National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Arimoclomol for treating Niemann-Pick disease Type C ID1312

Response to consultee and commentator comments on the draft remit and draft scope

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Great Ormond Street Hospital NHS Trust	This topic is appropriate for referral to NICE for evaluation under the HST process.	Thank you for your comment. No action needed.
	Niemann-Pick UK	We support the referral of this topic to NICE for evaluation.	Thank you for your comment. No action needed.
	Orphazyme	Yes. It would be appropriate to refer this topic to NICE for evaluation.	Thank you for your comment. No action needed.
	Birmingham Women's and Children's NHSFT	Yes this is entirely appropriate. This is a potential high cost drug for an ultra-rare disease and therefore clearly falls into the remit of the NICE HST process.	Thank you for your comment. No action needed.

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	Salford Royal Foundation NHS Trust	Yes	Noted
Wording	Great Ormond Street Hospital NHS Trust	The wording is appropriate.	Thank you for your comment. No action needed.
	Niemann-Pick UK	We agree with the remit as drafted	Thank you for your comment. No action needed.
	Orphazyme	Yes. The remit wording is appropriate.	Thank you for your comment. No action needed.
	Birmingham Women's and Children's NHSFT	Yes	Noted
	Salford Royal Foundation NHS Trust	Yes	Noted
Timing Issues	Great Ormond Street Hospital NHS Trust	This evaluation should be undertaken as promptly as possible to determine if this important treatment option will be made available.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing

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			authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Niemann-Pick UK	NPC imposes a major burden upon patients, their families, health services and society. NPC is a progressive neurodegenerative disease consequently access to effective therapies are time critical. It would be unethical to delay this evaluation.	Thank you for your comment. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted.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.
	Orphazyme	Urgent, given the seriousness of this disease and the unmet needs of patients.	Thank you for your comment. 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

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			programme. No action needed.
	Birmingham Women's and Children's NHSFT	It is appropriate to be scoping this now as Phase 3 data have just been published and a new drug application has been filed with FDA /EMA. There are patients in England who have been taking part in clinical trials of arimoclomol for NPC and there remains an unmet need for better therapies for this condition.	Thank you for your comment. 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.
	Salford Royal Foundation NHS Trust	Newer therapies are eagerly awaited which may address some of these unmet needs with the current licenced treatment	Thank you for your comment. 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.

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Additional comments on the draft remit	Orphazyme	No additional comments	Comment noted

Comment 2: the draft scope

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Background information	Great Ormond Street Hospital NHS Trust	For clarity, the two subtypes NPC1 and NPC2 are due to various mutations in two different genes (not “different gene mutations”). It should be emphasised that NPC is a progressive neurodegenerative disorder; the various symptoms described are not “static” but would be expected to deteriorate and worsen over time. As described current treatment is multidisciplinary supportive management plus miglustat. Supportive management will include physiotherapy, medication for control of seizures, feeding support (due to dysphagia) that may include gastrostomy feeding, occupational therapy, ophthalmology.	Thank you for your comment. The background section has been amended in line with the comment.
	Niemann-Pick UK	Adequate	Noted
	Orphazyme	The background information is accurate except for one point – narcolepsy is not a symptom – it should be cataplexy.	Thank you for your comment. This has been updated.
	Birmingham Women’s and	This is mostly accurate. It captures the clinical heterogeneity of the disorder although maybe suggests that there is a distinct “children” and “adult” form of the disease whereas there is in reality a continuous spectrum. Some patients may be diagnosed as children (eg with cholestasis and splenomegaly) but	Thank you for your comment. No change to the scope required.

