NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Eliglustat for treating type 1 Gaucher disease [ID709]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)**

2. **Consultee and commentator comments on the Evaluation Consultation Document** from:
   - Genzyme Therapeutics
     - ECD response letter
     - ECD detailed response
   - Gauchers Association
   - Shire Human Genetic Therapies UK

   Please note notification of no comments was received from the Department of Health

3. **Comments on the Evaluation Consultation Document from experts:**
   - **Clinical expert**, nominated by Genzyme and Gauchers Association
   - **Patient expert**, nominated by Gauchers Association
   - **Patient expert**, nominated by Gauchers Association

4. **Evidence Review Group response to updated PAS and company ECD response**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Eliglustat for treating type 1 Gaucher disease

Response to consultee, commentator and public comments on the Evaluation Consultation Document (ECD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Evaluation Determination (FED). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Evaluation Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ECD separately from the organisations that nominated them. They do not have the right of appeal against the FED other than through the nominating organisation.

Commentators – Organisations that engage in the evaluation process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FED. These organisations include manufacturers of comparator technologies, Welsh Government, Healthcare Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council); other groups (for example, the NHS Confederation, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ECD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the evaluation committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

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.

Comments received from consultees

Consultee	Comment	Response
Sanofi Genzyme	SanofiGenzyme hopes that the information provided in this response together with the provision of new data and revised terms of the Patient Access Scheme allows the committee to revise its decision for the benefit of patients with type 1 Gaucher Disease.	See FED section 1.1 Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers, when the company provides it with the discount agreed in the patient access scheme.
Sanofi Genzyme	4.3 This paragraph excludes oral evidence provided by the clinical experts in the Committee meeting in September 2016 in which the clinicians commented that they followed the Gaucher disease standard operating procedure but that they recognised ERT doses the UK were lower than many other European countries, that they rounded up and down when calculating dose, that price was a factor when considering dose and that literature, the Dutch/German study (de Fost et al 2006) indicated there could be long-term sequelae as a result of the dosing approach in England.	Section 4 summarises the evidence submissions received and the ERG critique of the company's submission. The discussion that took place at the committee meeting is captured in section 5.
Sanofi Genzyme	4.7 It should be noted that while this is a statistically significant difference between arms the change in haemoglobin level is not clinically meaningful as the reduction noted for eliglustat is still within normal range for 'normal' population. This information was provided in response to the ERG factual accuracy check.	This section has been updated to include 'The company stated that this difference was not clinically meaningful because it remained within the normal range.'

Sanofi Genzyme	4.18 The rationale for the 25% margin is described above. SGZ finds this statement disingenuous as there has not been discussion that a 15% non-inferiority margin. A 15% non-inferiority margin would have been impractical and potentially unethical, given the size of this patient population. The 25% non-inferiority margin allows for a potential 10% difference between imiglucerase and eliglustat and 15% for inherent variability in estimation of the difference between these two treatments. To power the study to achieve a tighter non-inferiority margin would have taken more patients than is feasible in a rare disease. Both clinicians at the first meeting agreed that a 10% reduction in efficacy is clinically insignificant. The lower margin of the 95% confidence interval, post-hoc, reached 17.6% so was within the 20% margin, which was preferred and recommended by the EMA. In addition, the reported result from the primary publication is calculated using Agresti and Caffo's adjusted Wald method. Other methods were explored, including the Newcombe's hybrid score interval, as requested by the ERG at the clarification stage. Of the 16 methods explored only two methods reported a lower 95% CI not within a 20% non-inferiority margin. Table 2 (see committee papers for full details)	This section presents the ERG critique, the committee's considerations of the evidence base are presented in section 5. See section 5.3.
Sanofi Genzyme	4.19 ERT-stable Since the submission of the eliglustat dossier, four year data have become available for ENCORE and ENGAGE. In the ENCORE trial eliglustat treatment resulted in stable haemoglobin concentration, platelet count and spleen and liver volumes for up to four years. Mean bone mineral density Z-scores also remained stable and were maintained in the health reference range (Cox et al 2017), see Appendix 2 Figure 3 at the end of this document for endpoint results. Analysis of the primary composite endpoint was repeated for all patients for whom data were available, see the first figure below, while the second figure reports results with ENCORE patients when the Pastores 2004 therapeutic goals are applied. Treatment-naïve Again, since the dossier was submitted, matched-pair analysis has been carried out comparing eliglustat and ERT in treatment-naïve patients, see figure below for a summary of the results, from which we can conclude that similar outcomes for these parameters were observed (Ibrahim et al 2016). (see committee papers for full details)	This section reflects the ERG report, the committee's considerations are reflected in section 5. However, this section has been clarified to state 'The ERG stated that the trials were of reasonable quality and well conducted, but at the time of their review highlighted that long-term data for eliglustat were limited'.

Sanofi Genzyme	4.21 While the outcomes in the trial had the potential for inter-investigator variability, they are not 'subjective' outcomes. The open-label design was considered the more practical option than a double-blind study for the following reasons. Cerezyme and eliglustat have different routes of administration, which in a double-blind, double-dummy design would require the patient to take a placebo and active treatment of either oral or intravenous infusion, placing a undue burden on patients and dissuading participation in the setting of other marketed treatments. The open-label design permits the important comparison of the patient reported assessment of treatment preference between oral and intravenous. SGZ recognise the potential of bias in open label trials, however, all of the primary composite (spleen and liver volumes, haemoglobin and platelet levels) and the secondary endpoints in ENCORE, are objective measurements that are unlikely to be affected by the open-label design. The secondary endpoint of bone marrow burden has a large inter-observer variability, however to minimise this, the same observer was used throughout the study, therefore any difference is likely to be real. The tertiary quality of measures (SF-36, Fatigue Severity Score, Brief Pain Inventory, and Gaucher DS3) could potentially be considered subjective endpoints, however validated tools were used for these measures.	This section reflects the ERG report, the committee's considerations are reflected in section 5.

Sanofi Genzyme	4.22 The company has already provided the information needed to address this issue in response to the ERG report publication in July 206. We reiterate it here: The ENCORE trial ended on a calendar date, not after a prespecified time on treatment. All enrolled patients had the opportunity to be treated with eliglustat for at least 2 years, but some patients ended up being in the trial for much longer, due to the fact that trial enrolment was spread out over 2 full years. People who enrolled early were in the trial for the longest. In total, 130/157 eliglustat-treated patients (82%) either completed the trial or were switched to commercial therapy when it became available in the United States. The smaller number of patients with 4-year data in ENCORE is due to the timing of their enrolment and/or the group they were in during the primary analysis. ENCORE patients who enrolled very early, were randomized to eliglustat, and did not live in the US, had the opportunity to be on eliglustat for 4 years or longer (one patient had 5-year data). On the other extreme, patients who enrolled very late, were randomized to imiglucerase for the first year, and lived in the US would have had the opportunity to be on eliglustat for only 2.3 years before the trial ended. 36 patients were switched to commercial product, 48 had timed out of the trial and 12 patients withdrew due to adverse events, of these, 4 were withdrawals due to AEs considered related to eliglustat; 10 patients wished to withdraw, 4 patients withdrew due to pregnancy, 2 to noncompliance, and 1 was lost to follow up. Patient disposition is given below. (see committee papers for full details)	This section has been removed from the FED.
Sanofi Genzyme	4.23 SGZ believe that the sample size was not small in relation to the rarity of the disease. For a non-inferiority or equivalence trial comparing eliglustat to imiglucerase in treatment naïve Gaucher Disease, a sample size of at least 70 patients would be required. It was simply not feasible to recruit that many treatment-naive patients. The ENGAGE study, with 40 patients, took 2 full years to enrol and is actually the largest clinical trial ever of treatment-naïve Gaucher Disease patients.	This section reflects the ERG report, the committee's considerations are reflected in section 5.

Sanofi Genzyme	4.23 SGZ agree that 9 months is insufficient time to show improvements in bone outcome. However, that is why bone marrow burden was evaluated in ENGAGE, because we believe it is an early measure of evolving bone disease. We did see a statistically significant improvement in BMB score in eliglustat-treated patients compared to placebo. Changes in bone mineral density were not significant, but trended in the right direction (Mistry et al. JAMA 2015). In the ENCORE trial of patients previously stabilized on ERT (mean prior duration of ERT 10 years), there was a small but statistically significant improvement in least square mean lumbar spine Z-score after 4 years of eliglustat (0.29, P<0.0001) In the phase 2 trial of treatment naïve patients, mean lumbar spine T score, which was in the osteopenic range at baseline improved to the normal range after 4 years of treatment (Lukina et al. BCMD 2014). Of note, T-score continued to improve gradually during the subsequent 4 years of the trial and after 7-8 years of eliglustat among the 19 patients who completed the trial, the proportion of patients with normal, osteopenic or osteoporotic lumbar spine Z scores shifted from 26%, 42%, and 32%, respectively, to 63%, 32% and 5% (8 year data – Genzyme data on file). In addition, the placebo-controlled trial design was considered ethically justifiable given that patients were untreated adults who would have a 50% chance of receiving eliglustat during the first 9 months and a 100% chance upon successful completion of the 9 month PAP.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.24 SGZ would like to explain the loss of patients over time. Majority of these occurred during the first year; 3 patients withdrew because of pregnancy (after 4, 6, and 13 months on eliglustat); 2 patients withdrew on Day 1 of treatment due to asymptomatic NSVTs detected during routine Holter monitoring when plasma levels of eliglustat were undetectable; 1 patient withdrew after 1 year due to a bone lesion that was retrospectively identified at baseline (this was a protocol violation), and 1 patient chose to withdraw after 2 years on eliglustat. Trial withdrawals are described in detail in the published manuscripts (Lukina et al. BCMD 2014). Of note, this trial recently ended after 7-8 years on eliglustat, and there were no further trial withdrawals during the final 4 years of the trial (19 patients completed the trial) (Genzyme data on file).	Section 4.24 has been amended following the company's explanation.

Sanofi Genzyme	4.25 SGZ recognise that a non-inferiority or equivalence trial comparing eliglustat to imiglucerase in treatment naïve GD1 patients would have been ideal, but would have required a sample size of at least 70 patients. It was simply not feasible to recruit that many treatment-naive patients. The ENGAGE study, with 40 patients, took 2 full years to enrol and is actually the largest clinical trial ever of treatment-naïve Gaucher patients. We refer to the section above which presents the results from the Ibrahim et al study, that found similar outcomes in matched treatment naïve patients initiated on imiglucerase and eliglustat.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.26 It is the understanding of SGZ that in the UK clinicians do start higher than 30U/kg, especially in children, where they tend to keep the dose the same as the child grows, therefore gradually reducing the dose/kg, and in those with severe symptoms or particularly severe blood results. Clinicians would then titrate the dose downwards to the patients clinical haemoglobin, platelet and chitotriosidase levels	This section reflects the ERG report, the experts' comments and the committee's considerations are reflected in section 5.

Sanofi Genzyme	4.43 We assumed that a patient's probability of being in a particular health state, except for death, at a particular time (year) depends on the health state in the previous period, the length of time the patient was receiving treatment (1, 2, or ≥ 3 years), the patient's starting DS3 category (mild, moderate, marked, or severe), and whether patient has had a splenectomy. We included treatment duration to capture the effect of disease stabilization over time as reported by Weinreb et al (2013) and Zimran et al (2015); we truncated treatment duration at 3 years based on the literature and clinical input that patients stabilize after about 3 years of treatment. We included splenectomy status because it can directly influence a patient's likelihood of being in spleen-related health states. We included the ignition DS3 category because of clinical input we received that indicated that disease severity when starting treatment can influence how quickly patients improve. These assumptions are presented in Ganz et al (2017). The equation for determining a patient's current health state is rather simple. The reason, we suppose, that the ERG finds the method complicated is that there 9 health states and, therefore, the transition probabilities (81 of them) are derived from a ordinal logistic regression model. The methods are fully explained in the appendix to Ganz et al (2017). The long-term transition probabilities were derived from patients enrolled in a GD1 disease registry, 99% of whom started therapy with ERT. We applied the same long-term transition probabilities to all arms in the model because we lacked information on the long-term trajectories of patients using eliglustat and because we assumed that the long-term outcomes would be similar between ERT and eliglustat based on the non-inferiority results of the clinical trials. The regression model could be modified so that the patient's DS3 category at the start of the long-term phase is used rather than	This section reflects the ERG report, no change required.

	4.43 This interpretation of the GD-DS3 scoring tool is not correct. The tool is not insensitive to changes in disease statue. It was constructed to identify minimal clinically important difference (MCID) in patients with Gaucher Disease. The reason it doesn't reflect differences between treatments observed in the trial is, as stated in our covering letter, very few of these differences are clinically meaningful. In the ENCORE trial only three patients out of the 99 per protocol patients on the eliglustat arm had clinically meaningful changes in their disease status at 52 weeks according to Therapeutic Goals. The GD-DS3 scoring system was developed with nine GD1 experts from across the globe in an effort to define patient cohorts in this chronic disease that has heterogeneous manifestations. Through a survey, domains of disease manifestation and items within each domain were selected for inclusion within the scoring system. The scaling of and maximum scores for individual assessments within DS3 were optimized to maximize the correlation between total scores and the consensus CGI-S scores utilizing a Generalized Reduced Gradient-2 algorithm. Participating physicians then conducted an exercise to determine the minimal clinically important difference (MCID), which represents a change in score, either increase or decrease, that would indicate a change in some aspect of the disease or trigger an adjustment in medical care or prognosis. Physicians were provided a sample of 20 patients and came to a consensus (at least 75% of physicians agreeing) on there being a change in prognosis. The MCID for improvement was found to be a decrease of -3.17 and for worsening was +3.86. Additionally, cases scored as no change in prognosis by at least 75% had changes that fell in between these two values. With MCID in mind, while clinical efficacy on a biomarker and organ level may differ nominally between treatment arms, unless they result in a change of -3.17 or +3.86, they are unlikely to modify patient's prognosis. During model development there was discussion regarding perceived lack of sensitivity and so health states were constructed to reflect the GD-DS3 but also clinician feedback on the most important drivers of quality of life, costs and disease path. Spleen status and severe skeletal complications (SSC) were identified as being the biggest drivers. However, in the age of ERT, spleen status is fixed after initiation of ERT (if you begin ERT with a spleen, you will not be splenectomized). Additionally, SSC did not represent a MCID via the DS3 scoring system (+/- 1 total point) but it did affect quality of life and costs due to both the event and subsequent management. Therefore, the mild, moderate, marked and severe states were further divided into with or without SSC in order to be sensitive to changes in a patient's disease status. Mild without SSC was further divided to be those with and without moderate, severe or extreme bone pain for further sensitivity within the most frequent health state patients receiving ERT experienced. The GD-DS3 may not directly replicate the findings from the ENCORE trial, however, it does measure MCID, that would drive differences in treatments or prognosis and therefore be relevant to the evaluation of comparative effectiveness underway.	This section reflects the ERG report, no changes required.

Sanofi Genzyme	4.44 Long term state transition matrices are populated based on the baseline state a patient begins in. Patients begin in the same state distribution and transition based on their treatment-specific transition matrix, the dependency on the baseline state has the effect of making the transition matrices the same for both treatment arms. While there is a difference in a patient's state path because of the treatment effect difference at one year, there is convergence to the same state path since the same transition matrices are applied to both arms. Although the analysis of the data indicated that transition matrices were dependent on the baseline state, this criticism is valid. We have explored alternative analyses and implementation of the long term data to test the impact of basing the long term the long term transitions on where they end up after the trial treatment effect. SGZ ran some exploratory analyses changing the way the patient cohort moved onto the transition matrices. Rather than these being determined by the patients' baseline characteristics, two options were explored, the first takes the distribution of patients, both imiglucerase and eliglustat arms, at the end of the 52 weeks of ENCORE. This end of trial distribution then determines where the patients enter the transition matrices, thereafter the matrices are applied as in the base case model. The second option uses the ENCORE four-year eliglustat data, so that the final state distribution is based on the completion of 4 years of eliglustat therapy. These changes mostly affected the frequency of time in mild vs. moderate health states. Eliglustat transition matrices tracked similarly to that of the long term transition data leading to generally similar results. This analysis was done on the company's base case: total incremental QALY gain 2.28. The first approach (using the 52 week data) led to revised total QALYs of 2.27. The second approach (using 4 year data) led to total incremental QALYs of 2.29. There is minimal change in costs as the only changes were in the health state costs, which are not the drivers of costs in this model. We are confirming that similar affects would be observed with the ERG base case, so from 1.05 QALY gain to 1.04 using one approach and 1.06 using the other approach, we will confirm this when the results are available.	This section has been updated to state ' …and had the potential to impact on estimated incremental QALYs'.
Sanofi Genzyme	4.44 This is an overstatement of the impact that amending the long-term transition probabilities has on the incremental QALYs for plausible changes to the model. Our exploratory analysis above suggests, based on the company's base case analysis, that depending on the approach used total QALY gain may increase or decrease by 0.01, from a base of 2.28. We are confirming that similar affects would be observed with the ERG base case, so from 1.05 QALY gain to 1.04 using one approach and 1.06 using the other approach, we will confirm this when the results are available.	

Sanofi Genzyme	4.45 As discussed earlier, the decision was made to base the model on an independently developed and validated scoring tool designed to measure minimal clinically important differences in disease progression. By using this tool the model is able to compare established standard of care with eliglustat on clinically, as opposed to statistically, meaningful outcomes that would directly impact the NHS from a total health outcomes and a total cost perspective. Because ERT controls GD1 deterioration, patients with GD1 today are very unlikely to be measured as marked or severe on the GD-DS3 tool. However, and given comments in this document that suggest the committee is querying ERT, if these treatments were not available the impact on patients' quality of life would be substantial. As such, SGZ felt the complexity related to using a 10-state as opposed to a 3 or 4 state model were justified. We acknowledge that for more severe health states there are limited data, an artefact of there being few patients who end up with this level of disease now effective treatment options are available	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.46 Using ENCORE data to population the ERT arm of the treatment-naïve model would not be a robust way of addressing the data gap. The inclusion criteria for the ENCORE trial required patients to have been on ERT for a minimum of three years, patients had in fact been on ERT for a mean of 9.8 years in the eliglustat arm and 10.0 years in the imiglucarase arm. For at least 6 of the 9 months prior to randomisation the patient had to have received a total monthly dose of 30U/kg to 130U/kg of ERT and have reached GD therapeutic goals. In ENCORE, these ERT patients continue on ERT or switch to eliglustat. This ERT-stable population is very different to a treatment-naïve population being stable patients as opposed to patients seeking to control disease symptoms for the first time.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.48 This is a legitimate challenge that the company accepts. However, it suggests there is some misunderstanding regarding the premise of the assumption: given the availability of ERT, time in the marked and severe state is short and transitory. Amendments to treatment plans can return people to better health states so that it is unlikely people with GD on active treatment will be in the marked and severe health states for any notable period of time. However, we accept the principle that were a person in a marked and severe health state for a long period of time they are likely to have a greater risk of mortality, as such we accept this proposition.	This section reflects the ERG report, the committee's considerations are reflected in section 5.

Sanofi Genzyme	4.49 The statement in 4.49 is not representative of the data presented in Wyatt 2012. Wyatt conducted an observational study of a UK cohort identified in treatment centres. Their baseline characteristics at enrollment are in Tables 12 and 13, with Table 12 only presenting the characteristics for adults. The ERG has used the "age of treatment initiation" as the mean age at which treatment is started among treatment naïve patients with GD1; however, this is likely to be biased as it likely includes patients who began treatment after having GD1 for years prior to the introduction of ERT. The ERG made the mean starting age for the stable on treatment population to be the average age of the study cohort from Wyatt 2012, which are not equivalent statistics. The average age of the cohort in Wyatt is biased for the same reasons listed above for the treatment naïve population, and literature has shown that patients stabilize on ERT within 2-5 years of their initiation, not 10 as indicated by the value used by the ERG (Weinreb 2015; Weinreb 2002). Data from the Ibrahim et al (2016) study reports mean age of treatment initiation being 32-35 years	This section has been deleted based on the ERG's updated response that this is not a key issue.
Sanofi Genzyme	4.50 The final statement in this paragraph is misleading. It would be correct to say that clinically meaningful change in disease was a driver of the model, but as discussed earlier the differences between arms are minimally meaningful from a clinical perspective. Further, the information on the PK/PD modelling that was undertaken as part of eliglustat's regulatory assessment indicated that with there was no difference in the efficacy outcomes between the 100mg BID and 150mg BID dose with the exception of a 4% change in spleen volume. This 4% change in spleen volume was still within normal ranges and therefore not considered clinically meaningful (Turpault et al 2015_poster).	The final statement has been removed from this section.

Sanofi Genzyme	4.51 We accept that a consideration of the cost of homecare and hospital treatment is appropriate. We dispute the ERG's conclusion that that it is 'implausible' for the cost of homecare to be greater than hospital care. Nurse time in the home has no economies of scale and far more limited economies of scope than nurse time in a hospital. As such, whether homecare or hospital care is more expensive is a factor of the perspective of the costing analysis. Consideration of the cost 'per hour of nurse time' and the activities that the nurse can deliver in that time leads to different results to the 'nurse cost per infusion'. Costing differences are also dependent upon the composition of the costs, for example is there a portion of cost ascribed to sunk capital costs, training costs, support staff costs and sundries, in which case a NHS nurse with all the accompanying NHS organisation costs to include is likely to be more expensive in the hospital or giving care in the home, than a nurse from a smaller, third party homecare organisation. If using the gold standard costing compendium from the PSSRU as the source for unit costs, costs can be consistently applied across resources. However, PSSRU doesn't have a cost for homecare delivered by a third party organisation. Because of this we sought to find a publicly available price for homecare delivery, which we reported. While we accept that cost attributed to home delivery may be a high estimate in the basecase, and the ERGs simplifying approach is reasonable, we suggest there is uncertainty with the ERGs estimated and costs may be higher.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.51 SGZ agree it is appropriate to include a dispensary fee. Work with key stakeholders to date would suggest that they expect eliglustat to be delivered every month/two months/three months, therefore it may be necessary for the frequency that this dispensary fee is applied to be adjusted.	This section reflects the ERG report, the committee's considerations are reflected in section 5.

Sanofi Genzyme	4.52 'The ERG noted concerns with the costs for ERT in the model. The ERG was concerned that the company did not include any vial wastage.' In developing the economic model for this submission SGZ heard from treating clinicians, and based on the content of the Gaucher Disease Standard Operating Procedure, that ERT was not wasted and all doses were rounded up or down to avoid wastage. In not including wastage the base case disadvantaged eliglustat, including wastage would have increased ERT costs. In the first evaluation committee meeting the expert clinicians stated that they rounded up and down their dosing. The base case model presented give a cost for total units of ERT required, (based on mean dose in U/kg and weight). We agree with the approach the ERG took in looking at the distribution of GD patients in the ENCORE trial and calculating a distribution of ERT based on the distribution of weight and dose and relating that to the most likely whole vial. However, SGZ does not know how clinicians make decisions about when to round the dose up or down, as we discuss below there is uncertainty regarding the 'usual English dose of ERT. As a result we believe the approach taken in the base case to report costs on a per unit basis based on the trial data is the most consistent approach.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.52 See responses above regarding usual UK dose, UK weight and efficacy assumptions.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.52 'The ERG also noted that patients who had not had previous treatment in the model were assumed to have had the same dose of ERT as patients whose disease was stable. However, the clinical adviser to the ERG suggested that newly diagnosed patients are typically less severely affected than patients who start treatment in childhood and so do not need such intensive dosing.' We suggest that the committee seeks clarification on this issue. It is true that patients with childhood onset tend to have more severe disease. However, it is not accurate to say all patients diagnosed in adulthood have mild disease that requires lower dosing. Given the rareness of the disease, patients can go undiagnosed and therefore untreated for a number of years and therefore could require high doses of ERT. Equally, adult onset patients may have less severe disease and require lower doses. This also is inconsistent with the SOP that suggests a higher starting dose and titrating down.	This section reflects the ERG report, the committee's considerations are reflected in section 5.

Sanofi Genzyme	4.54 'additional administration costs for eliglustat (£14.40 monthly dispensary cost)' We accept that a dispensary cost should be included. Eliglustat might be delivered every one, two or three months, we request the ERG adjust the frequency the dispensary cost is applied accordingly.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.54 'revised administration costs for ERT treatments (home therapy cost equal to hospital cost)' See discussion above, it is plausible for homecare to be more costly than hospital care. However, we don't dispute the approach the ERG have used, nor the simple fix for implementation in the model. However, it is very much an assumption. It should be noted that the ERG appear not to have been able to find a better estimate for the cost of a nurse-led home infusion than SGZ was.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.54 'revised estimate of the QALY benefits of oral therapy (estimate of 0.05)' Post the submission of the HST dossier for eliglustat in April 2016 SGZ recognised that the original value submitted for oral benefit of 0.12 double counted some aspects of the adverse events due to intravenous infusion. Had an ECD been produced after the September committee meeting, SGZ would have shared this information. SGZ accepts the committee's most plausible utility value for QALY benefit of an oral treatment in this therapy area is 0.05.	This section reflects the ERG report, the committee's considerations are reflected in section 5.
Sanofi Genzyme	4.54 'revised modelling of mortality to allow for increased mortality risk for people with marked and severe disease ' This is a legitimate challenge that the company accepts. However, it suggests there is some misunderstanding regarding the premise of the assumption: given the availability of ERT, time in the marked and severe state is short and transitory. Amendments to treatment plans can return people to better health states so that it is unlikely people with GD on active treatment will be in the marked and severe health states for any notable period of time. However, we accept the principle that were a person in a marked and severe health state for a long period of time they are likely to have a greater risk of mortality, as such we accept this proposition.	This section reflects the ERG report, the committee's considerations are reflected in section 5.

Sanofi Genzyme	4.54 ‘reduction in dose of ERT to bring it in line with UK practice (25 U/kg)’ As mentioned previously, this represents an inconsistent and flawed consideration of the available data. It is inappropriate to implement a dose of 25U/kg, as representing usual UK practice, without taking into account the weight of usual UK Gaucher Disease patients, reported above. Further, there is no consideration about how this dosing would affect the efficacy estimate in the model, which is inconsistent with the discussion on the 100mg BID/150mg BID eliglustat dose (while recognising they may have different dose/response relationships) . SGZ would requests NICE/the ERG consider what a plausible adjustment to estimates of ERT efficacy would be at this dose, specifically to consider if this affects the long-term efficacy given the potential relationship between lower doses and poorer bone outcomes (Deegan et al 2011; de Fost 2006)	This section reflects the ERG report, the committee’s considerations are reflected in section 5.
Sanofi Genzyme	4.54 ‘ using ENCORE effectiveness data in the treatment-naive population during the first cycle.’ SGZ strongly refutes this suggestion. Given that patients in the ENCORE trial had to have been on ERT for a minimum of three years, to have documented stability for the last 6 months and to be on a dose ranging from 30U/kg – 130U/kg, and that the mean patient across both of the per protocol arms had been on ERT for a mean of 10 years, we consider the assumption that these patients are equivalent to treatment-naive patients is flawed. The study by Ibrahim et al, and reported in the EPAR appears to demonstrate that very similar outcomes are achieved in the first-year of active treatment with eliglustat or ERT	This section reflects the ERG report, the committee’s considerations are reflected in section 5.
Sanofi Genzyme	4.55 Given the company has submitted a simple PAS and the NHS would not pay list price, these results are not relevant to a discussion about value for money for the NHS.	The committee’s decision was made on results based on the discounts available, but these cannot be publically presented because of their confidential nature. NICE is committed to transparency and therefore presents the list price results in this situation, noting that discounts are available.

Sanofi Genzyme	5.2 There are limited data on poor metabolisers. There were no poor metabolisers in the ENGAGE study. There were 4% poor metabolisers in the ENCORE study, and when pooling patients from ENCORE, EDGE and Phase II there were 4% PMs. Verbal evidence in the first committee meeting from SGZ was that there is variability in the estimated proportion of GD1 patients who are poor metabolisers: it ranges from 3% to 7% depending on what information you are looking at. In summary, the few data are due to small patient numbers, observed data and outputs of PK/PD modelling suggests that at the dose of 100mg QD there will be no difference in clinical outcomes or TEAEs. Consideration needs to be given to drug-drug interactions and contraindications relating to the CYP2D6 metabolic pathway, as in needed for IM/EM, and there are slightly different for PMs.	See section 5.7, 'The company submission stated that up to 7% of the Gaucher population are poor metabolisers. Following consultation, the company stated that its pharmacokinetic\pharmacodynamic modelling suggested that similar clinical outcomes are expected for poor metabolisers having the lower dose of eliglustat.'
Sanofi Genzyme	5.2 Sanofi Genzyme undertook modelling that showed selecting a 100 mg BID dose for the IM and EM population will allow for safe and efficacious exposure of this target population, in the same range as observed in our positive clinical trials and without the need for plasma monitoring. A PK/PD-efficacy modelling approach was used to show that the exposures predicted in a CYP2D6 phenotype-based dosing scenario would achieve the same range that has been shown to be safe and efficacious in the pivotal studies. (see committee papers for full details)	See section 5.6, the committee noted that the company's pharmacokinetic\pharmacodynamic modelling suggested only minor differences in plasma levels with the higher dosage, and that it would be associated with a negligible difference in clinical response. The committee was satisfied that using the efficacy data for eliglustat from the ENCORE trial would not introduce major bias to the results.
Sanofi Genzyme	5.4 SGZ considers this a more accurate representation of the dose issue in the UK than paragraph 4.52 above	This section represents the committee's deliberations.
Sanofi Genzyme	5.4 'The committee also heard that there were no differences in the effect of eliglustat in the ENCORE trial when stratified according to ERT dose.' SGZ suggests this is a mis-interpretation of the table below (see committee papers) to conclude that outcomes seen with a mean of 42.4U/kg would be achieved with a mean dose of 25U/kg. The ENCORE data were analyses by doses ≥35U and <35U. The mean dose in the <35U population was 27U while the mean dose in the ≥35U dose was 51.23U (last dose received, ITT population). The committee have assumed a 'flat dose' of 51U/kg is equal to a 'flat dose' 27U/kg and thereafter 25U/kg without taking into account that does of ERT will be affected by patient weight, baseline characteristics and disease severity. What the <35 and ≥35U data show is that, if patients are well managed on doses are ERT uniquely tailored to their characteristics then ERT leads to maintained stability over 52 weeks. It does not show that if every patient on the ERT arm of the ENCORE study had received 27U the same outcomes would have been achieved.	See section 5.5, the committee discussed this and heard from the ERG that that the data showed that, in people having lower doses of ERT, their condition continues to respond to treatment. The committee was satisfied that using the efficacy data for ERT from ENCORE was appropriate.

