National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Response to consultee and commentator comments on the draft remit, draft scope (pre-referral) and provisional matrix

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Royal Free Hospital LSD Unit	Yes	Thank you for your comment. No changes to the scope required.
	Gauchers Association	Yes	Thank you for your comment. No changes to the scope required.
	NHS England	Yes. This is a competitor for the existing very expensive enzyme replacements therapies.	Thank you for your comment. No changes to the scope required.
	Genzyme Therapeutics	Yes	Thank you for your comment. No changes to the scope required.
	Royal Free London NHS Foundation Trust	This draft remit addresses an important and timely issue for the therapy of patients with Gaucher disease.	Thank you for your comment. No changes to the scope required.
Wording	Royal Free Hospital LSD Unit	Yes	Thank you for your comment. No action required.
	Gauchers Association	No Comment	Thank you for your comment. No action required.
	NHS England	Yes	Thank you for your comment. No action required.
	Genzyme Therapeutics	Yes, the wording of the draft remit is appropriate.	Thank you for your comment. The

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		We note that the scope refers to the evaluation relating to National Commissioning in NHS England. We would comment that should the NICE HST process be extended to provide guidance to NHS Wales (as is the case for NICE Single and Multiple Technology Appraisals) than that extension should be reflected in the scope and span of the final recommendations.	remit of NICE is to provide guidance on the use of highly specialised technologies in the context of national commissioning by NHS England only, and therefore recommendations cannot be extended to NHS Wales. No action required.
Timing Issues	Royal Free Hospital LSD Unit	The intervention is likely to be approved by FDA and EMEA in 2014 so the timing is appropriate.	Thank you for your comment. NICE aims to schedule evaluations into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to publish guidance within 6 months of a technology receiving its marketing authorisation in the UK or becoming commercial available in the UK (if this is significantly later than the marketing authorisation). No changes to the scope required.
	Gauchers Association	To ensure that once the product is licensed by the EMA that patients do not have to wait too long to be able to access it.	Thank you for your comment. NICE aims to schedule evaluations into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to publish guidance within 6 months of a technology receiving its marketing authorisation in the UK or becoming commercial available in the UK (if this is significantly later than the marketing authorisation). No changes to the scope required.
	NHS England	This drug may offer substantial savings over current therapy and is for that reason urgent.	Thank you for your comment. NICE aims to schedule evaluations into the

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			work programme to provide timely guidance to the NHS. Where possible, NICE aims to publish guidance within 6 months of a technology receiving its marketing authorisation in the UK or becoming commercial available in the UK (if this is significantly later than the marketing authorisation). No changes required.
	Shire	This technology should be evaluated after a positive CHMP opinion in line with NICE HSTE process.	Thank you for your comment. NICE aims to schedule evaluations into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to publish guidance within 6 months of a technology receiving its marketing authorisation in the UK or becoming commercial available in the UK (if this is significantly later than the marketing authorisation). No changes to the scope required.
	Genzyme Therapeutics	We believe that NHS national commissioning will need to receive timely guidance on eliglustat to inform commissioning decisions and the place of this new therapy in current treatment pathways.	Thank you for your comment. NICE aims to schedule evaluations into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to publish guidance within 6 months of a technology receiving its marketing authorisation in the UK or becoming commercial available in the UK (if this is significantly later than the marketing authorisation). No changes to the scope required.

Section	Consultees	Comments	Action
	Royal Free London NHS Foundation Trust	Impending market authorisation of this oral alternative for patients with Gaucher disease	Thank you for your comment. NICE aims to schedule evaluations into the work programme to provide timely guidance to the NHS. Where possible, NICE aims to publish guidance within 6 months of a technology receiving its marketing authorisation in the UK or becoming commercial available in the UK (if this is significantly later than the marketing authorisation).No changes to the scope required.
Additional comments on the draft remit	Gauchers Association	Gaucher's should be Gaucher Disease throughout the document.	Thank you for your comment. "Gaucher's disease" has been amended to "Gaucher disease" throughout the scope.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Charles Dent Metabolic Unit, UCLH	This is not entirely accurate. The second sentence is unclear: Gaucher is caused by a deficiency of glucocerebrosidase which leads to storage of complex lipids. The estimate for the number of people affected in England and Wales also seems too low to me: we do have a significant Ashkenazi population which may put the numbers up.	Thank you for your comment. The background information in the scope is only intended to provide a brief summary of the nature of the condition and current management options. More detailed information, including epidemiological estimates for England will be included in the evidence submissions from consultees during the course of the evaluation. The

