National Institute for Health and Care Excellence

Health Technology Evaluation

Pegunigalsidase alfa for treating Fabry disease [ID3904]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Amicus	The evaluation of pegunigalsidase alfa with other enzyme replacement therapies (ERTs) (agalsidase alfa or agalsidase beta) as comparators is appropriate; however, Amicus would like the draft scope to be changed to reflect the current NHS Fabry treatment pathway in the following four ways: **1. Best supportive care (BSC) removed as a comparator in final scope** Since the introduction of ERTs in 2001, BSC is no longer prescribed for patients who have treatable Fabry disease and as such BSC should be removed as a comparator from the final scope. Communication with clinical experts indicates that the treatments for Fabry disease currently used in the NHS are documented in the UK Fabry treatment SOP (standard operating procedure [Hiwot, Hughes, and Ramaswami])[1]; this document, written by Fabry disease clinical experts, does not include BSC as a treatment option, hence its inclusion in the draft scope is not reflective of current clinical practice.[1] The inclusion of BSC in the draft scope represents a retrograde step in clinical management and does not align with the NHS Rare Disease	Comment noted. Following the consultation and scoping workshop the following changes have been made to the scope: 1. Best supportive care has been removed as a comparator. 2. Migalastat has been retained as a comparator for a population subgroup

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		Framework which highlights the need to ensure access to innovative treatments for people with rare diseases.[2] **2. Migalastat removed as a comparator in final scope** The treatment options available for Fabry patients are dependent on whether the patient has a migalastat-amenable mutation. If a patient has the amenable mutation nearly all patients will be treated with migalastat first line and then an ERT (either agalsidase alfa or agalsidase beta) second line. If the patient does not have the miglastat mutation then the first-line treatment is an ERT (either agalsidase alfa or agalsidase beta), and the second-line treatment is a different ERT (either agalsidase alfa or agalsidase beta). The patient cohort that migalastat can be prescribed for in the NHS is clearly defined in the migalastat NICE guidance and the UK Fabry treatment SOP. As such, it is clear that migalastat is prescribed in a different patient cohort to ERTs and is not a direct comparator to pegunigalsidase alfa; the final scope should be changed to reflect this. **3. Include the UK treatment SOP in the final scope** As mentioned above, the treatment options prescribed as standard clinical practice are outlined in the UK Fabry treatment SOP. This treatment SOP was written by Fabry clinical experts and is implemented in all the specialist Fabry treatment centres. This treatment SOP should be referenced and included in the final scope. **4. The reference to the NHS Rare Disease Framework needs to be updated in the final scope and the 4 policy priorities included in the appraisal** In the section "Related national policy" the UK Rare Disease Framework is listed as a relevant policy document. The document referenced in the draft scope is from 2013 which is out of date and has been superseded by the following:	which have amenable mutations. This decision was made following confirmation from clinical experts at the scoping workshop that patients with an amenable mutation may be treated with either migalastat or enzyme replacement therapy. The decision of whether to take migalastat or ERT as 1st line therapy would be influenced by a range of factors (including disease severity and suitability for oral treatment). 3. Reference to the BIMDG treatment guidelines has been added to the scope. 4. The reference to the NHS Rare Disease

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		• In January 2021, the revised UK Rare Disease Framework was published: (https://www.gov.uk/government/publications/uk-rare-diseases-framework) • In February 2022 the UK rare disease action plan for England was published: (https://www.gov.uk/government/publications/england-rare-diseases-action-plan-2022/england-rare-diseases-action-plan-2022). Both these recent documents highlight that the pathway, treatment, and access to medicines for rare diseases needs to improve. As a consequence, Amicus would like the objectives of the most recent UK NHS Rare Disease Framework and action plan to be included in this appraisal.[2] 1. Hiwot T, Hughes D, Ramaswami U. BIMDG: Guidelines for the treatment of Fabry Disease 2020 [Available from: http://www.bimdg.org.uk/store/lsd//FabryGuide_LSDSS_Jan2020_700523_11032020.pdf (last accessed 1st September) 2. Department of Health and Social Care. The UK Rare Diseases Framework London: DHSC; 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950651/the-UK-rare-diseases-framework.pdf	Framework has been updated.
	Cambridge University Hospitals	We would wish to see some clarification/explanation regarding the choice of single technology appraisal rather than using the highly specialised technology route?	Comment noted. Following the consultation and scoping workshop it was decided that this topic will proceed as a Single Technology Appraisal. This decision was informed by

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			information such as the disease prevalence, size of eligible population and availability of existing treatments, in consideration of the updated highly specialised technologies routing criteria.
	Chiesi Limited	The only NICE-approved treatment for Fabry disease, migalastat, was assessed through the highly specialised technology route (HST4).[1] However, migalastat is only available for the treatment of patients over 16 years of age with an amenable mutation. Patients with Fabry disease have limited treatment options, and those who are treated with current therapies still experience disease progression, and patients can develop neutralising antibodies to enzyme replacement therapies (ERT) which may reduce effectiveness.[2] As such there is still a substantial unmet need for effective new treatments for patients with Fabry disease. To ensure equity in decision-making across the same indication, Chiesi strongly calls for PRX-102 to be considered via the same route as migalastat via HST, not STA or MTA. In addition, the standard STA process is not designed to assess orphan medicines for the treatment of rare conditions such as Fabry disease. PRX-102 has orphan drug status that was awarded in 2017 (EU orphan status EU/3/17/1953).[3] Treatments for orphan diseases require a different approach to health technology assessment due to the challenges in performing clinical trials in rare and heterogeneous patient populations, which is the reason why HST exists.	Comment noted. Using input from the consultation and scoping workshop the technology was considered against the highly specialised technologies routing criteria. It was decided that this topic will proceed as a Single Technology Appraisal. This decision was informed by information such as the disease prevalence, size of eligible population and availability of existing treatments.

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		We believe that assessing PRX-102 under the STA process discriminates against patients with a rare condition such as Fabry disease, as these patients should have access to additional treatment options that are assessed using a fair and equitable approach that takes into account the rarity of their condition. 1. National Institute for Health and Care Excellence (NICE). Migalastat for treating Fabry disease: Highly specialised technologies guidance. 2017. (Updated: 22 February 2017) Available at: https://www.nice.org.uk/guidance/hst4/chapter/1-Recommendations. Accessed: 20 April 2022. 2. Cairns T, Muntze J, Gernert J, et al. Hot topics in Fabry disease. *Postgrad Med J*. 2018; 94(1118):709-13. 3. European Medicines Agency. EU/3/17/1953: Orphan designation for the treatment of Fabry disease. 2017. Available at: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171953#:~:text=On%2012%20December%202017%2C%20orphan,%2C%20Italy%2C%20in%20May%202019. Accessed: 20 April 2022.	The patient population for HST4 was people aged 16 years and older with a confirmed diagnosis of Fabry disease and who have an amenable mutation. This is different (and smaller) than the population for this appraisal, which is adults with Fabry disease. As outlined in NICE's Process and Methods manual, "standard technology appraisals methods and processes are designed to be flexible and adaptable for all technologies and conditions. So, they are suitable for most technologies that treat rare conditions and small populations."
	Genetic Alliance UK	We have concerns over the choice of routing for this technology. The STA route is likely to disadvantage pegunigalsidase alfa given the rarity of Fabry disease.	Comment noted. Using input from the consultation and

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		A previous treatment for Fabry disease (migalastat) went through an HST route so it is unclear as to why this technology has been routed through STA. The population is stated in the background information as 1 in 49,000. The new HST criteria states that the population should be no more than 1 in 50,000. Though we value the more objective nature of the criteria, it would be helpful to see how they are being applied in topic selection. Migalastat has been recommended for use in individuals with Fabry disease aged 16 and above with amenable mutations however, the majority of people with Fabry disease do not have the required mutations therefore they have limited alternative treatment options.	scoping workshop the technology was considered against the highly specialised technologies routing criteria. It was decided that this topic will proceed as a Single Technology Appraisal. This decision was informed by information such as the disease prevalence, size of eligible population and availability of existing treatments. The patient population for HST4 was people aged 16 years and older with a confirmed diagnosis of Fabry disease and who have an amenable mutation. This is different (and smaller) than the population for this appraisal, which is adults with Fabry disease.