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	Children's NHSFT	then remain neurologically stable for many years into adolescence and even adulthood. The statement "patients with neurological onset early in life deteriorate faster and have a shorter life expectancy than those with adult onset" is mostly true but there can be patients who may develop ophthalmoplegia earlier in life and then have a long gap before developing cognitive impairment.	
	Salford Royal Foundation NHS Trust	Difficulty with swallowing or unsafe swallowing is one of the important features as the disease progresses particularly in adults. This leads to needs of PEG feeding as a part of supportive management. Unfortunately majority of adult patients die due to aspiration pneumonia	Thank you for your comment. The background section has been amended in line with the comment.
The technology/ intervention	Great Ormond Street Hospital NHS Trust	Arimoclomol is an inducer of the Heat Shock Protein system that increases the molecular chaperone systems within "stressed" cells. The "technology" (Arimoclomol) would be used in addition to current supportive care and together with miglustat in patients treated with this drug.	Thank you for your comment. The technology section has been amended in line with the comment.
	Niemann-Pick UK	No Comments	Noted
	Orphazyme	The description of the technology is accurate.	Thank you for your comment. No change to the scope required.
	Birmingham Women's and Children's NHSFT	It should be emphasised in this description that (1) arimoclomol is a small molecule able to cross the blood-brain barrier and (2) the mechanism of action of HSP70 proteins is not just thought to be that of a chaperone protein assisting with protein misfolding but also protective effects within the cell and	Thank you for your comment. The technology section has been amended.

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		especially on the lysosomes (eg reversing lysosome aggregation, preventing membrane permeabilisation and stress-induced cell death) This dual mechanism of action is relevant to consider as although treatment effects may be expected to be better in patients with missense mutations, there is still a rationale to explore its use in patients with one or two null mutations.	
	Salford Royal Foundation NHS Trust	Yes	Noted
Population	Great Ormond Street Hospital NHS Trust	The population described includes all patients (paediatric and adult) diagnosed with NPC. This is appropriate.	Thank you for your comment. No change to the scope required.
	Niemann-Pick UK	NP-C is a complex disease involving a combination of visceral, neurological and psychiatric symptoms. It is commonly classified according to the age of onset of neurological symptoms, although patients do not fit neatly into each group.: (Patterson et al,2 Geberhiwot et al 2018). Niemann-Pick disease type C subgroups: Pre-/Perinatal period (< 2 months) Early infantile period (2 months < 2 years) Late infantile period (2 years < 6 years) Juvenile (classical) (6 years to 15 years) Adolescent and adult (>15 years)	Thank you for your comment. The subgroups have been amended and now include subgroups defined by severity at onset.

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	Orphazyme	Yes. The population is defined appropriately. There are no sub-groups that should be considered separately.	Thank you for your comment. No change to the scope required.
	Birmingham Women's and Children's NHSFT	The population just states "children and adults with NPC". Clinical trials have only been performed in patients with neurological symptoms of NPC to my knowledge and the approval of Miglustat also specifies only patients with neurological symptoms. This is relevant because patients may be diagnosed in childhood who may not develop neurological symptoms for many years and to date it is not proven whether starting treatment presymptomatically improves outcome. I would suggest that the population is restricted to "children and adults with one or more neurological symptoms of NPC".	Thank you for your comment. The population in the scope is intended to be broad 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.
Comparators	Great Ormond Street Hospital NHS Trust	"Best alternative care" would currently include holistic supportive care +/- miglustat, and the comparator should be this (rather than comparing miglustat versus arimoclomol).	Thank you for your comment. The comparators have been updated in line with the comment.
	Niemann-Pick UK	Miglustat plus holistic care. Evidence shows miglustat works synergistically with arimoclomol, increasing patient benefit. If clinically appropriate, the most effective patient care would be a combination of both therapies.	Thank you for your comment. The comparators have been updated in line with the comment.

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	Orphazyme	Suggest changing to: Established clinical management including miglustat where appropriate.	Thank you for your comment. The comparators have been updated in line with the comment.
	Birmingham Women's and Children's NHSFT	Yes – Miglustat and supportive care would be considered "best alternative care" currently. Other therapeutic agents (cyclodextrins) are in clinical trials but cannot be considered standard care at present	Thank you for your comment. The comparators have been updated in line with the comment.
	Salford Royal Foundation NHS Trust	Yes	Noted
Outcomes	Great Ormond Street Hospital NHS Trust	The outcomes described in broad terms cover the important outcome domains. Specific measures/ scales/ assessments that would be able to quantify these outcomes would need to be established. There are NPC specific severity scales already in use. It is important that changes in the defined outcome measures compared to what would be expected with "best standard care" is assessed. A positive outcome may be improvement, stabilisation, or less-severe deterioration in some of these domains.	Thank you for your comment. The list of outcomes is not exhaustive, and the company may submit evidence of additional outcomes if they deem these relevant. The list has been updated to included swallowing.
	Niemann-Pick UK	Therapeutic goals should be clearly listed in line with clinical guidelines on standards of care and consideration given as to how to monitor change over time.	Thank you for your comment. The list of outcomes is not exhaustive, and the