Section	Consultees	Comments	Action
			background section of the scope has been amended slightly for clarity in line with some comments received during consultation.
	Royal Free Hospital LSD Unit	Adequate	Thank you for your comment. No action required.
	Gauchers Association	The overall frequency should be 1 in 50,000 to 1 in 100,000 and the frequency in Ashkenazi family origin should be 1 in 500 to 1 in 1,000. Miglustat is licensed for Type 1 Gaucher Disease.	Thank you for your comment. The incidence estimates in the background section of the scope have been amended in line with the suggested changes. More detailed epidemiological estimates for England will be included in the evidence submissions from consultees during the course of the evaluation.
	NHS England	No comment	Thank you for your comment. No action required.
	Genzyme Therapeutics	We would suggest that the following wording would more accurately reflect the background of the disease *"Gauchers disease is an inherited lysosomal storage disorder. It is caused by a deficiency of an enzyme (glucocerebrosidase) which is essential in the degradation of glucocerebroside, a complex lipid. Failure to be degraded causes the lipid to build up in certain types of cells, which become abnormal (Gaucher cells) and which are seen throughout the liver, spleen, bone marrow, and occasionally the lungs. There are 3 subtypes of Gauchers disease, of which type 1 (non-neuronopathic) is the most prevalent. All types of Gauchers disease are associated with a variety of*	Thank you for your comment. The background information in the scope is only intended to provide a brief summary of the nature of the condition and current management options. More detailed information will be included in the evidence submissions from consultees during the course of the evaluation. The background section of the scope has been amended slightly for clarity in line with comments received from consultees during consultation.

Section	Consultees	Comments	Action
		symptoms, including pain, fatigue, anaemia, thrombocytopenia, jaundice, bone damage and pain, and enlargement of the liver and spleen. *There is limited data available on the epidemiology of Gauchers disease. Over 90% of people affected have type 1 Gauchers Disease. The overall frequency of all types of Gauchers disease is approximately 1 in 40,000 to 1 in 50,000 live births. The prevalence of type 1 Gaucher's disease is estimated as 1 in 200,000 in non-Ashkenazi Jewish Europeans, which equates to approximately 250 people in England and Wales. It is more common in people of Ashkenazi Jewish origin, with a frequency of approximately 1 in 450 live births.* *Treatment of Gauchers disease requires an individualised approach that begins with a comprehensive multi-systemic assessment of all possible disease manifestations to accurately classify disease burden. Current management options include enzyme replacement therapy (such as imiglucerase or velaglucerase alfa) or substrate reduction therapy (miglustat) for people for whom enzyme replacement therapy is not suitable (i.e., not a first-line treatment), alongside supportive therapy (which may include blood products, bisphosphonate therapy and/or analgesia)".*	
	Royal Free London NHS Foundation Trust	Specify enzyme replacement therapy with imiglucersase or velaglucerase is intravenous infusion administered every 2 weeks in the hospital or home by patient, relative or home care team.	Thank you for your comment. Specific details about current management options, including the route of administration and dosage of enzyme replacement therapies, will be presented in the evidence submissions from consultees during the course of the evaluation. No change to the scope

Section	Consultees	Comments	Action
			required.
The technology/ intervention	Charles Dent Metabolic Unit, UCLH	Eliglustat and miglustat both act by a mechanism called substrate reduction therapy (SRT). In SRT the aim is to reduce the level of synthesis of the storage molecule, in this case glucosyl ceramide, to a level where the patient's residual enzyme activity is able to digest the remaining substrate and reverse storage. There is extensive medical literature on SRT in LSDs and the term should certainly be included here.	Thank you for your comment. The term 'substrate reduction therapy' has been included in the description of the technology in the scope. More detailed information about the technology and the comparator treatments will be included in the evidence submission from the manufacturer and other consultees, and will be considered by the Evaluation Committee during the course of the evaluation.
	Royal Free Hospital LSD Unit	Yes	Thank you for your comment. No action required.
	Gauchers Association	No comment	Thank you for your comment. No action required.
	NHS England	Yes	Thank you for your comment. No action required.
	Shire	The technology should be described as a 'Substrate reduction therapy' There is limited available information about the long term downstream impact of the SRT mechanism of action. The study populations in SRT were limited to adults over 16 years of age. We note that treating children with SRT is not routine practice in the UK.	Thank you for your comment. The term 'substrate reduction therapy' has been included in the description of the technology in the scope. More detailed information about the technology will be included in the evidence submission from the manufacturer and other consultees and will be considered by the Evaluation Committee during the course of the evaluation. The technology will only be evaluated

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			within its licensed indication.
	Genzyme Therapeutics	The description of the technology in the 1st paragraph would be more accurately worded as follows, to differentiate the mode of action from existing ERT's and miglustat: *"Eliglustat is a novel SRT. Its mechanism of action, partial inhibition of the enzyme glucosylceramide synthase, is entirely distinct from that of the ERTs commonly used to treat GD1 (augmenting acid-α-glucosidase activity). Eliglustat is a highly selective and potent inhibitor of glucosylceramide synthase (McEachern, 2007, Mol Genet Metab). While eliglustat and the approved SRT, miglustat, share the same target enzyme (glucosylceramide synthase), their chemical structures, molecular properties and pharmacological effects are quite distinct.* *Miglustat resembles the glucose moiety of GL-1, whereas eliglustat is similar in structure to the ceramide moiety. The structural differences convey an approximately 1500 fold greater affinity of eliglustat for the target enzyme with much greater specificity. Eliglustat shows little or no inhibition of glycosidases, with no measurable inhibition of glycosidases and digestive disaccharidases (McEachern, 2007, Mol Genet Metab).* *These properties translate into an entirely different risk-benefit ratio and resulting therapeutic efficiency. Whereas the dose and duration of dosing with miglustat is limited by gastro-intestinal adverse events and severe neuropathy which is often found to be irreversible, this has not been the case with eliglustat, which has been shown in clinical trials to be suitable for long term dosing*	Thank you for your comment. The description in the scope is only intended to provide a brief overview of the technology. More detailed information about the technology, including its mechanism of action, will be included in the evidence submission from the manufacturer and other consultees, and will be considered by the Evaluation Committee during the course of the evaluation. The term 'substrate reduction therapy' has been included in the description of the technology in the scope.