Sanofi Genzyme	5.5 'it also noted the view of the European Medicines Agency's Committee for Medicinal Products for Human Use that the trial did not comprehensively show that the usual regulatory standard of -20% had been achieved' We acknowledge this statement is in the EPAR and we acknowledge that SGZ made the decision to go at a 25% non-inferiority margin in the face of advice from the CHMP that 20% was the preferred margin. However, as is reported in the cover letter to have met this 20% non-inferiority margin would have required nearly double the number of patients being exposed to the trial product (an extra 174 in addition to the 186 patients actually enrolled). Trial robustness needed to be balanced against practical issues (how to recruit double the patients in an ultra orphan disease area), ethical issues, exposing double patients to a pre-licence drug and of course commercial considerations: a larger trial would delay availability of the licenced product to Gaucher Disease patients across Europe. As stated earlier, using 14 different appropriate methods for analysing the data, the lower 95% confidence interval was within a 20% non-inferiority margin. It was outside the 20% NIM using two methods that can legitimately be considered less appropriate given the nature of the data being assessed.	See section 5.3, the committee understood the challenges in developing a clinical trial programme for a rare condition, and concluded that the ENCORE trial was sufficiently robust for its decision-making.
Sanofi Genzyme	5.5 'The committee heard from the clinical experts that they considered eliglustat to be equivalent, or very nearly equivalent, to ERT based on clinical measures such as haemoglobin levels and platelet counts, as well as in terms of how patients felt while having eliglustat.' SGZ agrees this is a critical commentary from the clinical experts and reflects the importance of distinguishing between clinically and statistically meaningful information	Noted, see section 5.8 in the FED. The committee concluded that eliglustat is an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty of effectiveness in comparison with ERT in the long term

Sanofi Genzyme	5.5 'The committee concluded that eliglustat could potentially be an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty about effectiveness in comparison with ERT, particularly in the long term' The long-term issue is the same for any novel medicinal product launching, it accounts for why the usual NICE HTA process has a three year re-review period. SGZ ran some exploratory analyses changing the way the patient cohort moved onto the transition matrices. Rather than these being determined by the patients' baseline characteristics, two options were explored, the first takes the distribution of patients, both imiglucerase and eliglustat arms, at the end of the 52 weeks of ENCORE. This end of trial distribution then determines where the patients enter the transition matrices, thereafter the matrices are applied as in the base case model. The second option uses the ENCORE four-year eliglustat data, so that the final state distribution is based on the completion of 4 years of eliglustat therapy. These changes mostly affected the frequency of time in mild vs. moderate health states. Eliglustat transition matrices tracked similarly to that of the long term transition data leading to generally similar results. This analysis was done on the company's base case: total incremental QALY gain 2.28. The first approach (using the 52 week data) led to revised total QALYs of 2.27. The second approach (using 4 year data) led to total incremental QALYs of 2.29. There is minimal change in costs as the only changes were in the health state costs, which are not the drivers of costs in this model.	Noted, see section 5.8 in the FED. The company presented 4 year data from ENCORE showing that the outcomes remained stable. The committee concluded that eliglustat is an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty of effectiveness in comparison with ERT in the long term
Sanofi Genzyme	5.7 SGZ is very concerned by the implications of this paragraph. This HST was for the assessment of eliglustat in the treatment of type 1 Gaucher Disease, not a multiple technology assessment of all treatments for Gaucher Disease. We remind the committee that the phrase 'value for money' is used in the HST process rather than cost-effectiveness because of societal preference for flexibility in defining a treatments value ie, not all diseases are equivalent and it is not always appropriate to apply efficiency measures. This is seen explicitly with the End of Life criteria for cancer treatments and in the design of the current HST process that explicitly precludes the utilitarian/efficiency reporting of outcomes as 'ICERs' as it was determined that this is not always appropriate. SGZ considers questioning the value for money of an established and effective treatment in the ECD to be out of scope for this evaluation and suggests the committee have gone outside of the remit of this evaluation in doing so.	Comments noted. The committee noted that its considerations on the value for money of eliglustat were based on the current evidence and clinical practice, but that they would need to be reconsidered if ERT was no longer available in routine practice. See section 5.10.

Sanofi Genzyme	5.8 'The company assumed that eliglustat and ERT have equal efficacy in patients who had not previously had treatment. The committee was aware that there was no direct evidence comparing eliglustat with ERT in this population. It agreed with the ERG that evidence from the ENCORE trial would have been more appropriate.' SGZ requests the committee reviews this decision in the face of information provided regarding the nature of the ENCORE trial design. ERT-stable patients are very different to treatment-naïve patients. There is variation in treatment-naïve patients (some with less severe illness as they have milder adult onset disease, some with more severe illness, and this can be due to long delays in diagnosis) that would lead to a variation in baseline disease state that is not seen in the ENCORE study.	See section 5.11. The committee agreed that both approaches had limitations. It heard that, because these transition probabilities were applied to the first cycle only, it had a very small impact on the results.
Sanofi Genzyme	5.10 'The company assumed long-term equivalence of eliglustat and ERT, and the ERG highlighted that this had a considerable impact on estimated incremental quality-adjusted life years QALYs).' SGZ requests this analysis is provided to us to be able to validate the veracity of this statement, the information we were able to find fro the ERG report dated July 2016 was that, 'The ERG attempted to incorporate differential efficacy into the analysis in order to demonstrate the impact on the results if the assumption of non-inferiority did not hold in the long-term. However, the ERG was unable to explore this scenario as any attempt to remove the assumption of non-inferiority resulted in inconsistent results, and a lack of transparency in the cost-effectiveness model prevented the identification of any errors'. This is quite a different proposition and the company would like to understand the basis for this statement. SGZs exploratory analysis suggests that from a base case of 2.28 QALY gain, a plausible difference would be a 0.01 increase/decrease in QALY gain.	See section 5.11, ' the ERG highlighted that this had the potential to impact on estimated incremental quality-adjusted life years.

Sanofi Genzyme	5.10 ‘ The committee agreed with the ERG that non-inferiority was not the same as equivalence, and that non-inferiority in the short term does not imply non-inferiority in the long term.’ SGZ agrees with the accuracy of this statement. However, this is not the same as stating the products have clinically meaningful difference in effectiveness. There is an indication of similar outcomes in the study by Ibrahim et al for treatment naïve patients. Considering how eliglustat might be used in ERT stable patients, and recognising that patients with sub-optimal outcomes would not be maintained on a product, there is likely not to be clinically meaningful difference in outcomes in ERT-stable patients in the long-term. Further the per protocol results for ENCORE at 1 year demonstrate that after 52 weeks of treatment, 92% of patients in the eliglustat group and 94% in the Cerezyme group were stable and "normal" as defined by the composite endpoint. (see committee papers for full details)	See section 5.11. The committee considered the 4 year data presented by the company following consultation (see section 5.8) and also noted that the company presented varied approaches to transition within the model, resulting in a negligible impact on total QALYs gained. The ERG, however, clarified that the assumption of long-term equivalence was not underpinned by how transition probabilities are calculated, but by using the same probabilities in the long term across both arms of the model. The committee maintained that there was uncertainty around the assumption of equivalence in the long term.
Sanofi Genzyme	5.10 ‘ Moreover, the committee was aware that 48% of patients in ENCORE had a higher dose of eliglustat and these data were used in the model’ See response above relating to the dosing in the ENCORE trial.	Noted, this issue is now discussed in section 5.6 and the committee was satisfied that using the efficacy data for ERT from ENCORE was appropriate.
Sanofi Genzyme	5.10 ‘ The committee considered that there was uncertainty around the assumption of equivalence, especially in the long term’ We would again agree with the principle of this statement. Regarding the absence of long-term data in a new product eliglustat is no different to any therapy, which is why NICE has a process option for a 3 year re-review process. Given the strong indication, that in patients who continue to meet well-established therapeutic goals, there is no clinically meaningful difference between ERT and eliglustat. For patients who do not meet these goals, in line with a conversation between patient and clinician, patients would be unlikely to be maintained. Further, there are unknowns with both treatments at the dose of ERT given in the UK and the indication from Dutch/German data that lower doses affect BMB outcomes (de Fost et al 2006) there is a plausible scenario in which eliglustat offers patients better long-term outcomes as the small molecule penetration provides better bone outcomes, the bone outcomes being the most troublesome to the patient and	See section 5.11. The committee maintained that there was uncertainty around the assumption of equivalence in the long term.

Sanofi Genzyme	5.10 ‘ dose of ERT used in the model was 42.4 U/kg, every 2 weeks, based on the mean dose of imiglucerase patients had in the ENCORE study. The committee recalled (see section 5.4) that a dose of between 15–30 U/kg was considered most reflective of clinical practice. The committee was aware that the dose of ERT was a key driver of results and that the ERG had explored the impact of including a dose of 25 U/kg. The committee considered that the ERG exploratory analysis that included a dose of 25 U/kg was appropriate’ It is true that dose is a key driver in the model. Dose is a composite of U/kg and weight (kg). Discussion of weight is omitted in the ECD document. The company submitted a base case of the dose/weight/efficacy directly from the ENCORE trial, as an alternative it reported the dose/weight combination reported in the velaglucerase submission to the AWMSG of 32U/kg and 75kg (average UK weight according to most recent, but old ONS data (2010) was 83.6KG for men and 70.2KG for women, a population average of 76.9kg). In response to this ECD the company has sought accurate GD1 patient weight information: Results presented in the base case give a price per unit, rather than per vial, and while the SGZ recognises that the SOP and usual practice is not to waste ERT, what is clear is that the ERG estimate is the only estimate that is close to 4 vials, all others are close to 5 vials. (see committee papers for full details)	See section 5.11. The ERG clarified that that dose of ERT in the ERG analyses was obtained from English prescribing data reporting average units per month, so the average weight in the model was not relevant. However, the ERG also presented exploratory analyses using estimates based on real world weight.
Sanofi Genzyme	5.10 ‘ especially because the results of the ENCORE trial showed no difference in the response to eliglustat in terms of the dose of the comparator ERT.’ This is a mis-representation of the ERT data. The ENCORE data were analyses by doses ≥35U and <35U. The mean dose in the <35U population was 27U while the mean dose in the ≥35U dose was 51.23 (last dose received, ITT population). This statement essentially assumes is that a ‘flat dose’ of 27U is equal to a ‘flat dose’ of 51U without taking into account a patient’s weight, baseline characteristics or disease severity. What the <35 and ≥35U data show is that, if patients are well managed on doses are ERT uniquely tailored to their characteristics then ERT leads to maintained stability over 52 weeks. It does not show that if every patient on the ERT arm of the ENCORE study had received 27U the same outcomes would have been achieved. (see committee papers for full details)	See section 5.5, the committee discussed this and heard from the ERG that that the data showed that, in people having lower doses of ERT, their condition continues to respond to treatment. The committee was satisfied that using the efficacy data for ERT from ENCORE was appropriate.

Sanofi Genzyme	5.10 ‘ The company assumed that the mortality risk does not increase with disease severity. The committee considered that this was an unrealistic assumption. It noted that the ERG explored the impact of increased mortality risk for patients in the ‘marked’ and ‘severe’ health states.’ This is a legitimate challenge that the company accepts. However, it suggests there is some misunderstanding regarding the premise of the assumption: given the availability of ERT, time in the marked and severe state is short and transitory. Amendments to treatment plans can return people to better health states so that it is unlikely people with GD on active treatment will be in the marked and severe health states for any notable period of time. However, we accept the principle that were a person in a marked and severe health state for a long period of time they are likely to have a greater risk of mortality, as such we accept this proposition.	Comments noted, no change was made.
Sanofi Genzyme	5.10 ‘ The company assumed that there are no administration costs associated with eliglustat because it is an oral therapy. The committee considered that the ERG’s exploration including a monthly dispensary cost for eliglustat was appropriate, noting that this had a minor impact on the results.’ The company assumed that there are no administration costs associated with eliglustat because it is an oral therapy. The committee considered that the ERG’s exploration including a monthly dispensary cost for eliglustat was appropriate, noting that this had a minor impact on the results.	See section 5.11, the ERG explored including a monthly dispensary cost for eliglustat but, following consultation, the company stated that eliglustat could be dispensed less frequently. The committee agreed with the ERG that there was uncertainty around the frequency and, because this had a minor impact on the results, the ERG’s approach of including a monthly dispensary cost was pragmatic.

Sanofi Genzyme	5.10 ‘ The ERG highlighted that the administration costs for ERT were likely to be overestimated in the company’s model because they were higher than the costs of hospital administration. The committee agreed that this was implausible and noted that the ERG had explored this assumption.’ We accept that a consideration of the cost of homecare and hospital treatment is appropriate. We dispute the ERG’s conclusion that that it is ‘implausible’ for the cost of homecare to be greater than hospital care. Nurse time in the home has no economies of scale and far more limited economies of scope than nurse time in a hospital. As such, whether homecare or hospital care is more expensive is a factor of the perspective of the costing analysis. Consideration of the cost ‘per hour of nurse time’ and the activities that the nurse can deliver in that time leads to different results to the ‘nurse cost per infusion’. Costing differences are also dependent upon the composition of the costs, for example is there a portion of cost ascribed to sunk capital costs, training costs, support staff costs and sundries, in which case a NHS nurse with all the accompanying NHS organisation costs to include is likely to be more expensive in the hospital, and giving care in the home, than a nurse from a smaller, third party homecare organisation. If using the gold standard costing compendium from the PSSRU as the source for unit costs, costs can be consistently applied across resources. However, PSSRU doesn’t have a cost for homecare delivered by a third party organisation. Because of this we sought to find a publicly available price for homecare delivery, which we reported. While we accept that cost attributed to home delivery may be a high estimate in the basecase, and the ERGs simplifying approach is reasonable, we suggest there is uncertainty with the ERGs estimated and costs may be higher.	See section 5.11, ‘The company stated that this would depend on the perspective of the costing analysis, but the ERG confirmed that all data available supported lower costs for home administration. The committee agreed that the ERG’s exploration assuming equal cost was appropriate, and potentially overestimates the cost of ERT’.

Sanofi Genzyme	5.10 In line with comments above: Post the submission of the HST dossier for eliglustat in April 2016 SGZ recognised that the original value submitted for oral benefit of 0.12 double counted some aspects of the adverse events due to intravenous infusion. Had an ECD been produced after the September committee meeting, SGZ would have shared this information. SGZ accepts the committee's most plausible utility value for QALY benefit of an oral treatment in this therapy area is 0.05. However, we are concerned that oral utility discussions from previous NICE submissions: adverse events and the benefits of other oral therapies estimated in previous NICE submissions may be being inappropriately applied to this HST evaluation. The references in the ERG report used to defend a lower utility value were all being taken from cancers with a poor survival prognosis (Liu et al 1997; Twelves et al 2006; Tabberer et al 2006; and NICE 2007). It is a very different proposition being asked if you prefer an oral therapy or an IV therapy in the last 6 months of life than being asked if you prefer an oral therapy or an IV therapy at the start of a treatment plan that will last for the next 50-60 years. The ERG postulates a scenario in which it states the original utility value submitted (0.12) would suggest people were prepared to trade-off 2.29 years of life in full health for the convenience of an oral therapy [over 50-60 years]. The ERG poses this as a ridiculous assumption. While SGZ would accept 0.12 is too high and therefore 2.29 years is too long, we would challenge that this is a ridiculous assumption and suggest that it is patients that should be making that decision.	Comments noted, no change required.
Sanofi Genzyme	5.10 SGZ would point out that there is a revised PAS agreed with the Department of Health. SGZ requests documented confirmation that the confidential discount offered by Shire for VPriv meets the requirements of a discount to be acceptable for the use in a NICE assessment:	NICE confirms that the confidential discounts are based on CMU prices and are considered appropriate for use in an evaluation.

Sanofi Genzyme	5.11 As already stated, SGZ acknowledges that the poor metaboliser (PM) population is small. There were no PMs in the ENGAGE trial, 4% of patients in the ENCORE trial were PMs (6/146) Across all eliglustat trials (Phase 2, ENGAGE, ENCORE and EDGE), 14 patients (3.6%) were poor metabolizers (14/393) (Peterschmitt et al 2017). Observed data from the Phase III clinical trials supported by PK/PD modelling demonstrate that similar clinical outcomes are expected for poor metabolisers at the 100mg QD dose, and that no difference in TEAEs were reported with the PM populations (EMA 2015). Consideration is given in the SmPC regarding considerations that needs to be made once metaboliser status is confirmed, specifically relating to drug-drug interactions and contraindications. In summary, the few data are due to small patient numbers, observed data and outputs of PK/PD modelling suggests that at the dose of 100mg QD there will be no difference in clinical outcomes or TEAEs. Consideration needs to be given to drug-drug interactions and contraindications relating to the CYP2D6 metabolic pathway, as in needed for IM/EM, and there are slightly different for PMs.	See section 5.14. The committee concluded that eliglustat offered value for money in people with poor metaboliser status.

Sanofi Genzyme	5.16 SGZ suggests this paragraph is a little misleading. It reads as thought zero mortality, no treatment stopping and adding in the 4% poor metabolisers account for the jump in budget impact, when in fact it is the previous ERG assumption around units of ERT used that drive the cost difference. SGZ is surprised by the approach the ERG adopted: 1 patient over 5 years. The advice in the STA User Guide is, 'State the estimated annual budget impact on the NHS in England (NICE 2015)'. Reviewing the HST interim methods guide we couldn't see any recommendations to use a different, per patent, approach (NICE 2013). Given the perspective is NHS-England, it is usual that a budget impact analysis includes an assumption for mortality and, although this varies by therapy area, treatment stopping. The principle being that if a patient dies within the 5 year timeframe of the BI analysis they are no longer costing the NHS money. It may have been fair to question if an annualised mortality rate would have been more appropriate, or some other estimate for the number of patients in the Gaucher Disease population that would die in a 5 year period. Regarding treatment stopping, the same principle applies, if a patients asks for a treatment break for a period of time and the NHS is not funding their treatment then there is no cost and this should be included. SGZ agrees that for simplicity this stopping rule can be removed. SGZ accepts that the poor metaboliser population should have been included in the budget impact analysis and agrees that a rate of 4% is appropriate.	Comments noted. See section 5.18. 'Following consultation, the company stated that it was inappropriate to exclude mortality because any deaths would mean the NHS is no longer paying for treatment. The ERG, however, considered that the company's approach potentially double counted mortality and preferred to exclude mortality and stopping treatment from the cost–consequence model and only include it in the budget impact model. The committee considered that, while approaches could differ, it was important that the approach used was internally consistent and did not double count the impact of mortality on budget impact.'
Sanofi Genzyme	5.20 'The committee understood that type 1 Gaucher disease can be a debilitating condition that has severe effects on the lives of people with the condition, and their families and carers. It agreed that there was uncertainty about the equivalence of eliglustat compared with ERT. However, the committee considered that, because it is an oral treatment, it could potentially provide important quality-of-life benefits for people currently having intravenous ERT, as well as for people who have not previously had treatment.' SGZ agrees with this statement.	Comment noted.

Sanofi Genzyme	Procedural concern: While the Interim Process Guide sets out in broad terms the procedure that will be followed and the principles that will be applied by the Evaluation Committee in considering an HST, the precise methodology and assessment of "value for money" remains unclear. As a consequence and in circumstances where there are few precedents, it is difficult for stakeholders to understand how decisions are made and what is required in order to obtain a positive outcome. While the HST process purports to recognise the challenges associated with developing a treatment for a rare and life-long disease, the Interim Process Guide provides no indication as to how this should be reflected in the evaluation, with the result that the ECD for eliglustat criticises the data on the basis that the studies are not larger (in fact ENGAGE is the largest study ever conducted in treatment-naïve Gaucher patients) and longer term data (data up to 8 years have been submitted) are not available.	Comments noted. A consultation has taken place on elements of the interim Methods Guide, including value for money, and the guide is being updated. Please note that section 4 in the ECD reflects the critique of the Evidence Review Group. The committee's deliberations are reflected in section 5. The committee understood the challenges in developing a clinical trial programme for a rare condition, and concluded that the ENCORE trial was sufficiently robust for its decision-making. It noted that the placebo-controlled ENGAGE study, which included a treatment-naive population, also allowed inclusion of people who had previously had ERT provided they were not having treatment at the time of entry into the trial. Additionally, there were no comparative data with ERT for patients who had not had previous treatment. The committee concluded that it would need to take these uncertainties into account in its decision-making.

Sanofi Genzyme	Procedural concern: The Committee questions whether eliglustat represents value for money for the NHS on the basis that the comparator products have not themselves been evaluated. NICE's Methods of Technology Appraisal states at paragraph 6.2.3: "The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s). When the assessment suggests that an established practice may not be considered a good use of NHS resources relative to another available treatment, the Committee will decide whether to include it as an appropriate comparator in the appraisal, after reviewing an incremental cost–utility analysis. The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so embedded in clinical practice that its use will continue unless and until it is replaced by a new technology. The Committee will also take into account the uncertainty associated with the estimates of clinical and cost effectiveness, and whether the new technology under appraisal could provide a cost-saving alternative". ERT plainly constitutes established NHS treatment for Gaucher Disease (as recognised by the Evaluation Committee at paragraph 5.2 of the ECD) and the Committee does not suggest that use will cease in the absence of a replacement technology. In these circumstances, there is no basis for refusing to recommend use of eliglustat based on a comparison with ERT. Any suggestion to the contrary must be based on evidence that ERT is not established treatment for NHS patients. Should NICE propose to introduce a policy that comparators must themselves have undergone evaluation and be the subject of a positive recommendation, even where such treatment constitutes established practice within the NHS, this policy cannot be applied retrospectively, but should be stated explicitly in NICE's process guides. In those circumstances, NICE should not schedule an HST evaluation until the relevant comparator has already undergone evaluation. That did not happen in this case - presumably because ERT is established treatment within the NHS; NICE has certainly published no plans to conduct an evaluation of ERT for Gaucher Disease. The fact that ERT has not been evaluated by NICE is a matter for NICE and not for SGZ and should not prejudice the assessment of eliglustat.	See section 5.10, the committee noted that its considerations on the value for money of eliglustat were based on the current evidence and clinical practice, but that they would need to be reconsidered if ERT was no longer available in routine practice. The committee also encouraged the company, NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits of eliglustat and ERT for treating type 1 Gaucher disease.

Sanofi Genzyme	The ERG queried high 'loss to follow-up' in the ENCORE trial in its report in July 2016, even though no information in relation to this issue had been requested from SGZ at the clarification stage. SGZ was immediately able to provide information to explain the position, including the movement of US patients out of the trial and onto commercial product when it became available in Autumn 2014. In response the ERG stated *Although the ERG accepts the company's amendment may be true, we were not previously given access to the relevant information stated by the company. At this stage of the process we believe that we cannot incorporate new information or data into the report, and that the statement made by the ERG remains accurate based on the information we had available to us at the time.* SGZ was frustrated by the approach of the ERG, which was obstructive rather than co-operative and inconsistent with an assessment aimed at presenting a fair and accurate reflection of the data to assist all stakeholders (NICE, patients and clinicians as well as SGZ) to consider eliglustat. This "punitive" approach and inaccurate comment by the ERG has now been reflected in paragraph 4.22 of the ECD released on the 7th March 2017, even though the ERG has been in possession of SGZ's explanation since July 2016. It is unclear how the refusal by the ERG to incorporate the details provided by SGZ in relation to patient follow-up in ENCORE, have influenced the conclusions of the Evaluation Committee, however in circumstances where they are reported in the ECD, they must be assumed to have had some effect.	Comments noted. This section has been removed from the FED.
Sanofi Genzyme	Written information clarifying the patient disposition in ENCORE was provided to NICE/the ERG in July 2016, in response to the ERG's report. However, this is raised as a gap in SGZ's submission, even though the information has been with NICE/ERG since July last year.	Comments noted. Please note that section 5 of the FED explains the committee's deliberations – this takes into account all evidence received from stakeholders as well as the ERG report.
Sanofi Genzyme	Following the meeting on the 21st of September SGZ notified NICE that it had submitted a PAS for approval to PASLU. This may have affected the decision by NICE not to issue an ECD at that stage. Many of the clinical issues raised in the ECD of 7th March could have been raised in September if an ECD had been issued, which would have been a much more efficient way of dealing with the committees concerns. SGZ feels strongly an opportunity was missed for the company and other stakeholders to respond to clinical issues. Similarly, the ERG had information provided to it (for example in response to the report) that it has not formally taken into account yet, even though it has been sitting on the information since July, such as the above regarding patient disposition.	Following, the 1st committee meeting, the company advised NICE that the list price of eliglustat has been revised and that it had applied for a PAS. An ECD cannot be issued in the absence of a list price, and the results discussed at the committee meeting were no longer relevant. It is not part of the HST process to run a separate consultation on clinical aspects of an evaluation.

Sanofi Genzyme	After the postponement of the Committee meeting scheduled for January 2017 due to lack of quorum, the meeting was rescheduled, with only a month's notice for February 2017. The rescheduled meeting fell in the half term holidays and coincided with the most important annual global conference for Gaucher Disease clinicians in the US. In view of the limited notice and the timing, neither the expert clinicians nor the patient advocacy representative were able to attend. This situation (a scheduled meeting at short notice) was clearly unsatisfactory and inconsistent with NICE's procedures. Furthermore, in circumstances where it is important that the Evaluation Committee has access to clinical and patient expertise in relation to the manifestations and treatment of an ultra rare disease, it is unreasonable to schedule a meeting at a time when it is patently obvious that relevant experts are unlikely to be able to attend. While NICE set up TC conferences with the expert clinicians and patient specialists prior to the rescheduled meeting on the 16th Feb, this did not adequately correct the unfairness resulting from the absence of the experts at the meeting. SGZ was not invited to attend the TCs and did not therefore hear the perspectives of the clinical and patient experts at that time. Nor where did the resulting ECD appear to reflect their viewpoint. Details of the structure of these TCs are not known: who was in attendance (was it quorate for the Evaluation Committee members?), how many TCs there were. The ECD for eliglustat includes clinical conclusions that are controversial (e.g. the Committee's conclusions regarding the benefits of eliglustat versus ERT, their failure to adjust the efficacy of ERT to reflect the lower dose used in clinical practice as compared with clinical trials and their assessment of the modest effect on quality of life resulting from introduction of an oral treatment). It is likely that the absence of the clinical and patient experts from the February meeting prejudiced discussion on these matters.	Comments noted. The committee meeting was postponed because it could not be quorate, this was as a result of resignations and availability of remaining members. It was rescheduled to the earliest next availability. Because experts could not be present, a teleconference was organised separately with experts prior to meeting to explore queries raised from the additional information received from the company. Patient and clinical experts were advised and agreed to this process being undertaken due to them not being able to attend the meeting. The feedback from this teleconference was presented at meeting via slides and minutes were also included in committee papers. The main focus of second meeting was to discuss company's updated results (based on updated list prices and a patient access scheme discount) and updated patient estimates – clinical issues remained as discussed at the 1st meeting and were consulted on in the ECD released in March 2017.
Sanofi Genzyme	The ECD released on the 7th March 2017 raised issues that largely had been discussed in September 2016 and were not even raised in the committee meeting in February 2017 to allow the company to respond. As such, many issues that could have been responded to by SGZ are only now being raised.	The main focus of second meeting was to discuss company's updated results (based on updated list prices and a patient access scheme discount) and updated patient estimates – clinical issues remained as discussed at the 1st meeting and were consulted on in the ECD released in March 2017.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Gauchers Association	As part of our preparation for this appraisal we conducted a survey amongst our Members who were concerned and anxious about ongoing difficulties and the burden of venous access after in some cases 23 years on fortnightly (in the early days weekly) infusions. Yes, NICE outlines in para 5.2 'that patient experts highlighted that they were administered intravenously and that this could be burdensome for patients' but this does not recognise the fact that for some patient's venous access is a real challenge, which in the long term may result in not being able to continue on ERT with potentially severe consequences. It is well documented in the literature that there are sanctuary sites where ERT is not effective, even at high doses and in England, we have a few patients receiving eliglustat for lung involvement and mesenteric lymph nodes. Although the data to demonstrate the benefits of this combination therapy is very limited, due to the small numbers, does eliglustat not offer a treatment for unmet needs in these patients that ERT is not meeting, for those patients currently receiving it for this purpose and for those patients where there is a clinical need in the future. We must also consider that new patients will be diagnosed and may not be clinically suitable for ERT and if eliglustat is not available they will either not receive a treatment and quoting NICE in para 5.1 "The committee concluded that type 1 Gaucher disease is a debilitating condition that has a significant impact on quality of life" and therefore be condemning these patients to a poor quality of life impacting on their ability to work, be independent and in some cases early death. OR they will have to take Miglustat, which quoting NICE para 4.3 "The clinical and patient experts noted that people with type 1 Gaucher disease choose ERT whenever possible because Miglustat is associated with tolerability and safety issues, and modest efficacy" which is unethical when Eliglustat is a licensed treatment available for these patients.	Comments noted. Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers, when the company provides it with the discount agreed in the patient access scheme.

Gauchers Association	In para 5.19, it says “the committee heard from the clinical experts that the availability of eliglustat will reduce the need for the nursing support that is often needed for home infusions of ERT. The committee concluded that the impact of eliglustat on the delivery of specialised services is likely to be relatively negligible.” What this does not address is the enormous burden the impact of the homecare service has on in particular the Clinical Nurse Specialists and Pharmacists at the 8 Centres who have to monitor the Homecare service and deal with the day to day issues experienced by the patients and families, thus taking their time away from actually dealing with the clinical needs of the patient community. This has not been quantified and taken into consideration in the impact.	Comment noted, see section 5.20.
Gauchers Association	The Association would like to emphasise that unlike the Scottish Medicines Commission, ERT for Gaucher Disease has not been formally considered by NICE in England, however in 2007 a NIHR Health Technology Assessment programme was commissioned ‘The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders’ which concluded: *These data provide strong evidence for an association between time on ERT and a clinically significant improvement in platelet count and Hb in adults, irrespective of whether or not they have undergone splenectomy, and in children. There is also a strong, statistically significant association between time on ERT and a clinically important decrease in the likelihood of having an enlarged spleen or liver based on estimated spleen volumes from scans or on palpation. In all of these analyses the data appear to suggest very substantial improvements over the first years of treatment (lasting perhaps 5–10 years) and then a plateauing of the effect. (J Inherit Metab Dis. 2014 Nov; Epub: 2014 Feb 11).*	See section 5.10. The committee heard that the effectiveness of ERT is well established and the dose of ERT can be titrated to the lowest effective dose. The committee noted that its considerations on the value for money of eliglustat were based on the current evidence and clinical practice, but that they would need to be reconsidered if ERT was no longer available in routine practice.