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			As outlined in NICE's Process and Methods manual, "standard technology appraisals methods and processes are designed to be flexible and adaptable for all technologies and conditions. So, they are suitable for most technologies that treat rare conditions and small populations."
	The MPS Society	Whilst we feel that this technology is appropriate for NICE review, it would have been more conducive to have used the scope to define the appropriate appraisal route. Proceeding with a health technology evaluation with no defined pathway would have been preferred. This would have potentially given NICE the information it needed to be assured that the right decision and pathway had been decided. Currently NICE have proposed that this review follows an STA route but has not given any justification for this decision. It is unclear why HST has not been considered in this instance, given that it is: A) a rare condition, with a treatment recognised by MHRA as a rare treatment with accelerated access B)whist excluded as a criteria, it is important to note that clinical management and treatment protocol currently falls under a highly specialised service C) STA is not designed in our opinion to review complex rare diseases and technologies. This is especially as gene therapies are on the horizon for many of these treatments D) ERT's are high cost therapies with ICER's not appropriate for STA	Comment noted. Following the consultation and scoping workshop it was decided that this topic will proceed as a Single Technology Appraisal. This decision was informed by information such as the disease prevalence, size of eligible population and availability of existing treatments in consideration of the highly specialised

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		E) currently it is not clear whether this technology will address comorbidities not currently met, who the defined treatment population would be and the treatment protocols. F) we are concerned that if new technologies for this condition all go down a STA route and there is not enough evidence to prove clinical and cost effectiveness, no new therapies and their potential innovative properties will be considered and approved leading to a block in innovation and access. NICE have also posed the question as to whether this should be reviewed under a MTA as there are three treatments already commissioned by NHSE. This would be a complex approach and whilst not opposed we would be very concerned over the timescale needed to undertake such a task and would need to be very clear of the scope for this type of appraisal, its implications, as well as how inclusive, equitable and transparent the process would be. As NICE are aware, historically we have two ERT's commissioned pre NICE and one oral therapy that was recommended by NICE in 2016 under an HST evaluation. Previous attempts for these treatments to be reviewed have failed due to the lack of consistent long term data. It is also important to consider the different patient populations both current and proposed treatments are targeting • Agalsidase alpha and beta (children and adults) • Migalastat (16yrs and over with an amenable mutation) • Pegunigalsidase (adults 18yrs and over) It would also be difficult to illicit clinical opinion on pegunigalsidase as currently not all the results from the clinical studies are available.	technologies routing criteria. As outlined in NICE's Process and Methods manual, "standard technology appraisals methods and processes are designed to be flexible and adaptable for all technologies and conditions. So, they are suitable for most technologies that treat rare conditions and small populations."
Wording	Amicus	No comment.	No action required.

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	Cambridge University Hospitals	No objection	No action required.
	Chiesi Limited	Yes	No action required.
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	Appropriate	No action required.
Timing Issues	Amicus	No comment.	No action required.
	Cambridge University Hospitals	There remains unmet medical need in patients with Fabry disease	No action required.
	Chiesi Limited	PRX-102 is a highly innovative treatment for patients with Fabry disease: it is the first PEGylated alpha-galactosidase A, which has been designed with the aim of improving stability, a longer half-life, improved biodistribution and reducing the risk of immunogenicity compared to existing ERTs. It has been shown to be more stable than other commercially-available ERTs (agalsidase alfa and agalsidase beta), both in plasma and under lysosomal-like conditions where it remains active for 5 times as long.[4] The innovative nature of PRX-102 has been endorsed in the UK by the MHRA granting PRX-102 an Innovation Passport in August 2021 and PRX-102 is being assessed through the Innovative Licensing and Access Pathway.	Comment noted. NICE aims to publish final guidance for all new technologies within 90 days of receiving marketing authorisation.

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		The current proposed NICE timelines for the appraisal, with a proposed NICE submission date of February 2023, are not aligned with the current regulatory timelines submitted to NICE (see table below) and also do not reflect the urgency of patient access for this innovative treatment for a rare disease with a high unmet need. Therefore, we request that the timing of the submission is brought forward to align more closely to regulatory timelines allowing UK patients with Fabry disease access to this innovative treatment as quickly as possible. 4. Kizhner T, Azulay Y, Hainrichson M, et al. Characterization of a chemically modified plant cell culture expressed human alpha-Galactosidase-A enzyme for treatment of Fabry disease. *Mol Genet Metab*. 2015; 114(2):259-67.	
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	Needs to be in line with expected EMA / MHRA approval	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Amicus	The background section of the draft scope does not fully explain the treatment pathway available to patients treated in the NHS and needs to be updated. In particular, the draft scope does not mention the importance of	Comment noted. Following the consultation and

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		patient subgroups in determining the treatment options available to Fabry patients. Treatable Fabry patients either have the amenable migalastat mutation or not; if they have the amenable mutation the patient (subject to label) is eligible for migalastat and in nearly all cases in current UK clinical practice receives migalastat as a first-line therapy. If a patient does not have the migalastat-amenable mutation then the patient receives ERT as a first-line therapy. The following changes to the background section outlining the treatment options are requested: • A section explaining the importance of a patients' migalastat-amenable mutation status and the different treatment options in the amenable and non-amenable subgroups. • A section explaining that migalastat and ERTs are different types of medicine and are prescribed to different patient cohorts in NHS clinical practice. This section should highlight that migalastat is an oral therapy (the draft scope only mentions that ERTs are an infusion). In addition, Amicus would like the background section in the final scope to be updated to highlight and include two important documents in the treatment of Fabry patients: 1. UK Fabry treatment SOP: The treatment of Fabry patients is tightly defined and controlled through the UK treatment SOP (Hiwot 2020).[1] Current clinical practice is aligned with this SOP, which is widely used in specialist centres to determine Fabry treatment.[1] The UK treatment SOP should therefore be referenced in the final scope and the scope should be aligned to reflect current clinical practice. The UK Rare Disease Framework and implementation plan[2] set in place a strategy for the diagnosis, treatment and care of people with a confirmed diagnosis of Fabry disease. The framework sets in place four key priorities to: reduce the "diagnostic odyssey" and help patients to receive a diagnosis	scoping workshop, reference to the BIMDG guidelines have been added to the scope. In line with the BIMDG treatment guidelines and discussion at the scoping workshop, it has been noted in the scope that for people with an amenable mutation, 1st line therapy options are migalastat or enzyme replacement therapy. The clinical experts did not agree that 'nearly all' people with an amenable mutation would take migalastat. They said the decision of whether to take migalastat or ERT as 1st line therapy would be influenced by a range of factors (including disease severity and

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		faster (#1), ensure appropriate education and support of those involved in patient care (#2), improve coordination of care (#3), and improve access to specialist care, treatments and drugs (#4).[2] The draft scope currently references the 2013 NHS England policy document in the table entitled 'related policy'. Amicus request that the NHS Rare Disease Framework published in January 2021 and the England rare disease implementation plan published in February 2022 be referenced and their importance to the future appraisal described in the scope. In addition, Amicus request the future appraisal ensures any guidance is aligned to the four priorities set out in the framework to ensure Fabry patient care improves and access to innovative treatments is secured. 1. Hiwot T, Hughes D, Ramaswami U. BIMDG: Guidelines for the treatment of Fabry Disease 2020 [Available from: http://www.bimdg.org.uk/store/lsd//FabryGuide_LSDSS_Jan2020_700523_11032020.pdf (last accessed 1st September) 2. Department of Health and Social Care. The UK Rare Diseases Framework London: DHSC; 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950651/the-UK-rare-diseases-framework.pdf] (last accessed March 2022)	suitability for oral treatment).
	Cambridge University Hospitals	Treatment of angiokeratomas is generally not available within the NHS	No action required.
	Chiesi Limited	There are limited data in Fabry disease describing accurate and up-to-date prevalence estimates for the UK. The Brennan and Parkes (2014) reference	Comment noted. Following the