Section	Consultees	Comments	Action
		at levels which allow comparable therapeutic efficacy to enzyme replacement therapy as measured by all efficacy parameters. *In view of these factors it is appropriate to think of eliglustat as either a different class of therapy to miglustat or an entirely different generation of compound even though they are both inhibitors of the same enzyme."*	
	Royal Free London NHS Foundation Trust	Studies in naïve patients and those who have previously received imiglucerase.	Thank you for your comment. The scope has been amended to specify that eliglustat has been studied in people who have and have not previously received enzyme replacement therapy.
Population	Royal Free Hospital LSD Unit	This intervention should exclude children and pregnant females. It should be restricted to type 1 Gaucher adults.	Thank you for your comment. The technology will only be evaluated within its licensed indication.
	Gauchers Association	No comment	Thank you for your comment. No action required.
	NHS England	It may be worth considering separately symptomatic (present clinically) and asymptomatic (family case finding) patients	Thank you for your comment. The population in the scope has been amended to 'Adults with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers' in line with the marketing authorisation.
	Shire	The population should be: Adults with Type 1 Gaucher Disease for whom ERT is unsuitable.	Thank you for your comment. The technology will only be evaluated within

Section	Consultees	Comments	Action
			its licensed indication and has accordingly been amended to: 'Adults with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers'
	Genzyme Therapeutics	The population should be based on the proposed licenced indication (see planned indication for technology section).	Thank you for your comment. The technology will only be evaluated within its licensed indication. The population in the scope has been amended to 'Adults with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers' in line with the marketing authorisation .
	Royal Free London NHS Foundation Trust	It may be appropriate to specify people with type 1 Gaucher disease exhibiting clinical manifestations of the condition (as there are a proportion of patient who are asymptomatic).	Thank you for your comment. The population in the scope has been amended to 'Adults with type 1 Gaucher disease who are CYP2D6 poor metabolisers, intermediate metabolisers or extensive metabolisers' in line with the marketing authorisation.
Comparators	Charles Dent Metabolic Unit, UCLH	Yes. However, for eliglustat, miglustat should really be the direct comparator as they both work by the same mechanism. Miglustat is only licensed for those for whom ERT is unsuitable as it is less efficacious than ERT.	Thank you for your comment. At the Scoping Workshop, consultees agreed that eliglustat is likely to be used in clinical practice at the same point in the treatment pathway as enzyme replacement therapy (that is, first-line) or as a second line treatment instead of miglustat (substrate reduction

Section	Consultees	Comments	Action
			therapy) in patients for whom enzyme replacement therapy (imiglucerase or velaglucerase) is unsuitable. Therefore, imiglucerase, velaglucerase alfa and miglustat were considered to be the most appropriate comparators. No change to the scope required.
	Royal Free Hospital LSD Unit	These are the appropriate comparators; velaglucerase and imiglucerase were found equivalent in a recent study.	Thank you for your comment. No action required.
	Gauchers Association	Miglustat is for Type 1	Thank you for your comment. At the Scoping Workshop, it was agreed that eliglustat is likely to be used in clinical practice at the same point in the treatment pathway as enzyme replacement therapy (that is, first-line) or as a second line treatment instead of miglustat (substrate reduction therapy) in patients for whom enzyme replacement therapy is unsuitable. Therefore, imiglucerase, velaglucerase alfa and miglustat were considered to be the most appropriate comparators. No change to the scope required.
	NHS England	The comparators are correctly described.	Thank you for your comment. No action required.
	Shire	The technology should be compared to all the currently licensed and funded therapies for Gaucher Disease type 1 available on the NHS in England, and should be considered as a second line therapy.	Thank you for your comment. At the Scoping Workshop, it was agreed that eliglustat is likely to be used in clinical practice at the same point in the

Section	Consultees	Comments	Action
			treatment pathway as enzyme replacement therapy (that is, first-line) or as a second line treatment instead of miglustat (substrate reduction therapy) in patients for whom enzyme replacement therapy is unsuitable. Therefore, imiglucerase, velaglucerase alfa and miglustat were considered to be the most appropriate comparators. No change to the scope required.
	Genzyme Therapeutics	The ERTs listed (imiglucerase and velaglucerase alfa) are appropriate comparators. However, we do not believe that miglustat should be included as a comparator as follows: • The proposed label and likely clinical positioning for eliglustat would position it as an oral first line alternative to Enzyme Replacement Therapies (imiglucerase and velaglucerase alfa). • In contrast the Summary of Product Characteristics for miglustat (Zavesca) states that (see section 4.1 – Indications) *"Zavesca is indicated for the oral treatment of adult patients with mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable (see sections 4.4 and 5.1)".* • Similarly current national commissioning guidance on the management of Adult Gaucher Disease state that *"Miglustat remains a second line agent for patients unable or unwilling to take enzyme therapy"* (SOP for Adult Gauchers	Thank you for your comment. At the Scoping Workshop, it was agreed that eliglustat is likely to be used in clinical practice at the same point in the treatment pathway as enzyme replacement therapy (that is, first-line) or as a second line treatment instead of miglustat (substrate reduction therapy) in patients for whom enzyme replacement therapy is unsuitable. Therefore, imiglucerase, velaglucerase alfa and miglustat were considered to be the most appropriate comparators. No change to the scope required.