Gauchers Association	It is crucial to point out that the patients currently receiving eliglustat are receiving this treatment through the company's compassionate programme and that it is not being funded by NHS England. These patients have been prescribed Eliglustat for clinical reasons by their treating clinicians at one of the 8 Expert Centres in England, and fall into the following categories: 1. They are unable to take ERT 2. Their Gaucher disease was not responding to ERT 3. They have poor venous access 4. They are receiving eliglustat in addition to ERT to manage untreated symptoms of their Gaucher disease not addressed by ERT. If NICE refuse to fund eliglustat for these patients, they will either not receive a treatment and quoting NICE in para 5.1 "The committee concluded that type 1 Gaucher disease is a debilitating condition that has a significant impact on quality of life" and therefore be condemning these patients to a poor quality of life impacting on their ability to work, be independent and in some cases early death. OR they will have to take Miglustat, which quoting NICE para 4.3 "The clinical and patient experts noted that people with type 1 Gaucher disease choose ERT whenever possible because Miglustat is associated with tolerability and safety issues, and modest efficacy" which is unethical when Eliglustat is a licensed treatment available for these patients.	Comments noted. Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers, when the company provides it with the discount agreed in the patient access scheme.
Gauchers Association	In NICE's recent approval of Migalastat for Fabry disease, it says "NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits of migalastat and ERT for treating Fabry disease, which should inform a future evaluation of the costs and benefits of all treatment options for Fabry disease". We would ask NICE to consider recommending eliglustat along the same lines and then implement a Managed Access Scheme for all treatments for Gaucher disease to collect the evidence needed for future evaluations and be proactive rather than reactive.	Comments noted. Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers, when the company provides it with the discount agreed in the patient access scheme. The committee also encouraged the company, NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits of eliglustat and ERT for treating type 1 Gaucher disease.

Patient	As a patient Expert for Eiglustat, I would like to register my disappointment with NICE's decision not to fund Eiglustat on the NHS on the following grounds: As a Gauchers Disease Type I patient, I was put on ERT for a number of years where I experienced a number of side effects including constant diarrhoea and vanishing veins. My quality of life and mental wellbeing was suffering compared to normal person. I was than taken off ERT and put on Miglustat to improve my quality of life. Being on miglustat for the past 4 years has been a horrendous experience as it has permanently damaged 25% of my kidneys, having normal kidneys before being put on Miglustat. On compassionate grounds, I was put on Eiglustat funded by the company (not the NHS). This improved my quality of life and mental wellbeing by taking one tablet a day and preserving the rest of my kidneys. To be told by NICE that NHS will not fund this medicine is a severe blow not only to my quality of life but also for my mental wellbeing. Taking a tablet a day has enabled me to carry on with my life as a normal person. I hope and believe that NICE will re-consider its decision in light of the above said.	Comments noted. Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers, when the company provides it with the discount agreed in the patient access scheme.

Patient	I was diagnosed with Gaucher aged 17, and there was no cure or even treatment, but a whisper of a new treatment in the USA gave my parents & myself fresh hope. I started taking the Ceredase twice a week -this was infusions and involved two days a week in hospital, my Mother had to give up work and our lives pretty much revolved around hospital visits & stays. Two infusions a week with poor intravenous access, eventually took its toll and after endless failed attempts at access and every option exhausted including between my fingers & toes, wrists & neck used for infusions. Due to the constant trauma, I ended up with acute needle phobia and with no more places to gain access I was given a portacath., still requiring a needle, but in a designated spot and guaranteed access every time. Though still very unpleasant and somewhat uncomfortable I managed to get 18 years use from the port until it blocked and became unusable. At this point Zavesca (Miglustat) was available, my relief was indescribable, a tablet! The side effects of Zavesca were not pleasant. Unfortunately, after taking Zavesca for 5 years I noticed tingling & loss of feeling in my fingers & toes … I was instructed to stop taking the tablet with immediate effect - the tablet had caused peripheral neuropathy - I was devastated and terrified about having to start having infusions again. [redacted] told me he was trying to get Eliglustat for me on compassionate grounds, this was major news and the feeling of relief was overwhelming. He pulled out of all the stops to get the drug for me on the compassionate basis of I'd been without treatment for 9 months and fearing my markers were not looking good but eventually after another fight for treatment I got the Eliglustat, a far superior drug to Zavesca in every way from the efficiency of treating Gaucher to the dreaded side effects. The relief was overwhelming, I started the tablets in March 2015, the results have been brilliant, much better than when I was on Zavesca, my health has improved, there are no side effects and again I have the promise of normality! To find out that I might now lose this treatment is devastating - for me there is no other option for treatment. Eliglustat is my only option, to find that I may now lose this is terrifying, it's taking away my health, my fear of this is impalpable - when the treatment is there and WORKS. For me as a patient there is no other treatment for me to take to treat my Gaucher disease, to take this away from me is condemning me to a future of uncertainty and without doubt major deterioration health wise. On Eliglustat, my illness is managed easily and effectively, with a safe, stable & reliable drug. My biomarkers have dropped, as much as 30% in just one year! To take this away from me would feel like a death sentence. Which is why I urge that you reconsider your decision on this drug. It is not a miracle cure per se but for myself (and hopefully other Gaucher patients) it is a miracle treatment.	Comments noted. Eliglustat is recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers, when the company provides it with the discount agreed in the patient access scheme.

Clinical expert	4.13 I have reservations about the continued cynicism expressed about the scientific basis for the non-inferiority margin in the ENCORE trial. Justification of these parameters is clearly set out in all the documentation and was accepted in full dialogue with FDA and EMA. It was further clarified at the first session of NICE. The statistical confidence margin was based on 'real-life' data, objectively and independently obtained in the clinical study of enzyme therapy given either every two weeks or monthly (Kishnani PS, Di Rocco M, Kaplan P, Mehta A, Pastores GM, Smith SE, Puga AC, Lemay RM, Weinreb NJ. (2019) Mol Genet Metab. 96:164-70). The parameters chosen and agreed by the regulatory authorities took account of variation in haematological and visceral volumetrics determined by MRi in the baseline stability population enrolled in this clinical trial.	Comments noted. This section reflects the ERG report, the committee's considerations are reflected in section 5. See section 5.3, the committee understood the challenges in developing a clinical trial programme for a rare condition, and concluded that the ENCORE trial was sufficiently robust for its decision-making.
Clinical expert	4.21 The suggestion that the (inescapable) open-label nature of the ENCORE trial led to subjective evaluations of therapeutic responses appears to me to be officious: the responses were based on haemoglobin concentrations; platelet counts; and spleen and liver volumes, and in secondary measures by DEXA scintigraphy determined by a blinded set of off-site radiologists who analysed serial data. In the context of clinical trial regulation and monitoring I cannot conceive of how the evaluations of the primary individual and composite endpoint primary endpoint data could be rendered more objective.	Comments noted. This section reflects the ERG report, the committee's considerations are reflected in section 5. See section 5.3, the committee understood the challenges in developing a clinical trial programme for a rare condition, and concluded that the ENCORE trial was sufficiently robust for its decision-making.

Clinical expert	4.22 It is disingenuous to claim that there was no explanation for the four-year ENCORE follow-up data involving 46/7 patients. At the first meeting in NICE this matter was set out clearly. It is also further explained in detail in the recent publications. Again: Time on the drug within the conditions of the ENCORE trial was determined by the date of enrolment (which in the many participating centres worldwide spanned 2 years, from September 2009 until November 2011), the initial treatment group to which patients were randomly assigned, and their country of residence. After approval of the drug by the FDA in the Autumn of 2014, US trial participants left the study and received commercial eliglustat; it has been reimbursed in the US and elsewhere for 2½ years. Long-term safety and efficacy with respect to years of exposure for all 157 eliglustat-treated patients in ENCORE is available; in 46 of these, trial data are reported for a period of 4 years. (see Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM et al (2017). Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. Blood. Feb 6. pii: blood-2016-12-758409). In this publication, of ENCOREdata at four years, outcomes are carefully depicted for the whole cohort and also for those in the subset for whom only four year data were available: no material difference was found (see Figure 2, Cox TM et al (2017).	This section has been removed from the FED.

Clinical expert	In ENCORE, clinical stability was maintained with respect to haemoglobin concentration, platelet count, liver and spleen volume, bone mineralization density and widely accepted Gaucher biomarkers for up to 4 years - well beyond the interval that might be attributed to residual effects of prior long-term enzyme therapy. By its nature, since active bone disease was an exclusion criterion in the stable population, this trial cannot comprehensively address the capacity of the drug to reverse bone disease, but as cited in the NICE report there are indications of a strong primary effect of the drug over all aspects of the phase 2 and phase 3 trial outcomes. A further important point set out in Table 2 of this publication relates to the demonstration of efficacy in the ENCORE trial: which sets out changes from baseline in haematological, visceral, and bone parameters over each year on the study drug. Using the appropriate analysis in the repeated measures mixed model of least-square mean changes from baseline in these efficacy parameters, attained after a mean of 10 years of enzyme therapy, mean values for haemoglobin concentration, platelet count, spleen and liver volumes in the subset of patients who had 4-year data (Figure 2, A-D), there were small but statistically significant reductions in least-square mean liver (3%, P=0.02) and spleen volumes (13%, P<0.001) after 4 years of eliglustat treatment (Table 2). Also after treatment with eliglustat, lumbar spine least-square mean Z scores of BMD increased by 0.29 (significantly).	Comments noted. See section 5.8, the committee concluded that eliglustat is an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty of effectiveness in comparison with ERT in the long term.
Clinical expert	The committee and NICE is impressive for its general willingness to make its decisions partly on behalf of patients and in relation to those at the centre of the illness and its possible treatments. However, on this occasion, I have strong reservations about the procedure adopted. The committee fixed the dates firmly for the two hearings but then changed the date of the second hearing at short notice and at a time when none of the experts nor patient representatives could attend. It is thus appears counter to usual practice that the committee has in effect met and apparently decided upon several weighty matters related to this drug in camera. Despite being immediately informed about this matter by several advisors, the committee went ahead. I contend that full appreciation of the patients' concerns and experiences with the different agents could not have been fully taken in at one brief session.	Comments noted. The committee meeting was postponed because it could not be quorate, and it was rescheduled to the earliest next availability. Because experts could not be present, a teleconference was organised separately with experts prior to meeting. Experts agreed to participate. The feedback from this teleconference was presented at meeting via slides and minutes were also included in committee papers. The main focus of second meeting was to discuss company's updated results (based on updated list prices and a patient access scheme discount) and updated patient estimates – clinical issues remained as discussed at the 1st meeting.

Clinical expert	In view of this negative recommendation, there is a feeling that something went wrong with the evaluation process – at least so far. The patients' voice has been inadequately heard in relation to the take up and attractiveness of an oral therapy - specifically in terms of cost, labour, efficiency, practical advantage and acceptability. As an (unpaid) international investigator in the clinical phase 3 programme and earlier a participant in the international safety monitoring committee, I can report that with continuing evidence of safety, tolerability and efficacy, the international take-up of eliglustat has exceeded expectations. The international Phase II and Phase III clinical studies undertaken with eliglustat over more than a decade represent the largest programme of therapeutic investigation ever conducted in any ultra-orphan disease (as defined by Sir Michael Rawlins a disease that affects less - much fewer - than 500 patients in the UK). Hitherto, data from 1400 patient years of exposure are available with comprehensive studies of 225 patients for up to 12 years. It is salutary also to note that the agent is the first ever of six therapies accepted for Gaucher disease to be investigated in the formal setting of a randomized controlled double-blind, placebo-controlled and cross-over clinical trial. While one understands that the report from the NICE Evaluation Committee is, to date, a preliminary recommendation, recent approvals by the Institute in relation to ultra-orphan diseases seem to have adopted very different standards for acceptance on grounds that do not seem to have been subject to equally rigorous scientific consideration. Given some inaccuracies in the assumptions (from the first meeting) and the unprecedented depth and quality of the clinical trial findings obtained with the enrolment of British patients suffering from Gaucher disease over many years, it appears likely that matters of cost must have taken priority in the decision-making so far. After approval by the FDA in August 2014 and EMSA in early 2015, eliglustat is approved or about to be recommended for reimbursement in most eligible countries. Given the weight of evidence for its tolerability, safety and efficacy and the huge advantage for most patients of a first-line oral agent, I can only comment from experience, that the case for its acceptance for NHS reimbursement is incredibly strong. Without wishing to overreach the limits of expert opinion, I personally take the view that, subject to reasonable cost negotiations, it would be an injustice and disservice to UK patients were the drug to be denied them in the NHS specialist centres or elsewhere.	

Comments received from commentators

Commentator	Comment	Response
Shire	We note the Committee's consideration of the uncertainties in the clinical trials and wish to express our agreement with the points highlighted in the ECD.	Comments noted. See section 5.8, the committee concluded that eliglustat is an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty of effectiveness in comparison with ERT in the long term.
Shire	We note the Committee's consideration that adverse effects associated with eliglustat would be acceptable to patients, especially in the context of the advantages of oral administration. It is likely that the adverse effects of eliglustat may have a negative impact on adherence rates and subsequently, on health outcomes. As such, in the long run, oral intake may not be advantageous to some patients.	Comments noted. See section 5.19 The committee noted that, because eliglustat is an oral therapy, it would give people the freedom to travel and attend university, and remove the need for people to take time off work for intravenous infusion appointments. It heard that the drug would be associated with important indirect mental health benefits because it allows people to live a more normal life.
Shire	Section 4.16 states that 83% of patients who switched from ERT to eliglustat expressed preference for oral therapy. However, it is well documented that adherence to oral therapies is inconsistent; therefore presenting a risk in achieving full benefits for patients.	Comments noted. See section 5.19 The committee noted that, because eliglustat is an oral therapy, it would give people the freedom to travel and attend university, and remove the need for people to take time off work for intravenous infusion appointments. It heard that the drug would be associated with important indirect mental health benefits because it allows people to live a more normal life.

Sheela Upadhyaya
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4 April 2017

Dear Sheela,

Re. NICE Highly Specialised Technology Evaluation: Eliglustat for treating type 1 Gaucher Disease [ID709]

Sanofi Genzyme (SGZ) welcomes the opportunity to respond to the Evaluation Consultation Document for eliglustat in the treatment of type 1 Gaucher Disease.

We believe eliglustat offers a truly beneficial option for patients suffering from this chronic rare disease. We consider the evidence provided supports this position and further, that the availability of eliglustat would not place additional financial burden on the NHS in light of the adjustment to the Patient Access Scheme.

The four-year data from ENCORE demonstrated sustained clinically meaningful effectiveness in ERT-stable patients. Similarly, the four year data from ENGAGE show similar outcomes with eliglustat for treatment naïve patients across key clinical parameters; haemoglobin level and platelet count, spleen and liver volume, in line with ERT therapeutic goals for this disease.

The four year data from ENCORE and ENGAGE have recently been accepted by the Committee for Medicinal Products for Human Use (CHMP) as further evidence of the positive risk/benefit profile of this important new oral therapy.

We have a number of concerns regarding the following elements in the Evaluation Consultation Document:

- The committee's challenge to the regulatory assessment of the clinical value of eliglustat:
    - The trial programme demonstrates that eliglustat is a clinically comparable option for treatment-naïve and ERT-stable patients, when comparing with ERT at doses far above those routinely used in the UK a position supported by CHMP and FDA market authorisation.

- The utilisation of real world dose without adjustment for either real world weight or the effectiveness delivered by trial doses
    - With the exception of the ERG's preferred assumption all sources of UK weight data including RWD indicate that patients require five vials of ERT per infusion. The dose deemed most plausible in the ECD equates to four vials per infusion. This approach lacks methodological consistency and is a flawed basis from which to determine value for money for the NHS.

- Recognition of the true benefit of an oral therapy on a individual's quality of life in a chronic, rare condition
    - Despite compelling evidence from patient representatives, it appears the committee hasn't recognised in their decision that the substantial QALY gain associated with eliglustat reflects the genuine influence on an individual's quality of life of oral therapy over a lifetime of care.

Our response to the consultation is in a number of parts;

1) This covering letter provides a summary response focusing on the critical issues:
    a. are there clinically meaningful effectiveness differences between eliglustat and ERT in both treatment-naïve and ERT-stable patients; and,
    b. what level of uncertainty is there in the economic analysis and therefore in the assessment of eliglustat being good value for money for the NHS

2) A confidential appendix providing revised cost consequence and budget impact results based on the revised patient access scheme for eliglustat and taking into account commercial arrangements in place for the ERT products.
3) A summary appendix of our concerns regarding the HST process in general and, in particular, as it has been implemented in this evaluation
4) A comprehensive accompanying document that responds to the ECD point by point

As part of this response to the ECD, SGZ is submitting a number of concerns regarding process elements associated with this HST assessment (Appendix 2).

SGZ also requests confirmation from NICE that the commercial arrangements in place for the ERTs meet the criteria needed to be taken into account in formal NICE evaluations, in that the prices are 'consistently available across the NHS, and if the period for which the specified price is available is guaranteed' (NICE 2014).

The next part of this letter addresses the clinical and economic issues raised in the ECD in turn.

From the point of view of the clinical and economic evidence submitted SGZ considers there to be a very strong argument for eliglustat to be available to patients with Gaucher Disease receiving treatment in the NHS in England.

We hope that the committee will reconsider their initial decision in light of the evidence we present below, in order to benefit patients with this rare condition.

Yours sincerely

Claire Grant
Head of Health Outcomes
Sanofi UK and Ireland

a. Clinically meaningful effectiveness, comparing eliglustat and ERT in treatment-naïve and ERT-stable patients

The trial programme for eliglustat: the phase II study, ENGAGE, ENCORE and EDGE is the largest trial programme for any lysosomal storage disorder. However, this is an ultra-orphan disease and there are data gaps in the evidentiary package that SGZ acknowledges. The trial programme demonstrates that eliglustat is a clinically comparable option for treatment-naïve and ERT-stable patients, when comparing with ERT at doses far above those routinely used in the UK a position supported by CHMP and FDA market authorisation.

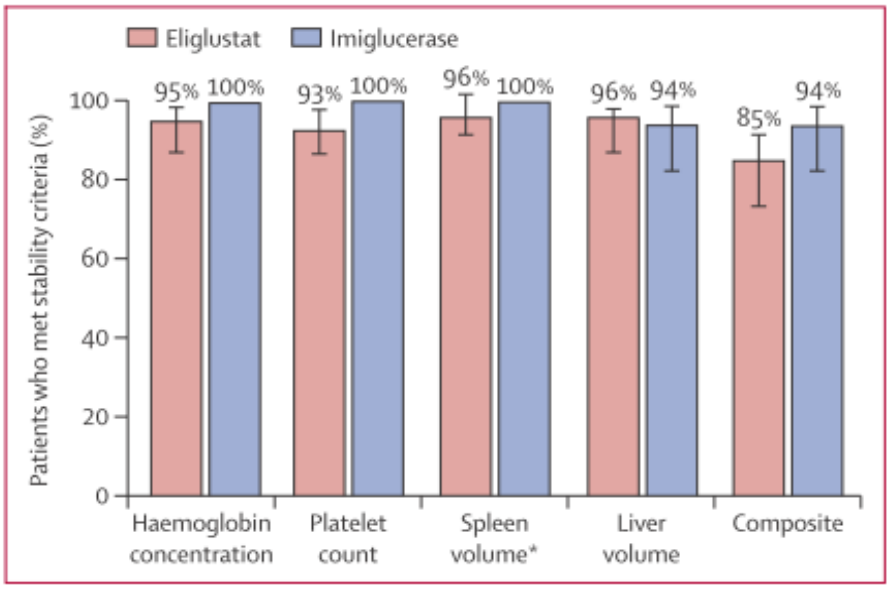
ERT-stable patients

Taking first the ERT-stable patients, the objective of the ENCORE trial was to evaluate non-inferior maintenance of stability at one year for patients switched from ERT to eliglustat compared with patients that continued on ERT. In order to be eligible for ENCORE patients had to have been on ERT for a minimum of three years, patients had in fact been on ERT for a mean of 9.8 years in the eliglustat arm and 10.0 years in the imiglucarase arm. For at least 6 of the 9 months prior to randomisation the patient had to have received a total monthly dose of 30U/kg to 130U/kg of ERT and patients had to have reached GD therapeutic goals (Cox et al., 2015). It is notable that UK patients would have been excluded from the trial at the dose of ERT that the evaluation committee takes to be the most plausible UK dose. Maintaining stability when moving from a product a patient has been on for a mean of 10 years to a novel therapy is a notable hurdle.

ENCORE's primary outcome was a composite of four domains: two haematologic (haemoglobin level and platelet count) and two organ volume measures (spleen and liver volume). Meeting the primary endpoint, i.e., maintaining stability, required the patient to be stable in all four components, based on changes from baseline that did not exceed pre-specified thresholds, at 52 weeks. Failure to meet one parameter meant failure of the primary endpoint. These pre-specified endpoints were not the same as the therapeutic treatment goals used in routine clinical practice (Pastores et al 2004). The ENCORE thresholds also did not take into account patients' baseline values across the four parameters.

The primary endpoint for ENCORE, non-inferiority of eliglustat compared with ERT, was demonstrated (Cox et al 2015). While the pre-specified non-inferiority margin was 25%, the lower 95% confidence interval was actually -17.6%, well within the 20% non-inferiority range requested by the Committee for Medicinal Products for Human Use (CHMP). The difference in trial primary endpoint can be seen in Figure 1 below.

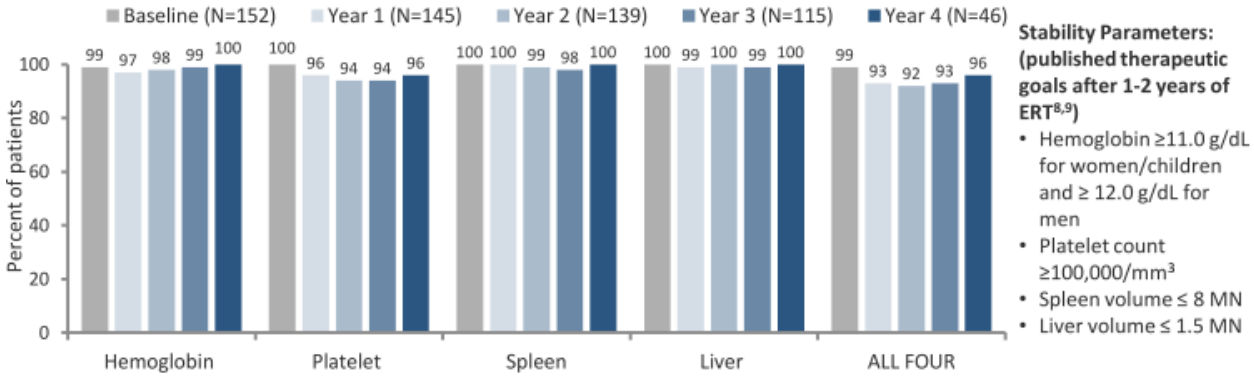
Figure 1 Percentage of patients who met stability criteria by individual components and composite endpoint 12 months after treatment initiation (if black and white eliglustat are the left hand bars)



Per-protocol population. Error bars represent exact 95% CIs around the proportion.
*Spleen percentages are based on the total number of non-splenectomised patients in each treatment group.

The ENCORE composite primary endpoint, while built out of evidence, is an artificial construct for the ENCORE trial alone. Therefore the ENCORE trial data were also analysed according to the more widely used therapeutic treatment goals (Pastores et al 2004) and the results are presented below (Cox et al 2016), Figure 2.

Figure 2: Stability with respect to published therapeutic goals (absolute value)



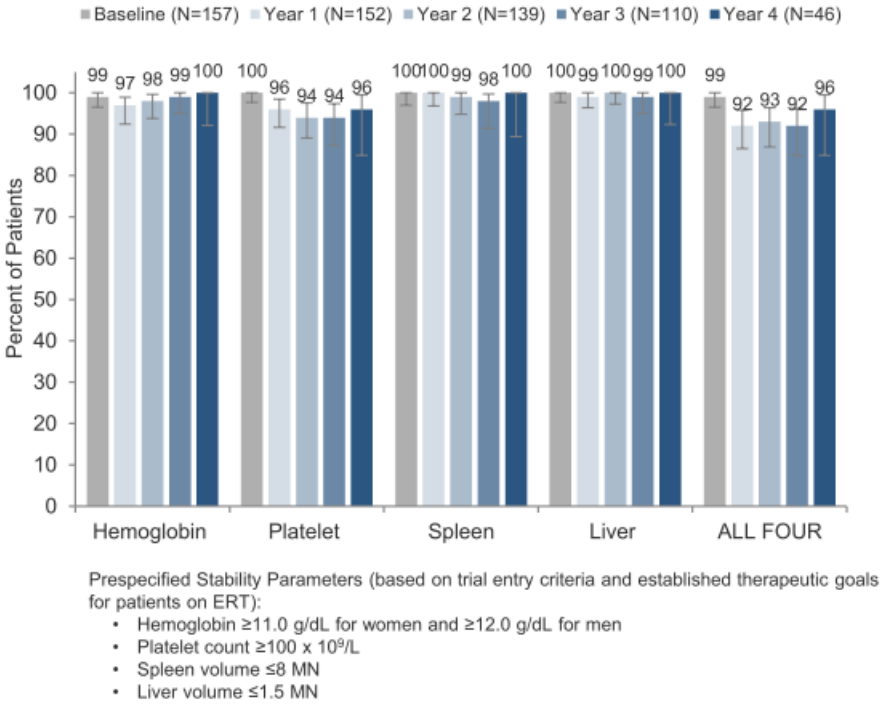
Some patients who switched from ERT to eliglustat in the ENCORE trial did not maintain stability at 52 weeks. Of the 18 patients who did not meet the primary endpoint in ENCORE (15 on eliglustat and three on imiglucerase), 16 missed on only one criterion, one patient on eliglustat missed on two criteria (spleen volume and platelet count). One patient on eliglustat was counted as a failure because this patient voluntarily switched to imiglucerase after 9 months, although all stability criteria were met at the time of the switch. Criteria that were not met in the eliglustat treatment group were haemoglobin concentration (four patients), platelet count (six patients), liver volume (three patients), and spleen volume (two patients). The criterion that was not met in the three patients treated with imiglucerase was liver volume.

However, failure to meet the trial endpoint did not mean that the patient had deteriorated clinically. For example, a patient would “fail” both the platelet and the composite endpoint if platelet count went from 260 x109/L at baseline to 200 x109/L after 12 months, a 30% decrease. This is not a clinically relevant change in platelet value: 200 x109/L is a platelet value within the range of normal platelet values for the ‘normal’ population and well above the allowable therapeutic goal threshold for GD patients. Based on the GD1 therapeutic goals for patients receiving ERT, 12 out of the 15 patients in the eliglustat group who did not meet the primary endpoint were maintained stability from a clinically meaningful perspective (see Figure 2).

As such, it can be concluded that after 52 weeks, only three out of 99 eliglustat per protocol patients had a clinically meaningful change in parameters after being challenged with a novel therapy having been on ERT for three years previously, a mean duration of ERT of 9.8 years and documented stability 6 months prior to enrolment.

The four year data for ENCORE, that have become available since the HST dossier was submitted demonstrate that eliglustat treatment resulted in stable haemoglobin concentration, platelet count and spleen and liver volumes for up to four years. Mean bone mineral density Z-scores also remained stable and were maintained in the health reference range (Cox et al 2017).

Figure 3 Pre-specified therapeutic goals based on entry criteria and goals established for patients on enzyme therapy (absolute value). Error bars denote upper and lower 95% confidence intervals



The four-year ENCORE data for mean haemoglobin concentration, platelet count, and spleen and liver volumes remained stable for up to 4 years. Year to year, all four measures remained collectively stable (composite endpoint relative to baseline values) in ≥85% of patients, as well as individually in ≥92%. Mean bone mineral density Z-scores (lumbar spine and femur) remained stable and were maintained in the healthy reference range throughout. For the therapeutic goals endpoint stability measures were maintained in ≥92% of patients, as well as individually ≥94%.

Non-inferiority margin (NIM)

From a statistical perspective it is important the Evaluation Committee is aware that while the pre-specified non-inferiority margin was 25% rather than 20%, the lower 95% confidence interval (CI) was less than 20% in 14 out of 16, and all appropriate, methods reported. This information was provided to NICE/the ERG in response to clarification questions in May 2016 and we are disappointed that it appears not to have been taken into account in the committee discussions.

Given the hypothesis for the study is that eliglustat is non-inferior to cerezyme, i.e. eliglustat is not worse than Cerezyme by more than the non-inferiority margin. The acceptance of the hypothesis is

determined by the lower bound of 95% CI, therefore, given a lower confidence interval bound of 17.6% non-inferiority can be declared at a margin of <20%.

A non-inferiority margin of 25% was selected for this study based on considerations of an imiglucarase response rate of 95% for the defined composite primary endpoint for measuring stability, and assuming a response rate of 85% for eliglustat based on Phase 2 data. The 25% margin accounts for a 10% difference between the active-comparator (imiglucarase) and test treatment arms (eliglustat) as well as an additional 15% for the inherent variability in estimating the difference between these 2 treatments (corresponding to the lower bound of the 95% confidence interval [CI]).

The margin of 25%, rather than 20%, was also chosen because the rare patient population limited the size of the study see Table 1. Despite this caveat, the lower bound of the 95% CI for the observed difference between treatment arms was -17.6%.

Table 1 Number of trial participants needed to meet different trial designs

Patient numbers	Non-inferiority Margin	Significance
150	25%	One-sided 0.05 significance level
186	25%	Two-sided 0.025 significance level
360	20%	Two-sided 0.05 significance level
441	20%	Two-sided 0.025 significance level

Therefore, moving to a 90% powered trial with a non-inferiority margin of 20% would have required the trial to nearly double in size, an extra 174 patients. Such a change in recruitment numbers would expose nearly double the number of patients to a non-licensed product, delayed access to a licensed treatment of GD1 for patients across Europe and significantly increased the practical challenge of recruiting sufficient patients in this ultra orphan disease.

The main result from the primary publication is calculated using Agresti and Caffo's adjusted Wald method. Other methods were explored, including the Newcombe's hybrid score interval, as requested by the ERG at the clarification stage. Of the 16 methods explored only two methods reported a lower 95% CI not within a 20% non-inferiority margin. For more information see the clarification document provided in July 2016, the content of the relevant question is also repeated in the accompanying document that responds to the ECD point by point.

To summarise, using exact and asymptotic methods that have the necessary statistical properties, it eliglustat demonstrated non-inferiority with imiglucerase at a 20% non-inferiority margin.

100mg BID/150mg BID dosing

While 48% of patients in the ENCORE trial received 150mg BID dose, the outcome of the trial is stil valid. PK/PD modelling demonstrates that materially different conclusions would not have been drawn with the 100mg BID dose.

Two methods for dosing eliglustat have been considered during product development. The first, used in the clinical trials, dosed according to plasma levels of the drug. The second, which is the dosing in the product's marketing authorisation, is based on CYP2D6 phenotype. Both approaches yield similar outcomes (Turpault et al 2015) however, dosing by CYP2D6 phenotype has the advantage of simplicity.

We provide more detailed information on the modelling undertaken in the accompanying document however, to summarise here, the Phase II/III programme demonstrates that a 100 mg BID dosing regimen results in a favourable clinical response in both treatment-naïve as well as in ERT-stabilized IM and EM patients, regardless of the eliglustat Ctrough being less than, equal to or greater than 5 ng/mL. The small gain in clinical efficacy that is expected to be achieved with a higher daily dose in some EM patients is not clinically meaningful. The recommended 100 mg BID regimen is predicted to have similar efficacy outcomes for IMs and EMs, and importantly, has a more favourable risk/benefit profile because patients would be at lower risk for elevated exposures resulting from drug-drug interactions in the real-word (post-marketing) setting.

