningful impact on quality of life and should be included as an outcome measure.	Thank you for your comment. The list of outcomes has been amended to include a single bullet for angioedema attacks with examples of frequency, severity, location and duration. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list.

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		The company propose that the outcomes considered as part of the appraisal should be as follows: • frequency of angioedema attacks • severity of angioedema attacks • need for acute treatment • mortality • adverse effects of treatment • location of angioedema attacks • duration of angioedema attacks health-related quality of life	
	HAE UK	I am not sure how to phrase this but as a prophylaxis product it should be measured on attacks prevented rather number of attacks? However, this is not easy to quantify without withdrawing treatment altogether and risking a severe and possibly fatal attack. Reduction in severity of attacks meaning they are tolerated without need for rescue may be helpful?	Thank you for your comment. The list of outcomes provides a summary of main outcomes and is not intended to be an exhaustive list. The list of outcomes has been amended to include a single bullet for angioedema attacks with examples of frequency, severity, location and duration. It is anticipated that prevention of attacks

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			will be measured as part of this outcome.
Economic analysis	BioCryst Pharmaceuticals	There are no economic analysis issues to comment on.	Comment noted. No action needed.
	HAE UK	Owing to unavailability of the only other effective (and unlicenced) oral prophylaxis, the timing is very relative.	Comment noted. No action needed.
	UK Primary Immunodeficiency Network	The suggested economic analysis appears to be appropriate.	Comment noted. No action needed.
Equality and Diversity	BioCryst Pharmaceuticals	No comments	Noted. No action needed.
	HAE UK	Unlikely to be an issue	Comment noted. No action needed.
	UK Primary Immunodeficiency Network	Do not think that the proposed remit needs changing in relation to this.	Comment noted. No action needed.
Other considerations	BioCryst Pharmaceuticals	There are no additional issues to comment on.	Comment noted. No action needed.
	HAE UK	Current issues regarding availability of the unlicenced oral prophylaxis which in any case can have undesireable side effects such as masculinisaton for female patients, massive weight gain, aggressive behaviour and risk of liver cancer for all patients.	Thank you for your comment. During the development of the appraisal, the committee will consider the current treatment

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			pathway. NICE will also consider patient/carer, professional and clinical expert submissions. No action needed.
	UK Primary Immunodeficiency Network	No other suggestions at present	Comment noted. No action needed.
Innovation	BioCryst Pharmaceuticals	Orladeyo is the first orally available targeted kallikrein inhibitor for prevention of HAE attacks. In clinical trials, Orladeyo has demonstrated an ability to reduce the frequency of angioedema attacks. Over the course of the 24 weeks of the phase III APeX-2 trial 50% of patients treated with 150mg of Orladeyo QD experienced at least a 70% reduction in frequency of attacks from baseline.[9] [redacted] Orladeyo is the first effective treatment for HAE to offer both an oral administration route and an extremely low rate of adverse events. This is unique when comparing to the other prophylactic treatments within this space. Orladeyo thus offers an innovative new therapy option for HAE patients. For those patients appropriate for prophylaxis and ineligible (i.e. those patients who experience less than 2 attacks per week) or unable/unwilling to use IV or SC therapies, there is currently no licenced long-term prophylactic therapy that has been shown to be effective and safe in clinical trials. These patients therefore have to rely on a '*watch & rescue*' strategy. Orladeyo provides an effective treatment option for these patients.	Comment noted. During the development of the appraisal, the committee will consider the degree to which berotralstat is an innovative technology when making its recommendations. No action needed.

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		The company considers the following health related benefits that may have potential significance which are unlikely to be included in the QALY calculation. • Loss of workdays due to attacks. • Loss of carer workdays. • Loss of workdays due to training for self-administration of subcutaneous and intra-venous therapies. • The avoidance of undesirable side effects associated with Androgen use. Data on workdays lost due to attacks can be calculated using the mean duration of attacks and frequency of attacks to estimate the time patients spend incapacitated. Loss of carer workdays can be calculated in a similar way however only considering those patients under the age of 18 and applying a percentage of attacks requiring carer assistance. Loss of workdays due to training for self-administration of SC and IV therapies can be calculated as this training follows a set time structure and can be applied to all patients eligible for those therapies.	
	HAE UK	An effective, licenced oral prophylactic product represents a significant advance over the injectables. Hence it is very innovative! Use requires no training and requires no special abilities amongst patients. Current C1-INH requires intravenous administration and consequent damage to veins. Subcut lanadelumab raises issues over 'wash out' period and generally safety of long term kallikrien suppression (although this last applies to this product)	Comment noted. During the development of the appraisal, the committee will consider the degree to which berotralstat is an innovative technology when making its recommendations. No action needed.