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		Disease available at http://www.specialisedservices.nhs.uk/document/10024 Accessed 21/11/2013) • Further, a European consensus statement, recognizing that both imiglucerase and miglustat were licensed for the treatment of Gaucher disease, reviewed their therapeutic status and developed consensus guidelines for the use of this oral agent as a second-line agent in patients with mild-to-moderate Gaucher disease who are unable or unwilling to take enzyme therapy (Cox, Aerts et al. 2003). The positioning of miglustat is reflected in the small proportion of patients who are reported to be on this therapy. A recent UK longitudinal cohort study (Wyatt et al) showed that of 150 Gaucher diagnosed adults recruited to the study, 11 were not on ERT, 131 were on ERT and 8 on SRT (miglustat). (see page 79-80, Wyatt, K., W. Henley, et al. (2012). "The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders." Health Technol Assess **16**(39): 1-543).	
Outcomes	Charles Dent Metabolic Unit, UCLH	The NSS SOP for Gaucher disease describes all of the therapeutic goals in detail and I would suggest the clinical outcomes are explicitly related to this document, which is the standard of care in England and Wales.	Thank you for your comment. At the Scoping Workshop, it was agreed that the outcome 'type 1 Gaucher disease therapeutic goals' would encompass the Adult Gaucher Disease Standard Operating Procedures developed by the National Specialist Commissioning team in 2012. No change to the scope

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			required.
	Royal Free Hospital LSD Unit	The Gaucher 'Goals' does not include QoL and this should be assessed; alongside impact on blood counts, organ volumes and bone health	Thank you for your comment. Health related quality of life for patients and carers is included as an outcome in the scope. At the Scoping Workshop, it was agreed that the outcome 'type 1 Gaucher disease therapeutic goals' would encompass the Adult Gaucher Disease Standard Operating Procedures (including blood counts, organ volumes and bone health) developed by the National Specialist Commissioning team in 2012. No change to the scope required.
	Gauchers Association	The therapeutic goals should be clearly listed in line with the 2012 National Specialised Commissioning Advisory Group UK national guidelines for adult Gaucher disease.	Thank you for your comment. At the Scoping Workshop, it was agreed that the outcome 'type 1 Gaucher disease therapeutic goals' would encompass the Adult Gaucher Disease Standard Operating Procedures developed by the National Specialist Commissioning team in 2012. No change to the scope required.
	NHS England	Yes	Thank you for your comment. No action required.
	Shire	Given the lifelong need for therapy is enough known about the long term data on efficacy and safety?	Thank you for your comment. The Committee will consider any available evidence on long term efficacy and safety of eliglustat during the evaluation. Long term benefits of

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			treatment will also be estimated in the manufacturer's economic model. No action required.
	Genzyme Therapeutics	Yes the outcome measures listed are appropriate.	Thank you for your comment. No action required.
	Royal Free London NHS Foundation Trust	Outcomes should be consistent with those monitored in patients receiving the comparators according to NHS England Gaucher SOP and could be summarised by achievement of 'Goals of therapy' (Pastores et al 2004) however in practise these are individualised according to starting criteria.	Thank you for your comment. At the Scoping Workshop, it was agreed that the outcome 'type 1 Gaucher disease therapeutic goals' would encompass the Adult Gaucher Disease Standard Operating Procedures developed by the National Specialist Commissioning team in 2012. No change to the scope required.
Nature of condition	Charles Dent Metabolic Unit, UCLH	The current standard of care with ERT has transformed the lives of patients with Gaucher disease: imiglucerase and velaglucerase are highly efficacious.	Thank you for your comment. No action required.
	Royal Free Hospital LSD Unit	Current treatment options are fairly good but there are unmet needs and the new intervention could potentially meet some of them.	Thank you for your comment. A detailed description of the nature of the condition and current treatment options, including unmet need, will be included in the evidence submissions from the manufacturer and other consultees during the course of the evaluation. This information will be considered by the Evaluation Committee. No change to the scope required.
	Gauchers Association	No comment	Thank you for your comment. No