In treatment-naïve patients, the clinical response continues over time as seen in the 4-year Phase II study, with patients in both trough concentration groups reaching similar treatment goals. The large number of clinical responders with a Ctrough <5 ng/mL indicates that this threshold is not the sole determinant for the safe and efficacious use of eliglustat in the GD1 population.

The only exposure-response relationship observed in ERT-stabilized patients was with spleen volume, which showed a shallow slope predicting only a predicted 4% maximum increase in spleen volume following a reduction in dose from 150 mg BID to 100 mg BID, which is comparable to the test-test variability of organ volume measurement by MRI, and is not clinically meaningful.

Any small gain in efficacy resulting from 150 mg BID dosing would be outweighed by the logistical complexities of dosing based on plasma concentrations. The conditions of use in the real-world (post-marketing) setting need to be taken into account. In this setting, drug-drug interactions are less controllable than in clinical studies (even with adequate guidance in the label and educational materials), especially considering over-the counter medications and natural products (such as grapefruit juice) can decrease the metabolism of eliglustat). The potential for eliglustat exposures to reach the extremes of the range determined as safe in clinical studies needs to be considered as part of the risk/benefit ratio.

In conclusion, the results of the PK/PD modelling based on eliglustat trial programme data show that the 100 mg BID dose is associated with no differences in efficacy that are clinically meaningful, compared with the 150mg BID in either ERT-stable or treatment naïve patients. These findings justify the authorised dose of 100mg BID as approved by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP).

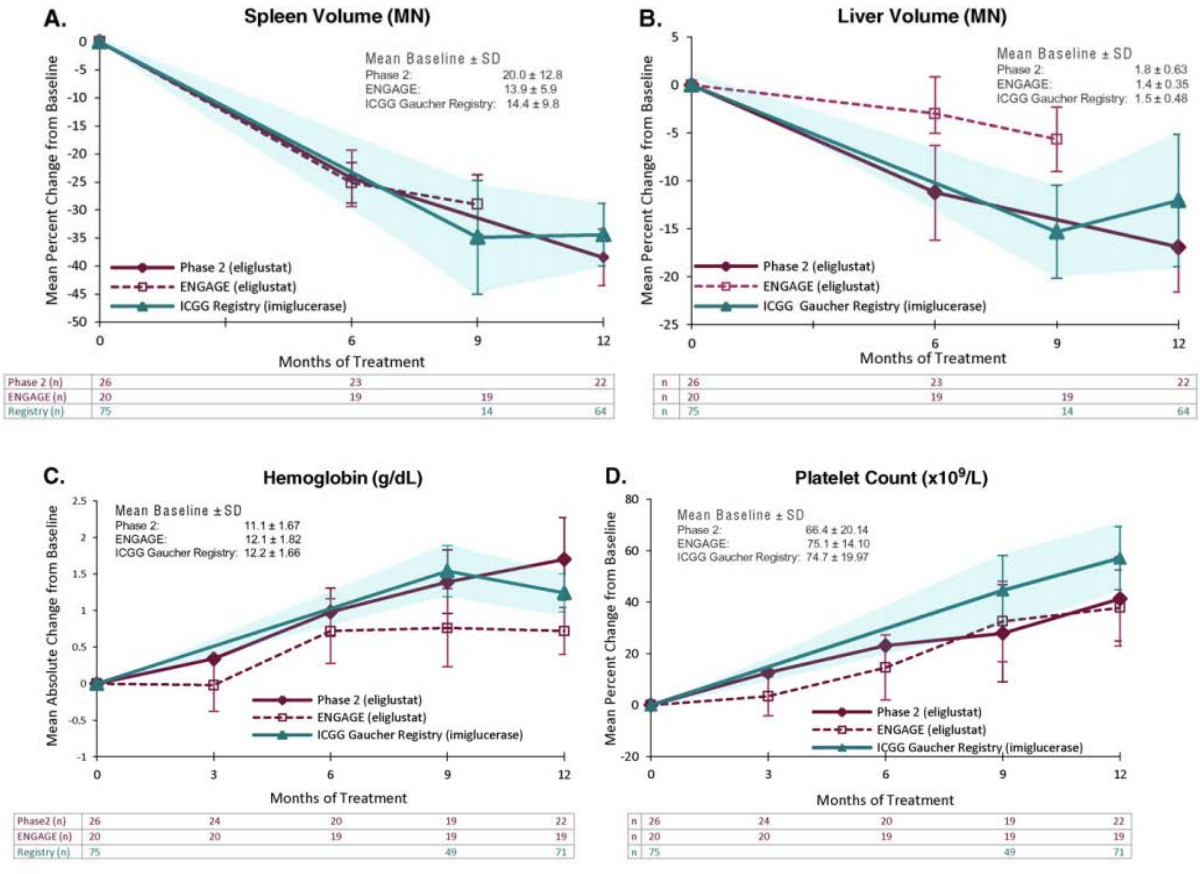
Treatment-naïve patients

While we do not have trial data comparing eliglustat with ERT in the treatment-naïve population, this was discussed with the CHMP and SGZ explored the possibility of a non-inferiority study. However, such a study would have needed at least 76 treatment-naïve patients to gain sufficient power. The CHMP agreed that given the rareness of the disease this was not considered feasible (EMA 2014).

SGZ carried out and submitted an indirect comparison of efficacy data of eliglustat with imiglucarase data from the International Collaborative Gaucher Group (ICGG) Registry to the CHMP (Ibrahim et al 2016). This has been published since the NICE submission (Ibrahim et al 2016). The CHMP concluded, this analysis indicated comparable treatment effects are seen for the most important endpoints during the 4 years of treatment [with eliglustat]. Further, continued improvement with eliglustat from 39 weeks of treatment to 78 weeks (1.5 years) in ENGAGE is shown on established clinical treatment outcomes for GD1, in addition to clinically meaningful effects on bone disease. Given the indirect comparison the CHMP concluded, 'a reasonable percentage of patients treated with eliglustat will achieve comparable results as are to be expected for the already registered ERT'.

The indirect comparison was a post-hoc analysis of treatment-naïve patients comparing the results of eliglustat treatment from the Phase II study (12 months) and ENGAGE (9 and 12 month data) with the results of imiglucarase treatment (up to 12 months) among a cohort of treatment-naïve patients with comparable baseline haematologic and visceral parameters from the International Collaborative Gaucher Group (ICGG) Registry. Organ volumes and hematologic parameters improved from baseline in both treatment groups, with a time course and degree of improvement in eliglustat-treated patients similar to imiglucerase-treated patients, see Figure 4. Mean ERT dose for the imiglucarase patients in the registry was 35U/kg, range 15U/kg-60U/kg.

Figure 4 Change from baseline in organ volumes and hematologic parameters



Upper and lower 95% confidence intervals are indicated by shading for imiglucerase and by brackets for eliglustat data.
Patients from the ENGAGE clinical trial had spleen and liver MRIs at the 9-month primary endpoint and, thus, did not have spleen or liver MRIs at 12 months.

This will be looked at in the biennial reports of Long term Eliglustat efficacy post marketing commitment. The first report is expected to be available by the latter half of 2017.

Based on this evidence SGZ is confident differences in the effectiveness between eliglustat and ERT in the two populations of interest are not clinically meaningful in patients maintained on eliglustat. This was supported by the clinical experts in the committee meeting in September 2016, however, their evidence appears to have been overlooked in this ECD.

b. Economic uncertainty and value for money for the NHS

The points raised in the ECD relating to uncertainty in the economic analysis are

1) the comparability of eliglustat and ERT effectiveness in the short- and long-term
2) uncertainty regarding the dose of ERT used in England and Wales treatment centres
3) the value of an oral, measured by utility

Comparability of eliglustat and ERT effectiveness in the short- and long-term

This point relates closely to the points discussed above regarding the accurate interpretation of the ENGAGE and ENCORE trial data. It is also critical to understand that the structure of the economic model is underpinned by the GD1 DS3 scoring tool. This is a robust and validated tool, developed independent of any HTA in 2010 to provide a standardised assessment for clinicians treating GD1. Using the GD1 DS3 scoring tool a difference of -3.17 or +3.86 is defined as being clinically meaningful (Weinreb et al 2010).

SGZ concludes that eliglustat and ERT are both effective treatments as measured on the GD1 DS3 tool, that patients treated with either product are likely to have a high chance of being maintained in the mild or moderate disease severity for many years, and while there may be minor effectiveness differences between products, between patients, from a population perspective, these have only a minor difference on long-term outcomes and the costs borne by the NHS.

It is imperative however, that ENCORE data are not considered appropriate for use in the treatment-naïve population, which is suggested in the ECD. As discussed above mean duration of treatment on ERT prior to the ECORE trial is 10 years. Such ERT-stable patients are very different and should not be used as a proxy due to an absence of data when the indirect data analysis (Ibrahim et al 2016) discussed above supports the assumption in the model that for treatment-naïve patients eliglustat and ERT can be considered clinically similar

We hope this addresses some of the committee's uncertainty and reassures them that there is not meaningful difference driven by clinical outcomes. Dose data on the other hand has a very significant effect.

SGZ ran some exploratory analyses changing the way the patient cohort moved onto the transition matrices. Rather than these being determined by the patients' baseline characteristics, two options were explored, the first takes the distribution of patients, both imiglucerase and eliglustat arms, at the end of the 52 weeks of ENCORE. This end of trial distribution then determines where the patients enter the transition matrices, thereafter the matrices are applied as in the base case model. The second option uses the ENCORE four-year eliglustat data, so that the final state distribution is based on the completion of 4 years of eliglustat therapy.

These changes mostly affected the frequency of time in mild vs. moderate health states. Eliglustat transition matrices tracked similarly to that of the long term transition data leading to generally similar results. This analysis was done on the company's base case: total incremental QALY gain 2.28. The first approach (using the 52 week data) led to revised total QALYs of 2.27. The second approach (using 4 year data) led to total incremental QALYs of 2.29. There is minimal change in costs as the only changes were in the health state costs, which are not the drivers of costs in this model.

This exploratory analysis lend credibility to the assumption in the base case model, and confirms that given the similarity in clinically meaningful disease control, in the long-term similar outcomes would be expected with both eliglustat and ERT.

Dose of ERT

Clinical expert input was taken into account regarding the dose of ERT used in routine clinical practice in the UK and determined that the most plausible dose for ERT is 25U/kg, rather than

42.4U/kg, the mean dose of imiglucarase from the ENCORE trial. SGZ does not dispute that the UK routinely uses lower dose than those reported in ENCORE. As such we accept that 25U/kg is a reasonable, if low, estimate. However, it is inconsistent to use real world dose data but ignore real world weight data; total administered dose being a product of dose and weight. In applying real world doses to ENCORE trial weight data the ERG's analysis is unbalanced and unfair. Similarly, the same effect cannot be assumed at RWE dosing as was achieved within the clinical trials on higher doses.

The estimated mean patient's dose at 25U/kg and ENCORE trial weight of 67.5kg gives a mean total dose of 1687U, or four vials. See Table 2 below for alternative estimates for dose and weight that have more internal consistency.

Table 2 Real world weight data for UK GD1 patients

	Weight (kg)	Unit/kg	Total dose	Dose rounded to nearest vial	No. vials
ENCORE trial	67.5	25	1687.5	1600	4
AWMSG (velaglucerase)	75	25	1875	2000	5
Royal Free Hospital (RFH 2017)	73.29	25	1832.25	2000	5
ICGG (Genzyme_Data on file, 2017a)	71.8 (last follow up)	25	1795	2000	5
Pooled UK patients from ENGAGE and ENCORE(Genzyme _Data on file, 2017b)	73.6 (study end)	25	1840	2000	5

What is notable, is that with the exception of the ERGs preferred assumption the majority of weight data points require five vials. The dose deemed most plausible in the ECD requires four vials. SGZ considers this to be an unreasonable approach, lacking methodological consistency and a flawed basis from which to determine value for money for the NHS and the current negative draft recommendation.

Appendix 1 provides revised cost consequence and budget impact estimated results based on the committee's preferred assumptions, but also considering the impact of applying real world UK weight data.

Further, while there is extensive discussion in the ECD of the validity of eliglustat efficacy data from the ENCORE trial where the doses considered are 100mg BID and 150mg BID, there is no discussion of adjusting ERT efficacy data to account for usual UK dose being more than 40% lower than the trial dose. SGZ disagrees with the committee's interpretation of the analysis by ERT <35U/kg/≥35U/kg dose, that there is no dose/response relationship with ERT, the mean dose in <35U/kg population is 27U/kg, while the mean dose in the ≥35U/kg population is 51U/kg. Of the five patients in ENCORE who had a dose of ≤25U/kg there were three males and 2 females, all of whom weighed less than 68kg, for information, average female weight in the UK was 70.2kg in 2010 (ONS 2010). SGZ would suggest the correct interpretation of these data is that similar outcomes can be achieved using doses of ERT tailored to an individual's specific weight, disease severity and other relevant baseline characteristics. Taking the approach that the efficacy results seen in ENCORE for ERT would be observed in usual UK practice potentially unfairly disadvantaged eliglustat.

Value of an oral treatment option

The QALY gain associated with the ERGs preferred assumptions was 1.05 per patient over the lifetime of the model. While this is lower that the company submitted base case of 2.28 (both for the ERT-stable IM/EM population) it is a notable QALY gain in a patient population that is well-managed to a large extent.

SGZ is concerned that comments in the ECD suggests the committee values QALY gains due to route of administration differentially to similar QALY gain due to, for example, reduced side-effects or

improved symptom control. GD1 requires lifetime treatment, oral administration should not be trivialised as improving convenience when the alternative is fortnight IV infusions for 30, 40, 50 years. In the ERG report and the ECD there are references to previous NICE submissions that have considered different routes of administration (Liu et al 1997; Twelves et al 2006; Tabberer et al 2006; and NICE 2007) what is not explicit to the reader, is that these reference terminal cancer treatments, at least one of which is specifically a palliative treatment. The impact the route of administration will on a person in the last months of life perhaps looking for life-extending treatment, compared with a person embarking on many years of chronic treatment for Gaucher Disease are considerably different.

The committee heard very compelling evidence from the patient representatives in the first meeting in September 2016 regarding the impact of oral treatment on quality of life. Expert clinician evidence submits the significant indirect mental health benefit of an oral. The committee accepts that the *Health* Related Quality of Life benefit of an oral is 0.05. However, it then undermines its own assumption by concluding, '*The committee was not convinced that these could be justified solely based on the benefits of an oral treatment*'. It appears the committee hasn't recognised that the substantial QALY gain is a summation of that 0.05 over a lifetime of treatment, reflecting how much more than convenience an oral option is, over a lifetime of care and a genuine influence on an individual's quality of life.

Appendix 1

NICE Highly Specialised Technology Evaluation: Eliglustat for treating type 1 Gaucher Disease [ID709]:

Revised results for the Cost Consequence and Budget Impact Models

Contents

SanofiGenzyme herewith submits revised results for the cost consequence and budget impact models. All information contained within this document is confidential.

Revised PAS price

SGZ has submitted a revised PAS price that was approved by the Department of Health on Friday 24 March 2017. This was communicated to NICE on Monday 27 March 2017. Prices relevant to this assessment are presented in Table 3 below. SGZ has asked for clarification that the commercial arrangement that Shire has in place for VPriv meets the required criteria for an arrangement to be considered in a formal NICE assessment: reduced prices are transparent and can be consistently available across the NHS, and when the period for which the specified price is available is guaranteed (NICE 2014).

As the holder of the Marketing Authorisation for Cerezyme, SGZ is aware of the price per vial at which it is sold into NHS-England. SGZ does not know the details of the commercial arrangement the Shire has for VPriv, however, given the commentary in the ECD it is clear that there is a discount in place. SGZ has run a set of revised analyses and scenarios as the prices listed in Table 3, using a best guess for the price of VPriv.

We also run an example one-way sensitivity analysis and a PSA looking at the ERT-stable, IM/EM population compared with velaglucerase using all the ERG's preferred assumptions. These sensitivity analyses don't use the UK weight we suggest is most plausible.

Table 3 – The price of Gaucher Disease Treatments to NHS England

	Capsule price	56-capsule pack price	Average cost per patient (IM/EM) per year
Eliglustat			
List price	£342.23	£19,164.96	£250,000
Revised PAS Price [redacted]	[redacted]	[redacted]	[redacted]
ERT			
Imiglucarase price per vial to NHS	[redacted]		
Velaglucerase price per vial to NHS	[redacted]		

The information provided in the ECD has allowed SGZ to respond to what the Committee has stated it is preferred and most plausible assumptions. Sanofi Genzyme accepts a number of these preferences, however some we contend.

We start with a summary of the results tables from the ERG report (16 December 2016). These are based on the following assumptions. See Table 4 and Table 5 for the ERGs cost consequence results and Table 6 and

Table 7 for the Budget impact results.

ERG preferred assumptions:

- Alternative discontinuation rates for eliglustat and ERT treatments;
- Alternative assumptions regarding the mortality of Gaucher patients;
- Alternative assumptions regarding the HRQoL benefits associated with oral therapy.
- Alternative assumptions made regarding the administrative costs of eliglustat and ERT
- Changes to the dose of eliglustat and ERT treatment assumed in the model;

ERG base case analysis (Tables 67 & 68 in the ERG report of 16 Dec 16)

Table 4: Incremental QALYs and Costs (Eliglustat (PAS price) vs. Imiglucerase (list price))

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	[redacted]	[redacted]
ERT stable PM	[redacted]	[redacted]
ERT naïve IM/EM	[redacted]	[redacted]
ERT naïve PM	[redacted]	[redacted]

IM= Intermediate Metaboliser; EM = Extensive Metaboliser, PM = Poor Metaboliser

Table 5: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	[redacted]	[redacted]
ERT stable PM	[redacted]	[redacted]
ERT naïve IM/EM	[redacted]	[redacted]
ERT naïve PM	[redacted]	[redacted]

IM= Intermediate Metaboliser; EM = Extensive Metaboliser, PM = Poor Metaboliser

Table 6: Budget Impact with Original Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

We replicated the analysis above, which is the ERG's preferred set of assumptions and which the committee have agreed with as far as we can ascertain, this time using the prices listed in Table 3. Results in Table 8 are the results versus imiglucarase, Table 9 is versus velaglucerase and Table 10 is the budget impact results using the revised uptake numbers and the prices listed in Table 3.

ERG preferred assumptions with revised PAS price

Table 8: REVISED PAS for eliglustat and estimated commercial arrangements for the ERTS: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	[redacted]	[redacted]
ERT stable PM	[redacted]	[redacted]
ERT naïve IM/EM	[redacted]	[redacted]
ERT naïve PM	[redacted]	[redacted]

IM= Intermediate Metaboliser; EM = Extensive Metaboliser, PM = Poor Metaboliser

Table 9: REVISED PAS for eliglustat and estimated commercial arrangements for the ERTS: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	[redacted]	[redacted]
ERT stable PM	[redacted]	[redacted]
ERT naïve IM/EM	[redacted]	[redacted]
ERT naïve PM	[redacted]	[redacted]

IM= Intermediate Metaboliser; EM = Extensive Metaboliser, PM = Poor Metaboliser

Table 10: REVISED PAS and other commercial arrangements: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

While these results would suggest that at the revised PAS price eliglustat offers value for money accepting all of the ERG's assumptions, SGZ does *not* accept all of the assumptions. Specifically using routine UK dose but not routine UK weight is inconsistent. Nor do we consider it plausible that ERT results from the ENCORE trial, at a mean dose of 42.4U/kg, can be simply mapped over to a much lower dose without consideration of adjustment for patient characteristics, such as weight and disease severity.

SGZ tested the Committee's preferred dose of 25U at two weights that are more plausible than that used by the ERG:

- 71.8kg (ICGG 2017 UK GD patient weight)
- 73.29 kg (Royal Free Hospital)

Revised PAS and 71.8kg (ICGG 2017 UK GD patient weight)

In running these analyses a simple mean weight was applied in the model rather than assigning any population/gender distributions.

Table 11: ERG assumptions but with UK patient weight applied (71.8kg): REVISED PAS for eliglustat and estimated commercial arrangements for the ERTS: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	[redacted]	[redacted]
ERT stable PM	[redacted]	[redacted]

ERT naïve IM/EM	[redacted]	[redacted]
ERT naïve PM	[redacted]	[redacted]

IM= Intermediate Metaboliser; EM = Extensive Metaboliser, PM = Poor Metaboliser

Table 12: ERG assumptions but with UK patient weight applied (71.8kg): REVISED PAS for eliglustat and estimated commercial arrangements for the ERTS: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	[redacted]	[redacted]
ERT stable PM	[redacted]	[redacted]
ERT naïve IM/EM	[redacted]	[redacted]
ERT naïve PM	[redacted]	[redacted]

IM= Intermediate Metaboliser; EM = Extensive Metaboliser, PM = Poor Metaboliser

Table 13: Weight 71.8kg, REVISED PAS and other commercial arrangements: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Revised PAS and 73.29 kg (Royal Free Hospital)

Table 14: ERG assumptions but with UK patient weight applied (73.29kg): REVISED PAS for eliglustat and estimated commercial arrangements for the ERTS: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	[redacted]	[redacted]
ERT stable PM	[redacted]	[redacted]
ERT naïve IM/EM	[redacted]	[redacted]
ERT naïve PM	[redacted]	[redacted]

IM= Intermediate Metaboliser; EM = Extensive Metaboliser, PM = Poor Metaboliser

Table 15: ERG assumptions but with UK patient weight applied (73.29g): REVISED PAS for eliglustat and estimated commercial arrangements for the ERTS: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	[redacted]	[redacted]
ERT stable PM	[redacted]	[redacted]
ERT naïve IM/EM	[redacted]	[redacted]
ERT naïve PM	[redacted]	[redacted]

IM= Intermediate Metaboliser; EM = Extensive Metaboliser, PM = Poor Metaboliser

Table 16: Weight 73.29kg, REVISED PAS and other commercial arrangements: Budget Impact with New Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

As can be seen when running a more plausible UK weight in the model, the cost savings are notable in the GD1 population. On top of this is the significant benefit that the oral formulation gives people with Gaucher Disease, for no clinically meaningful difference in efficacy. Given uncertainty regarding the long-term outcomes associated with the dosing level of ERT in the UK, specifically for bone manifestations, there could potentially be better outcomes with eliglustat.

One Way Sensitivity Analysis:

The sensitivity analyses below are run with the prices in **Table 3**, with the ERG's preferred assumptions, rather than SGZ'z preferred assumption from weight.

Figure 5: Change in QALYs with OWSA

Figure 6: Change in Costs OWSA

Probabilistic Sensitivity Analysis:

The basis for this analysis is the ERT-stable population, velaglucerase as the comparator, the prices in Table 3 and using the ERG base case, not SGZ's preferred weight assumptions. **The results of this show that in 84.1% of cases eliglustat was cost-saving and 100% of the time eliglustat accrued positive incremental QALYs in comparison to velaglucerase.**

Figure 7: PSA at discounted prices with ERGs assumptions implemented

Conclusion

The PSA and the one-way sensitivity analyses presented above give results with the ERGs preferred base case but with the prices from Table 1, including the revised PAS for eliglustat. With those assumptions there is a strong case that eliglustat offers value for money to the NHS. If a plausible UK weight were used for Gaucher Disease patients the results would be increasingly in favour of eliglustat, the results presented above are the 'worse case scenario' and as such suggest that 84% of the time eliglustat will be cost saving and 100% of the time associated with improved QALY outcomes.

Appendix 2

NICE Highly Specialised Technology Evaluation: Eliglustat for treating type 1 Gaucher Disease [ID709]:

Process issues in the evaluation of eliglustat for treating type 1 Gaucher Disease

Sanofi Genzyme (SGZ) is concerned that the process for the evaluation of HSTs is generally unclear and that in certain important respects, the consideration of eliglustat has been unfair. We strongly believe that these procedural issues have prejudiced the evaluation of eliglustat and contributed in the current draft decision.

Our procedural concerns include the following matters.

1) **Uncertain procedure for evaluating highly specialised technologies**
    - While the Interim Process Guide sets out in broad terms the procedure that will be followed and the principles that will be applied by the Evaluation Committee in considering an HST, the precise methodology and assessment of "value for money" remains unclear. As a consequence and in circumstances where there are few precedents, it is difficult for stakeholders to understand how decisions are made and what is required in order to obtain a positive outcome.
    - While the HST process purports to recognise the challenges associated with developing a treatment for a rare and life-long disease, the Interim Process Guide provides no indication as to how this should be reflected in the evaluation, with the result that the ECD for eliglustat criticises the data on the basis that the studies are not larger (in fact ENGAGE is the largest study ever conducted in treatment-naïve Gaucher patients) and longer term data (data up to 8 years have been submitted) are not available.

2) **The Committee's conclusion that the value for money of eliglustat treatment is uncertain because the comparator has not been evaluated by NICE is contrary to NICE's procedures, unfair and unreasonable**

    The Committee questions whether eliglustat represents value for money for the NHS on the basis that the comparator products have not themselves been evaluated.

    - NICE's Methods of Technology Appraisal states at paragraph 6.2.3:

        > "The Committee will normally be guided by established practice in the NHS when identifying the appropriate comparator(s). When the assessment suggests that an established practice may not be considered a good use of NHS resources relative to another available treatment, the Committee will decide whether to include it as an appropriate comparator in the appraisal, after reviewing an incremental cost–utility analysis. The Committee's overall decision on whether it is a valid comparator will be guided by whether it is recommended in other extant NICE guidance, and/or whether its use is so

embedded in clinical practice that its use will continue unless and until it is replaced by a new technology. The Committee will also take into account the uncertainty associated with the estimates of clinical and cost effectiveness, and whether the new technology under appraisal could provide a cost-saving alternative".

ERT plainly constitutes established NHS treatment for Gaucher Disease (as recognised by the Evaluation Committee at paragraph 5.2 of the ECD) and the Committee does not suggest that use will cease in the absence of a replacement technology. In these circumstances, there is no basis for refusing to recommend use of eliglustat based on a comparison with ERT. Any suggestion to the contrary must be based on evidence that ERT is not established treatment for NHS patients.

- Should NICE propose to introduce a policy that comparators must themselves have undergone evaluation and be the subject of a positive recommendation, even where such treatment constitutes established practice within the NHS, this policy cannot be applied retrospectively, but should be stated explicitly in NICE's process guides. In those circumstances, NICE should not schedule an HST evaluation until the relevant comparator has already undergone evaluation. That did not happen in this case - presumably because ERT is established treatment within the NHS; NICE has certainly published no plans to conduct an evaluation of ERT for Gaucher Disease. The fact that ERT has not been evaluated by NICE is a matter for NICE and not for SGZ and should not prejudice the assessment of eliglustat.

3) Information provided by the company was excluded by NICE/ERG and has not been incorporated into the decision making

- The ERG queried high 'loss to follow-up' in the ENCORE trial in its report in July 2016, even though no information in relation to this issue had been requested from SGZ at the clarification stage. SGZ was immediately able to provide information to explain the position, including the movement of US patients out of the trial and onto commercial product when it became available in Autumn 2014. In response the ERG stated

Although the ERG accepts the company's amendment may be true, we were not previously given access to the relevant information stated by the company. At this stage of the process we believe that we cannot incorporate new information or data into the report, and that the statement made by the ERG remains accurate based on the information we had available to us at the time.

SGZ was frustrated by the approach of the ERG, which was obstructive rather than co-operative and inconsistent with an assessment aimed at presenting a fair and accurate reflection of the data to assist all stakeholders (NICE, patients and clinicians as well as SGZ) to consider eliglustat. This "punitive" approach and inaccurate

comment by the ERG has now been reflected in paragraph 4.22 of the ECD released on the 7th March 2017, even though the ERG has been in possession of SGZ's explanation since July 2016.

It is unclear how the refusal by the ERG to incorporate the details provided by SGZ in relation to patient follow-up in ENCORE, have influenced the conclusions of the Evaluation Committee, however in circumstances where they are reported in the ECD, they must be assumed to have had some effect.

4) Information provided to NICE has not been taken into account in the ECD

By way of example:

- Written information clarifying the patient disposition in ENCORE was provided to NICE/the ERG in July 2016, in response to the ERG's report. However, this is raised as a gap in SGZ's submission, even though the information has been with NICE/ERG since July last year.

5) No ECD issued after the 21 September committee

- Following the meeting on the 21st of September SGZ notified NICE that it had submitted a PAS for approval to PASLU. This may have affected the decision by NICE not to issue an ECD at that stage.

  Many of the clinical issues raised in the ECD of 7th March could have been raised in September if a ECD had been issued, which would have been a much more efficient way of dealing with the committees concerns. SGZ feels strongly an opportunity was missed for the company and other stakeholders to respond to clinical issues.

  Similarly, the ERG had information provided to it (for example in response to the report) that it has not formally taken into account yet, even though it has been sitting on the information since July, such as the above regarding patient disposition.

6) Committee meeting 16th Feb no attendance by clinical or patient advocates

- After the postponement of the Committee meeting scheduled for January 2017 due to lack of quorum, the meeting was rescheduled, with only a month's notice for February 2017. The rescheduled meeting fell in the half term holidays and coincided with the most important annual global conference for Gaucher Disease clinicians in the US. In view of the limited notice and the timing, neither the expert clinicians nor the patient advocacy representative were able to attend. This situation (a scheduled meeting at short notice) was clearly unsatisfactory and inconsistent with NICE's procedures. Furthermore, in circumstances where it is important that the Evaluation Committee has access to clinical and patient expertise in relation to the

manifestations and treatment of an ultra rare disease, it is unreasonable to schedule a meeting at a time when it is patently obvious that relevant experts are unlikely to be able to attend.

- While NICE set up TC conferences with the expert clinicians and patient specialists prior to the rescheduled meeting on the 16th Feb, this did not adequately correct the unfairness resulting from the absence of the experts at the meeting. SGZ was not invited to attend the TCs and did not therefore hear the perspectives of the clinical and patient experts at that time. Nor where did the resulting ECD appear to reflect their viewpoint. Details of the structure of these TCs are not known: who was in attendance (was it quorate for the Evaluation Committee members?), how many TCs there were.
- The ECD for eliglustat includes clinical conclusions that are controversial (e.g. the Committee's conclusions regarding the benefits of eliglustat versus ERT,their failure to adjust the efficacy of ERT to reflect the lower dose used in clinical practice as compared with clinical trials and their assessment of the modest effect on quality of life resulting from introduction of an oral treatment). It is likely that the absence of the clinical and patient experts from the February meeting prejudiced discussion on these matters.

7) Content of the ECD reflects the September 2016 meeting

- The ECD released on the 7th March 2017 raised issues that largely had been discussed in September 2016 and were not even raised in the committee meeting in February 2017 to allow the company to respond. As such, many issues that could have been responded to by SGZ are only now being raised.

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NICE Highly Specialised Technology Evaluation: Eliglustat for treating type 1 Gaucher Disease [ID709]:

SanofiGenzyme's response to points raised in the Evaluation Consultation Document

This is the accompanying document to our cover letter responding to the Evaluation Consultation Document: a comprehensive document that responds to the ECD point by point.