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		Swallow is an important component and should be included. Consider use of the NPC 5 domain Severity Scoring Scale - ambulation, speech, cognition, swallow, fine motor - acknowledged by patients as being most important to address. Ref: Cortina-Borja M, Te Vruchte D, Mengel E, et al. Annual severity increment score as a tool for stratifying patients with Niemann-Pick disease type C and for recruitment to clinical trials. Orphanet J Rare Dis. 2018;13(1):143. Published 2018 Aug 16. doi:10.1186/s13023-018-0880-9	company may submit evidence of additional outcomes if they deem these relevant. The list has been updated to included swallowing.
	Orphazyme	The outcomes listed capture the most important health related benefits of the technology, with the exception of liver. While arimoclomol may influence liver function, it was seen as a diagnostic element rather than a disease defining condition and was not collected in the study. Given the multisystem nature of NPC disease, there are a number of other potential outcome measures, of which liver function is one example, that may be relevant but were not collected in the study. This should be a topic for discussion with the clinical experts in the scoping workshop.	Thank you for your comment. The list of outcomes is not exhaustive, and the company may submit evidence of additional outcomes if they deem these relevant. The list has been updated to included swallowing.
	Birmingham Women's and Children's NHSFT	I think these capture the most important health related benefits. It would be important to state that mortality would not be an important measure to focus on as studies have not really been long enough to detect a change in mortality. Also NPC has been shown to be associated with an increased incidence of Crohns Disease (including Very Early Onset Crohns Disease –VEOCD – which considerably affects quality of life) It would be useful to see if there is evidence to show whether arimoclomol impacts the incidence of this	Thank you for your comment. The list of outcomes is not exhaustive, and the company may submit evidence of additional outcomes if they deem these relevant. The list has been updated to included swallowing.

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		complication (especially as some of those patients may require additional high cost agents such as infliximab)	
	Salford Royal Foundation NHS Trust	Yes	Noted
Equality and Diversity	Great Ormond Street Hospital NHS Trust	No specific comments.	Noted
	Niemann-Pick UK	No issue identified	Noted
	Orphazyme	Orphazyme are not aware of any material equality issues.	Thank you for your comment. No change to the scope required.
	Birmingham Women's and Children's NHSFT	No concerns here	Noted
	Salford Royal Foundation NHS Trust	The clinic trial looked at the age up to 18y: Does it mean that a separate trial will be required for the adult diagnosed patients? Or the adult patients won't be eligible for this treatment if does prove to be effective in children	Thank you for your comment. No change to the scope required.

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Other considerations	Great Ormond Street Hospital NHS Trust	Sub-analysis by genotype: given the heterogeneous genotype (multiple mutations within NPC1 and NPC2 genes) it is unlikely that sufficient evidence for any one genotype would be available. More relevant may be analysis by severity of disease at baseline (I.e. appraisal in most severe infantile forms versus slower progressive adult forms)	Thank you for your comment. The subgroups have been amended in line with the comment.
	Niemann-Pick UK	Careful consideration to be given to the management of patients currently receiving arimoclomol post trial and in the period leading up to and post the NICE appraisal decision process.	Thank you for your comment. The appraisal committee will take this into account in its decision making. No change to the scope required.
	Orphazyme	No additional issues to raise.	Noted
	Birmingham Women's and Children's NHSFT	No additional issues recommended	Noted
Innovation	Great Ormond Street Hospital NHS Trust	Despite the treatment with miglustat, NPC remains a disorder that is progressive and causes significant morbidity and mortality. This technology has the potential to provide an additive benefit for this patient cohort.	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which arimoclomol is an innovative technology

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			when making its recommendations. No action needed.
	Niemann-Pick UK	Arimoclomol works by an entirely novel method and has been shown to be effective in NPC, a disease in which it is incredibly difficult to demonstrate clinical efficacy in the timescale of a trial, Furthermore, it has been shown to have synergistic benefits with Miglustat and as an oral therapy, arimoclomol does not require additional medical support, such as home care support to enable use. Arimoclomol has significant potential to make an impact on health outcomes for NPC patients	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which arimoclomol is an innovative technology when making its recommendations. No action needed.
	Orphazyme	Yes. We consider the technology to be a step-change for patients with NPC given its innovative mechanism of action which operates on a cellular level and its potential to impact significantly and substantially on both quality and length of life of NPC patients.	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which arimoclomol is an innovative technology when making its recommendations. No action needed.
	Birmingham Women's and	Yes – this is an innovative product and has applications outside of just this one condition. Given the noninvasive nature of the treatment (oral) it has the potential to be widely taken up by the patient population with good	Thank you for your comment. During the development of the