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			action required.
	Shire	The symptoms of Gaucher disease are well managed by the current standard of care (ERT). The current standard of care (ERT, replacing the deficient enzyme) provides a physiologically rational and effective therapy for the symptoms of the disease. The mode of action of SRT is to block a second enzyme and the physiological effects are unclear.	Thank you for your comment. A detailed description of the nature of the condition and current treatment options will be included in the evidence submissions from the manufacturer and other consultees during the course of the evaluation. This information will be considered by the Evaluation Committee. No change to the scope required.
	Genzyme Therapeutics	Gaucher disease is associated with a significant burden to patients and caregivers. Gaucher disease is an autosomal recessive lysosomal storage disorder caused by acid beta-glucosidase (glucocerebrosidase or glucosylceramidase) deficiency. The progressive accumulation of its substrates in the liver, spleen, bones, lungs, and other vital tissues results in a wide spectrum of disease severity (Beutler and Grabowski 2006). Clinical manifestations of the disease are multisystemic and clinically heterogeneous (Mistry, Sadan et al. 2007). Early disease manifestations can be “silent,” and Gaucher disease often goes undiagnosed, resulting in progressive, debilitating, and often life-threatening visceral, haematological, and skeletal manifestations (Beutler and Grabowski 2006; Mistry, Sadan et al. 2007; Andersson, Kaplan et al. 2008; Balwani, Fuerstman et al. 2010). Generally, three clinical subtypes of Gaucher disease are recognized: type 1 (non-neuropathic), type 2 (acute neuropathic), and type 3 (subacute/chronic neuropathic)	Thank you for your comment. A detailed description of the nature of the condition and current treatment options will be included in the evidence submissions from the manufacturer and other consultees during the course of the evaluation. This information will be considered by the Evaluation Committee. No change to the scope required.

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		(Grabowski, Kolodny et al. 2006). Type 1 Gaucher disease is the most common subtype in the US, Canada, and Europe, representing approximately 94% of the Gaucher disease population and is differentiated from types 2 and 3 by the absence of primary central nervous system involvement (Grabowski, Kolodny et al. 2006; Kaplan, Baris et al. 2012). The clinical hallmarks of type 1 Gaucher disease include enlargement and dysfunction of the liver and spleen, hematologic abnormalities, displacement of normal bone marrow by lipid-engorged storage cells (Gaucher cells), and bone damage leading to bone infarctions and fractures (Grabowski, Kolodny et al. 2006). Skeletal manifestations are the major source of morbidity and disability in patients with type 1 Gaucher disease; bone complications include chronic bone pain, bone crises, fractures, avascular necrosis (AVN), and loss of bone mineral density (BMD) leading to osteopenia and osteoporosis (Weinreb, Barranger et al. 2007; Khan, Hangartner et al. 2012). Patients with untreated type 1 Gaucher disease typically have a poor quality of life (QoL), and delays in treatment can result in suboptimal clinical outcomes (Mistry, Sadan et al. 2007; Weinreb, Barranger et al. 2007; Mistry, Deegan et al. 2009). In the UK current 1st line treatment options are Enzyme Replacement Therapy (imiglucerase and velaglucerase alfa) and the Substrate Reduction Therapy miglustat, which is a second line treatment for adult patients where ERT is unsuitable (see above). Supportive therapy is indicated for patients who decline ERT/SRT, but who require symptomatic supportive intervention with blood products, bisphosphonate therapy, and/or analgesia.	

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		Goals of therapy and the evidence base for treatment are summarised in the current national commissioning guidance on the management of Adult Gaucher (SOP for Adult Gauchers Disease available at http://www.specialisedservices.nhs.uk/document/10024 Accessed 21/11/2013)	
	Royal Free London NHS Foundation Trust	Patients receiving enzyme replacement therapy with the comparators show improvement in Goals of therapy to varying disease. Morbidity is experienced in terms of bone disease, clinical effects of anaemia (fatigue) and thrombocytopenia (bleeding) and long term complications including increased rates of malignancy, gall stones, glucose intolerance, pulmonary hypertension. There is reduction of quality of life particularly in relation to bone disease. Impact of regular intravenous infusions on quality of life should be recognised.	Thank you for your comment. A detailed description of the nature of the condition and the effectiveness of current treatment options will be included in the evidence submissions from the manufacturer and other consultees during the course of the evaluation. This information will be considered by the Evaluation Committee. No change to the scope required.
Cost to the NHS and Personal Social Services, and Value for Money	Charles Dent Metabolic Unit, UCLH	It is unlikely that this technology will have equal let alone superior efficacy or safety to ERT. The benefit lies in the fact that it is given orally and not by intravenous infusion, which may be more acceptable to patients and involve some savings for health services.	Thank you for your comment. The Committee will consider the clinical effectiveness of eliglustat and the value for money it represents compared with existing treatments during the course of the evaluation. No change to the scope required.
	Royal Free Hospital LSD Unit	Cost is not yet determined so cannot comment on the incremental benefit. If this intervention is more expensive than ERT then yes, there will be an impact on budgets.	Thank you for your comment. The Committee will consider the potential budget impact of eliglustat during the course of the evaluation. No change to the scope required.
	Gauchers Association	No comment.	Thank you for your comment. No