Given the summary of critical committee concerns reported towards the end of the ECD document tend to be most pertinent to the decision, we have taken the approach to respond to the points raised in the, 'Summary of evaluation committee's key conclusions' section first, and thereafter work through other points of clarification, correction and response in paragraph order.

Note – With apologies we were unable to use 'referencing to link our tables when embedded within this larger table. We hope that the text makes it clear what tables/figures are referred to. We apologise if not and will provide clarification.

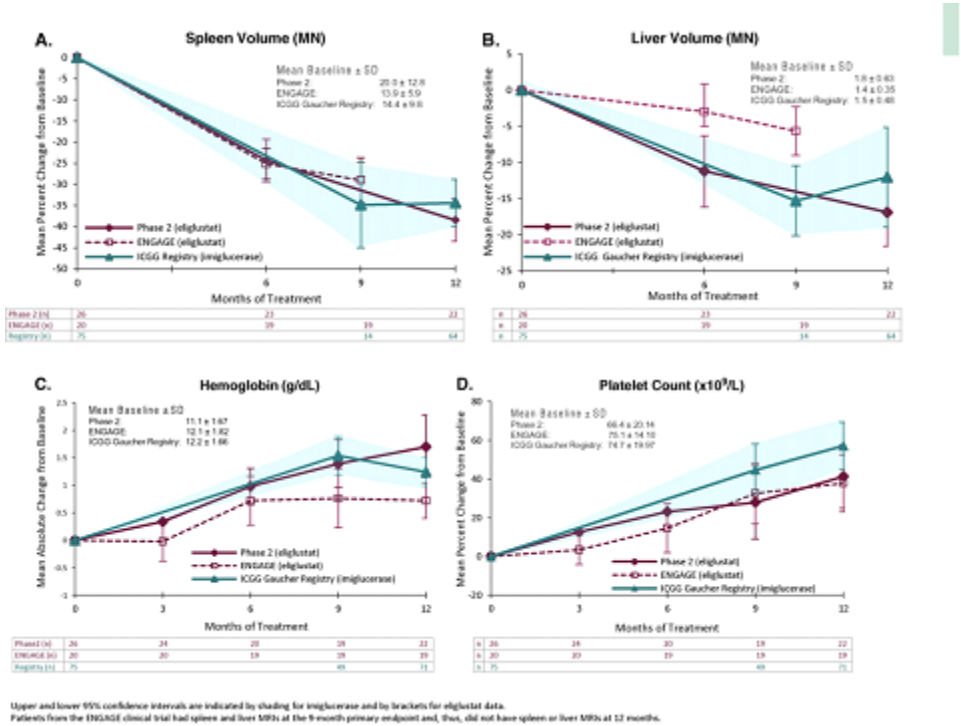
Paragraph number	Comment in ECD	SanofiGenzyme response
Summary of evaluation committee's key conclusions		
Key conclusions	The committee noted the substantial additional costs of eliglustat compared with ERT in people with intermediate and extensive metaboliser status. The committee was not convinced that these could be justified solely based on the benefits of an oral treatment.	SGZ believes that the revised PAS will reassure the committee regarding the value of eliglustat treatment. The committee accepted the utility value proposed by the ERG for an oral therapy of 0.05, in the treatment of this chronic ultra-orphan disease. Based on this (0.05) utility value, but affected by other assumptions in the economic model such as risk of mortality, over a lifetime a patient treated with eliglustat would have a QALY gain of 1.05 according to the ERGs assumptions, reflecting the frequency of administration needed to treat type 1 Gaucher Disease (GD1) and therefore the cumulative benefit or this oral option. This is a substantive gain in health outcomes. We request that the committee makes decisions based on the QALY gain and doesn't trivialise quality of life gains due to oral administration. Given the alternative dosing approach is fortnightly IV infusion for potentially 50 or 60 years, an oral option is substantially more than improved convenience, hence the size of the QALY gain in a lifetime model. A QALY gain of 1.05 is not more valuable if derived from reduced adverse events rather than from route of administration.

Paragraph number	Comment in ECD	SanofiGenzyme response
	The committee recognised that eliglustat potentially offered cost savings in people with poor metaboliser status, but was mindful of the very limited evidence base for this population.	SGZ acknowledges that the poor metaboliser (PM) population is small. There were no PMs in the ENGAGE trial, 4% of patients in the ENCORE trial were PMs (6/146) Across all eliglustat trials (Phase 2, ENGAGE, ENCORE and EDGE), 14 patients (3.6%) were poor metabolizers (14/393) (Peterschmitt et al 2017) Observed data from the Phase III clinical trials supported by PK/PD modelling demonstrate that similar clinical outcomes are expected for poor metabolisers at the 100mg QD dose, and that no difference in TEAEs were reported with the PM populations (REF EPAR page 61) The few data are due to small patient numbers, observed data and outputs of PK/PD modelling suggests that at the dose of 100mg QD there will be no difference in clinical outcomes or TEAEs. Consideration needs to be given to drug-drug interactions and contraindications relating to the CYP2D6 metabolic pathway, as in needed for IM/EM, and there are slightly different for PMs.
	The committee had concerns about the true value for money provided by eliglustat in this population, particularly *when considering that the value for money of ERT itself was not established.*	SGZ is very concerned by the implications of this paragraph. This HST was for the assessment of eliglustat in the treatment of type 1 Gaucher Disease, not a multiple technology assessment of all treatments for Gaucher Disease. We remind the committee that the phrase 'value for money' is used in the HST process rather than cost-effectiveness because of societal preference for flexibility in defining a treatments value ie, not all diseases are equivalent and it is not always appropriate to apply efficiency measures. This is seen explicitly with the End of Life criteria for cancer treatments and in the design of the current HST process that explicitly precludes the utilitarian/efficiency reporting of outcomes as 'ICERs' as it was determined that this is not appropriate in rare disease. SGZ considers questioning the value for money of an established and effective treatment in the ECD to be out of scope for this evaluation and suggests the committee have gone outside of the

Paragraph number	Comment in ECD	SanofiGenzyme response
		remit of this evaluation in doing so.
Uncertainties generated by the evidence	The committee had the following concerns: • the non-inferiority margin of 25% for the ENCORE trial was wider than normal	Unlike virtually all other switch trials in Gaucher patients, the stability thresholds defined in ENCORE were not arbitrary but were based on data from an earlier clinical trial of patients with Gaucher disease who were stabilized on enzyme therapy as well as reported measurement variability. The thresholds for the individual components of the composite endpoint are based on objective criteria using the 5th percentile (laboratory parameters) or 95th percentile (organ volumes) for the changes observed after 12 months of imiglucerase treatment in a matched subgroup of patients from the Phase 4 'Q2/Q4' trial (Kishnani et al. 2009), which compared every-other-week to once-a-month ERT. A non-inferiority margin of 25% was selected for this study based on considerations of a Cerezyme response rate of 95% for the defined composite primary endpoint for measuring stability, and assuming a response rate of 85% for eliglustat based on Phase 2 data. The 25% margin accounts for a 10% difference between the active-comparator (Cerezyme) and test treatment arms (eliglustat) as well as an additional 15% for the inherent variability in estimating the difference between these 2 treatments (corresponding to the lower bound of the 95% confidence interval [CI]). The margin of 25%, rather than 20%, was also chosen because the rare patient population limited the size of the study; despite this caveat, the lower bound of the 95% CI for the observed difference between treatment arms was -17.6% We acknowledge there is a statement in the EPAR that a 20% non-inferiority margin would have been better and we acknowledge that SGZ made the decision to go at a 25% non-inferiority margin in the face of advice from the CHMP that 20% was the preferred margin. However, as is reported in the cover letter to have met this 20% non-inferiority margin would have required nearly double the number of patients being exposed to the trial product (an extra 174 in addition to the 186 patients actually enrolled). Trial robustness needed to be balanced against practical issues (how to recruit double the patients in an ultra orphan disease area), ethical issues relating to exposing double the number of patients to a pre-licence drug and commercial considerations: a larger trial would delay availability of the licenced product to Gaucher Disease patients across Europe.

Paragraph number	Comment in ECD	SanofiGenzyme response
		Further, the lower 95% confidence interval was within a 20% non-inferiority margin using 14 different appropriate methods for analysing the data. It was outside the 20% NIM using two methods that can legitimately be considered less appropriate given the nature of the data being assessed. SGZ would like to highlight to the committee that the US Food and Drug Administration (FDA) recommended analysis for the efficacy endpoint will be percentage change in spleen volume (MN) from baseline to Week 52 using a 15% non-inferiority margin. This endpoint will be used to evaluate the non-inferiority of eliglustat compared to Cerezyme. The analysis of the per protocol population will be the primary analysis in this non-inferiority framework. For the FDA analysis the following were used to define the non-inferiority margin (endpoint percentage change in spleen volumes (in MN) from baseline to Week 52): • An assumed treatment difference of 0% at Week 52 in percentage changes from baseline in spleen volume (MN) between the eliglustat treatment group and the Cerezyme treatment arm • An assumed standard deviation of 15% at Week 52 in percentage changes from baseline in spleen volume (in MN) for the eliglustat and Cerezyme treatment arms. Consider the following 2 parameters: M_1 = the entire effect of the active control assumed to be present in the non-inferiority study M_2 = the largest clinically acceptable difference (degree of inferiority) of eliglustat compared to Cerezyme Based on the Gaucher Registry analysis (n=47), patients who stopped ERT treatment and met the primary inclusion criteria for this study had a mean increase in spleen volume of 22.5% and thus the M1 margin of 22.5% is assumed. A non-inferiority margin (M2) of 15% for percentage change in spleen volume (in MN) is a reasonable non-inferiority margin both from a statistical and clinical perspective

Paragraph number	Comment in ECD	SanofiGenzyme response
	• there were no comparative data with ERT for patients who had not had previous treatment	SGZ recognise that a non-inferiority or equivalence trial comparing eliglustat to imiglucerase in treatment naïve GD1 patients would have been ideal, but would have required a sample size of at least 76 patients to gain sufficient power. The ENGAGE study, with 40 patients, took 2 full years to enrol and is actually the largest clinical trial ever of treatment-naïve Gaucher patients further, 'the CHMP agreed that given the rareness of the disease this is not considered feasible' (EMA 2015). A *post hoc,* SanofiGenzyme led, comparison of treatment outcomes in treatment naive patients from the eliglustat clinical trials (ENGAGE and Phase 2) with a matched population of treatment naïve patients treated with imiglucerase patients from the ICGG Registry was published post submission by Ibrahim et al., 2016, MGM. This analysis suggests that the magnitude and time course of treatment response was similar with both treatments, with respect to haemoglobin, platelets, spleen volume, and liver volume, see figures below.

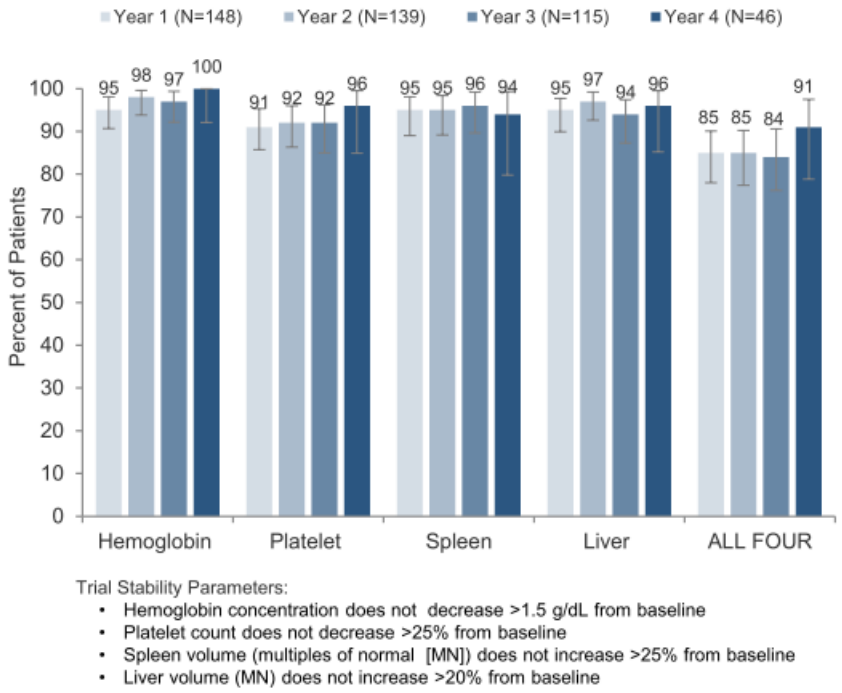
Paragraph number	Comment in ECD	SanofiGenzyme response
		Figure 1 Change from baseline in organ volumes and hematologic parameters  Upper and lower 95% confidence intervals are indicated by shading for imiglucerase and by brackets for eliglustat data. Patients from the ENGAGE clinical trial had spleen and liver MRIs at the 9-month primary endpoint and, thus, did not have spleen or liver MRIs at 12 months. Based on these results, SGZ would expect clinically similar results across these visceral and haematological parameters for treatment-naïve patients treated with either eliglustat or ERT.
	• there were few data on patients with poor metaboliser status	As already stated, SGZ acknowledges that the poor metaboliser (PM) population is small. There were no PMs in the ENGAGE trial, 4% of patients in the ENCORE trial were PMs (6/146)

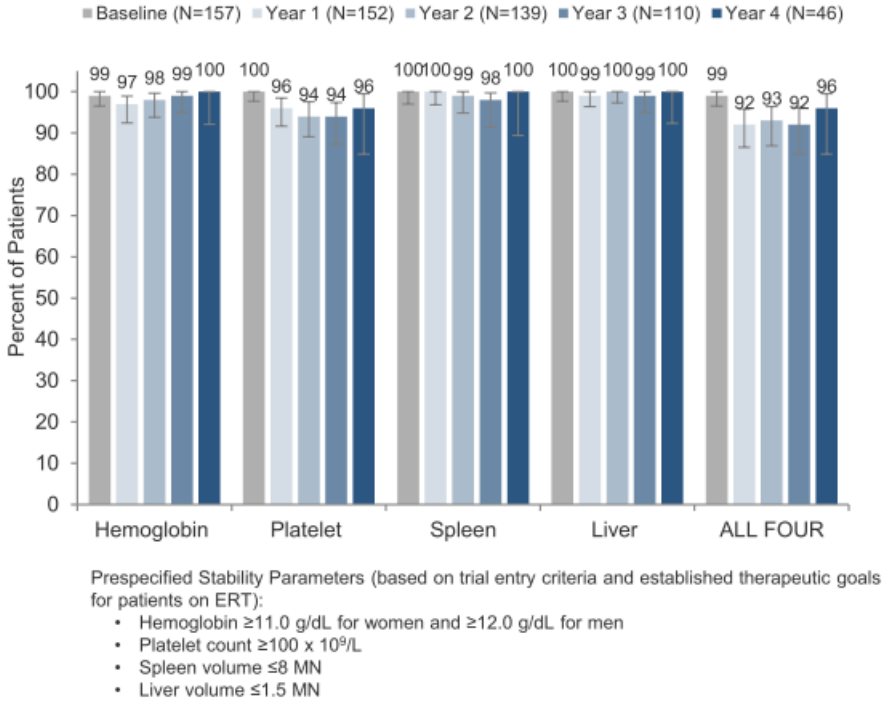
Paragraph number	Comment in ECD	SanofiGenzyme response
		Across all eliglustat trials (Phase 2, ENGAGE, ENCORE and EDGE), 14 patients (3.6%) were poor metabolizers (14/393) (Peterschmitt et al 2017) Observed data from the Phase III clinical trials supported by PK/PD modelling demonstrate that similar clinical outcomes are expected for poor metabolisers at the 100mg QD dose, and that no difference in TEAEs were reported with the PM populations (EMA 2015). Consideration is given in the SmPC regarding considerations that needs to be made once metaboliser status is confirmed, specifically relating to drug-drug interactions and contraindications. The few data are due to small patient numbers. Observed data and outputs of PK/PD modelling suggests that at the dose of 100mg QD there will be no difference in clinical outcomes or TEAEs. Consideration needs to be given to drug-drug interactions and contraindications relating to the CYP2D6 metabolic pathway, as in needed for IM/EM, and there are slightly different for PMs.
	• 48% of people in the ENCORE trial had a higher dosage of eliglustat than is specified in the marketing authorisation.	Sanofi Genzyme undertook modelling that showed selecting a 100 mg BID dose for the IM and EM population will allow for safe and efficacious exposure of this target population, in the same range as observed in our positive clinical trials and without the need for plasma monitoring. A PK/PD-efficacy modelling approach was used to show that the exposures predicted in a CYP2D6 phenotype-based dosing scenario would achieve the same range that has been shown to be safe and efficacious in the pivotal studies. These analyses were particularly important in the case of ENCORE. As noted by NICE almost half of the patients in ENCORE received a dose of 150 mg BID. Therefore, it was necessary to confirm that the ENCORE study population would still achieve comparable efficacy under a phenotype-based dosing regimen with a top dose of 100 mg BID for IMs and EMs. The ENCORE primary efficacy composite endpoint and its four individual components were evaluated for exposure-response relationships. The four components of the primary endpoint in ENCORE were evaluated for exposure-response relationships. There was no significant exposure-response relationship

Paragraph number	Comment in ECD	SanofiGenzyme response
		observed for absolute change in haemoglobin level, percent change in platelet count, or percent change in liver volume. The only parameter that showed a significant exposure-response relationship was % change in spleen volume. Given the limited range of exposure and the success of the trial in maintaining disease stability, it is not unexpected that most of the components of the primary composite endpoint did not show appreciable changes from baseline (when those values were already normal or near-normal). For exposure estimates in this modelling approach, PopPK-predicted PK parameters were used instead of observed PK parameters since the latter were confounded by the fact that dose was adjusted based on Ctrough during Phase II and III. Using the PK/PD model, percent changes in spleen volume (MN) from Baseline to Week 52 at the study level were predicted using PopPK-predicted exposures. This allowed Sanofi Genzyme to compare the observed study results from the ENCORE trial to the predicted study results if IM and EM patients were to receive 100 mg BID (as proposed in the commercial dosing). PK/PD analyses predicted that spleen volume treatment responses for IM and EM patients dosed at a fixed dose of 100 mg BID that would be similar to the observed spleen volume treatment effects in the study. The estimated treatment difference from Cerezyme using the simulations and the same Cerezyme data (observed) was also similar to the observed treatment difference in the study. To further confirm that the proposed phenotype-based dosing regimen would not impact the efficacy results of those IM and EM patients actually dosed 150 mg BID and who would be administered the lower dose of 100 mg BID, patient exposure projections were applied to the established PK/PD model with observed percent change in spleen volume to obtain projected percent change in spleen volume values for IM and EM patients when dosed at 100 mg BID. The maximum increase between the observed and projected values for spleen volume at Week 52, due to the reduction in dose from 150 mg BID to 100 mg BID, would be 4%. Four percent is a small change relative to the patients' essentially normal spleen volume (therapeutic goal for spleen volume is ≤2 to 8MN) and is comparable to the test-test variability of organ volume measurement by MRI determined during the ENGAGE study using the same methodology, and less than the 12% variability reported in the literature (Barton, 1991, New Engl J Med). Such a small change in

Paragraph number	Comment in ECD	SanofiGenzyme response
		patients with little or no splenomegaly would not be clinically or medically noticeable. Thus, 100 mg BID is an effective dose for IM and EM patients receiving chronic therapy aimed at maintaining stability of disease, and the added exposure from a 150 mg BID dose is not expected to provide any further meaningful clinical benefit. When considering the sufficiency of a 100 mg BID dose for the ENCORE patient population (clinical stable patients switching from ERT), it is important again to consider the efficacy demonstrated in treatment-naïve patients. The Phase 2 and ENGAGE trial, which treated patients with the highest disease burden (the treatment-naïve), have demonstrated the efficacy of the 100 mg BID dose in the most difficult to treat patient population. The ENCORE study enrolled patients who had received enzyme replacement therapy for >3 years, and consequently, these patients had low disease burden at the time of initiation of eliglustat treatment and were considered clinically stable by virtue of meeting pre-specified therapeutic goals. The 100 mg BID dose is therefore expected to also be effective in the patients with lower disease burden (ERT-stabilized patients). In conclusion, the analyses performed by Sanofi Genzyme not only support the proposed CYP2D6 phenotype-based dosing, but also demonstrate the continued validity of the ENCORE conclusions non-inferiority to imiglucerase) even with a top dose of 100 mg BID for IMs and EMs. For more detail see Appendix 1 in this document.
Uncertainties around and plausibility of assumptions and inputs in the economic model and budget impact analysis	**Cost–consequence analysis** The committee considered that there was uncertainty around the assumption of equivalence of eliglustat with ERT, especially in the long term.	In response to this statement SGZ suggests that for any clinically meaningful difference between eliglustat and ERT there is *not* a level of uncertainty that precludes the committee from recommending eliglustat. The committee heard the clinical experts 'considered eliglustat to be equivalent, or very nearly equivalent, to ERT based on clinical measures such as haemoglobin levels and platelet counts, as well as in terms of how patients felt while having eliglustat'. **Short-term** SGZ believes the trial data support the argument that there is *no* clinically meaningful difference in

Paragraph number	Comment in ECD	SanofiGenzyme response
		outcomes in the ERT-stable population for eliglustat patients compared with ERT patients, taking into account the trial design: • Patients who switched from ERT to eliglustat had been on ERT therapy for a mean of 9.8years, have been on ERT for a minimum of 3 years at a dose between 30U/kg and 130U/kg with documented disease stability in the 6 months prior to enrolment, • Of these, only 3 out of 99 per protocol patients had a loss of stability that would be deemed clinically meaningful using usual therapeutic treatment goals **Long-term** Since the submission of the eliglustat dossier, four year data have become available for ENCORE and ENGAGE. In the ENCORE trial eliglustat treatment resulted in stable haemoglobin concentration, platelet count and spleen and liver volumes for up to four years. Mean bone mineral density Z-scores also remained stable and were maintained in the health reference range (Cox et al 2017), see Appendix 2 Figure 3 in Appendix 2 at the end of this document for endpoint results. Analysis of the primary composite endpoint was repeated for all patients for whom data were available, see the first figure below, while the second figure reports results with ENCORE patients when the Pastores 2004 therapeutic goals are applied.

Paragraph number	Comment in ECD	SanofiGenzyme response
		Figure: Stability of hematologic and visceral parameters with respect to the composite primary endpoint (relative to change from baseline). Error bars denote upper and lower 95% confidence intervals  Trial Stability Parameters: • Hemoglobin concentration does not decrease >1.5 g/dL from baseline • Platelet count does not decrease >25% from baseline • Spleen volume (multiples of normal [MN]) does not increase >25% from baseline • Liver volume (MN) does not increase >20% from baseline

Paragraph number	Comment in ECD	SanofiGenzyme response
		Figure: Prespecified therapeutic goals based on entry criteria and goals established for patients on enzyme therapy (absolute value).Error bars denote upper and lower 95% confidence intervals  Prespecified Stability Parameters (based on trial entry criteria and established therapeutic goals for patients on ERT): • Hemoglobin ≥11.0 g/dL for women and ≥12.0 g/dL for men • Platelet count ≥100 x 10^9/L • Spleen volume ≤8 MN • Liver volume ≤1.5 MN Further, the economic model supports this argument that any differences between arms are

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		clinically minimal and over the lifetime of a patient cohort, in line with the NICE reference case for an economic evaluation, there is an advantage in having eliglustat as a treatment option for Gaucher Disease, both from the point of view of total health outcomes gained and cost to the NHS. The GD-DS3 scoring tool was constructed by clinicians to identify minimal clinically important difference (MCID) in patients with Gaucher Disease (Weinreb et al. 2010). Putting the outcomes of the trial through the economic model that is based on the GD-DS3 highlights that the statistically differences observed in the trial are not clinically meaningful in that they would be unlikely to lead to a difference in treatment plan or patient prognosis. The GD-DS3 may not directly replicate the findings from the ENCORE trial, however, it does measure MCID in treatments that is fundamental to this HST assessment. SGZ is also concerned that the company was not able to review the analysis upon which the statement in paragraph 5.10 was made: The company assumed long-term equivalence of eliglustat and ERT, and the *ERG highlighted that this had a considerable impact on estimated incremental quality-adjusted life years QALYs*. According to page 150 of the ERG report in July 2016 which states that, 'the long-term difference between the two treatments is unclear and there are issues regarding the assumption of non-inferiority as discussed further in Section 5.2.7. The ERG attempted to incorporate differential efficacy into the analysis in order to demonstrate the impact on the results if the assumption of non-inferiority did not hold in the long-term. *However, the ERG was unable to explore this scenario as any attempt to remove the assumption of non-inferiority resulted in inconsistent results, and a lack of transparency in the cost-effectiveness model prevented the identification of any errors*'. SGZ would suggest that there is a significant difference in being unable to amend a model to run an exploratory analysis and concluding *there is a considerable impact on estimated incremental quality-adjusted life years QALYs.* The company cannot find the analysis that suggests the ERG were able to run this analysis and make this conclusion.

Paragraph number	Comment in ECD	SanofiGenzyme response
		SGZ ran some exploratory analyses changing the way the patient cohort moved onto the transition matrices. Rather than these being determined by the patients' baseline characteristics, two options were explored, the first takes the distribution of patients, both imiglucerase and eliglustat arms, at the end of the 52 weeks of ENCORE. This end of trial distribution then determines where the patients enter the transition matrices, thereafter the matrices are applied as in the base case model. The second option uses the ENCORE four-year eliglustat data, so that the final state distribution is based on the completion of 4 years of eliglustat therapy. These changes mostly affected the frequency of time in mild vs. moderate health states. Eliglustat transition matrices tracked similarly to that of the long term transition data leading to generally similar results. This analysis was done on the company's base case: total incremental QALY gain 2.28. The first approach (using the 52 week data) led to revised total QALYs of 2.27. The second approach (using 4 year data) led to total incremental QALYs of 2.29. There is minimal change in costs as the only changes were in the health state costs, which are not the drivers of costs in this model (SGZ Data on file_2017c). We are confirming that similar affects would be observed with the ERG base case, so from 1.05 Q ALY gain to 1.04 using one approach and 1.06 using the other approach, we will confirm this when the results are available. NICE recognises that there are often data gaps with novel products, which it has a process option for a 3 year re-review, to prevent this uncertainty being a barrier to pragmatic decision making. In patients who continue to meet well-established therapeutic goals, there is no clinically meaningful difference between ERT and eliglustat. For patients who do not meet these goals, in line with a conversation between patient and clinician, patients would have the option to return to ERT. Further, we would suggest that there is less uncertainty regarding relative effectiveness of ERT and eliglustat if we accept the dose of ERT that the committee state is most plausible for UK Gaucher disease patients: 25U/kg. SGZ disagrees with the Committee's interpretation that there is no dose/response relationship with ERT, based on the results of the analysis of primary outcome by dose population <35U/kg/≥35U/kg in the ENCORE trial. SGZ's interpretation of these data would

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		be that similar outcomes can be achieved if patient-specific dosing plans are followed that take into account a patients' weight, baseline characteristics and disease severity. As far as SGZ is aware, the ERG has not undertaken such an analysis adjusting for these variables. As such, at a dose of 25U/kg ERT is likely to be associated with lower effectiveness outcomes in usual UK practice than in ENCORE, reducing any uncertainty regarding relative efficacy. Data from the Dutch/German analysis of real world data, in which Dutch patients had a mean ERT dose of 15-30U/kg every 4 weeks compared with German data in which patients had a mean dose of 80U/kg every 4 weeks concluded that bone marrow burden improved ore quickly and was more pronounced in the higher dose group. There was no difference in haematologic or visceral parameters (De Fost et al 2006). So, while recognising there is uncertainty in the data under consideration in this assessment, we would suggest that there is a plausible scenario in which eliglustat offers patients better long-term outcomes as the small molecule penetration provides better bone outcomes, compared with sustained low dosing of ERT. In recommending eliglustat the committee would facilitate a conversation between patient and clinician in which there is discussion of the limitations and benefits of both ERT or eliglustat: lack of long-term data in eliglustat, uncertainty regarding the long-term bone outcomes associated with the doses of ERT routinely given in the UK. Finally, a patient should not be maintained on a therapy to which they are having a sub-optimal response, as such SGZ would advocate that only patients who benefit from eliglustat should be maintained upon it, and patients with sub optimal response should receive ERT.
	There was uncertainty around the dosage of ERT used in the ENCORE trial, which was thought to be higher than that used in clinical	Clinical expert input was taken into account regarding the dose of ERT used in routine clinical practice in the UK and determined that the most plausible dose for ERT is 25U/kg, rather than 42.4U/kg, the mean dose of imiglucarase from the ENCORE trial. SGZ does not dispute that the UK routinely uses lower dose than those reported in ENCORE. As such we accept that 25U/kg is a

<table>
<tr><th>Paragraph number</th><th>Comment in ECD</th><th>SanofiGenzyme response</th></tr>
<tr><td></td><td>practice.</td><td>reasonable estimate. However, it is inconsistent to use real world dose data but ignore real world weight data; total dose being a product of dose and weight. In applying real world doses to ENCORE trial weight the ERG's analysis is unreasonably punitive against eliglustat.

The estimated mean patient's dose at 25U/kg and ENCORE trial weight of 67.5kg gives a mean total dose of 1687U, or four vials. See table below for alternative estimates for dose and weight that have more internal consistency.

Table 1 Real world weight data for UK GD1 patients
<table>
<tr><th></th><th>Weight (kg)</th><th>Unit/kg</th><th>Total dose</th><th>Dose rounded to nearest vial</th><th>No. vials</th></tr>
<tr><td>ENCORE trial</td><td>67.5</td><td>25</td><td>1687.5</td><td>1600</td><td>4</td></tr>
<tr><td>AWMSG (velaglucerase)</td><td>75</td><td>25</td><td>1875</td><td>2000</td><td>5</td></tr>
<tr><td>Royal Free Hospital (RFH 2017)</td><td>73.29</td><td>25</td><td>1832.25</td><td>2000</td><td>5</td></tr>
<tr><td>ICGG (SGZ_Data on file 2017a)</td><td>71.8 (last follow up)</td><td>25</td><td>1795</td><td>2000</td><td>5</td></tr>
<tr><td>Pooled UK patients from ENGAGE and ENCORE(SGZ Data on file_ 2017 b)</td><td>73.6 (study end)</td><td>25</td><td>1840</td><td>2000</td><td>5</td></tr>
<tr><td>UK population average weight (ONS 2010)</td><td>76.9</td><td>25</td><td>1922.5</td><td>2000</td><td>5</td></tr>
</table>
While wastage is not factored into the economic model due to guidance in the Standard Operating Procedure, it is interesting that the majority of weight data point to five vials being required, whereas the dose deemed most plausible in the ECD would limit to four vials. SGZ considers this to be an unreasonable approach, lacking methodological consistency and a flawed basis from which to determine value for money for the NHS and the current negative draft recommendation.