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	Children's NHSFT	compliance and has the potential to significantly alter the disease course for this devastating illness. Whether we have sufficient data already to answer this is for the committee to consider of course.	appraisal, the committee will consider the degree to which arimoclomol is an innovative technology when making its recommendations. No action needed.
	Salford Royal Foundation NHS Trust	The current means of therapy is not entirely satisfactory. Quite a few of the adult patients have come off miglustat as they have not found it much helpful. New therapy does offer a step change in the management	Thank you for your comment. During the development of the appraisal, the committee will consider the degree to which arimoclomol is an innovative technology when making its recommendations. No action needed.
Questions for consultation	Great Ormond Street Hospital NHS Trust	**How is arimoclomol expected to be used in clinical practice?** It would be expected to be used in all eligible patients and commenced early in the treatment pathway; with all these treatments it would be optimal to start early in the disease course. It would be expected to be used as an adjunct to miglustat in those patients already on this drug. **Have all relevant comparators for arimoclomol been included in the scope?**	Comments noted. Please refer to the related responses above.

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		- **Which treatments are considered established clinical practice in the NHS for NPC1 and NCP2? Are there any a differences?** As above, treatment is supportive management +/- miglustat - **Is miglustat used in clinical practice? And in which patients?** Yes, for patients with neurological progression as per guidelines. - **What supportive care options are considered for people with NPC?** Comments as above **Are the outcomes listed appropriate? Are there any other outcomes that should be included in the scope?** - **Would arimoclomol be expected to affect non-neurological aspects of NPC, such as liver function?** Arimoclomol would be expected to have systemic effect (not just neurological), although the main clinical problems in NPC are the neurological components (rather than liver dysfunction). **Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money?** - **Is it relevant to explore subgroups for types of NPC?** See comments above - **Should any or other groups be examined separately?**	

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		See comments above	
	Niemann-Pick UK	NPUK supports 107 patients affected by NPC. Arimoclomol therapy should be offered to patients as a first line therapy in combination with Miglustat, if clinically appropriate. Arimoclomol should be considered in all patients diagnosed with NPC Miglustat is the first line therapy for NPC patients Although NPC 2 represents 5% of the patient population it is clinically indistinguishable from NPC1 and has the different treatment option of BMT, distinct from NPC1. NPC is a complex multi system progressive disease. Supportive care may include management of psychiatric and psychological features (including dementia, psychosis and mood disorders), neurological complications (including epilepsy, dystonia, cataplexy), respiratory, hepatic, gastroenterological and musculoskeletal complications. In addition, it may involve the input of allied health services such as dieticians, SLT, (including referrals for Percutaneous feeding), physiotherapy, occupational therapy, wheelchair and mobility services. There is often a need for significant social and educational support, this may include the need for input from educational psychology, specialist schools, and support with access to learning, employment and housing.	Comments noted. These aspects will be considered further in evidence submission and by the appraisal committee.
	Orphazyme	**How many people have NPC in England, and how many would be offered Arimoclomol therapy?** • We estimate there to be around 120 patients of which we expect around 80% to be eligible for treatment with arimoclomol. Incidence and	Comment noted. These aspects will be considered further in evidence submission

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		prevalence figures are being calculated using currently available data and clinical expert opinion. **How is arimoclomol expected to be used in clinical practice?** **Is arimoclomol expected to be used as a monotherapy or an add on therapy in combination with miglustat?** • Arimoclomol is expected to be used as backbone therapy for NPC treatment due to its favourable adverse event profile. It is expected to be used in conjunction with current standard of care including miglustat where appropriate. **At what point in the treatment pathway would arimoclomol be considered?** • All eligible newly diagnosed patients will be considered for arimoclomol, as well as patients receiving best standard of care including miglustat where appropriate. **Is miglustat used in clinical practice? And in which patients?** • Yes, in about 80% of all patients with or without other supportive care. **Would arimoclomol be expected to affect non-neurological aspects of NPC, such as liver function?** • Yes, due to NPCs systemic disease pathology and the action of arimoclomol on a cellular level, an effect is possible but was not investigated in the trial **Which treatments are considered established clinical practice in the NHS for NPC1 and NCP2? Are there any differences?** • There are a wide range of treatments which make up established clinical practice. All patients undergo clinical assessments in	and by the appraisal committee.