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			action required.
	NHS England	This technology should substitute for one of the enzyme replacement therapies and so have no impact on the budget available for specialised commissioning, or provide a saving.	Thank you for your comment. The Committee will consider the potential budget impact of eliglustat during the course of the evaluation. No change to the scope required.
	Shire	Given the lifelong need for therapy is enough known about the long term data on efficacy and safety? Real world compliance rates with oral therapy in chronic conditions tend to decline over time and could lead to a lack of efficacy, whereas compliance with ERT is very high. As an SRT, close neurologic follow-up is recommended due to possible complications such as peripheral neuropathy and cognitive decline, which is not the case with ERT.	Thank you for your comment. The Committee will consider the evidence on long term efficacy and safety, compliance and need for monitoring during the course of the evaluation. No change to the scope required.
	Genzyme Therapeutics	In terms of the incremental benefit of this technology we would anticipate a health related quality of life benefit associated with the use of an oral product compared with continual biweekly ERT infusion. Compared with ERTs, eliglustat is likely to provide productive efficiency gains due to its oral route of delivery. Current first line ERTs are administered by intravenous infusion every 2 weeks. In addition to the service delivery costs and impacts of providing patients with biweekly infusions, the requirement for infusions can be burdensome and inconvenient to patients and caregivers, requiring time off work and placing limits on travel and independence.	Thank you for your comment. The Committee will consider the evidence on the potential benefits of eliglustat's mode of administration compared to the mode of administration of current treatment options during the course of the evaluation. No change to the scope required.

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	Royal Free London NHS Foundation Trust	Data thus far publically presented suggests comparable efficacy to the existing products. The drug is orally administered and will be administered with improved convenience to Gaucher patients. The rate of new diagnosis of Gaucher patients on an annual basis is low (less than 5%). Most patients receiving the new technology are therefore likely to be patients currently receiving enzyme replacement therapy with the comparators. Depending on relative price of eliglustat this is likely to represent a saving to the NHS special commissioning as home care infusion costs will not be required.	Thank you for your comment. The Committee will consider the clinical effectiveness of eliglustat and the value for money it represents compared with existing treatments during the course of the evaluation. No change to the scope required.
Impact of the technology beyond direct health benefits, and on the delivery of the specialised services	Royal Free Hospital LSD Unit	Benefits as listed in the document could be achieved. No staffing or infrastructure requirements. Current treatments are given by home care with saving of VAT; important to preserve this.	Thank you for your comment. The Committee will consider any non-health related benefits of eliglustat and its impact of the delivery of the specialised service during the evaluation process. No change to the scope required.
	Gauchers Association	No comment	Thank you for your comment. No action required.
	NHS England	As this is an oral therapy, staffing and infrastructure costs should be less than for ERT.	Thank you for your comment. The Committee will consider the impact of eliglustat on the delivery of the specialised service during the evaluation process. No change to the scope required.
	Shire	This technology is a second to market Substrate Reduction Therapy (SRT).	Thank you for your comment. No change to the scope required.

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	Genzyme Therapeutics	As an oral alternative to ERT, Eliglustat provides an opportunity for service re-design in relation to opportunities to disinvest or use resources for alternative NHS activity in current IV pharmacy compounding and infusion services required to support patients on biweekly ERT infusions. As a very rare disease there is a limited data set on cost associated with Gaucher Disease both internationally and within the UK. In the UK, Wyatt et al., *2012*, collected health- and social-care service-use data using a well-established questionnaire that was completed by patients or caregivers. However, the questionnaire was not modified to include disease specific questions (for example, services related specifically to ERT infusions). Unit costs were then applied to the resource use profiles to derive estimates for the mean annual NHS costs per patient (excluding medications). This study estimated the mean annual cost of care per adult GD patient to be £3000, of which four-fifths were as a result of hospital services, approximately half (£1200 per patient per year) were from outpatient, and about a third (£830) from inpatient stays. Overall, 17% of the adults who provided valid service-use data reported inpatient stays (23 patients); however this accounted for more than one-third of the hospital costs. Separately the study reported the breakdown of NHS and social services costs outside the NHS hospital setting, reporting a median annual cost for other nurses or health visitors at £2100 and for home helps at £2,800 per year, indicating that costs are significant outside the hospital setting and outside the NHS and PSS.	Thank you for your comment. The Committee will consider the impact of eliglustat on the delivery of the specialised service during the course of the evaluation. No change to the scope required.

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		Wyatt, K., W. Henley, et al. (2012). "The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders." Health Technol Assess **16**(39): 1-543	
	Royal Free London NHS Foundation Trust	Home Care infusion nurses will not be required.	Thank you for your comment. The Committee will consider the impact of eliglustat on the delivery of the specialised service during the course of the evaluation. No change to the scope required.
Equality and Diversity	Royal Free Hospital LSD Unit	No issues identified.	Thank you for your comment. No action required.
	Gauchers Association	No comment.	Thank you for your comment. No action required.
	Genzyme Therapeutics	No comments.	Thank you for your comment. No action required.
Innovation	Charles Dent Metabolic Unit, UCLH	The technology may have a useful role to play if it can provide a comparable effect to ERT at a much lower cost. A truly efficacious and safe oral therapy would be a step change.	Thank you for your comment. Consultees are encouraged to describe the innovative nature of eliglustat in their evidence submissions. The Committee will consider this information during the evaluation process. No change to the scope required.
	Royal Free Hospital LSD Unit	Yes	Thank you for your comment. No action required.
	Gauchers Association	Eliglustat is an oral therapy; almost all Gaucher patients	Thank you for your comment.