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		cited in the draft scope describes the 1 in 49,000 figure as the estimated prevalence for symptomatic diagnosed Fabry disease in England. We request that the wording in the draft scope is updated to ensure accuracy as this figure is only for symptomatic diagnosed patients, not for all patients with Fabry disease. Please add the most recent BIMDG Fabry Guidelines in Related National policy: FabryGuide_LSDSS_Jan2020_700523_11032020.pdf (bimdg.org.uk) Due to the withdrawal of the NICE Pathways service , please remove the below from the Related NICE recommendations: *Endocrine, nutritional and metabolic conditions overview NICE pathway* *Endocrine, nutritional and metabolic conditions overview - NICE Pathways* Regarding current therapies, it is important to note that current ERTs have short circulatory half-lives, which may contribute to limited efficacy and continuous disease progression in patients, including deterioration in renal function.[2, 4] Current ERTs can also induce the production of neutralizing anti-drug antibodies (ADAs), which can limit efficacy and prevent long-term clinical benefit.[5, 6] As described above, in the 'Timing Issues', comment, PRX-102 has been designed to have a 5 x longer half-life than other ERTs.[4] This may allow for a reduced frequency of infusions every 4 weeks when compared with current ERTs' infusion schedule of every 2 weeks, as shown by results of the BRIGHT clinical study.[7] In addition, PEGylation and chemical modification of pegunigalsidase alfa has been shown to reduce immunogenicity by masking immunogenic epitopes, and potentially induce immunotolerance through enhanced enzyme exposure. In patients previously treated with other ERTs,	consultation and scoping workshop the word 'symptomatic' has been added to the 1 in 49,000 prevalence figure in the scope. The Brennan and Parkes reference states that this is the expected prevalence of symptomatic Fabry if there was an improved uptake in cascade testing (whereby blood relatives of known Fabry cases are also tested). Since this is a hypothetical situation based on the study findings, it was considered it may be misleading to add 'diagnosed' to the wording. A sentence has also been added to reflect the fact that when presymptomatic or asymptomatic patients are included, the

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		switching to PRX-102 has been shown reduce cross-reactivity with pre-existing ADAs, thereby reducing serum-mediated enzyme inhibition of PRX-102.[7, 8] These are important points to highlight in the technology section of the background. 2. Cairns T, Muntze J, Gernert J, et al. Hot topics in Fabry disease. *Postgrad Med J*. 2018; 94(1118):709-13. 4. Kizhner T, Azulay Y, Hainrichson M, et al. Characterization of a chemically modified plant cell culture expressed human alpha-Galactosidase-A enzyme for treatment of Fabry disease. *Mol Genet Metab*. 2015; 114(2):259-67. 5. Hollak CE and Linthorst GE. Immune response to enzyme replacement therapy in Fabry disease: impact on clinical outcome? *Mol Genet Metab*. 2009; 96(1):1-3. 6. Lenders M, Hennermann JB, Kurschat C, et al. Multicenter Female Fabry Study (MFFS) - clinical survey on current treatment of females with Fabry disease. *Orphanet journal of rare diseases*. 2016; 11(1):88-. 7. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of BRIDGE Phase III Open-Label, Switch-Over Clinical Trial Evaluating Pegunigalsidase Alfa for the Treatment of Fabry Disease. 2020. (Updated: 30 December 2020) Available at: https://www.prnewswire.com/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-final-results-of-the-bright-phase-iii-clinical-trial-evaluating-prx-102-for-the-treatment-of-fabry-disease-301505728.html. Accessed: 20 April 2022. 8. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of the BRIGHT Phase III Clinical Trial Evaluating PRX-102 for the Treatment of Fabry Disease. 2022. (Updated: 18 March 2022) Available at: https://www.prnewswire.com/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-	prevalence is expected to be much higher. The scope already notes that “the enzyme is chemically modified in a way that makes it more stable than current enzyme replacement therapies, potentially extending the time between treatments”. We typically would not include any further detail on the technology at this stage. The additional benefits noted can be included in the company submission.

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		final-results-of-the-bright-phase-iii-clinical-trial-evaluating-prx-102-for-the-treatment-of-fabry-disease-301505728.html. Accessed: 20 April 2022.	
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	Appropriate	No action required.
Population	Amicus	No comment.	No action required.
	Cambridge University Hospitals	Yes	No action required.
	Chiesi Limited	PRX-102 will be positioned as a treatment option for any patient with symptomatic Fabry disease who would usually be offered ERT or migalastat. The phase III clinical trial programme for PRX-102 (BRIDGE, BRIGHT and BALANCE) provides compelling and consistent effectiveness and safety data in both treatment–naïve and ERT–experienced patients with Fabry disease.[7-9] PRX-102 would be used to treat patients for symptomatic Fabry disease who would be offered ERT or migalastat. Therefore, there are no other subgroups of patients not currently being treated for whom PRX-102 would be considered.	Comment noted. As discussed at the scoping workshop the population has been updated to specify that the population is adults with Fabry disease. It was clarified that the starting criteria for treatment would be consistent with current BIMDG starting criteria. It was agreed that the

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		In patients with an amenable mutation who are treated with migalastat and who experience deteriorating kidney function (not indicated in patients with eGFR <30 ml/min), usually a switch to ERT would be recommended in clinical practice.[10] The decision to use agalsidase alfa, agalsidase beta, PRX-102 or migalastat would be a decision led by clinician and taking into account patient choice.	word 'symptomatic' would not be included in the scope population.

7. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of BRIDGE Phase III Open-Label, Switch-Over Clinical Trial Evaluating Pegunigalsidase Alfa for the Treatment of Fabry Disease. 2020. (Updated: 30 December 2020) Available at: https://www.prnewswire.com/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-final-results-of-the-bright-phase-iii-clinical-trial-evaluating-prx-102-for-the-treatment-of-fabry-disease-301505728.html. Accessed: 20 April 2022.
8. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of the BRIGHT Phase III Clinical Trial Evaluating PRX-102 for the Treatment of Fabry Disease. 2022. (Updated: 18 March 2022) Available at: https://www.prnewswire.com/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-final-results-of-the-bright-phase-iii-clinical-trial-evaluating-prx-102-for-the-treatment-of-fabry-disease-301505728.html. Accessed: 20 April 2022.
9. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Topline Results from the 24-Month Phase III BALANCE Clinical Trial of PRX-102 for the Treatment of Fabry Disease. 2022. (Updated: 7 April 2022) Available at: https://www.chiesi.com/en/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-topline-results-from-the-24-month-phase-iii-balance-clinical-trial-of-prx-102-for-the-treatment-of-fabry-disease/. Accessed: 20 April 2022.

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		10. BIMDG. Guidelines for the treatment of Fabry Disease 2020. Available at: https://www.bimdg.org.uk/store/lsd/FabryGuide_LSDSS_Jan2020_700523_11032020.pdf. Accessed: 20 April 2022.	
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	Whilst the figure quoted for England is probably correct, the overall number of people living with Fabry in the UK is nearer to 1500. We believe the current population consists of: 1/3 male 2/3 female	No action required.
Subgroups	Amicus	Therapeutic indications and marketing authorisations has not be confirmed. Our understanding is that the treatment will be intended for adults (18 years and over) and we assume patients would be assessed against the current treatment guidelines for Fabry disease. https://bimdg.org.uk/site/guidelines-lsd.asp?t=1	No action required.
	Cambridge University Hospitals	Yes: published evidence on cost effectiveness has shown greater benefit in males with classic disease	Comment noted. Where evidence allows, the cost-effectiveness of the technology in relevant subgroups will be considered by the committee during appraisal.