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		specialist centres and treatment and care is determined by clinicians based on the full range of disease and patient-specific factors. There are no treatment differences between NPC1 and NPC 2 **What supportive care options are considered for people with NPC?** • There are a wide variety including speech training, physiotherapy, psychological therapy, work and school support, as well as various drug treatments to prevent and treat symptoms. Patients may receive up to 10 different supportive care treatments. Supportive care options and how patients access these are well defined by multi-disciplinary teams working at each of the specialist centres.	
	Birmingham Women's and Children's NHSFT	**How many people have NPC in England, and how many would be offered arimoclomol therapy?** This will vary across centres but NHSE should have data for patients currently receiving Miglustat and I would expect anyone eligible for Miglustat would be offered arimoclomol if appropriate **How is arimoclomol expected to be used in clinical practice?** **- Is arimoclomol expected to be used as a monotherapy or an add on therapy in combination with miglustat?** At present probably an add-on as there have not been many Miglustat-naïve patients included in arimoclomol trials and evidence suggests that the effect of arimoclomol is in addition to/independent from any Miglustat effect. This may well be an option for future clinical trials however. **At what point in the treatment pathway would arimoclomol be considered?**	Comment noted. These aspects will be considered further in evidence submission and by the appraisal committee.

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		I think based on current data for children it would be considered at the onset of neurological symptoms in combination with Miglustat given the more rapid disease course. For adults it may be offered after a period of Miglustat therapy to patients intolerant of Miglustat and/or showing disease progression despite Miglustat. **Have all relevant comparators for arimoclomol been included in the scope?** **- Which treatments are considered established clinical practice in the NHS for NPC1 and NCP2? Are there any a differences?** Correct in the remit **Is miglustat used in clinical practice? And in which patients?** Yes – currently offered to most English patients at the onset of neurological symptoms in NPC. Very early onset NPC expected to show very rapid deterioration of neurological symptoms already advanced at diagnosis may not be offered Miglustat (or may have stricter stopping criteria applied) **What supportive care options are considered for people with NPC?** Supportive care is for symptom control. Physiotherapy and mobility aids for ataxia – and subsequently wheelchair provision and home adaptations. Enteral feeding tubes when bulbar dysfunction affects swallowing. Anticonvulsant medications for seizures. Sometimes imipramine/amitryptilline for cataplexy. Surgical treatments including scoliosis surgery. Input of palliative care services **Are the outcomes listed appropriate? Are there any other outcomes that should be included in the scope?** **- Would arimoclomol be expected to affect non-neurological aspects of NPC, such as liver function?**	

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		Theoretically yes it should impact on disease anywhere where lysosomal dysfunction occurs. However liver function is variable in NPC – many infants with cholestasis have a self-resolving cholestasis which does not lead to chronic liver disease (a small minority have rapidly progressive liver failure). So the underlying issues in liver disease are not completely understood. Most patients with NPC die from their neurological complications with near normal liver function at the time of death. As described above it would be good to know if arimoclomol had any effect on the incidence of Crohns disease in this group of patients at higher risk. **Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money?** **- Is it relevant to explore subgroups for types of NPC?** **- Should any or other groups be examined separately?** The very early onset neurological NPC patients may simply progress too quickly for any oral agent to impact on significantly. It might be appropriate to consider this group separately as a potential group to be excluded from the treatment indication – clinical trials have been reported based on neurological symptoms >4yrs of age.	
Additional comments on the draft scope	Orphazyme	No	Noted
	Salford Royal Foundation NHS Trust	I would expect the new technology to be offered as first line therapy. It is unlikely that treatment would be of much benefit in advanced disease. Managed Access agreement would be the right path for this treatment and other already licensed treatment as well	Thank you for your comment. No change to scope required.

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

Metabolic Support UK