SGZ further requests the committee be even handed in its consideration of efficacy adjustments between the trial and real world setting. SGZ is providing information in this response to the ECD that hopefully addresses concerns regarding any efficacy differential between the 100mg BID and</td></tr>
</table>

Paragraph number	Comment in ECD	SanofiGenzyme response
		150mg BID dose. However, the committee takes the results of the analysis of outcomes by ERT dose the population <35U/kg and ≥35U/kg (see table below) to conclude that outcomes seen with a mean of 42.4U/kg would be achieved with a mean dose of 25U/kg.

Proportion of Patients Stable at 12 months: Per Protocol Population

	Eliglustat			Imiglucerase		
	Pre Study ERT			Pre Study ERT		
	< 35 /kg/q2w (N=38)	≥ 35 U/kg/q2w (N=61)	Overall (N=99)	< 35 /kg/q2w (N=18)	≥ 35 U/kg/q2w (N=29)	Overall (N=47)
Proportion, n (%) 95% CI remaining stable	32 (84·2) (68·7, 94·0)	52 (85·2) (73·8, 93·0)	84 (84·8) (76·2, 91·3)	17 (94·4) (72·7, 99·9)	27 (93·1) (77·2, 99·2)	44 (93·6) (82·5, 98·7)
Difference in proportion vs imiglucerase and 95% CI	-10·2 (-25·2, 10·2)	-7·9 (-20·0, 7·6)	-8·8 (-17·6, 4·2)	N/A	N/A	N/A

The ENCORE data were analyses by doses ≥35U and <35U. The mean dose in the <35U population was 27U while the mean dose in the ≥35U dose was 51.23U (last dose received, ITT population). The committee have assumed a 'flat dose' of 51U/kg is equal to a 'flat dose' 27U/kg and thereafter 25U/kg without taking into account that does of ERT will be affected by patient weight, baseline characteristics and disease severity. What the <35 and ≥35U data show is that, if patients are well managed on doses are ERT uniquely tailored to their characteristics then ERT leads to maintained stability over 52 weeks. It does not show that if every patient on the ERT arm of the ENCORE study had received 27U the same outcomes would have been achieved.

Only 5 patients in the ENCORE trial had doses ≤25U/kg, their weight range was from 62kg to 69

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		kg, so all patients, so receiving a low dose, but a dose equivalent to an average british male 83.62kg, receiving a dose of 25U/kg. While the SOP and consensus is that in the UK doses are adjusted to the lowest effective dose, effective is not defined. Clinical practice appears to be based on haematological and visceral measures not, long-term bone health. Reports in the literature find correlation between fewer bone crises and higher doses of ERT (Deegan et al 2011) and the SmPC for Cerezyme (SmPC). Therefore, there is an unresolved question as to whether the UK dosing leads to poorer long-term outcomes. The data seem to be ambiguous that low doses of ERT lead to poor bone outcomes, conversely it is not to be ambiguous that higher doses of ERT are associated with improved bone outcomes (de Fost et al 2006; Deegan et al 2011; Cerezyme SmPC 2017). In treatment naïve patients this discrepancy in dose between usual UK dose of ERT and trial doses is even greater, with mean doses being in the range of 60U/kg (Ben Turkia 2013)
	The committee considered that the company's assumption that mortality risk does not increase with disease severity was unrealistic.	This is a legitimate challenge that the company accepts. However, it suggests there is some misunderstanding regarding the premise of the assumption: given the availability of ERT, time in the marked and severe state is short and transitory. Amendments to treatment plans can return people to better health states so that it is unlikely people with GD on active treatment will be in the marked and severe health states for any notable period of time. However, we accept the principle that were a person in a marked and severe health state for a long period of time they are likely to have a greater risk of mortality, as such we accept this proposition.
	The utility increment (0.12) assumed for oral treatment was considered to be too high. The true value was uncertain, but the alternative value (0.05) used by the	Post the submission of the HST dossier for eliglustat in April 2016 SGZ recognised that the original value submitted for oral benefit of 0.12 double counted some aspects of the adverse events due to intravenous infusion. Had an ECD been produced after the September committee meeting, SGZ would have shared this information. SGZ accepts the committee's most plausible utility value for QALY benefit of an oral treatment in

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	ERG was more appropriate.	this therapy area is 0.05.
	Budget impact model The committee concluded that company's estimates of budget impact were additionally uncertain because: • the model excluded poor metabolisers • the dosage of ERT was assumed to be higher than in clinical practice • of incorporation of mortality and stopping treatment in estimated total costs.	SGZ is surprised by the approach the ERG adopted: 1 patient over 5 years. The advice in the STA User Guide is, 'State the estimated annual budget impact on the NHS in England' (NICE 2015). Reviewing the HST interim methods guide we couldn't see any recommendations to use a different approach (NICE 2013). Given the perspective is NHS-England, it is usual that a budget impact analysis includes an assumption for mortality and, although this varies by therapy area, treatment stopping. The principle being that if a patient dies within the 5 year timeframe of the BI analysis they are no longer costing the NHS money. It may have been fair to question if an annualised mortality rate would have been more appropriate, or some other estimate for the number of patients in the Gaucher Disease population that would die in a 5 year period. Regarding treatment stopping, the same principle applies, if a patients asks for a treatment break for a period of time and the NHS is not funding their treatment then there is no cost and this should be included. However, SGZ accepts that for simplicity this stopping rule can be removed. SGZ agrees that the poor metaboliser population should have been included in the budget impact analysis and agrees that a rate of 4% is appropriate.
Incorporation of health-related quality-of-life benefits and utility values	The committee noted the ERG's comments that a utility increment of 0.12 (assumed by the company) was substantial when compared with the decrements from significant adverse events and the benefits of other oral therapies estimated in previous NICE	As already stated, post submission in April 2016 SGZ recognised that the original value submitted for oral benefit of 0.12 double counted some aspects of the adverse events due to intravenous infusion. Had an ECD been produced after the September committee meeting, SGZ would have shared this information. SGZ accepts the committee's most plausible utility value for QALY benefit of an oral treatment in this therapy area is 0.05.

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	submissions The committee concluded that, although the true value was uncertain, the alternative value (0.05) used by the ERG was more appropriate.	
Cost to the NHS and PSS	It understood that this increased the costs in year 5 from £571,487 to £11,123,765 and increased the cumulative cost over 5 years from £1,623,219 to £34,701,740 based on list prices for all technologies.	SGZ requests that this text is amended to make clear that the majority of this cost difference is driven by different dose of ERT assumptions. SGZ acknowledges the model is sensitive to ERT dose however, the way the text is currently presented is disingenuous as it appears to suggest there are many substantial cost issues in the budget impact model.
	However, the committee considered that the budget impact remained considerable,	SGZ hopes that the revised PAS addresses this issue
	especially in the context that benefits of eliglustat over ERT *related solely to the benefits of an oral treatment.*	SGZ is concerned about the implication of this statement. It appears that the committee values QALY gains due to route of administration differently to the way it would value a similarly substantial QALY gain driven by, for example, reduced adverse events. We suggest that it is not the role of the committee to presuppose societal preference for one type of QALY gain versus another, i.e., extension of life versus reduced adverse events versus increased symptom control versus route of administration. We refer the committee to the evidence (section 5.18 of the ECD) that '…the drug would be associated with important indirect mental health benefits because it allows people to live a more normal life'. And the committee's conclusion that, 'eliglustat is likely to have a significant impact on people's lives beyond its direct health benefits'. We would request clarity in the document that is missing at the moment that the oral route of administration provides a tangible impact on health-related quality of life, due in large part to its impact on mental health as well as issues regarding venous access, pain and distress associated with

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		infusions, as well as impact on non-health related quality of life. We request clarity on whether the positive discussion on non-health quality of life is factored into the committee's decision not to recommend this product, given guidance to the committee only to consider *health*-related quality of life.
Value for money	The committee had concerns about the true value for money provided by eliglustat, particularly when *considering that the value for money of ERT itself was not established.*	SGZ is very concerned by the implications of this paragraph. This HST was for the assessment of eliglustat in the treatment of type 1 Gaucher Disease, not a multiple technology assessment of all treatments for Gaucher Disease. We remind the committee that the phrase 'value for money' is used in the HST process rather than cost-effectiveness because of societal preference for flexibility in defining a treatments value ie, not all diseases are equivalent and it is not always appropriate to apply efficiency measures. This is seen explicitly with the End of Life criteria for cancer treatments and in the design of the current HST process that explicitly precludes the utilitarian/efficiency reporting of outcomes as 'ICERs' as it was determined that this is not always appropriate.. SGZ considers questioning the value for money of an established and effective treatment in the ECD to be out of scope for this evaluation and suggests the committee have gone outside of the remit of this evaluation in doing so.
	The committee appreciated the important advantages of *an oral treatment but considered that this alone did not justify* the additional price charged by the company.	SGZ believes that the revised PAS will reassure the committee regarding the price of treatment. As stated above, we request that the committee assess value for money based on the QALY gain and doesn't presume to represent societal preference for QALYs derived from one source over another.
	The committee recognised that eliglustat potentially offered cost savings in people with poor metaboliser status, *but was mindful of the very*	As already stated, SGZ acknowledges that the poor metaboliser (PM) population is small. There were no PMs in the ENGAGE trial, 4% of patients in the ENCORE trial were PMs (6/146) Across all eliglustat trials (Phase 2, ENGAGE, ENCORE and EDGE), 14 patients (3.6%) were poor metabolizers (14/393) (Peterschmitt et al 2017).

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	limited evidence base for this population. The committee was not convinced that eliglustat offered value for money in people with poor metaboliser status.	Observed data from the Phase III clinical trials supported by PK/PD modelling demonstrate that similar clinical outcomes are expected for poor metabolisers at the 100mg QD dose, and that no difference in TEAEs were reported with the PM populations (EMA 2015). Consideration is given in the SmPC regarding considerations that needs to be made once metaboliser status is confirmed, specifically relating to drug-drug interactions and contraindications. In summary, the few data are due to small patient numbers, observed data and outputs of PK/PD modelling suggests that at the dose of 100mg QD there will be no difference in clinical outcomes or TEAEs. Consideration needs to be given to drug-drug interactions and contraindications relating to the CYP2D6 metabolic pathway, as in needed for IM/EM, and there are slightly different for PMs.
1.1	Eliglustat is not recommended within its marketing authorisation for treating type 1 Gaucher Disease	SanofiGenzyme hopes that the information provided in this response together with the provision of new data and revised terms of the Patient Access Scheme allows the committee to revise its decision for the benefit of patients with type 1 Gaucher Disease.
4.3	NHS England and clinical experts stated that current clinical practice in England is to titrate the dose of ERT and use the lowest effective dose	This paragraph excludes oral evidence provided by the clinical experts in the Committee meeting in September 2016 in which the clinicians commented that they followed the Gaucher disease standard operating procedure but that they recognised ERT doses the UK were lower than many other European countries, that they rounded up and down when calculating dose, that price was a factor when considering dose and that literature, the Dutch/German study (de Fost et al 2006) indicated there could be long-term sequelae as a result of the dosing approach in England.
4.7	…the difference was statistically significant between treatment groups only for absolute and percentage changes in haemoglobin levels, for which there was a larger reduction for	It should be noted that while this is a statistically significant difference between arms the change in haemoglobin level is not clinically meaningful as the reduction noted for eliglustat is still within normal range for 'normal' population. This information was provided in response to the ERG factual accuracy check.

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	eliglustat (-0.28, 95% CI -0.52 to -0.03, p=0.03)	
4.18	The company submission did not clearly explain how the pre-specified non-inferiority margin was derived for the ENCORE trial	This is dealt with in detail above, we believe we have now clearly explained the derivation of the non-inferiority margin: Unlike virtually all other switch trials in Gaucher patients, the stability thresholds defined in ENCORE were not arbitrary but were based on data from an earlier clinical trial of patients with Gaucher disease who were stabilized on enzyme therapy as well as reported measurement variability. The thresholds for the individual components of the composite endpoint are based on objective criteria using the 5th percentile (laboratory parameters) or 95th percentile (organ volumes) for the changes observed after 12 months of imiglucerase treatment in a matched subgroup of patients from the Phase 4 'Q2/Q4' trial (Kishnani et al. 2009), which compared every-other-week to once-a-month ERT. A non-inferiority margin of 25% was selected for this study based on considerations of a Cerezyme response rate of 95% for the defined composite primary endpoint for measuring stability, and assuming a response rate of 85% for eliglustat based on Phase 2 data. The 25% margin accounts for a 10% difference between the active-comparator (Cerezyme) and test treatment arms (eliglustat) as well as an additional 15% for the inherent variability in estimating the difference between these 2 treatments (corresponding to the lower bound of the 95% confidence interval [CI]). The margin of 25%, rather than 20%, was also chosen because the rare patient population limited the size of the study; despite this caveat, the lower bound of the 95% CI for the observed difference between treatment arms was -17.6%
4.18	It commented that the non-inferiority margin of 25% was wider than would normally have been accepted, and suggested that a margin of 15% would have been robust.	The rationale for the 25% margin is described above. SGZ finds this statement disingenuous as there has not been discussion that a 15% non-inferiority margin. A 15% non-inferiority margin would have been impractical and potentially unethical, given the size of this patient population. The 25% non-inferiority margin allows for a potential 10% difference between imiglucerase and eliglustat and 15% for inherent variability in estimation of the difference between these two treatments. To power the study to achieve a tighter non-inferiority margin would have taken more

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		patients than is feasible in a rare disease. Both clinicians at the first meeting agreed that a 10% reduction in efficacy is clinically insignificant. The lower margin of the 95% confidence interval, post-hoc, reached 17.6% so was within the 20% margin, which was preferred and recommended by the EMA. In addition, the reported result from the primary publication is calculated using Agresti and Caffo's adjusted Wald method. Other methods were explored, including the Newcombe's hybrid score interval, as requested by the ERG at the clarification stage. Of the 16 methods explored only two methods reported a lower 95% CI not within a 20% non-inferiority margin. Table 2 Lower 97.5% confidence limits of the difference between the proportions of patients remaining stable on eliglustat compared to patients on imiglucerase for the Per-Protocol and Full Analysis Sets using various statistical methods

Analysis Type	Method	Per-Protocol	Full Analysis Set
Exact (non-stratified)	1. Santner and Snell (1980)	-0.2594	-0.2420
	2. Chan and Zhang (1999)	-0.1875	-0.1794
	3. Agresti and Min (2001)	-0.1880	-0.1795
	4. Reiczigel et al. (2008)	-0.1830	-0.1769
	5. Shan and Wang (2013)	-0.1945	-0.1805
Asymptotic (stratified)	6. Agresti-Caffo (MH)+	-0.1756	-0.1706
	7. Wald (MH)	-0.1870	-0.1820
	8. Newcombe-Wilson (MH)	-0.1810	-0.1750
Asymptotic (non-stratified)	9. Agresti-Caffo (2000)	-0.1814	-0.1761
	10. Wald (1940)	-0.1870	-0.1818

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	11. Wald (cc)	-0.2027	-0.1959
	12. Newcombe-Wilson (1998)	-0.1811	-0.1739
	13. Newcombe-Wilson (cc)	-0.1795	-0.1724
	14. Hauck-Anderson (1986)	-0.1985	-0.1920
	15. Farrington-Manning (1990)	-0.1854	-0.1774
	16. Miettinen-Nurminen (1985)	-0.1852	-0.1775
Key: cc, continuity-correction; MH, Mantel-Haenszel weights **Notes:** +, primary efficacy analysis method			

All methods tested exclude the 20% non-inferiority margin with the exception of the Santner and Snell method (PP and FA sets) and continuity corrected Wald test (PP set).11 The Santner and Snell and the continuity corrected Wald test have exact type I error rates of 0.0006 and 0.0093, respectively, when a 95% imiglucerase response rate is assumed so are extremely conservative and would not have been considered for the primary analysis when the non-inferiority analysis method was selected. The Wald method with continuity correction is not recommended in the literature due to its conservativeness.

In summary, exact and asymptotic methods, that have the necessary statistical properties, robustly demonstrate non-inferiority between eliglustat and imiglucerase using a 20% NIM

Efficacy Endpoint as recommended by the FDA - Spleen

The US Food and Drug Administration (FDA) recommended the efficacy endpoint for its analysis will be percentage change in spleen volume (MN) from baseline to Week 52. This endpoint will be used to evaluate the non-inferiority of eliglustat compared to Cerezyme. The analysis of the per protocol population will be the primary analysis in this non-inferiority framework.
For the FDA analysis the following were used to define the non-inferiority margin (endpoint percentage change in spleen volumes (in MN) from baseline to Week 52):

- An assumed treatment difference of 0% at Week 52 in percentage changes from baseline in

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		spleen volume (MN) between the eliglustat treatment group and the Cerezyme treatment arm • An assumed standard deviation of 15% at Week 52 in percentage changes from baseline in spleen volume (in MN) for the eliglustat and Cerezyme treatment arms. Consider the following 2 parameters: M_1 = the entire effect of the active control assumed to be present in the non-inferiority study M_2 = the largest clinically acceptable difference (degree of inferiority) of eliglustat compared to Cerezyme Based on the Gaucher Registry analysis (n=47), patients who stopped ERT treatment and met the primary inclusion criteria for this study had a mean increase in spleen volume of 22.5% and thus the M1 margin of 22.5% volume (in MN) is a reasonable non-inferiority margin both from a statistical and clinical perspective
4.19	Long term data for Eliglustat were limited, especially in the context of a lifelong condition	**ERT-stable** Since the submission of the eliglustat dossier, four year data have become available for ENCORE and ENGAGE. In the ENCORE trial eliglustat treatment resulted in stable haemoglobin concentration, platelet count and spleen and liver volumes for up to four years. Mean bone mineral density Z-scores also remained stable and were maintained in the health reference range (Cox et al 2017), see Appendix 2 Figure 3 at the end of this document for endpoint results. Analysis of the primary composite endpoint was repeated for all patients for whom data were available, see the first figure below, while the second figure reports results with ENCORE patients when the Pastores 2004 therapeutic goals are applied.

Paragraph number	Comment in ECD	SanofiGenzyme response
		Figure: Stability of hematologic and visceral parameters with respect to the composite primary endpoint (relative to change from baseline). Error bars denote upper and lower 95% confidence intervals

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		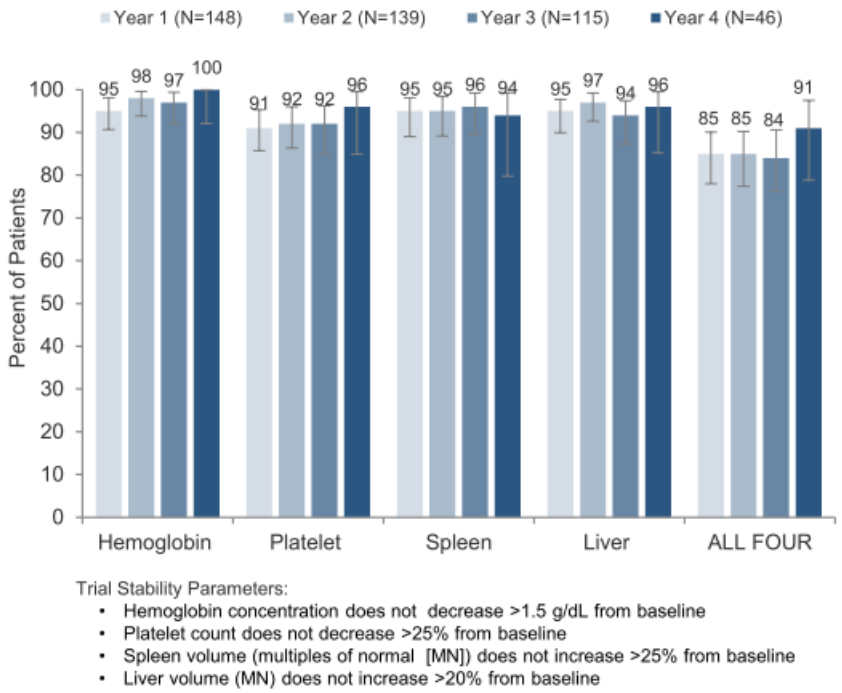 Figure: Prespecified therapeutic goals based on entry criteria and goals established for patients on enzyme therapy (absolute value).Error bars denote upper and lower 95% confidence intervals

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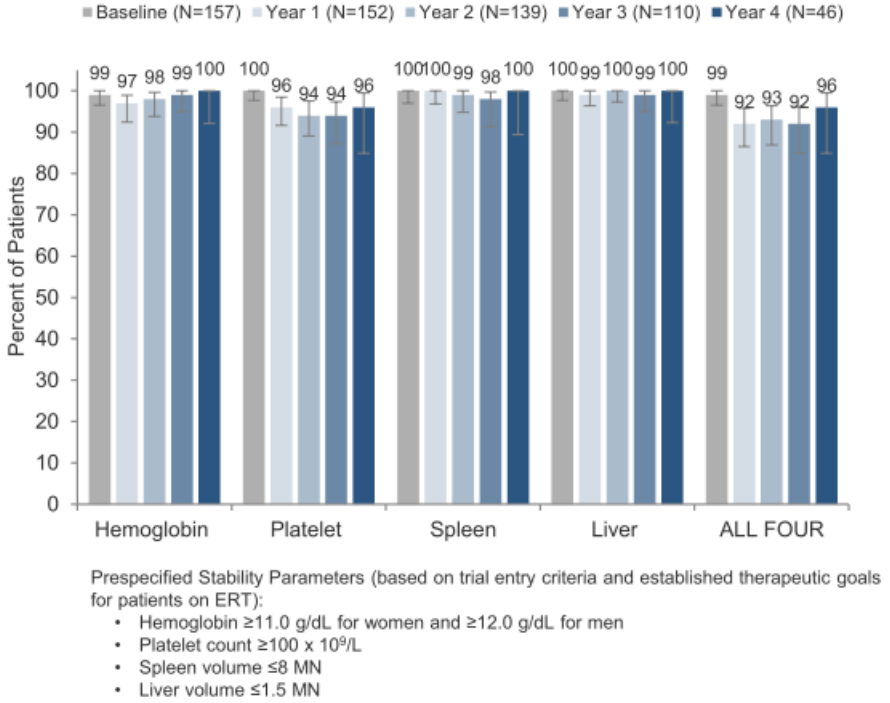
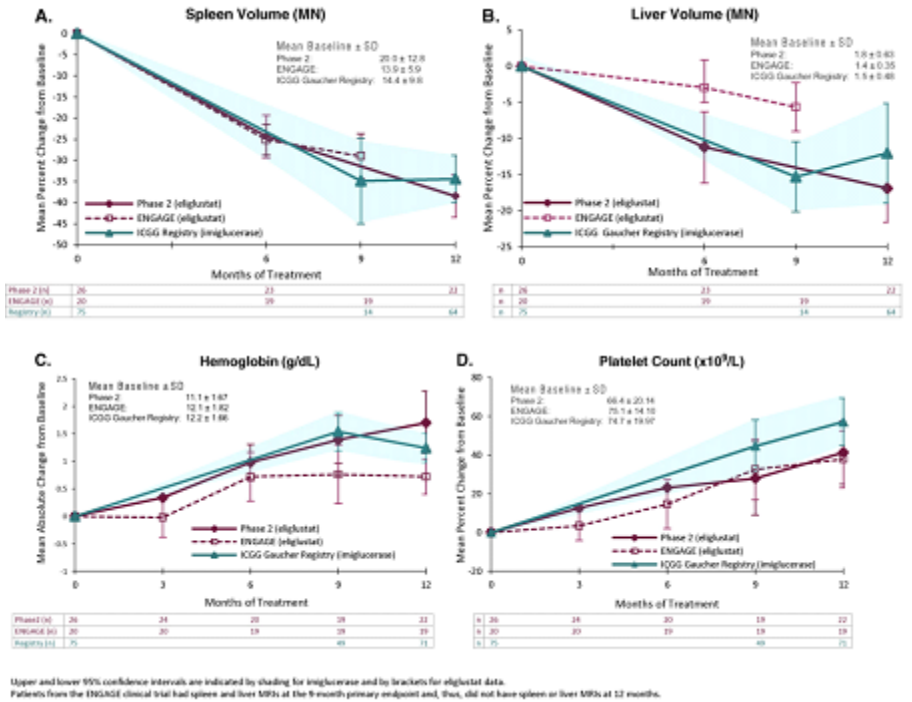
		 Prespecified Stability Parameters (based on trial entry criteria and established therapeutic goals for patients on ERT): • Hemoglobin ≥11.0 g/dL for women and ≥12.0 g/dL for men • Platelet count ≥100 x 10^9/L • Spleen volume ≤8 MN • Liver volume ≤1.5 MN **Treatment-naive** Again, since the dossier was submitted, matched-pair analysis has been carried out comparing eliglustat and ERT in treatment-naïve patients, see figure below for a summary of the results, from which we can conclude that similar outcomes for these parameters were observed (Ibrahim et al 2016). **Figure 2 Change from baseline in organ volumes and hematologic parameters**

Paragraph number	Comment in ECD	SanofiGenzyme response
		 Upper and lower 95% confidence intervals are indicated by shading for imiglucerase and by brackets for eliglustat data. Patients from the ENGAGE clinical trial had spleen and liver MRIs at the 9-month primary endpoint and, thus, did not have spleen or liver MRIs at 12 months. Further, 4 year results are also available for the ENGAGE trial, summary results are presented

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		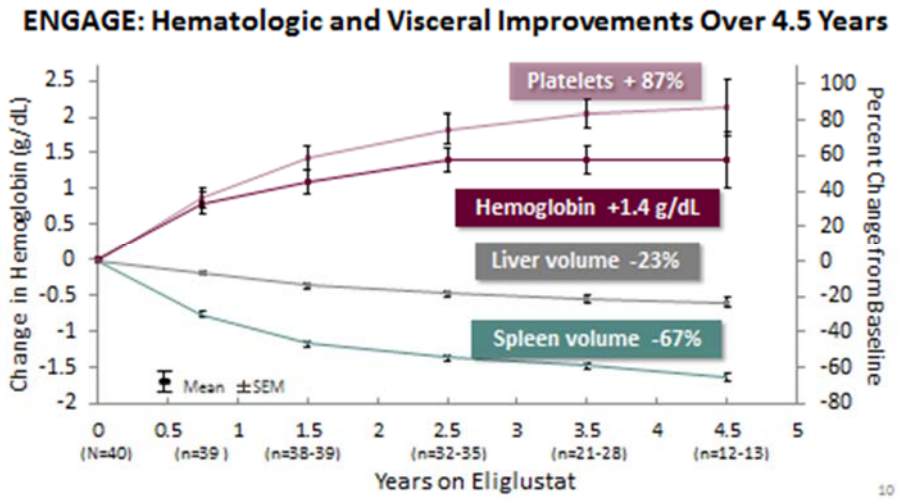 (Mistry 2017)
4.21	The ERG commented that, because of the open-label nature of the trial, there was a high risk of bias for any subjective outcomes.	While the outcomes in the trial had the potential for inter-investigator variability, they are not 'subjective' outcomes. The open-label design was considered the more practical option than a double-blind study for the following reasons. Cerezyme and eliglustat have different routes of administration, which in a double-blind, double-dummy design would require the patient to take a placebo and active treatment of either oral or intravenous infusion, placing a undue burden on patients and dissuading participation in the setting of other marketed treatments. The open-label design permits the important comparison of the patient reported assessment of treatment preference between oral and intravenous. SGZ recognise the potential of bias in open label trials, however, all of the primary composite (spleen and liver volumes, haemoglobin and platelet levels) and the secondary endpoints in ENCORE, are objective measurements that are unlikely to be affected by the open-label design. The secondary endpoint of bone marrow burden has a large inter-observer variability, however to minimise this, the same observer was used throughout the study, therefore any difference is likely to be real.

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		The tertiary quality of measures (SF-36, Fatigue Severity Score, Brief Pain Inventory, and Gaucher DS3) could potentially be considered subjective endpoints, however validated tools were used for these measures.
4.22	The ERG noted that, although few patients withdrew from ENCORE because of adverse events, only 44 of the 159 patients who started the trial were in the analysis at 4 years	The company has already provided the information needed to address this issue in response to the ERG report publication in July 206. We reiterate it here: The ENCORE trial ended on a calendar date, not after a prespecified time on treatment. All enrolled patients had the opportunity to be treated with eliglustat for at least 2 years, but some patients ended up being in the trial for much longer, due to the fact that trial enrolment was spread out over 2 full years. People who enrolled early were in the trial for the longest. In total, 130/157 eliglustat-treated patients (82%) either completed the trial or were switched to commercial therapy when it became available in the United States. The smaller number of patients with 4-year data in ENCORE is due to the timing of their enrolment and/or the group they were in during the primary analysis. ENCORE patients who enrolled very early, were randomized to eliglustat, and did not live in the US, had the opportunity to be on eliglustat for 4 years or longer (one patient had 5-year data). On the other extreme, patients who enrolled very late, were randomized to imiglucerase for the first year, and lived in the US would have had the opportunity to be on eliglustat for only 2.3 years before the trial ended. 36 patients were switched to commercial product, 48 had timed out of the trial and 12 patients withdrew due to adverse events, of these, 4 were withdrawals due to AEs considered related to eliglustat; 10 patients wished to withdraw, 4 patients withdrew due to pregnancy, 2 to noncompliance, and 1 was lost to follow up. Patient disposition is given below.

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		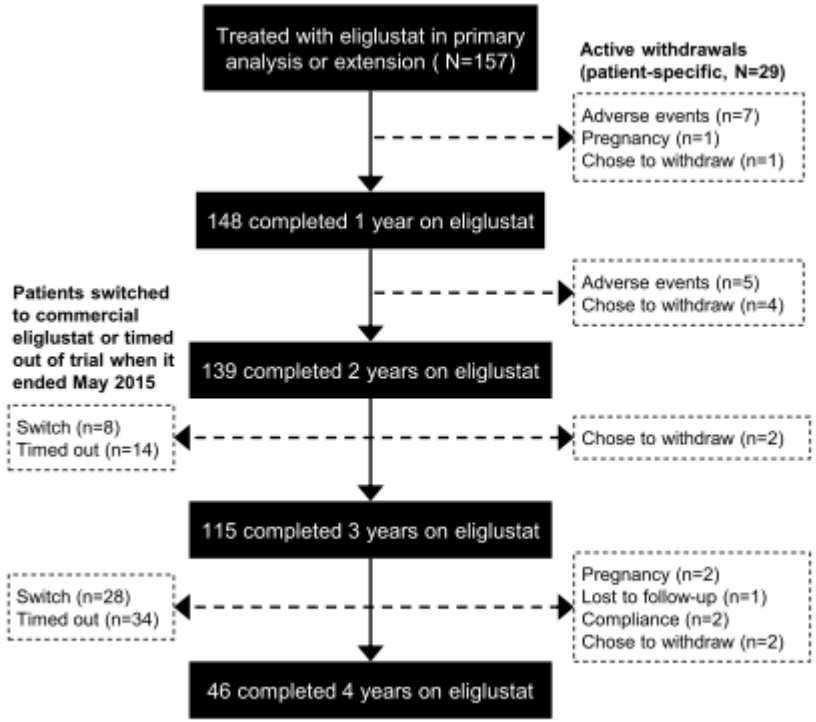 (Cox et al 2017)
4.23	The ERG highlighted that the sample size in the ENGAGE trial was very small (n=40)	SGZ believe that the sample size was not small in relation to the rarity of the disease. For a non-inferiority or equivalence trial comparing eliglustat to imiglucerase in treatment naïve Gaucher Disease, a sample size of at least 70 patients would be required. It was simply not feasible to recruit that many treatment-naive patients. The ENGAGE study, with 40 patients, took 2 full years to enrol and is actually the largest clinical trial ever of treatment-naïve Gaucher Disease patients.