Section	Consultees	Comments	Action
		in England use Enzyme Replacement Therapy which is a two weekly infusion that require support from a homecare service to varying degrees. Eliglustat does not require homecare support (except delivery); the oral drug would enable patients to travel without having to plan their travel around infusions or delay infusions. Newly diagnosed patients would benefit from Eliglustat as they would not need to attend their centre of excellence for the first three months for their ERT infusions which would save them time and money and mean they wouldn't have to take time off work or studying. Eliglustat would offer patients who do not want a fridge or homecare services to take an oral everyday therapy. Eliglustat would be suitable for patients who are needle phobic. Eliglustat is taken twice a day whereas ERT is a two weekly infusion, some patients may find it challenging to remember to take the oral therapy.	Consultees are encouraged to describe the innovative nature of eliglustat and the benefits it offers patients and their families and/or carers in their evidence submissions. The Committee will consider this information during the evaluation process. No change to the scope required.
	NHS England	An effective oral therapy is a step change for patients above intravenous infusions.	Thank you for your comment. Consultees are encouraged to describe the innovative nature of eliglustat in their evidence submissions. The Committee will consider this information during the evaluation process. No change to the scope required.
	Shire	This technology is a second to market Substrate Reduction Therapy (SRT). It should be considered as a second line therapy in adult patients in whom ERT is unsuitable.	Thank you for your comment. Consultees are encouraged to describe the innovative nature of eliglustat and its likely position in the

Section	Consultees	Comments	Action
			current clinical pathway for type 1 Gaucher disease in their evidence submissions. The Committee will consider this information during the evaluation process. No change to the scope required.
	Genzyme Therapeutics	We believe that eliglustat is an innovative technology as it provides an oral alternative with a favourable risk benefit profile to current first line ERTs, which are administered by intravenous infusion every 2 weeks. The requirement for infusions can be burdensome and inconvenient to patients and caregivers, requiring time off work and placing limits on travel and independence. Further as a small molecule, eliglustat offers the potential for better bio-distribution to affected tissues compared with current ERT. As such we consider it to be a step change in the management of this condition.	Thank you for your comment. Consultees are encouraged to describe the innovative nature of eliglustat in their evidence submissions. The Committee will consider this information during the evaluation process. No change to the scope required.
	Royal Free London NHS Foundation Trust	This is a significant advance for the therapy of Gaucher patients in providing an effective oral alternative to enzyme replacement therapy that will be relevant to potentially all patients requiring treatment	Thank you for your comment. Consultees are encouraged to describe the innovative nature of eliglustat in their evidence submissions. The Committee will consider this information during the evaluation process. No change to the scope required.
Other considerations	Royal Free Hospital LSD Unit	None	Thank you for your comment. No action required.
	Genzyme Therapeutics	No comments	Thank you for your comment. No action required.

Section	Consultees	Comments	Action
Questions for consultation	Charles Dent Metabolic Unit, UCLH	The therapeutic goals can be specifically defined with reference to the National Specialised Services SOP for Gaucher (http://www.specialisedservices.nhs.uk/document/10024) I think it is likely that eligustat will be used for people who cannot have ERT, for whatever reason and, possibly, as an oral alternative to ERT in people whose disease has initially been optimised by ERT. In principle eliglustat may act synergistically with ERT in patients whose disease does not respond to ERT.	Thank you for your comment. At the Scoping Workshop, it was agreed that the outcome 'type 1 Gaucher disease therapeutic goals' would encompass the Adult Gaucher Disease Standard Operating Procedures developed by the National Specialist Commissioning team in 2012. Clinical specialists at the scoping workshop considered that eliglustat is likely to be used instead of enzyme replacement therapy (first-line), or instead of substrate reduction therapy (second-line) in people for whom enzyme replacement therapy is unsuitable. It was noted that eliglustat would only rarely be used as an adjunct to enzyme replacement therapy, and adjunct use will only be considered during the evaluation if it is permitted by the marketing authorisation. No change to the scope required.
	Royal Free Hospital LSD Unit	See above	Thank you for your comment. No action required.
	Gauchers Association	1. Current treatments for Gaucher disease in England are Cerezyme, VPRIV and Miglustat. 2. Eliglustat would be suitable for those patients who are currently on ERT and newly diagnosed patients following advice from their clinician. 3. The outcome should align with the 2012 National Specialised Commissioning Advisory Group UK	Thank you for your comment. At the Scoping Workshop, it was agreed that the comparators in the scope were appropriate, and that the outcome 'type 1 Gaucher disease therapeutic goals' would encompass the Adult Gaucher Disease Standard Operating Procedures developed by the National