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	Chiesi Limited	No subgroups of interest have been identified.	No action required.
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	Therapeutic indications and marketing authorisations has not be confirmed. Our understanding is that the treatment will be intended for adults (18 years and over) and we assume patients would be assessed against the current treatment guidelines for Fabry disease. https://bimdg.org.uk/site/guidelines-lsd.asp?t=1	No action required.
Comparators	Amicus	The comparators specified in the NICE final scope should reflect current clinical practice, the current UK treatment SOP,[1] and priorities set out in the UK Rare Disease Framework.[2] To achieve this two changes need to be made to the final scope: **1. BSC removed as a comparator in final scope** Since the introduction of ERTs in 2001, BSC is no longer prescribed for patients with treatable Fabry disease and as such should be removed from the final scope as a comparator. Communication with clinical experts indicates that the treatments for Fabry disease currently used in the NHS are documented in the UK Fabry treatment SOP[1]; this document, written by Fabry disease clinical experts, does not include BSC as a treatment option, hence its inclusion in the draft scope is not reflective of current clinical practice.[1] The inclusion of BSC in the draft scope represents a retrograde step in clinical management and does not align with the Rare Disease Framework which highlights the need to ensure access to innovative treatments for people with rare diseases.[2] **2. Migalastat removed as a comparator in final scope**	Comment noted. Following the consultation and scoping workshop, best supportive care has been removed as a comparator. Migalastat has been retained as a comparator for the amenable population, following confirmation from clinical experts at the scoping workshop that patients with an amenable mutation may be treated with either

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		The treatment options available for Fabry patients are dependent on whether the patient has a migalastat-amenable mutation. If a patient has the amenable mutation, they are usually treated with miglastat first line and then an ERT (either agalsidase alfa or agalsidase beta) second line. If the patient does not have the migalastat mutation then the first-line treatment is an ERT (either agalsidase alfa or agalsidase beta), and the second-line treatment is a different ERT (either agalsidase alfa or agalsidase beta). The patient cohort that migalastat can be prescribed for in the NHS in is clearly defined in the migalastat NICE guidance and the UK Fabry treatment SOP. As such, it is clear that migalastat is prescribed in a different patient cohort to ERTs and is not a direct comparator to pegunigalsidase; the final scope should be changed to reflect this. Furthermore, pegunigalsidase alfa is an ERT and as such it is expected that it will be another treatment option to current ERT therapies, agalsidase alfa and agalsidase beta, hence the ERTs are suitable comparators in the appraisal of pegunigalsidase alfa. 1. Hiwot T, Hughes D, Ramaswami U. BIMDG: Guidelines for the treatment of Fabry Disease 2020 [Available from: http://www.bimdg.org.uk/store/lsd//FabryGuide_LSDSS_Jan2020_700523_11032020.pdf (last accessed 1st September) 2. Department of Health and Social Care. The UK Rare Diseases Framework London: DHSC; 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950651/the-UK-rare-diseases-framework.pdf] (last accessed March 2022)	migalastat or enzyme replacement therapy. The population with amenable mutations has been defined as a separate subgroup.

Section	Consultee/ Commentator	Comments [sic]	Action
	Cambridge University Hospitals	Yes, however evidence in relation to best supportive care will be extremely limited	Comment noted. Following the consultation and scoping workshop best supportive care has been removed as a comparator.
	Chiesi Limited	PRX-102 will be offered as a treatment option for patients with symptomatic Fabry disease who would usually be offered ERT or migalastat in line with BIMDG guidelines, therefore the inclusion of best supportive care as a comparator is not appropriate, as these patients would always receive therapy in clinical practice. Chiesi agrees that the other comparators for this appraisal should be: • Agalsidase alfa • Agalsidase beta • Migalastat (for those aged over 16 years with an amenable mutation) Future treatments in Fabry disease, such as substrate reduction therapy (SRT) and gene therapy will not be available until late 2026 at the earliest, therefore are not appropriate to be considered within the appraisal.	Comment noted. Following the consultation and scoping workshop best supportive care has been removed as a comparator.
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	Appropriate	Comment noted. Following the consultation and scoping workshop best

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		It is our understanding that 2/3s of the population are receiving treatment (All males- equating to 1/3 of entire population and 1/3 of the remaining 2/3s of females). Both ERT's are used for treating all patients (children and adults) Migalastat is for those 16yrs and over with an amenable mutation Eligibility for treatment is assessed using the current treatment guidelines https://bimdg.org.uk/site/guidelines-lsd.asp?t=1 Best supportive care needs to be patient centric with a MDT approach. BSC includes; • Neuropathic pain management (pain crisis, pain in hands and feet, heat intolerance, impaired ability to sweat) • Management of GI symptoms (nausea, vomiting, diarrhoea, constipation, abdominal pain) • Dietary support • Management of skin (angiokeratomas) • Opthamology including cornea verticillara • Hearing (hearing loss, titannus, vertigo) • Bones and joints (osteoporosis) • Mental Health / psychological support (depression, anxiety) • Renal management Kidney transplants • Cardiac /vascular management interventions • TIA / Stroke management • Respiratory management / function	supportive care has been removed as a comparator. People with amenable mutations will be considered as a separate subgroup.

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		• Physical impact – Energy, fatigue, headaches / migraines / dizziness / loss of balance / mobility • Palliative care	
Outcomes	Amicus	All outcome measures specified in the draft scope are appropriate.	No action required.
	Cambridge University Hospitals	Ability to participate in education/work effectively Impact on mental health	Comment noted. Where relevant and appropriate, benefits associated with technologies but not fully captured by the clinical outcome or the economic model may be considered by the committee during appraisal.
	Chiesi Limited	Yes, the outcomes listed are appropriate. In addition, we expect there to be benefits to both patients and caregivers compared to agalsidase alfa and agalsidase beta due to the potential reduced dosing frequency of PRX-102 Q2W and Q4W dosing[7] and reduced immunogenicity and IRRs.[7-9] 7. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of BRIDGE Phase III Open-Label, Switch-Over Clinical Trial Evaluating Pegunigalsidase Alfa for the Treatment of Fabry Disease. 2020. (Updated: 30 December 2020) Available at: https://www.prnewswire.com/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-final-results-of-the-bright-phase-iii-	Comment noted. Health-related quality of life for patients and carers is one of the outcomes in scope. Where evidence allows, benefits associated with the technology in comparison with other treatments will be considered by the

Section	Consultee/ Commentator	Comments [sic]	Action
		clinical-trial-evaluating-prx-102-for-the-treatment-of-fabry-disease-301505728.html. Accessed: 20 April 2022. 8. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of the BRIGHT Phase III Clinical Trial Evaluating PRX-102 for the Treatment of Fabry Disease. 2022. (Updated: 18 March 2022) Available at: https://www.prnewswire.com/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-final-results-of-the-bright-phase-iii-clinical-trial-evaluating-prx-102-for-the-treatment-of-fabry-disease-301505728.html. Accessed: 20 April 2022. 9. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Topline Results from the 24-Month Phase III BALANCE Clinical Trial of PRX-102 for the Treatment of Fabry Disease. 2022. (Updated: 7 April 2022) Available at: https://www.chiesi.com/en/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-topline-results-from-the-24-month-phase-iii-balance-clinical-trial-of-prx-102-for-the-treatment-of-fabry-disease/. Accessed: 20 April 2022.	committee during appraisal.
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	GI management and outcomes have not been included. HRQofL impacts on patients have not been captured (as listed above)	Comment noted. Following the consultation and scoping workshop, GI issues have been added to the scope as an outcome. Health-related quality of life has already been

Section	Consultee/ Commentator	Comments [sic]	Action
			included as an outcome in the draft scope.
Equality	Amicus	Of particular importance, Amicus believe that the inclusion of BSC as a comparator in the appraisal is a retrograde step in clinical treatment and that its inclusion in the scope of the appraisal would significantly increase the risk of some eligible patients not having access to standard of care innovative medicines. Therefore, Amicus would like the priorities set out in the Rare Disease Framework published in January 2021[2] to be included in the appraisal and BSC to be removed as a comparator to ensure that any decision supports the improvement of Fabry patients' care and does not increase the inequity in care many people with Fabry disease face. 2. Department of Health and Social Care. The UK Rare Diseases Framework London: DHSC; 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950651/the-UK-rare-diseases-framework.pdf] (last accessed March 2022)	Comment noted. Following the consultation and scoping workshop, best supportive care has been removed as a comparator.
	Cambridge University Hospitals	No comment	No action required.
	Chiesi Limited	None identified.	No action required.
	Genetic Alliance UK	No comment.	No action required.