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4.23	Randomised phase of the trial was too short (39 weeks) to measure improvements in bone outcomes for people with type 1 Gaucher disease.	SGZ agree that 9 months is insufficient time to show improvements in bone outcome. However, that is why bone marrow burden was evaluated in ENGAGE, because we believe it is an early measure of evolving bone disease. We did see a statistically significant improvement in BMB score in eliglustat-treated patients compared to placebo. Changes in bone mineral density were not significant, but trended in the right direction (Mistry et al. JAMA 2015). In the ENCORE trial of patients previously stabilized on ERT (mean prior duration of ERT 10 years), there was a small but statistically significant improvement in least square mean lumbar spine Z-score after 4 years of eliglustat (0.29, P<0.0001) In the phase 2 trial of treatment naïve patients, mean lumbar spine T score, which was in the osteopenic range at baseline improved to the normal range after 4 years of treatment (Lukina et al. BCMD 2014). Of note, T-score continued to improve gradually during the subsequent 4 years of the trial and after 7-8 years of eliglustat among the 19 patients who completed the trial, the proportion of patients with normal, osteopenic or osteoporotic lumbar spine Z scores shifted from 26%, 42%, and 32%, respectively, to 63%, 32% and 5% (8 year data – Genzyme data on file). In addition, the placebo-controlled trial design was considered ethically justifiable given that patients were untreated adults who would have a 50% chance of receiving eliglustat during the first 9 months and a 100% chance upon successful completion of the 9 month PAP.
4.24	The ERG noted the trial had a small sample size (n=26) and there was an unexplained loss of patients from later time points in the study.	SGZ would like to explain the loss of patients over time. Majority of these occurred during the first year; 3 patients withdrew because of pregnancy (after 4, 6, and 13 months on eliglustat); 2 patients withdrew on Day 1 of treatment due to asymptomatic NSVTs detected during routine Holter monitoring when plasma levels of eliglustat were undetectable; 1 patient withdrew after 1 year due to a bone lesion that was retrospectively identified at baseline (this was a protocol violation), and 1 patient chose to withdraw after 2 years on eliglustat. Trial withdrawals are described in detail in the published manuscripts (Lukina et al. BCMD 2014). Of note, this trial recently ended after 7-8 years on eliglustat, and there were no further trial withdrawals during the final 4 years of the trial (19 patients completed the trial) (Genzyme data on file).

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4.25	The ERG highlighted that no data comparing eliglustat with ERT were presented from patients who had not previously had treatment.	SGZ recognise that a non-inferiority or equivalence trial comparing eliglustat to imiglucerase in treatment naïve GD1 patients would have been ideal, but would have required a sample size of at least 70 patients. It was simply not feasible to recruit that many treatment-naive patients. The ENGAGE study, with 40 patients, took 2 full years to enrol and is actually the largest clinical trial ever of treatment-naïve Gaucher patients. We refer to the section above which presents the results from the Ibrahim et al study, that found similar outcomes in matched treatment naïve patients initiated on imiglucerase and eliglustat.
4.26	The ERG noted that the summary of product characteristics for imiglucerase and velaglucerase alfa recommend higher starting doses of 60 U/kg every 2 weeks. However, the standard operating procedure developed by expert consensus in England reports that a maintenance dose of 15–30 U/kg is appropriate for most patients	It is the understanding of SGZ that in the UK clinicians do start higher than 30U/kg, especially in children, where they tend to keep the dose the same as the child grows, therefore gradually reducing the dose/kg, and in those with severe symptoms or particularly severe blood results. Clinicians would then titrate the dose downwards to the patients clinical haemoglobin, platelet and chitotriosidase levels
4.43	The ERG considered the company's approach to generating long-term transition probabilities to be complicated, stating that it reduced the transparency of the model, so making validation difficult. The ERG stated that, because the same transition probabilities were applied to both treatment and comparator groups, it was unclear	We assumed that a patient's probability of being in a particular health state, except for death, at a particular time (year) depends on the health state in the previous period, the length of time the patient was receiving treatment (1, 2, or ≥ 3 years), the patient's starting DS3 category (mild, moderate, marked, or severe), and whether patient has had a splenectomy. We included treatment duration to capture the effect of disease stabilization over time as reported by Weinreb et al (2013) and Zimran et al (2015); we truncated treatment duration at 3 years based on the literature and clinical input that patients stabilize after about 3 years of treatment. We included splenectomy status because it can directly influence a patient's likelihood of being in spleen-related health states. We included the ignition DS3 category because of clinical input we received that indicated that disease severity when starting treatment can influence how quickly patients improve. These assumptions are presented in Ganz et al (2017). The equation for determining a patient's current health state is

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	why a simpler approach was not used.	rather simple. The reason, we suppose, that the ERG finds the method complicated is that there 9 health states and, therefore, the transition probabilities (81 of them) are derived from a ordinal logistic regression model. The methods are fully explained in the appendix to Ganz et al (2017). The long-term transition probabilities were derived from patients enrolled in a GD1 disease registry, 99% of whom started therapy with ERT. We applied the same long-term transition probabilities to all arms in the model because we lacked information on the long-term trajectories of patients using eliglustat and because we assumed that the long-term outcomes would be similar between ERT and eliglustat based on the non-inferiority results of the clinical trials. The regression model could be modified so that the patient's DS3 category at the start of the long-term phase is used rather than
4.43	Additionally, the ERG stated that the GD-DS3 score appeared to be insensitive to changes in disease status, so did not reflect differences between the treatments seen in the ENCORE trial. This meant that differences between the treatment and comparators were not accounted for in the model. This resulted in a bias towards equivalence in clinical benefits, so underestimating the differences between eliglustat and imiglucerase seen in the ENCORE study.	This interpretation of the GD-DS3 scoring tool is not correct. The tool is not insensitive to changes in disease statue. It was constructed to identify minimal clinically important difference (MCID) in patients with Gaucher Disease. The reason it doesn't reflect differences between treatments observed in the trial is, as stated in our covering letter, very few of these differences are clinically meaningful. In the ENCORE trial only three patients out of the 99 per protocol patients on the eliglustat arm had clinically meaningful changes in their disease status at 52 weeks according to Therapeutic Goals. The GD-DS3 scoring system was developed with nine GD1 experts from across the globe in an effort to define patient cohorts in this chronic disease that has heterogeneous manifestations. Through a survey, domains of disease manifestation and items within each domain were selected for inclusion within the scoring system. The scaling of and maximum scores for individual assessments within DS3 were optimized to maximize the correlation between total scores and the consensus CGI-S scores utilizing a Generalized Reduced Gradient-2 algorithm. Participating physicians then conducted an exercise to determine the minimal clinically important difference (MCID), which represents a change in score, either increase or decrease, that would indicate a change in some aspect of the disease or trigger an adjustment in medical care or prognosis. Physicians were provided a sample of 20 patients and came to a consensus (at least 75% of physicians agreeing) on there being a change in prognosis. The MCID for improvement was

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		found to be a decrease of -3.17 and for worsening was +3.86. Additionally, cases scored as no change in prognosis by at least 75% had changes that fell in between these two values. With MCID in mind, while clinical efficacy on a biomarker and organ level may differ nominally between treatment arms, unless they result in a change of -3.17 or +3.86, they are unlikely to modify patient's prognosis. During model development there was discussion regarding perceived lack of sensitivity and so health states were constructed to reflect the GD-DS3 but also clinician feedback on the most important drivers of quality of life, costs and disease path. Spleen status and severe skeletal complications (SSC) were identified as being the biggest drivers. However, in the age of ERT, spleen status is fixed after initiation of ERT (if you begin ERT with a spleen, you will not be splenectomized). Additionally, SSC did not represent a MCID via the DS3 scoring system (+/- 1 total point) but it did affect quality of life and costs due to both the event and subsequent management. Therefore, the mild, moderate, marked and severe states were further divided into with or without SSC in order to be sensitive to changes in a patient's disease status. Mild without SSC was further divided to be those with and without moderate, severe or extreme bone pain for further sensitivity within the most frequent health state patients receiving ERT experienced. The GD-DS3 may not directly replicate the findings from the ENCORE trial, however, it does measure MCID, that would drive differences in treatments or prognosis and therefore be relevant to the evaluation of comparative effectiveness underway.
4.44	The ERG stated that assuming long-term equivalence of eliglustat and ERT underpinned the calculation of long-term benefits, and had a considerable impact on estimated incremental QALYs. The ERG considered that this assumption had not been adequately justified	Long term state transition matrices are populated based on the baseline state a patient begins in. Patients begin in the same state distribution and transition based on their treatment-specific transition matrix, the dependency on the baseline state has the effect of making the transition matrices the same for both treatment arms. While there is a difference in a patient's state path because of the treatment effect difference at one year, there is convergence to the same state path since the same transition matrices are applied to both arms. Although the analysis of the data indicated that transition matrices were dependent on the baseline state, this criticism is valid. We have explored alternative analyses and implementation of the long term data to test the impact

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	in the company's submission. It stated that short-term non-inferiority results in the ENCORE trial did not imply non-inferiority in the long term.	of basing the long term the long term transitions on where they end up after the trial treatment effect. SGZ ran some exploratory analyses changing the way the patient cohort moved onto the transition matrices. Rather than these being determined by the patients' baseline characteristics, two options were explored, the first takes the distribution of patients, both imiglucerase and eliglustat arms, at the end of the 52 weeks of ENCORE. This end of trial distribution then determines where the patients enter the transition matrices, thereafter the matrices are applied as in the base case model. The second option uses the ENCORE four-year eliglustat data, so that the final state distribution is based on the completion of 4 years of eliglustat therapy. These changes mostly affected the frequency of time in mild vs. moderate health states. Eliglustat transition matrices tracked similarly to that of the long term transition data leading to generally similar results. This analysis was done on the company's base case: total incremental QALY gain 2.28. The first approach (using the 52 week data) led to revised total QALYs of 2.27. The second approach (using 4 year data) led to total incremental QALYs of 2.29. There is minimal change in costs as the only changes were in the health state costs, which are not the drivers of costs in this model. We are confirming that similar affects would be observed with the ERG base case, so from 1.05 QALY gain to 1.04 using one approach and 1.06 using the other approach, we will confirm this when the results are available.
4.44	and had a considerable impact on estimated incremental QALYs	This is an overstatement of the impact that amending the long-term transition probabilities has on the incremental QALYs for plausible changes to the model. Our exploratory analysis above suggests, based on the company's base case analysis, that depending on the approach used total QALY gain may increase or decrease by 0.01, from a base of 2.28. We are confirming that similar affects would be observed with the ERG base case, so from 1.05 QALY gain to 1.04 using one approach and 1.06 using the other approach, we will confirm this when the results are available.

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4.45	The ERG questioned whether the inclusion of a large number of health states was necessary. The ERG acknowledged that more health states can improve the accuracy of a model. However, the advantage of this approach is offset when the model has a greater complexity and reduced transparency as a result. The ERG commented that this was particularly important because data for type 1 Gaucher disease are limited.	As discussed earlier, the decision was made to base the model on an independently developed and validated scoring tool designed to measure minimal clinically important differences in disease progression. By using this tool the model is able to compare established standard of care with eliglustat on clinically, as opposed to statistically, meaningful outcomes that would directly impact the NHS from a total health outcomes and a total cost perspective. Because ERT controls GD1 deterioration, patients with GD1 today are very unlikely to be measured as marked or severe on the GD-DS3 tool. However, and given comments in this document that suggest the committee is querying ERT, if these treatments were not available the impact on patients' quality of life would be substantial. As such, SGZ felt the complexity related to using a 10-state as opposed to a 3 or 4 state model were justified. We acknowledge that for more severe health states there are limited data, an artefact of there being few patients who end up with this level of disease now effective treatment options are available
4.46	The ERG questioned the company's assumption that eliglustat and ERT were equivalent in people who had not had previous treatment. It considered that the evidence from the ENCORE trial should have been incorporated instead.	Using ENCORE data to population the ERT arm of the treatment-naïve model would not be a robust way of addressing the data gap. The inclusion criteria for the ENCORE trial required patients to have been on ERT for a minimum of three years, patients had in fact been on ERT for a mean of 9.8 years in the eliglustat arm and 10.0 years in the imiglucarase arm. For at least 6 of the 9 months prior to randomisation the patient had to have received a total monthly dose of 30U/kg to 130U/kg of ERT and have reached GD therapeutic goals. In ENCORE, these ERT patients continue on ERT or switch to eliglustat. This ERT-stable population is very different to a treatment-naïve population being stable patients as opposed to patients seeking to control disease symptoms for the first time.
4.48	The ERG stated that mortality risk would increase with severity of disease, so disagreed with the company's assumption on mortality. The ERG explored this	This is a legitimate challenge that the company accepts. However, it suggests there is some misunderstanding regarding the premise of the assumption: given the availability of ERT, time in the marked and severe state is short and transitory. Amendments to treatment plans can return people to better health states so that it is unlikely people with GD on active treatment will be in the marked and severe health states for any notable period of time. However, we accept the principle

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	assumption in its analyses.	that were a person in a marked and severe health state for a long period of time they are likely to have a greater risk of mortality, as such we accept this proposition.
4.49	The ERG identified the Wyatt et al. study (2012), which showed that the mean age at which treatment was started was 35.2 years in the treatment-naive population and was 46.4 years in those who were stable on treatment with ERT. The ERG considered that the starting age in the model was underestimated, therefore overestimating lifetime differences. The ERG explored this in its analyses	The statement in 4.49 is not representative of the data presented in Wyatt 2012. Wyatt conducted an observational study of a UK cohort identified in treatment centres. Their baseline characteristics at enrollment are in Tables 12 and 13, with Table 12 only presenting the characteristics for adults. The ERG has used the "age of treatment initiation" as the mean age at which treatment is started among treatment naïve patients with GD1; however, this is likely to be biased as it likely includes patients who began treatment after having GD1 for years prior to the introduction of ERT. The ERG made the mean starting age for the stable on treatment population to be the average age of the study cohort from Wyatt 2012, which are not equivalent statistics. The average age of the cohort in Wyatt is biased for the same reasons listed above for the treatment naïve population, and literature has shown that patients stabilize on ERT within 2-5 years of their initiation, not 10 as indicated by the value used by the ERG (Weinreb 2015; Weinreb 2002). Data from the Ibrahim et al (2016) study reports mean age of treatment initiation being 32-35 years.
4.50	The ERG considered that the dose of eliglustat in the model was in line with practice. However, the ERG noted that the efficacy data were taken from ENCORE, in which 48% of patients had a higher dosage of eliglustat (150 mg twice daily) for most of the trial. The ERG highlighted that this was a key driver in the model.	The final statement in this paragraph is misleading. It would be correct to say that clinically meaningful change in disease was a driver of the model, but as discussed earlier the differences between arms are minimally meaningful from a clinical perspective. Further, the information on the PK/PD modelling that was undertaken as part of eliglustat's regulatory assessment indicated that with there was no difference in the efficacy outcomes between the 100mg BID and 150mg BID dose with the exception of a 4% change in spleen volume. This 4% change in spleen volume was still within normal ranges and therefore not considered clinically meaningful (Turpault et al 2015_poster).
4.51	The ERG disagreed that there will be no administration costs	SGZ agree it is appropriate to include a dispensary fee. Work with key stakeholders to date would suggest that they expect eliglustat to be delivered every month/two months/three months, therefore

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	associated with eliglustat because it is an oral therapy, and explored incorporating a minimum pharmacy dispensary cost.	it may be necessary for the frequency that this dispensary fee is applied to be adjusted.
4.51	Additionally, the ERG considered that the company overestimated the administrative costs for ERT delivered at home because it was implausible that it would be higher than the cost of hospital administration.	We accept that a consideration of the cost of homecare and hospital treatment is appropriate. We dispute the ERG's conclusion that that it is 'implausible' for the cost of homecare to be greater than hospital care. Nurse time in the home has no economies of scale and far more limited economies of scope than nurse time in a hospital. As such, whether homecare or hospital care is more expensive is a factor of the perspective of the costing analysis. Consideration of the cost 'per hour of nurse time' and the activities that the nurse can deliver in that time leads to different results to the 'nurse cost per infusion'. Costing differences are also dependent upon the composition of the costs, for example is there a portion of cost ascribed to sunk capital costs, training costs, support staff costs and sundries, in which case a NHS nurse with all the accompanying NHS organisation costs to include is likely to be more expensive in the hospital or giving care in the home, than a nurse from a smaller, third party homecare organisation. If using the gold standard costing compendium from the PSSRU as the source for unit costs, costs can be consistently applied across resources. However, PSSRU doesn't have a cost for homecare delivered by a third party organisation. Because of this we sought to find a publicly available price for homecare delivery, which we reported. While we accept that cost attributed to home delivery may be a high estimate in the basecase, and the ERGs simplifying approach is reasonable, we suggest there is uncertainty with the ERGs estimated and costs may be higher.
4.52	The ERG noted concerns with the costs for ERT in the model. The ERG was concerned that the company did not include any vial wastage.	In developing the economic model for this submission SGZ heard from treating clinicians, and based on the content of the Gaucher Disease Standard Operating Procedure, that ERT was not wasted and all doses were rounded up or down to avoid wastage. In not including wastage the base case disadvantaged eliglustat, including wastage would have increased ERT costs. In the first evaluation committee meeting the expert clinicians stated that they rounded up and down their dosing. The base case model presented give a cost for total units of ERT required, (based on

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		mean dose in U/kg and weight). We agree with the approach the ERG took in looking at the distribution of GD patients in the ENCORE trial and calculating a distribution of ERT based on the distribution of weight and dose and relating that to the most likely whole vial. However, SGZ does not know how clinicians make decisions about when to round the dose up or down, as we discuss below there is uncertainty regarding the 'usual English dose of ERT. As a result we believe the approach taken in the base case to report costs on a per unit basis based on the trial data is the most consistent approach.
4.52	The ERG reiterated that there was considerable evidence to suggest that substantially lower doses of ERT are used in practice (see section 4.26), so the higher dose of ERT treatment assumed in the model overestimated the ERT acquisition cost.	See responses above regarding usual UK dose, UK weight and efficacy assumptions.
4.52	The ERG also noted that patients who had not had previous treatment in the model were assumed to have had the same dose of ERT as patients whose disease was stable. However, the clinical adviser to the ERG suggested that newly diagnosed patients are typically less severely affected than patients who start treatment in childhood and so do not need such intensive dosing.	We suggest that the committee seeks clarification on this issue. It is true that patients with childhood onset tend to have more severe disease. However, it is not accurate to say all patients diagnosed in adulthood have mild disease that requires lower dosing. Given the rareness of the disease, patients can go undiagnosed and therefore untreated for a number of years and therefore could require high doses of ERT. Equally, adult onset patients may have less severe disease and require lower doses. This also is inconsistent with the SOP that suggests a higher starting dose and titrating down.

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4.54	additional administration costs for eliglustat (£14.40 monthly dispensary cost)	We accept that a dispensary cost should be included. Eliglustat might be delivered every one, two or three months, we request the ERG adjust the frequency the dispensary cost is applied accordingly.
4.54	revised administration costs for ERT treatments (home therapy cost equal to hospital cost)	See discussion above, it is plausible for homecare to be more costly than hospital care. However, we don't dispute the approach the ERG have used, nor the simple fix for implementation in the model. However, it is very much an assumption. It should be noted that the ERG appear not to have been able to find a better estimate for the cost of a nurse-led home infusion than SGZ was.
4.54	revised estimate of the QALY benefits of oral therapy (estimate of 0.05)	Post the submission of the HST dossier for eliglustat in April 2016 SGZ recognised that the original value submitted for oral benefit of 0.12 double counted some aspects of the adverse events due to intravenous infusion. Had an ECD been produced after the September committee meeting, SGZ would have shared this information. SGZ accepts the committee's most plausible utility value for QALY benefit of an oral treatment in this therapy area is 0.05.
4.54	revised modelling of mortality to allow for increased mortality risk for people with marked and severe disease	This is a legitimate challenge that the company accepts. However, it suggests there is some misunderstanding regarding the premise of the assumption: given the availability of ERT, time in the marked and severe state is short and transitory. Amendments to treatment plans can return people to better health states so that it is unlikely people with GD on active treatment will be in the marked and severe health states for any notable period of time. However, we accept the principle that were a person in a marked and severe health state for a long period of time they are likely to have a greater risk of mortality, as such we accept this proposition.
	reduction in dose of ERT to bring it in line with UK practice (25 U/kg)	As mentioned previously, this represents an inconsistent and flawed consideration of the available data. It is inappropriate to implement a dose of 25U/kg, as representing usual UK practice, without taking into account the weight of usual UK Gaucher Disease patients, reported above. Further, there is no consideration about how this dosing would affect the efficacy estimate in the model, which is inconsistent with the discussion on the 100mg BID/150mg BID eliglustat dose (while recognising they may have different dose/response relationships) .

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		SGZ would requests NICE/the ERG consider what a plausible adjustment to estimates of ERT efficacy would be at this dose, specifically to consider if this affects the long-term efficacy given the potential relationship between lower doses and poorer bone outcomes (Deegan et al 2011; de Fost 2006)
	using ENCORE effectiveness data in the treatment-naive population during the first cycle.	SGZ strongly refutes this suggestion. Given that patients in the ENCORE trial had to have been on ERT for a minimum of three years, to have documented stability for the last 6 months and to be on a dose ranging from 30U/kg – 130U/kg, and that the mean patient across both of the per protocol arms had been on ERT for a mean of 10 years, we consider the assumption that these patients are equivalent to treatment-naive patients is flawed. The study by Ibrahim et al, and reported in the EPAR appears to demonstrate that very similar outcomes are achieved in the first-year of active treatment with eliglustat or ERT
4.55		Given the company has submitted a simple PAS and the NHS would not pay list price, these results are not relevant to a discussion about value for money for the NHS.
5.2	There were few data on patients with poor metaboliser state … the company submission states that 7% of the Gaucher population are poor metabolisers, while 3% of people had poor metaboliser status in the ENGAGE trial	There are limited data on poor metabolisers. There were no poor metabolisers in the ENGAGE study. There were 4% poor metabolisers in the ENCORE study, and when pooling patients from ENCORE, EDGE and Phase II there were 4% PMs. Verbal evidence in the first committee meeting from SGZ was that there is variability in the estimated proportion of GD1 patients who are poor metabolisers: it ranges from 3% to 7% depending on what information you are looking at. In summary, the few data are due to small patient numbers, observed data and outputs of PK/PD modelling suggests that at the dose of 100mg QD there will be no difference in clinical outcomes or TEAEs. Consideration needs to be given to drug-drug interactions and contraindications relating to the CYP2D6 metabolic pathway, as in needed for IM/EM, and there are slightly different for PMs.
	About 48% of patients in the ENCORE trial had a higher dosage of eliglustat (150 mg twice daily)	Sanofi Genzyme undertook modelling that showed selecting a 100 mg BID dose for the IM and EM population will allow for safe and efficacious exposure of this target population, in the same range as observed in our positive clinical trials and without the need for plasma monitoring. A PK/PD-

Paragraph number	Comment in ECD	SanofiGenzyme response
	than the recommended dosage stated in the summary of product characteristics. The committee was aware that efficacy data from ENCORE were used in the model, and was concerned that this reflected use of a higher dosage than in the marketing authorisation for eliglustat. The company stated that their modelling suggested only minor differences in plasma levels with the higher dose, and that it would be associated with a negligible gain. The committee understood, however, that the basis for this modelling were the blood concentration data from the trials in which dose adjustments had been made in response blood concentration measurements. Therefore, it concluded that the predictions were subject to bias.	efficacy modelling approach was used to show that the exposures predicted in a CYP2D6 phenotype-based dosing scenario would achieve the same range that has been shown to be safe and efficacious in the pivotal studies. These analyses were particularly important in the case of ENCORE. As noted by NICE almost half of the patients in ENCORE received a dose of 150 mg BID. Therefore, it was necessary to confirm that the ENCORE study population would still achieve comparable efficacy under a phenotype-based dosing regimen with a top dose of 100 mg BID for IMs and EMs. The ENCORE primary efficacy composite endpoint and its four individual components were evaluated for exposure-response relationships. The four components of the primary endpoint in ENCORE were evaluated for exposure-response relationships. There was no significant exposure-response relationship observed for absolute change in haemoglobin level, percent change in platelet count, or percent change in liver volume. The only parameter that showed a significant exposure-response relationship was % change in spleen volume. Given the limited range of exposure and the success of the trial in maintaining disease stability, it is not unexpected that most of the components of the primary composite endpoint did not show appreciable changes from baseline (when those values were already normal or near-normal). For exposure estimates in this modelling approach, PopPK-predicted PK parameters were used instead of observed PK parameters since the latter were confounded by the fact that dose was adjusted based on Ctrough during Phase II and III. Using the PK/PD model, percent changes in spleen volume (MN) from Baseline to Week 52 at the study level were predicted using PopPK-predicted exposures. This allowed Sanofi Genzyme to compare the observed study results from the ENCORE trial to the predicted study results if IM and EM patients were to receive 100 mg BID (as proposed in the commercial dosing). PK/PD analyses predicted that spleen volume treatment responses for IM and EM patients dosed at a fixed dose of 100 mg BID that would be similar to the observed spleen volume treatment effects in the study. The estimated treatment difference from Cerezyme using the simulations and the same Cerezyme data (observed) was also similar to the observed treatment difference in the study. To further confirm that the proposed phenotype-based dosing regimen would not impact the

Paragraph number	Comment in ECD	SanofiGenzyme response
		efficacy results of those IM and EM patients actually dosed 150 mg BID and who would be administered the lower dose of 100 mg BID, patient exposure projections were applied to the established PK/PD model with observed percent change in spleen volume to obtain projected percent change in spleen volume values for IM and EM patients when dosed at 100 mg BID. The maximum increase between the observed and projected values for spleen volume at Week 52, due to the reduction in dose from 150 mg BID to 100 mg BID, would be 4%. Four percent is a small change relative to the patients' essentially normal spleen volume (therapeutic goal for spleen volume is ≤2 to 8MN) and is comparable to the test-test variability of organ volume measurement by MRI determined during the ENGAGE study using the same methodology, and less than the 12% variability reported in the literature (Barton, 1991, New Engl J Med). Such a small change in patients with little or no splenomegaly would not be clinically or medically noticeable. Thus, 100 mg BID is an effective dose for IM and EM patients receiving chronic therapy aimed at maintaining stability of disease, and the added exposure from a 150 mg BID dose is not expected to provide any further meaningful clinical benefit. When considering the sufficiency of a 100 mg BID dose for the ENCORE patient population (clinical stable patients switching from ERT), it is important again to consider the efficacy demonstrated in treatment-naïve patients. The Phase 2 and ENGAGE trial, which treated patients with the highest disease burden (the treatment-naïve), have demonstrated the efficacy of the 100 mg BID dose in the most difficult to treat patient population. The ENCORE study enrolled patients who had received enzyme replacement therapy for >3 years, and consequently, these patients had low disease burden at the time of initiation of eliglustat treatment and were considered clinically stable by virtue of meeting pre-specified therapeutic goals. The 100 mg BID dose is therefore expected to also be effective in the patients with lower disease burden (ERT-stabilized patients). In conclusion, the analyses performed by Sanofi Genzyme not only support the proposed CYP2D6 phenotype-based dosing, but also demonstrate the continued validity of the ENCORE conclusions non-inferiority to imiglucerase) even with a top dose of 100 mg BID for IMs and EMs
5.4	It heard from clinical experts that	SGZ considers this a more accurate representation of the dose issue in the UK than paragraph 4.52

<table>
<tr><th>Paragraph number</th><th>Comment in ECD</th><th>SanofiGenzyme response</th></tr>
<tr><td></td><td>the approach in practice is to titrate the dose of ERT and use the lowest effective dose. It heard that patients generally start on 30 U/kg, followed by close monitoring for the first 12 months, with further dose reductions depending on response. The clinical experts stated that some people with newly diagnosed type Gaucher disease occasionally have very severe disease and may need a higher starting dose.</td><td>above</td></tr>
<tr><td>5.4</td><td>The committee also heard that there were no differences in the effect of eliglustat in the ENCORE trial when stratified according to ERT dose.</td><td>SGZ suggests this is a mis-interpretation of the table below to conclude that outcomes seen with a mean of 42.4U/kg would be achieved with a mean dose of 25U/kg.