Section	Consultees	Comments	Action
		national guidelines for adult Gaucher disease. 4. Eliglustat could potentially be used to address areas that ERT is shown not be as effective i.e. lungs, although this wold require further studies to support Eliglustat alongside ERT.	Specialist Commissioning team in 2012. Attendees agreed that substrate reduction therapy may be more effective than enzyme replacement therapy when there is pulmonary involvement. The scope has been amended to include consideration of subgroups of people with symptomatic type 1 Gaucher disease with and without pulmonary involvement, if the evidence allows.
	Genzyme Therapeutics	**Have all relevant comparators for eliglustat been included in the scope? Which treatments are considered to be established practice for treating type 1 Gauchers disease in England?** The proposed label and likely clinical positioning for eliglustat would position it as an oral first line alternative to Enzyme Replacement Therapies (imiglucerase and velaglucerase alfa). As such imiglucerase and velaglucerase would be appropriate comparators. We do not believe that miglustat should be included as a comparator as it is indicated as a second line treatment for patients who cannot tolerate ERT and is also listed as a second line agent in current clinical guidelines. **What are the most appropriate outcomes to be included in the scope? Can type 1 Gauchers disease therapeutic goals be more specifically defined?** The outcomes included in the scope are appropriate. The goals of treating Gaucher disease are usefully outlined in the SOP for Adult Gauchers Disease available at	Thank you for your comment. At the Scoping Workshop, it was agreed that eliglustat is likely to be used at the same point in the treatment pathway as enzyme replacement therapy (first line) or substrate reduction therapy (second line, for people in whom enzyme replacement therapy is unsuitable), and that imiglucerase, velaglucerase alfa and miglustat were therefore appropriate comparators. No change to the scope required. Thank you for your comment. No change required.

Section	Consultees	Comments	Action
		http://www.specialisedservices.nhs.uk/document/10024 Accessed 21/11/2013) **Where in the treatment pathway is eliglustat likely to be used?** • **Is it likely to be used for people who have previously received treatment, or for those who have not previously received treatment, or both?** • **Is eliglustat expected to be used as monotherapy only, or will use in combination with imiglucerase and/or other enzyme replacement therapies be possible?** Eliglustat will be used as first-line therapy for people with type 1 Gaucher disease who prefer oral treatment and for whom eliglustat is not contraindicated. We expect eliglustat will be used by both newly diagnosed people, and those currently taking ERT. We anticipate the majority of those taking eliglustat will be those who are currently treated with ERT or ultimately would be treated with ERT. Therefore, we anticipate eliglustat will replace ERT more than create additional market growth. We do not expect eliglustat will be used in combination with ERT. We lack data to support such usage and are not seeking combination use within our EMA marketing application. **Are there any subgroups of people in whom the technology is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?** No **Please tell us what evidence should be obtained to**	Thank you for your comment. At the Scoping Workshop, it was agreed that eliglustat is likely to be used at the same point in the treatment pathway as enzyme replacement therapy (first line) or substrate reduction therapy (second line, in people for whom enzyme replacement therapy is unsuitable). No change to the scope required. Thank you for your comment. No action required.

Section	Consultees	Comments	Action
		enable the Highly Specialised Technologies Evaluation Committee to identify and consider such impacts. No comments **Do you consider the technology 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)?** See above	Thank you for your comment. No action required. Thank you for your comment. No action required.
	Royal Free London NHS Foundation Trust	Eliglustat is likely to be used in both previously treated Gaucher patients who are stable and well after years of enzyme replacement therapy and naïve patients, newly diagnosed who prefer oral therapy. Patients presenting with more severe disease may receive a period of enzyme replacement therapy prior to oral substrate reduction. Patients receiving drugs which impact on eliglustat metabolism will require close monitoring.	Thank you for your comment. No action required.

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

Association of Renal Technologists

The Renal Association

Royal College of Nursing

Department of Health

Comment 3: the provisional matrix

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Remove Afiya Trust	NICE Secretariat		Removed	This organisation's interests are not directly related to the evaluation topic and as per our inclusion criteria the Equalities National Council has not been included in the matrix of consultees and commentators.
2.	Remove Equalities National Council	NICE Secretariat		Removed	This organisation's interests are not directly related to the evaluation topic and as per our inclusion criteria the Equalities National Council has not been included in the matrix of consultees and commentators.
3.	Remove Muslim Health Network	NICE Secretariat		Removed	This organisation is no longer operational and has therefore been removed.
4.	Remove Rare Disease UK	NICE Secretariat		Removed	This organisation is a subset of Genetic Alliance UK who are already included on the provisional matrix.

5.	Add Cochrane Metabolic & Endocrine Disorders Group	NICE Secretariat		Added	This organisation has an area of interest directly related to this evaluation topic and meets the selection criteria to participate in this evaluation. Cochrane Metabolic & Endocrine Disorders Group has been added to the matrix of consultees and commentators under 'relevant research groups'.
6.	Remove Health Research Authority	NICE Secretariat		Removed	This organisation has requested removal from all matrices.
7.	Remove Black Health Agency	NICE Secretariat		Removed	This organisation's interests are not directly related to the evaluation topic and as per our inclusion criteria the Black Health Agency has not been included in the matrix of consultees and commentators.
8.	Remove MPS Society	NICE Secretariat		Removed	This organisation does not have patients with or any relationship to Gaucher disease and has therefore been removed.

9.	Remove British Association of Urological Nurses	NICE Secretariat		Removed	This organisation's interests (Urology) are not directly related to Gaucher disease and has therefore been removed.
10.	Remove British Association of Urological Surgeons	NICE Secretariat		Removed	This organisation's interests (Urology) are not directly related to Gaucher disease and has therefore been removed.
11.	Remove Urology Foundation	NICE Secretariat		Removed	This organisation's interests (Urology) are not directly related to Gaucher disease and has therefore been removed.