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	The MPS Society	Whilst the remit of this evaluation is targeted to adult patients, it is important to take into consideration the benefits of treating children and young people before onset of significant disease burden. We are concerned that the current STA process will block any new therapies being approved due to the inability of the process to review rare conditions with limited clinical and cost effectiveness data.	Comment noted. The remit of NICE is to assess the clinical- and cost-effectiveness of the technology within its marketing authorisation. As outlined in NICE's Process and Methods manual, "standard technology appraisals methods and processes are designed to be flexible and adaptable for all technologies and conditions. So, they are suitable for most technologies that treat rare conditions and small populations." No action required.
Other considerations	Amicus	None	No action required.
	Cambridge University Hospitals	No comment	No action required.
	Chiesi Limited	The BALANCE study, the first randomised head-to-head study comparing active treatments in patients with Fabry disease, has successfully met the	Comment noted. Where relevant and

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		primary endpoint, demonstrating that PRX-102 is non-inferior to agalsidase beta in the primary outcome of kidney function.[9] It also demonstrated a favourable tolerability and immunogenicity profile for PRX-102 compared with agalsidase beta over 24 months.[9] As such, a cost-comparison approach to the economic modelling and subsequent appraisal may also be appropriate, as part of a HST assessment of PRX-102. 9. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Topline Results from the 24-Month Phase III BALANCE Clinical Trial of PRX-102 for the Treatment of Fabry Disease. 2022. (Updated: 7 April 2022) Available at: https://www.chiesi.com/en/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-topline-results-from-the-24-month-phase-iii-balance-clinical-trial-of-prx-102-for-the-treatment-of-fabry-disease/. Accessed: 20 April 2022.	appropriate, evidence relating to the clinical- and cost-effectiveness of the technology will be considered by the committee during appraisal. No action required.
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	No comment.	No action required.
Questions for consultation	Amicus	The response to the following two questions is similar so the questions have been grouped together to avoid repetition • **Would patients currently having migalastat be eligible for pegunigalsidase alfa?**	Comment noted. Clinical input during the scoping workshop confirmed that people with amenable

Section	Consultee/ Commentator	Comments [sic]	Action
		• **For people with Fabry disease and amenable mutations, would pegunigalsidase alfa be used after migalastat, or as an alternative to migalastat in clinical practice?** As pegunigalsidase alfa is an ERT, it is expected it will not be used in the same patient cohort as migalastat; that is, in patients with the amenable mutation, in line with the UK treatment SOP.[1] Current clinical practice is aligned with the UK treatment SOP[1] and, for people with a confirmed diagnosis of Fabry disease and meeting treatment initiation criteria with a migalastat-amenable mutation, migalastat is the recommended first-line treatment.[1,3] In the non-amenable population, migalastat is not recommended and ERTs are the first-line treatment.[1] Data show very few patients in the amenable population who meet the NICE funding criteria are prescribed ERTs. **Where do you consider pegunigalsidase alfa will fit into the existing 'Endocrine, nutritional and metabolic conditions overview' NICE pathway'?** As pegunigalsidase alfa is an ERT, it is expected it will fit into the NICE pathway in the same way as the other two ERTs. **Have all relevant comparators for pegunigalsidase alfa been included in the scope?** As noted in the 'comparator' section to this response Amicus would like the following comparators removed from the scope of the appraisal. • **Best supportive care removed as a comparator in final scope** Since the introduction of ERTs in 2001, BSC is no longer prescribed for patients with treatable Fabry disease and as such should be removed from the final scope as a comparator. Communication with clinical experts	mutations may receive either ERT or migalastat. The clinical experts disagreed that 'very few' patients in the amenable population are prescribed ERTs, and said the decision of whether to take migalastat or ERT as 1st line therapy would be influenced by a range of factors (including disease severity and suitability for oral treatment). It was agreed that the amenable population should be considered as a subgroup, with both ERT and migalastat as 1st line therapy options.

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		indicates that the treatments for Fabry disease currently used in the NHS are documented in the UK Fabry treatment SOP[1]; this document, written by Fabry disease clinical experts, does not include BSC as a treatment option, hence its inclusion in the draft scope is not reflective of current clinical practice.[1] The inclusion of BSC in the draft scope represents a retrograde step in clinical management and does not align with the Rare Disease Framework which highlights the need to ensure access to innovative treatments for people with rare diseases.[2] • **Migalastat removed as a comparator in final scope** The treatment options available for Fabry patients are dependent on whether the patient has a migalastat-amenable mutation. If a patient has the amenable mutation, they are usually treated with migalastat first line and then an ERT (either agalsidase alfa or agalsidase beta) second line. If the patient does not have the miglastat mutation then the first-line treatment is an ERT (either agalsidase alfa or agalsidase beta), and the second-line treatment is a different brand of ERT (either agalsidase alfa or agalsidase beta). **How should best supportive care be defined?** As outlined in the comparator section of this response Amicus recommends that BSC is not included in this appraisal as a comparator as it is not routinely used in clinical practice to treat Fabry patients. As a consequence, it should not be required to define BSC in order to conduct this appraisal. **Which treatments are considered to be established clinical practice in the NHS for Fabry disease?** The treatment of Fabry patients is tightly defined and controlled through the UK treatment SOP (Hiwot 2020).[1] Current clinical practice is aligned with this	Best supportive care has been removed as a comparator. Informed by clinical input and BIMDG guidelines, migalastat will remain as a comparator for the subgroup with amenable mutations.

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		SOP, which is widely used in specialist centres to determine Fabry treatment. Aligned with the UK Fabry prescribing SOP,[1] eligible patients are treated with ERT or migalastat. Migalastat is the first-line treatment for people with a confirmed diagnosis of Fabry disease (aged 16 years-plus) with a migalastat-amenable mutation who meet treatment initiation criteria.[1,3] ERTs, agalsidase alfa and agalsidase beta, are the first-line treatment for people with a confirmed diagnosis of Fabry disease (aged 16 years-plus), and meeting treatment initiation criteria. As such, ERT is therefore a suitable comparator in the appraisal of pegunigalsidase alfa. ERT and migalastat are both commissioned routinely by NHS Highly Specialised Services and are both firmly embedded in clinical practice. **Are the outcomes listed appropriate?** Yes, the outcomes listed in the draft scope are appropriate. **What important benefits have the other enzyme replacement therapies currently in routine use (agalsidase alfa or agalsidase beta) and migalastat provided to people with the condition?** Migalastat was evaluated by NICE in 2017 (HST4),[3] and by the Scottish Medicines Consortium (SMC) as an ultra-orphan medicine in 2016.[4] As an oral therapy, migalastat addressed the limitations of ERT administration and so had additional benefits beyond direct health benefits. For this reason, NICE guidance reflected this benefit in its consideration of the innovativeness of migalastat and SMC recognised migalastat as a therapeutic advancement in the treatment of Fabry disease patients with amenable mutations.[3,4] Therefore, while ERT and migalastat are both standard of care therapies, in	