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	UK Primary Immunodeficiency Network	Yes, the technology is innovative in its potential to have a significant impact. The oral preventative treatment options in the UK are currently androgens (danazol) or tranexamic acid. Danazol is unlicensed and currently having supply issues, the long-term outcome of which is uncertain. There is also the issue of androgenic side effects, which affect women more. Tranexamic acid is of limited effectiveness. C1 inhibitor requires injections usually twice weekly for prevention, and has a significant burden of treatment. Lanadelumab requires fewer injections but still requires injection. At present, there is no effective licensed oral therapy for prevention of attacks in HAE.	Comment noted. During the development of the appraisal, the committee will consider the degree to which berotralstat is an innovative technology when making its recommendations. No action needed.
Questions for consultation	BioCryst Pharmaceuticals	The current treatment pathway for hereditary angioedema specifies that: 1. No prophylactic treatments are prescribed for patients experiencing less than 2 attacks per month, meaning these patients must rely on the standard of care.[7] This involves the use of acute therapies such as '*Berinert*', '*Cinryze*', '*Firazyr*' and '*Ruconest*' at the onset of attacks to reduce the severity and durations of the symptoms. 2. Regular oral administration of attenuated androgens are available for patients experiencing 2 or more attacks per month.[7] This is prescribed alongside acute therapies for the treatment of acute attacks. 3. Those patients that are intolerable to attenuated androgens are considered for tranexamic acid as a long term preventative treatment, even though large proportions of patients experience no/little clinical benefit and are then discontinued.[10] Again, acute attacks are treated using acute therapies. 4. Regular injections of C1-inhibitors and/or lanadelumab are prescribed for patients experiencing 2 or more clinically significant attacks per week over 8 weeks despite oral preventive therapy, or oral therapy is contraindicated or not tolerated.[4] Again, acute therapies are used in the treatment of acute attacks.	Thank you for your comment. The current list of comparators only includes treatments for the prevention of acute attacks, in line with the draft remit and clinical trial population. No action needed.

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		Orladeyo is expected to fit into the treatment pathway for patients aged 12 years and older with hereditary angioedema, [redacted] The company are confident that the wording of the proposed remit and scope will not result in any discrimination against patients protected by the equality legislation. The company feel it is appropriate to appraise Orladeyo through the Single Technology Appraisal process. The company suggest it is not appropriate to use the cost comparison methodology for this appraisal. This is because the technology has proven to have significantly dissimilar clinical efficacy and resource use compared with the current treatments for HAE. No clinical trials for the comparator technologies in HAE that are expected to complete within the next 12 months have been identified	
	UK Primary Immunodeficiency Network	It may be helpful to look at subgroups of HAE patients with very severe disease separately to see if they benefit more from the technology.	Comment noted. The use of subgroups will depend on the availability of data from the clinical trial. During the development of the appraisal the committee will consider relevant subgroups raised in the

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			submission. No action required.
Additional comments on the draft scope	UK Primary Immunodeficiency Network	No other comments.	Noted. No action needed.
Stakeholder list	UK Primary Immunodeficiency Network	Is there a reason why NHS West Essex CCG and NHS Oldham CCG have been chosen from the list of CCGs to comment on this? Is there a reason why the South Asian Health Foundation (rather than other groups representing ethnic communities) have been asked to comment? (As HAE does not selectively affect people of south Asian origin)	Thank you for your comments. 2 CCGs are randomly selected to be a stakeholder for each topic. The South Asian Health Foundation is a standard consultee that is added to all stakeholder lists. No action needed.

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