Section	Consultee/ Commentator	Comments [sic]	Action
		patients with amenable mutations, migalastat has distinct benefits over ERT,[2,5-51] which warrant its preferential use in these patients. 1. Hiwot T, Hughes D, Ramaswami U. BIMDG: Guidelines for the treatment of Fabry Disease 2020 [Available from: http://www.bimdg.org.uk/store/lsd//FabryGuide_LSDSS_Jan2020_700523_11032020.pdf (last accessed 1st September) 2. Department of Health and Social Care. The UK Rare Diseases Framework London: DHSC; 2021 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950651/the-UK-rare-diseases-framework.pdf] (last accessed March 2022) 3. National Institute for Health and Care Excellence (NICE). Migalastat for treating Fabry disease (HST4) Manchester: NICE; 2017 [Available from: https://www.nice.org.uk/guidance/hst4/resources/migalastat-for-treating-fabry-disease-pdf-1394900887237] (last accessed March) 4. Scottish Medicines Consortium. Migalastat, 123mg hard capsules (Galafold®) SMC No. (1196/16). Glasgow: SMC; 2016. 5. Amicus Therapeutics. Study to compare the efficacy and safety of oral AT1001 and enzyme replacement therapy in patients with Fabry disease. NCT01218659. In: ClinicalTrials.gov [Internet]. Bethesda (MD):National Library of Medicine (US). 2010 [accessed 7.5.19]. Available from: https://clinicaltrials.gov/ct2/show/NCT01218659) 6. Amicus Therapeutics. Open-label long-term safety study of AT1001 (migalastat hydrochloride) in participants with Fabry disease who have completed a previous AT1001 study. NCT00526071. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) 2007 [accessed 7.5.19] [updated September 17, 2007]. Available from: https://clinicaltrials.gov/show/NCT00526071)	

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		7. Amicus Therapeutics. Long-term safety study of AT1001 in people with Fabry disease. EUCTR2007-001838-13-GB. In: EU Clinical Trials Register [Internet]. London: European Medicines Agency 2007 [accessed 7.5.19] [updated 05/05/2009]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-001838-13) 8. Amicus Therapeutics. Study of the effects of oral AT1001 (migalastat hydrochloride) in patients with Fabry disease. NCT00925301. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) 2009 [accessed 7.5.19] [updated August 2009]. Available from: http://clinicaltrials.gov/show/NCT00925301) 9. Amicus Therapeutics. Open-label phase 3 long-term safety study of migalastat. NCT01458119. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US) 2011 [accessed 7.5.19] [updated October 14, 2011]. Available from: https://clinicaltrials.gov/show/NCT01458119) 10. Barisoni L, Jennette J, Colvin R, Skuban N, Castelli J. Migalastat reduces globotriaosylceramide (GL-3) inclusions in renal peritubular capillaries in patients with Fabry disease and migalastat-amenable mutations: post hoc analyses from FACETS. Poster presented at 15th Annual WORLD Symposium; 4-8 February 2019; Orlando (FL); 32. 2019. 11. Barlow C. Clinical results using a GLP-validated pharmacogenetic test identifies subjects responsive to migalastat HCl in the FACETS study. Presented at 10th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium; 10-14 February 2014; San Diego (CA). Molecular Genetics and Metabolism. 2014;111(2):S23. 12. Barlow C, Benjamin ER YJ, France N, Ludington E, Lockhart DJ. Phase 3 study (FACETS) of migalastat HCl for Fabry disease: post hoc GLA mutation-based identification of subjects likely to show a drug effect. Mol Genet Metab. 2014;111:S24.	

Section	Consultee/ Commentator	Comments [sic]	Action
		13. Benjamin ER, Hamler R, Brignol N, Boyd R, Yu J, Bragat A, et al. Migalastat reduces plasma globotriaosylsphingosine (lyso-Gb3) in Fabry patients: results from the FACETS phase 3 study. Presented at the Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); 2-5 September 2014; Innsbruck (Austria). Journal of Inherited Metabolic Disease. 2014;37(1 Suppl 1):S161. 14. Bichet DG, Barth JA, Williams H, Skuban N. Effect of long-term migalastat treatment on plasma globotriaosylsphingosine (lyso-Gb3) levels in patients with Fabry disease previously treated with enzyme replacement therapy: results from ATTRACT and open-label extension studies. Molecular Genetics and Metabolism. 2019;126:S31. 15. Bichet DG, Nicholls K, Giugliani R, Hughes DA, Sunder-Plassmann G, Krusinska E, et al. Poster LB-06. Migalastat Has a Low Incidence Rate of Composite Clinical Outcomes at Long-term Follow-up in Patients With Fabry Disease Who Previously Received Enzyme Replacement Therapy. 16th Annual WORLD Symposium; Orlando, FL2020. 16. Bichet DG, Germain DP, Giugliani R, Hughes D, Schiffmann R, Wilcox W, et al. Subjects treated with migalastat continue to demonstrate stable renal function in a phase 3 extension study of Fabry disease. Presented at American Society of Human Genetics (ASHG) Annual Meeting 2014; 18-22 October 2014; San Diego (CA). 2014. 17. Feldt-Rasmussen U, Giugliani R, Germain D, et al. Efficacy and safety of migalastat, an oral pharmacologic chaperone for Fabry disease: results from two randomized phase 3 studies, FACETS and ATTRACT. Podium presentation. Molecular Genetics and Metabolism. 2017;1:S45-S6. 18. Feldt-Rasmussen U, Hughes D, Sunder-Plassmann G, Shankar S, Olivotto I, Ortiz D, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 30-month results from the randomized phase 3 ATTRACT study. Molecular Genetics and Metabolism. 2019;126:S53.	

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		19. Germain D, Giugliani R, Bichet D, et al. Efficacy of migalastat in a cohort of male patients with the classic Fabry phenotype in the FACETS phase 3 study. Mol Genet Metab. 2017(120):S52. 20. Germain D, Nicholls K, Bichet D, et al. Efficacy of migalastat in a cohort of male patients with the classic Fabry phenotype in the FACETS phase 3 study. American College of Medical Genetics and Genomics; Phoenix, AZ2017. 21. Germain D, Nicholls K, Wilcox W, et al. Effects of treatment with migalastat on the combined endpoint of kidney globotriaosylceramide accumulation and diarrhea in patients with Fabry disease: results from the phase 3 FACETS study. American College of Medical Genetics and Genomics; Prescott, AZ2017. 22. Germain D, Nicholls K, Wilcox W, Holdbrook F, Barth J, Schiffmann R. Effects of migalastat on the combined endpoint of kidney globotriaosylceramide accumulation and diarrhea in patients with Fabry disease In FACETS. Presented at the American College of Medical Genetics and Genomics (ACMG) Annual Clinical Genetics Meetin 2017; 21-25 March 2017; Prescott (AZ). American College of Medical Genetics Annual Clinical Genetics Meeting 2017. 2017. 23. Germain DP, Schiffmann R, Jovanovic A, et al. Cardiac outcomes with long-term migalastat treatment in patients with Fabry disease: results from phase 3 trials (Poster LB-18). Presented at the 14th Annual WORLD Symposium February 5-9, 2018; San Diego, CA2018. 24. Germain DP, Bichet D, Giugliani R, Hughes D, Schiffmann R, Wilcox W, et al. Treatment with migalastat results in reduced levels of disease substrate and stable renal function in a phase 3 study of Fabry disease. Presented at the Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM): 2-5 September 2014; Innsbruck (Austria). Journal of Inherited Metabolic Disease. 2014;37(1 Suppl 1):S43.	

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		25. Germain DP, Bichet DG, Giugliani R, Hughes D, Schiffmann R, Wilcox W, et al. Subjects treated with migalastat continue to demonstrate stable renal function and reduced left ventricular mass index over 3 years in a long-term extension study of Fabry disease. Presented at the Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); 1-4 September 2015; Lyon (France). Journal of Inherited Metabolic Disease. 2015;38((1 Supppl 1):S56. 26. Germain DP, Bichet DG, Giugliani R, Hughes DA, Schiffmann R, Wilcox W, et al. Subjects treated with migalastat demonstrate stable renal function, reduced left ventricular mass and gastrointestinal symptom improvement in phase 3 and a long-term extension study of Fabry disease. Presented at European Society of Human Genetics (ESHG) Conference; 6-9 June 2015; Glasgow (UK). 2015. 27. Germain DP, Giugliani R, Pastores GM, Nicholls K, Shankar S, Schiffmann R, et al. Long-term safety of migalastat HCl in patients with Fabry disease. Presented at the American Society of Human Genetics (ASHG) Annual Meeting 2012; 6-10 November 2012; San Francisco (CA). 2012. 28. Germain DP, Hughes DA, Nicholls K, Bichet DG, Giugliani R, Wilcox WR, et al. Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat. New England Journal of Medicine. 2016;375(6):545-55. 29. Germain DP, Nicholls K, Giugliani R, Bichet DG, Hughes DA, Barisoni LM, et al. Efficacy of the pharmacologic chaperone migalastat in a subset of male patients with the classic phenotype of Fabry disease and migalastat-amenable variants: data from the phase 3 randomized, multicenter, double-blind clinical trial and extension study. Genet Med. 2019;21(9):1987-97. 30. Hughes D, Nicholls K, Shankar S, et al. Response of patients with Fabry disease with the amenable GLA mutation p.N215S to treatment with migalastat (ATTRACT study). American College of Medical Genetics and Genomics; Phoenix, AZ2017.	

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		31. Hughes D, Bichet DG, Giugliani R, Schiffmann R, Wilcox WR, Benjamin E, et al. Long-term efficacy and safety of migalastat compared to enzyme replacement therapy in Fabry disease: phase 3 study results. Presented at 11th Annual Research Meeting of the Lysosomal Disease Network, WORLDSymposium; 9-12 February 2015; Orlando (FL). Molecular Genetics and Metabolism. 2015;114(2):S57. 32. Hughes DA, Nicholls K, Germain DP, Shankar SP, Sunder-Plassmann G, Bichet DG, et al. Response of patients with Fabry disease with the amenable GLA mutation p.N215S to treatment with migalastat. Molecular Genetics and Metabolism. 2017;120(1):S68-S9. 33. Hughes DA, Nicholls K, Shankar SP, Sunder-Plassmann G, Koeller D, Nedd K, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J Med Genet. 2017;54(4):288-96. 34. Hughes DA, Nicholls K, Sunder-Plassmann G, Jovanovic A, Feldt-Rasmussen U, Schiffmann R, et al. Safety of switching to Migalastat from enzyme replacement therapy in Fabry disease: Experience from the Phase 3 ATTRACT study. Am J Med Genet A. 2019;179(6):1069-73. 35. Jovanovic A, Schiffmann R, Nicholls K, et al. Improvements in Cardiac Mass With Long-Term Migalastat Treatment in Patients With Fabry Disease: Results From Phase 3 Trials (Abstract LBN 02). 13th International Congress of Inborn Errors of Metabolism; Rio de Janeiro, Brazil 2017. 36. Lourenco C, Schiffmann R, Nicholls K, Bichet DG, Feldt-Rasmussen U, Hughes D, et al. Long-term migalastat treatment stabilizes renal function in patients with Fabry disease: results from a phase 3 clinical study (at1001-041). Presented at the 13th International Congress on Inborn Errors of Metabolism (ICIEM); 5-8 September 2017; Rio De Janeiro (Brazil). Journal of Inborn Errors of Metabolism and Screening. 2017;5:357.	

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		37. Narita I, Ohashi T, Sakai N, Hamazaki T, Skuban N, Castelli JP, et al. Efficacy and safety of migalastat in a Japanese population: a subgroup analysis of the ATTRACT study. Clin Exp Nephrol. 2020;24(2):157-66. 38. Nicholls K, Feliciani C, Shankar S, Ezgu F, Janmohamed SG, Laing SM, et al. Phase 3 study of migalastat HCl for Fabry disease: stage 1 results. Presented at American Society of Human Genetics (ASHG) Annual Meeting 2012; 6-10 November 2012; San Francisco (CA). 2012. 39. Nicholls K, Germain DP, Feliciani C, Shankar S, Ezgu F, Janmohamed SG, et al. Phase 3 study of migalastat HCl for Fabry disease: Stage 1 results. Presented at the 9th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium; 13-15 February 2013; Orlando (FL). Molecular Genetics and Metabolism. 2013;108(2):S70. 40. Nicholls K, Giugliani R, Schiffmann R, Hughes D, Jain V, Holdbrook F, et al. Renal outcomes with up to 9 years of migalastat in patients with Fabry disease: results from an open-label extension study. Poster presented at 14th Annual WORLD Symposium; 5-9 Feb 2018; San Diego (CA); 270. 2018. 41. Nicholls K, Olivotto I, Ohashi T, Williams H, Jain V, Skuban N. The effects of long-term migalastat treatment in patients with Fabry disease who have migalastat-amenable variants with relatively low alpha-galactosidase A response in the in vitro migalastat amenability assay. Poster presented at 15th Annual WORLD Symposium; 4-8 Feb 2019; Orlando (FL); 256. 2019. 42. Schiffmann R, Bichet D, Hughes D, et al. Migalastat improves gastrointestinal signs and symptoms in patients with Fabry disease: patient-level responder analyses from the double-blind, placebo-controlled phase 3 trial (FACETS). 13th Annual WORLD Symposium; San Diego, CA 2017. 43. Schiffmann R, Bichet DG, Aerts JM, Skuban N, Mehta AB. Lyso-Gb3 Is Not a Predictive Biomarker of Treatment Response in Migalastat-treated Patients with Migalastat-amenable Variants (Poster 372). 16th Annual WORLD Symposium; February 10-13; Orlando, FL 2020.	

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		44. Schiffmann R, Bichet D, Germain D, Giugliani R, Hughes D, Nicholls K, et al. Effects of long-term migalastat treatment on renal function by baseline proteinuria in patients (PTS) with Fabry disease. Presented at 55th Annual Congress of the European Renal Association-European Dialysis and Transplant Association, ERA-EDTA; 24-27 May 2018; Copenhagen (Denmark). Nephrology Dialysis Transplantation. 2018;33(Suppl 1):i346-7. 45. Schiffmann R, Bichet DG, Germain DP, Giugliani R, Hughes DA, Wilcox W, et al. Improvement in gastrointestinal symptoms observed in the phase 3 FACETS (AT1001-011) study of migalastat in patients affected with Fabry disease. Presented at 11th Annual Research Meeting of the Lysosomal Disease Network, WORLD Symposium; 9-12 February 2015; Orlando (FL). Molecular Genetics and Metabolism. 2015;114(2):S103-4. 46. Schiffmann R, Bichet DG, Hughes D, Giugliani R, Wilcox W, Shankar SP, et al. Migalastat improves gastrointestinal symptoms in patients with Fabry disease: results from a double-blind, placebo-controlled phase 3 trial (FACETS). Presented at the Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM); 6-9 September 2016; Rome (Italy). Journal of Inherited Metabolic Disease. 2016;39(Suppl 1):S218. 47. Schiffmann R, Bichet DG, Jovanovic A, Hughes DA, Giugliani R, Feldt-Rasmussen U, et al. Migalastat improves diarrhea in patients with Fabry disease: clinical-biomarker correlations from the phase 3 FACETS trial. Orphanet Journal of Rare Diseases. 2018;13(1):68. 48. Schiffmann R, Hughes D, Bichet DG, Wilcox WR, Holdbrook F, Viereck C, et al. Effects of treatment with migalastat on the combined endpoint of kidney globotriaosylcermide accumulation and diarrhea in patients with Fabry disease: results from the phase 3 facets study. Presented at the 13th International Congress on Inborn Errors of Metabolism (ICIEM); 5-8 September 2017; Rio De Janeiro (Brazil). Journal of Inborn Errors of Metabolism and Screening. 2017;5:358-9.	

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		49. Sunder-Plassmann G, Jovanovic A, Feldt-Rasmussen U, Jain V, Peceny M, Skuban N, et al. Clinical outcomes after switching to migalastat from agalsidase alfa or agalsidase beta in patients with Fabry disease: Post hoc analysis from ATTRACT. Molecular Genetics and Metabolism. 2019;126:S141. 50. Sunder-Plassmann G, Shankar S, Wilcox W, Nicholls K, Giugliani R, Lagast H, et al. Occurrence of cerebrovascular events during long-term treatment with migalastat in patients with Fabry disease. Poster presented at 15th Annual WORLD Symposium; 4-8 Feb 2019; Orlando (FL); LP-49. 2019. 51. Torra R, Germain D, Bichet D, Schiffmann R, Yu J, Castelli J, et al. Clinical outcomes with migalastat in patients with Fabry disease based on degree of renal impairment: results from phase 3 trials. Presented at 55th Annual Congress of the European Renal Association-European Dialysis and Transplant Association, ERA-EDTA; 24-27 May 2018; Copenhagen (Denmark). Nephrology Dialysis Transplantation. 2018;33(Suppl 1):i346.	
	Cambridge University Hospitals	**Would patients currently having enzyme replacement therapy be eligible for pegunigalsidase alfa?** Yes **Would patients currently having migalastat be eligible for pegunigalsidase alfa?** Yes **Are there people with Fabry disease who are not currently having enzyme replacement therapy or migalastat for whom pegunigalsidase alfa could be considered?** No	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Would pegunigalsidase alfa be used after other enzyme replacement therapies, or as an alternative to enzyme replacement therapies in clinical practice? Both **For people with Fabry disease and amenable mutations, would pegunigalsidase alfa be used after migalastat, or as an alternative to migalastat in clinical practice?** Both **Other questions for discussion at the meeting**	
	Chiesi Limited	*Would pegunigalsidase alfa be a candidate for managed access?* PRX-102 is being studied in a comprehensive clinical trial programme which will provide substantial clinical data in patients previously treated with ERTs and in treatment naïve patients. BALANCE being a pivotal phase III randomised controlled trial and is the first head-to-head study comparing active treatments in patients with Fabry disease, and provides 24-month data in 78 adult patients, so a requirement for managed access and further data collection is not anticipated. *What important benefits have the other enzyme replacement therapies currently in routine use (agalsidase alfa or agalsidase beta) and migalastat provided to people with the condition?* There is no cure for Fabry disease, and prior to the launch of ERT in 2001, people with Fabry disease only received palliative care. ERTs have demonstrated significant benefits and reductions in fatigue and	Comment noted. Following the consultation and scoping workshop it was decided that this topic will be appraised via single technology appraisal process. The extent to which the technology may or may not be innovative will be considered in any appraisal of the technology. Where relevant and appropriate, health-related benefits not fully captured in QALY

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		gastrointestinal symptoms for patients with Fabry disease and young adults with Fabry disease expect to have better disease outcomes than older generations due to access to ERT from a much earlier age.[1] Migalastat the most recently approved treatment for Fabry disease, provides an additional treatment option but only for patients over 16 years with an amenable mutation. Current ERTs have short circulatory half-lives and sub-optimal dose regimens, leading to limited efficacy and continuous disease progression in patients, including deterioration in renal function,[4]and induce the production of neutralizing ADAs, which can limit efficacy and prevent long-term clinical benefit.[5, 6] Therefore, there is still a clear unmet need for a new treatment for Fabry disease that provides sustained efficacy, without inducing an immune response or infusion-related reactions. *Do you consider pegunigalsidase alfa to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* As described above, PRX-102 was granted an Innovation Passport in 2021 by the MHRA meeting all of the following criteria: (1) the condition is life-threatening or seriously debilitating; (2) the program is intended for a rare disease or special population; and (3) the medicine has the potential to offer benefits to patients. The longer half-life of PRX-102 may allow for reduced immunogenecity and a reduced frequency of infusions every 4 weeks when compared with current ERTs' infusion schedule of every 2 weeks, whilst maintaining similar efficacy.[4, 7]	calculation may be considered by the committee during appraisal.

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		Do you consider that the use of pegunigalsidase alfa can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? The reduced infusion burden of the option of Q4W dosing schedule of PRX-102 for some patients may improve the productivity and social lives of both patients and carers when compared with current ERTs which are dosed Q2W. *Is there any reason to evaluate this as a Multiple Technology Appraisal (MTA) Process?* Chiesi strongly believes that it is entirely inappropriate for PRX-102 to be evaluated under an MTA. As described above, PRX-102 is a treatment for an orphan condition, and due to the unique challenges of evidence generation in rare diseases, should not be assessed under the standard methods for technology appraisal, whether single or multiple. An MTA would be even more challenging in a rare disease such as Fabry due to the heterogeneous nature of the small trial populations in clinical trials. There is a recognised lack of robust data in Fabry disease, which is an essential requirement to perform the indirect treatment comparisons or meta-analyses involved in MTAs. In HST4, an indirect treatment comparison of migalastat and ERTs was deemed unfeasible for these reasons.[1] Finally, an MTA involves a lengthy HTA process, longer than that of HST, which would delay patient access to this innovative therapy, and would contradict the award of the Innovation Passport and ILAP which is designed to accelerate access of these treatments to patients in the UK.	

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		1. National Institute for Health and Care Excellence (NICE). Migalastat for treating Fabry disease: Highly specialised technologies guidance. 2017. (Updated: 22 February 2017) Available at: https://www.nice.org.uk/guidance/hst4/chapter/1-Recommendations. Accessed: 20 April 2022. 4. Kizhner T, Azulay Y, Hainrichson M, et al. Characterization of a chemically modified plant cell culture expressed human alpha-Galactosidase-A enzyme for treatment of Fabry disease. *Mol Genet Metab*. 2015; 114(2):259-67. 5. Hollak CE and Linthorst GE. Immune response to enzyme replacement therapy in Fabry disease: impact on clinical outcome? *Mol Genet Metab*. 2009; 96(1):1-3. 6. Lenders M, Hennermann JB, Kurschat C, et al. Multicenter Female Fabry Study (MFFS) - clinical survey on current treatment of females with Fabry disease. *Orphanet journal of rare diseases*. 2016; 11(1):88-. 7. Chiesi Group. Protalix BioTherapeutics and Chiesi Global Rare Diseases Announce Final Results of BRIDGE Phase III Open-Label, Switch-Over Clinical Trial Evaluating Pegunigalsidase Alfa for the Treatment of Fabry Disease. 2020. (Updated: 30 December 2020) Available at: https://www.prnewswire.com/news-releases/protalix-biotherapeutics-and-chiesi-global-rare-diseases-announce-final-results-of-the-bright-phase-iii-clinical-trial-evaluating-prx-102-for-the-treatment-of-fabry-disease-301505728.html. Accessed: 20 April 2022.	
	Genetic Alliance UK	No comment.	No action required.

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	The MPS Society	It is our understanding that depending on licensing stipulations, pegunigalsidase would be considered as a treatment option for adults following the current treatment guidelines. Appropriate treatment pathways would be in discussion between patient and clinician. It is our understanding that as not all data has been released from the clinical trials, it is not possible to answer the question in respect of switching patients Current UK treatment pathways, determine eligibility and assessment criteria for starting, monitoring and stopping treatment. Patients with clinical support and guidance choose the treatment most appropriate to them. Treatment helps prevent / delay disease progression with positive outcomes seen in both the kidneys and heart if caught early enough. Patients report Q of L improvements in areas such as pain (fewer or less frequent pain crisis, less pain in hands and feet), improved stamina and activity levels, headaches / migraines / GI symptoms, ability to sweat / better temperature control. Clinical Currently without costs being available, It is unclear whether patients treated at the extended treatment protocol of every 4 weeks would provide greater value for money compared to those treated every two weeks. We do anticipate a potential cost saving in homecare costs if treated every four weeks.	Thanks for the comment. The positioning of the technology in the treatment pathway, as well as its clinical and cost-effectiveness, will be considered and appraised by the committee during the appraisal. Stakeholders will be invited to submit evidence and statements and all will be considered.

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		Initial findings from the clinical trials indicates that pegunigalsidase has a longer circulating half-life compared to standard ERT's and that the rate of developing neutralizing AD antibodies may be less than current ERT's.	
Additional comments on the draft scope	Amicus	None	No action required.
	Cambridge University Hospitals	None	No action required.
	Chiesi Limited	None	No action required.
	Genetic Alliance UK	No comment.	No action required.
	The MPS Society	No comment	No action required.

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

n/a