Proportion of Patients Stable at 12 months: Per Protocol Population [these data were provided by biostats]
<table>
<tr><th></th><th colspan="3">Eliglustat</th><th colspan="3">Imiglucerase</th></tr>
<tr><th></th><th colspan="2">Pre Study ERT</th><th></th><th colspan="2">Pre Study ERT</th><th></th></tr>
<tr><th></th><th>< 35 /kg/q2w (N=38)</th><th>≥ 35 U/kg/q2w (N=61)</th><th>Overall (N=99)</th><th>< 35 /kg/q2w (N=18)</th><th>≥ 35 U/kg/q2w (N=29)</th><th>Overall (N=47)</th></tr>
<tr><td>Proportion, n (%) 95% CI remaining stable</td><td>32 (84·2) (68·7, 94·0)</td><td>52 (85·2) (73·8, 93·0)</td><td>84 (84·8) (76·2, 91·3)</td><td>17 (94·4) (72·7, 99·9)</td><td>27 (93·1) (77·2, 99·2)</td><td>44 (93·6) (82·5, 98·7)</td></tr>
<tr><td>Difference in proportion vs imiglucerase and 95% CI</td><td>-10·2 (-25·2, 10·2)</td><td>-7·9 (-20·0, 7·6)</td><td>-8·8 (-17·6, 4·2)</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
</table>
The ENCORE data were analyses by doses ≥35U and <35U. The mean dose in the <35U population</td></tr>
</table>

Paragraph number	Comment in ECD	SanofiGenzyme response
		was 27U while the mean dose in the ≥35U dose was 51.23U (last dose received, ITT population). The committee have assumed a 'flat dose' of 51U/kg is equal to a 'flat dose' 27U/kg and thereafter 25U/kg without taking into account that does of ERT will be affected by patient weight, baseline characteristics and disease severity. What the <35 and ≥35U data show is that, if patients are well managed on doses are ERT uniquely tailored to their characteristics then ERT leads to maintained stability over 52 weeks. It does not show that if every patient on the ERT arm of the ENCORE study had received 27U the same outcomes would have been achieved.
5.5	it also noted the view of the European Medicines Agency's Committee for Medicinal Products for Human Use that the trial did not comprehensively show that the usual regulatory standard of -20% had been achieved	We acknowledge this statement is in the EPAR and we acknowledge that SGZ made the decision to go at a 25% non-inferiority margin in the face of advice from the CHMP that 20% was the preferred margin. However, as is reported in the cover letter to have met this 20% non-inferiority margin would have required nearly double the number of patients being exposed to the trial product (an extra 174 in addition to the 186 patients actually enrolled). Trial robustness needed to be balanced against practical issues (how to recruit double the patients in an ultra orphan disease area), ethical issues, exposing double patients to a pre-licence drug and of course commercial considerations: a larger trial would delay availability of the licenced product to Gaucher Disease patients across Europe. As stated earlier, using 14 different appropriate methods for analysing the data, the lower 95% confidence interval was within a 20% non-inferiority margin. It was outside the 20% NIM using two methods that can legitimately be considered less appropriate given the nature of the data being assessed.
5.5	The committee heard from the clinical experts that they considered eliglustat to be equivalent, or very nearly equivalent, to ERT based on clinical measures	SGZ agrees this is a critical commentary from the clinical experts and reflects the importance of distinguishing between clinically and statistically meaningful information

Paragraph number	Comment in ECD	SanofiGenzyme response
	such as haemoglobin levels and platelet counts, as well as in terms of how patients felt while having eliglustat.	
5.5	The committee concluded that eliglustat could potentially be an effective treatment for type 1 Gaucher disease, but remained concerned about the uncertainty about effectiveness in comparison with ERT, particularly in the long term	The long-term issue is the same for any novel medicinal product launching, it accounts for why the usual NICE HTA process has a three year re-review period. SGZ ran some exploratory analyses changing the way the patient cohort moved onto the transition matrices. Rather than these being determined by the patients' baseline characteristics, two options were explored, the first takes the distribution of patients, both imiglucerase and eliglustat arms, at the end of the 52 weeks of ENCORE. This end of trial distribution then determines where the patients enter the transition matrices, thereafter the matrices are applied as in the base case model. The second option uses the ENCORE four-year eliglustat data, so that the final state distribution is based on the completion of 4 years of eliglustat therapy. These changes mostly affected the frequency of time in mild vs. moderate health states. Eliglustat transition matrices tracked similarly to that of the long term transition data leading to generally similar results. This analysis was done on the company's base case: total incremental QALY gain 2.28. The first approach (using the 52 week data) led to revised total QALYs of 2.27. The second approach (using 4 year data) led to total incremental QALYs of 2.29. There is minimal change in costs as the only changes were in the health state costs, which are not the drivers of costs in this model.
5.7	The committee noted that the main comparator for this evaluation was ERT. It also noted that, because NICE has not evaluated ERT, there was uncertainty about its benefits and value for money and, by	SGZ is very concerned by the implications of this paragraph. This HST was for the assessment of eliglustat in the treatment of type 1 Gaucher Disease, not a multiple technology assessment of all treatments for Gaucher Disease. We remind the committee that the phrase 'value for money' is used in the HST process rather than cost-effectiveness because of societal preference for flexibility in defining a treatments value ie, not

Paragraph number	Comment in ECD	SanofiGenzyme response
	extension, the benefits and value for money of eliglustat. The committee noted the statement from NHS England that the risks around value for money offered by ERT were lower for Gaucher disease compared with the risks for conditions such as Fabry disease. This is because it believed, in Gaucher disease, the effectiveness of ERT is well established and because the dose of ERT can be titrated to the lowest effective dose and the number of patients is lower. However, the committee was mindful that the benefits and value for money of ERT has not been formally considered. The committee concluded that this would add to any uncertainty around the value for money of eliglustat.	all diseases are equivalent and it is not always appropriate to apply efficiency measures. This is seen explicitly with the End of Life criteria for cancer treatments and in the design of the current HST process that explicitly precludes the utilitarian/efficiency reporting of outcomes as 'ICERs' as it was determined that this is not always appropriate.. SGZ considers questioning the value for money of an established and effective treatment in the ECD to be out of scope for this evaluation and suggests the committee have gone outside of the remit of this evaluation in doing so.
5.8	The company assumed that eliglustat and ERT have equal efficacy in patients who had not previously had treatment. The committee was aware that there was no direct evidence comparing	SGZ requests the committee reviews this decision in the face of information provided regarding the nature of the ENCORE trial design. ERT-stable patients are very different to treatment-naïve patients. There is variation in treatment-naïve patients (some with less severe illness as they have milder adult onset disease, some with more severe illness, and this can be due to long delays in diagnosis) that would lead to a variation in baseline disease state that is not seen in the ENCORE study.

Paragraph number	Comment in ECD	SanofiGenzyme response
	eliglustat with ERT in this population. *It agreed with the ERG that evidence from the ENCORE trial would have been more appropriate*.	
5.10	The company assumed long-term equivalence of eliglustat and ERT, and the *ERG highlighted that this had a considerable impact on estimated incremental quality-adjusted life years QALYs).*	SGZ requests this analysis is provided to us to be able to validate the veracity of this statement, the information we were able to find fro the ERG report dated July 2016 was that, *'The ERG attempted to incorporate differential efficacy into the analysis in order to demonstrate the impact on the results if the assumption of non-inferiority did not hold in the long-term. However, the ERG was unable to explore this scenario as any attempt to remove the assumption of non-inferiority resulted in inconsistent results, and a lack of transparency in the cost-effectiveness model prevented the identification of any errors'.* This is quite a different proposition and the company would like to understand the basis for this statement. SGZs exploratory analysis suggests that from a base case of 2.28 QALY gain, a plausible difference would be a 0.01 increase/decrease in QALY gain.
	The committee agreed with the ERG that non-inferiority was not the same as equivalence, and that non-inferiority in the short term does not imply non-inferiority in the long term.	SGZ agrees with the accuracy of this statement. However, this is not the same as stating the products have clinically meaningful difference in effectiveness. There is an indication of similar outcomes in the study by Ibrahim et al for treatment naïve patients. Considering how eliglustat might be used in ERT stable patients, and recognising that patients with sub-optimal outcomes would not be maintained on a product, there is likely not to be clinically meaningful difference in outcomes in ERT-stable patients in the long-term. Further the per protocol results for ENCORE at 1 year demonstrate that after 52 weeks of treatment, 92% of patients in the eliglustat group and 94% in the Cerezyme group were stable and "normal" as defined by the composite endpoint.

<table>
<tr><th>Paragraph number</th><th>Comment in ECD</th><th>SanofiGenzyme response</th></tr>
<tr><td></td><td></td><td>Summary of Percentage of Patients who are Stable and Normal at Week 52: Secondary Endpoint - Per Protocol Set
<table><tr><th>Variable</th><th>Eliglustat (N=99)</th><th>Cerezyme (N=47)</th></tr><tr><td>Patients Stable and Normal for 52 Weeks, n (%)
Exact 95% CI on Proportion Stable and Normal</td><td>91 (91.9)
(0.847, 0.964)</td><td>44 (93.6)
(0.825, 0.987)</td></tr></table></td></tr>
<tr><td></td><td>Moreover, the committee was aware that 48% of patients in ENCORE had a higher dose of eliglustat and these data were used in the model</td><td>See response above relating to the dosing in the ENCORE trial.</td></tr>
<tr><td></td><td>The committee considered that there was uncertainty around the assumption of equivalence, especially in the long term</td><td>We would again agree with the principle of this statement.
Regarding the absence of long-term data in a new product eliglustat is no different to any therapy, which is why NICE has a process option for a 3 year re-review process. Given the strong indication, that in patients who continue to meet well-established therapeutic goals, there is no clinically meaningful difference between ERT and eliglustat. For patients who do not meet these goals, in line with a conversation between patient and clinician, patients would be unlikely to be maintained.

Further, there are unknowns with both treatments at the dose of ERT given in the UK and the indication from Dutch/German data that lower doses affect BMB outcomes (de Fost et al 2006) there is a plausible scenario in which eliglustat offers patients better long-term outcomes as the small molecule penetration provides better bone outcomes, the bone outcomes being the most troublesome to the patient and</td></tr>
<tr><td></td><td>The dose of ERT used in the model</td><td>It is true that dose is a key driver in the model. Dose is a composite of U/kg and weight (kg).</td></tr>
</table>

<table>
<tr><th>Paragraph number</th><th>Comment in ECD</th><th>SanofiGenzyme response</th></tr>
<tr><td></td><td>was 42.4 U/kg, every 2 weeks, based on the mean dose of imiglucerase patients had in the ENCORE study. The committee recalled (see section 5.4) that a dose of between 15–30 U/kg was considered most reflective of clinical practice. The committee was aware that the dose of ERT was a key driver of results and that the ERG had explored the impact of including a dose of 25 U/kg. The committee considered that the ERG exploratory analysis that included a dose of 25 U/kg was appropriate,</td><td>Discussion of weight is omitted in the ECD document. The company submitted a base case of the dose/weight/efficacy directly from the ENCORE trial, as an alternative it reported the dose/weight combination reported in the velaglucerase submission to the AWMSG of 32U/kg and 75kg (average UK weight according to most recent, but old ONS data (2010) was 83.6KG for men and 70.2KG for women, a population average of 76.9kg).

In response to this ECD the company has sought accurate GD1 patient weight information:

<table>
<tr><th>Source</th><th>Weight</th><th>Total dose @25U</th><th>Vials</th></tr>
<tr><td>ERG proposition</td><td>67.5kg</td><td>1687.5</td><td>4</td></tr>
<tr><td>Royal Free Hospital (RFH 2017)</td><td>73.29</td><td>1832.25</td><td>5</td></tr>
<tr><td>ICGG (SGZ Data on file_2017a)</td><td>71.8 (last follow up)</td><td>1795</td><td>5</td></tr>
<tr><td>Pooled UK patients from ENGAGE and ENCORE(SGZ Data on file_2017b)</td><td>73.6 (study end)</td><td>1840</td><td>5</td></tr>
<tr><td>UK national average</td><td>76.9kg</td><td>1922.5</td><td>5</td></tr>
</table>
Table 3 UK data for weight of Gaucher Disease patients

Results presented in the base case give a price per unit, rather than per vial, and while the SGZ recognises that the SOP and usual practice is not to waste ERT, what is clear is that the ERG estimate is the only estimate that is close to 4 vials, all others are close to 5 vials.</td></tr>
<tr><td></td><td>..especially because the results of</td><td>This is a mis-representation of the ERT data. The ENCORE data were analyses by doses ≥35U and</td></tr>
</table>

<table>
<tr><th>Paragraph number</th><th>Comment in ECD</th><th>SanofiGenzyme response</th></tr>
<tr><td></td><td>the ENCORE trial showed no difference in the response to eliglustat in terms of the dose of the comparator ERT.</td><td><35U. The mean dose in the <35U population was 27U while the mean dose in the ≥35U dose was 51.23 (last dose received, ITT population). This statement essentially assumes is that a ‘flat dose’ of 27U is equal to a ‘flat dose’ of 51U without taking into account a patient’s weight, baseline characteristics or disease severity. What the <35 and ≥35U data show is that, if patients are well managed on doses are ERT uniquely tailored to their characteristics then ERT leads to maintained stability over 52 weeks. It does not show that if every patient on the ERT arm of the ENCORE study had received 27U the same outcomes would have been achieved.

Proportion of Patients Stable at 12 months: Per Protocol Population
<table>
<tr><th></th><th colspan="3">Eliglustat</th><th colspan="3">Imiglucerase</th></tr>
<tr><th></th><th colspan="2">Pre Study ERT</th><th></th><th colspan="2">Pre Study ERT</th><th></th></tr>
<tr><th></th><th>< 35 /kg/q2w (N=38)</th><th>≥ 35 U/kg/q2w (N=61)</th><th>Overall (N=99)</th><th>< 35 /kg/q2w (N=18)</th><th>≥ 35 U/kg/q2w (N=29)</th><th>Overall (N=47)</th></tr>
<tr><td>Proportion, n (%) 95% CI remaining stable</td><td>32 (84·2) (68·7, 94·0)</td><td>52 (85·2) (73·8, 93·0)</td><td>84 (84·8) (76·2, 91·3)</td><td>17 (94·4) (72·7, 99·9)</td><td>27 (93·1) (77·2, 99·2)</td><td>44 (93·6) (82·5, 98·7)</td></tr>
<tr><td>Difference in proportion vs imiglucerase and 95% CI</td><td>-10·2 (-25·2, 10·2)</td><td>-7·9 (-20·0, 7·6)</td><td>-8·8 (-17·6, 4·2)</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
</table></td></tr>
<tr><td></td><td>The company assumed that the mortality risk does not increase with disease severity. The committee considered that this was an unrealistic assumption. It noted that the ERG explored the impact of increased mortality risk</td><td>This is a legitimate challenge that the company accepts. However, it suggests there is some misunderstanding regarding the premise of the assumption: given the availability of ERT, time in the marked and severe state is short and transitory. Amendments to treatment plans can return people to better health states so that it is unlikely people with GD on active treatment will be in the marked and severe health states for any notable period of time. However, we accept the principle that were a person in a marked and severe health state for a long period of time they are likely to have a greater risk of mortality, as such we accept this proposition.</td></tr>
</table>

Paragraph number	Comment in ECD	SanofiGenzyme response
	for patients in the 'marked' and 'severe' health states.	
	The company assumed that there are no administration costs associated with eliglustat because it is an oral therapy. The committee considered that the ERG's exploration including a monthly dispensary cost for eliglustat was appropriate, noting that this had a minor impact on the results.	This is a legitimate challenge that the company accepts, except to point out that pre-launch discussions with relevant stakeholders suggest that treatment would be sent out every one, two or three months, therefore frequency of dispensary costs may need to be adjusted. .
	The ERG highlighted that the administration costs for ERT were likely to be overestimated in the company's model because they were higher than the costs of hospital administration. The committee agreed that this was implausible and noted that the ERG had explored this assumption.	We accept that a consideration of the cost of homecare and hospital treatment is appropriate. We dispute the ERG's conclusion that that it is 'implausible' for the cost of homecare to be greater than hospital care. Nurse time in the home has no economies of scale and far more limited economies of scope than nurse time in a hospital. As such, whether homecare or hospital care is more expensive is a factor of the perspective of the costing analysis. Consideration of the cost 'per hour of nurse time' and the activities that the nurse can deliver in that time leads to different results to the 'nurse cost per infusion'. Costing differences are also dependent upon the composition of the costs, for example is there a portion of cost ascribed to sunk capital costs, training costs, support staff costs and sundries, in which case a NHS nurse with all the accompanying NHS organisation costs to include is likely to be more expensive in the hospital, and giving care in the home, than a nurse from a smaller, third party homecare organisation. If using the gold standard costing compendium from the PSSRU as the source for unit costs, costs can be consistently applied across resources. However, PSSRU doesn't have a cost for homecare delivered by a third party organisation. Because of this we sought to find a publicly available price for homecare delivery, which we reported. While we accept that cost attributed to home delivery may be a high estimate in the basecase, and the ERGs simplifying approach is reasonable, we suggest there is uncertainty with the ERGs estimated and costs may be higher.
	The committee discussed the utility	In line with comments above: Post the submission of the HST dossier for eliglustat in April 2016

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	increment used in the company's model for oral therapy, which it understood was the key driver of QALY benefits. It heard from the patient and clinical experts that the availability of an oral treatment would have a huge impact on health-related quality of life compared with an intravenous infusion. The committee took note of several patient testimonies describing the positive impact of an oral treatment and the potential this offered for them to return to a more normal life. The committee heard from the ERG that it agreed that oral therapy would provide a clear quality-of-life benefit but questioned the extent of the benefit assumed by the company, even though this was based on a vignette study. The ERG highlighted that an increment of 0.12 was substantial when compared with the decrements from *significant adverse events and the benefits of other oral therapies estimated in previous NICE submissions*. The	SGZ recognised that the original value submitted for oral benefit of 0.12 double counted some aspects of the adverse events due to intravenous infusion. Had an ECD been produced after the September committee meeting, SGZ would have shared this information. SGZ accepts the committee's most plausible utility value for QALY benefit of an oral treatment in this therapy area is 0.05. However, we are concerned that oral utility discussions from previous NICE submissions: *adverse events and the benefits of other oral therapies estimated in previous NICE submissions* may be being inappropriately applied to this HST evaluation. The references in the ERG report used to defend a lower utility value were all being taken from cancers with a poor survival prognosis (Liu et al 1997; Twelves et al 2006; Tabberer et al 2006; and NICE 2007). It is a very different proposition being asked if you prefer an oral therapy or an IV therapy in the last 6 months of life than being asked if you prefer an oral therapy or an IV therapy at the start of a treatment plan that will last for the next 50-60 years. The ERG postulates a scenario in which it states the original utility value submitted (0.12) would suggest people were prepared to trade-off 2.29 years of life in full health for the convenience of an oral therapy [over 50-60 years]. The ERG poses this as a ridiculous assumption. While SGZ would accept 0.12 is too high and therefore 2.29 years is too long, we would challenge that this is a ridiculous assumption and suggest that it is patients that should be making that decision.

Paragraph number	Comment in ECD	SanofiGenzyme response
	committee was aware that the ERG explored an alternative utility increment of 0.05. The committee concluded that, although the true value was uncertain, the alternative value used by the ERG was more appropriate.	
5.10	Based on list prices …	SGZ would point out that there is a revised PAS agreed with the Department of Health.
	Based on list prices …	SGZ requests documented confirmation that the confidential discount offered by Shire for VPriv meets the requirements of a discount to be acceptable for the use in a NICE assessment:
5.11	The committee was also concerned that the trials included very few people with poor metaboliser status, so questioned whether the results from the model could be generalised to this population.	As already stated, SGZ acknowledges that the poor metaboliser (PM) population is small. There were no PMs in the ENGAGE trial, 4% of patients in the ENCORE trial were PMs (6/146) Across all eliglustat trials (Phase 2, ENGAGE, ENCORE and EDGE), 14 patients (3.6%) were poor metabolizers (14/393) (Peterschmitt et al 2017*).* Observed data from the Phase III clinical trials supported by PK/PD modelling demonstrate that similar clinical outcomes are expected for poor metabolisers at the 100mg QD dose, and that no difference in TEAEs were reported with the PM populations (EMA 2015). Consideration is given in the SmPC regarding considerations that needs to be made once metaboliser status is confirmed, specifically relating to drug-drug interactions and contraindications. In summary, the few data are due to small patient numbers, observed data and outputs of PK/PD modelling suggests that at the dose of 100mg QD there will be no difference in clinical outcomes or TEAEs. Consideration needs to be given to drug-drug interactions and contraindications relating to the CYP2D6 metabolic pathway, as in needed for IM/EM, and there are slightly different for PMs.

Paragraph number	Comment in ECD	SanofiGenzyme response
		.
5.16	The committee discussed the ERG's exploratory analyses of the budget impact analysis. It noted that the ERG revised several assumptions that were the same as its exploratory analysis of the company's cost–consequence model, with the additional assumptions of zero mortality, no treatment stopping, and that 4% of eliglustat patients were poor metabolisers. The committee was satisfied that these explorations reflected the committee's preferences. The committee understood that this increased the costs in year 5 from £571,487 to £11,123,765 and increasing the cumulative cost over 5 years from £1,623,219 to £34,701,740 based on list prices for all technologies. The committee noted that, taking into account the confidential discounts available for eliglustat and ERT, the budget impact associated with eliglustat	SGZ suggests this paragraph is a little misleading. It reads as thought zero mortality, no treatment stopping and adding in the 4% poor metabolisers account for the jump in budget impact, when in fact it is the previous ERG assumption around units of ERT used that drive the cost difference. SGZ is surprised by the approach the ERG adopted: 1 patient over 5 years. The advice in the STA User Guide is, 'State the estimated annual budget impact *on the NHS in England* (NICE 2015)'. Reviewing the HST interim methods guide we couldn't see any recommendations to use a different, per patent, approach (NICE 2013). Given the perspective is NHS-England, it is usual that a budget impact analysis includes an assumption for mortality and, although this varies by therapy area, treatment stopping. The principle being that if a patient dies within the 5 year timeframe of the BI analysis they are no longer costing the NHS money. It may have been fair to question if an annualised mortality rate would have been more appropriate, or some other estimate for the number of patients in the Gaucher Disease population that would die in a 5 year period. Regarding treatment stopping, the same principle applies, if a patients asks for a treatment break for a period of time and the NHS is not funding their treatment then there is no cost and this should be included. SGZ agrees that for simplicity this stopping rule can be removed. SGZ accepts that the poor metaboliser population should have been included in the budget impact analysis and agrees that a rate of 4% is appropriate.

Paragraph number	Comment in ECD	SanofiGenzyme response
	compared with ERT decreased. However, the committee considered that the budget impact remained considerable, especially in the context that benefits of eliglustat over ERT related solely to the benefits of it being an oral treatment.	
5.20	The committee understood that type 1 Gaucher disease can be a debilitating condition that has severe effects on the lives of people with the condition, and their families and carers. It agreed that there was uncertainty about the equivalence of eliglustat compared with ERT. However, the committee considered that, because it is an oral treatment, it could potentially provide important quality-of-life benefits for people currently having intravenous ERT, as well as for people who have not previously had treatment.	SGZ agrees with this statement
		Responses to the paragraphs that follow have been made elsewhere in this document.

Appendix 1: PK/PD Modeling methodology

Sanofi Genzyme acknowledges that a higher dose (150 mg) was used in the ENCORE primary analysis period (PAP), and that this dose was also made available during the extension (post-PAP) period of ENGAGE. However, Sanofi Genzyme maintains that a proposed 100 mg commercial regimen for IMs and EMs is well supported by the data derived from the eliglustat clinical trial program, and that the ENCORE study non-inferiority result versus imiglucerase remains valid in the context of that regimen.

Phase 2/3 eliglustat program demonstrates that eliglustat tartrate doses of 100 mg BID dosing resulted in a favourable clinical response in both treatment-naïve as well as in ERT-stabilized patients. The small gain in clinical efficacy expected to be achieved with a higher daily dose is not clinically meaningful, and the 100 mg BID regimen is predicted to be an adequate dose for IMs and EMs that maintains a favourable risk/benefit profile.

In addition, the risk of a sub-optimal response in individual patients will be discussed, along with a proposal for regular evaluation of the disease and treatment response using existing treatment goals for Gaucher disease with the use of ERT (Pastores, 2004).

Phenotype-Based Dosing Overview - 100 mg for IMs and EMs

Introduction

In this section, Sanofi Genzyme will address the first part of the question, and will justify that 100 mg BID is the optimal dose for CYP2D6 IMs and EMs, and that there is no need for an additional dose-strength of eliglustat for further dose titration in this population.

Dosing by CYP2D6 phenotype, which obviates the need for dose titration based on plasma concentrations, provides for a safe therapy that is comparably effective to the standard of care, ERT, in both treatment-naïve patients and those with stable disease. Eliglustat also provides unique benefits, such as the increased convenience of its oral formulation as compared to ERT.

In this section we will show:

- The eliglusat Ctrough threshold of 5 ng/ml (as employed in the clinical studies to escalate doses) is not the sole determinant for the safe and efficacious use of eliglustat in the GD1 population, and is not necessarily a predictor of efficacy (Phase 2 study and the Phase 3 studies ENGAGE and ENCORE).
- Treatment-naïve patients with GD1, having significant baseline disease, are the most relevant patient population to appreciate treatment effects of eliglustat at specific dose levels on clinical outcome parameters. In treatment-naïve patients, eliglustat tartrate doses up to 100 mg BID resulted in a statistically significant and clinically relevant response (Phase 2 study and the Phase 3 study ENGAGE). Results from the extension period of ENGAGE (from Week 39 to Week 78 of the overall study) demonstrate that the clinical outcomes of treatment-naïve patients who had previously, during the Primary Analysis Period (PAP), received placebo for39 weeks and then received eliglustat doses up to 150 mg BID for 39 weeks did not differ from those who received eliglustat tartrate doses up to 100 mg BID for 39 weeks during the PAP. Further, the rate of spleen volume reduction did not change over time in the patients originally randomized to eliglustat in the PAP, even after many had transitioned to the higher dose of 150 mg BID in the extension period after Week 39. This indicates that up-titration to 150 mg BID does not provide clinically significant improvements in effect in treatment-naïve patients.
- Pharmacokinetic/pharmacodynamic (PK/PD)-efficacy modelling in ERT-stabilized patients (ENCORE) show that a dose of 100 mg BID will achieve the exposure range proven to be safe and effective in the target patient population in clinical trials. PK/PD modeling predicted similar spleen volume responses of ERT-stabilized IM and EM patients dosed at 100 mg BID to the

observed treatment effects in the study. Importantly, PK/PD modeling also projected only a small and not-clinically-meaningful increase in spleen volume for IM and EM patients who were treated at 150 mg BID in the study and would be treated at 100 mg BID with the proposed dosing regimen. The analyses did not suggest the potential for under-treatment in this population at the proposed dose.

Based on these efficacy arguments and the desire to keep exposure levels within the range established to be safe and effective under the conditions of use in the real-world (post-marketing) setting, Sanofi Genzyme considers 100 mg BID to be the optimal dose for IM and EM patients. Since drug-drug interactions are less controllable in the post-marketing setting than in clinical studies (even with adequate guidance in the label and educational materials), the potential for eliglustat exposures to reach the extremes of the range determined as safe in clinical studies needs to be considered. Increasing the eliglustat dose without the expectation of a clinically relevant effect on efficacy is considered to decrease the overall favourable benefit/risk ratio of eliglustat.

Phenotype-based Dosing Rationale

In the eliglustat Phase 2/3 clinical studies, patients initially received eliglustat 50 mg BID, with the potential for subsequent dose increases based on plasma Ctrough. This method of dose titration, based on PK, separated patients into dose groups according to their ability to metabolize eliglustat. In clinical practice, this approach would be complicated by the need for repeated testing of plasma concentrations in the setting of potentially large fluctuations in concentration over the 12-hour dosing interval, requiring the health care provider and patient to precisely time the last dose so that the plasma concentration could be accurately interpreted. This observation is at least partly explained by the PK characteristics of eliglustat. Its rapid clearance requires precise timing of drug administration and concentration determination in order to obtain accurate and consistent Ctrough values. As observed in the clinical trials, many individuals on stable eliglustat doses showed Ctrough values that fluctuated above and below 5 ng/mL over time. This variability in the clinical trial setting would be further magnified in the real-world setting, where an inability to exactly control these timing variables could lead to confusion and potentially unnecessary dose adjustments, or other erroneous treatment decisions. In addition, the 5 ng/mL threshold does not appear to be necessary for efficacy. On the other hand, a PopPK analysis using data from healthy subjects and GD1 patients showed that CYP2D6 phenotype is the most significant determinant of eliglustat exposure. Therefore, an optimized dosing regimen based on CYP2D6 phenotype has been proposed that builds upon knowledge gleaned from the clinical trials, consisting of a single recommended dosing regimen of 100 mg eliglustat tartrate BID for IM and EM patients, and 100 mg QD for PM patients.
To evaluate the use of this CYP2D6 phenotype-based dosing regimen, which would not have the dosing complexities conferred by dose titration using plasma Ctrough in a real-world (post-marketing) setting, a pharmacokinetic/pharmacodynamic (PK/PD)-efficacy modelling approach was used. The exposures predicted in a CYP2D6 phenotype-based dosing scenario would achieve the same range that has been shown to be safe and efficacious in the pivotal studies. Evaluation of the potential need for the 150 mg BID dose particularly centers around the efficacy of eliglustat in EM patients, as all IM patients except for one were treated with doses lower than 150 mg BID in our clinical programme. The proposed fixed dose (100 mg BID) in this group of interest (EMs) will therefore be discussed below, with attention to the three critical points mentioned above: the 5 ng/mL threshold, sufficiency of 100 mg in treatment-naïve patients, and modeling of ENCORE efficacy results with the proposed 100 mg IM and EM commercial dose.

Achieving a 5 ng/mL Ctrough threshold is not necessary for successful treatment

Analysis across all studies indicates that achieving a 5 ng/mL Ctrough threshold is not necessary for successful treatment. The data from the treatment-naïve patient populations represented in the Phase 2 and ENGAGE studies (PAP), where patients had significant baseline disease and the ability to show significant observable changes in response to treatment, represent the best dataset from which to analyze efficacy by plasma C trough level in EM patients dosed with 100 mg BID. The large number of clinical responders in Phase 2 and ENGAGE at <5 ng/mL C trough indicates that this threshold is not the sole determinant of efficacy. While some minor efficacy differences were observed between the <5 and ≥5 ng/mL group, these changes were not statistically significant and can be explained by differences in baseline severity. Importantly, the efficacy endpoints converged over time, with both groups achieving the same final level of disease control. The data from ENCORE support this conclusion as well, as most patients in both Ctrough groups maintained stability in the primary outcome variable.
In order to demonstrate the efficacy of the 100 mg BID dose in EM patients, and to evaluate how it relates to a patient's ability to achieve a C trough threshold of 5 ng/mL, it is best to look at treatment-naïve patients (Phase 2 and ENGAGE) who have a high substrate load and disease burden. This in contrast to the enzyme replacement therapy (ERT)-stabilized patients, who have a low substrate load and low disease burden (ENCORE) and for whom the target is in essence to demonstrate maintenance of stability. Consequently, reducing disease burden in treatment-naïve patients provides a much clearer measure of efficacy and reflects a high treatment hurdle. In ERT-stabilized patients, this assessment is not feasible since patients first need to re-accumulate substrate to a critical level before clinical changes occur. Baseline disease status and treatment duration are other important variables that must be considered when interpreting treatment response, as greater clinical responses generally occur in more severely affected patients and in those who are treated for longer periods of time. The clinical impact of efficacy endpoint changes observed in ERT-stabilized patients can be misleading because the changes are occurring on normal or near-normal baseline values and result in values that remain within the therapeutic goals (Pastores, 2004). Since Gaucher disease is a chronic condition with largely reversible features, gradual improvements that continue beyond the timeframe of a short-term clinical trial are clinically acceptable and expected, as evidenced by the long-term therapeutic goals for ERT that extend out to 2 to 5 years to reach.

The following data analyses demonstrate that both treatment-naïve and ERT-stabilized EM patients who were treated with 100 mg BID and had low Ctrough values (i.e., mean <5 ng/mL) still showed clinically meaningful responses in our clinical trials. The small gain in clinical efficacy that is predicted to occur with the use of a higher daily dose in some EM patients is not of a sufficient magnitude to be clinically meaningful, and the use of 100 mg BID maintains a favourable risk/benefit ratio (i.e. minimising the risk should the patient take concomitant inhibitors, while maintaining a comparable benefit). Additionally, the analyses indicate that a Ctrough ≥5 ng/mL is not the sole determinant of meaningful clinical benefit in patients, as many patients with low Ctrough in the Phase 2 and Phase 3 clinical trials had a significant and adequate clinical response to eliglustat treatment.

Treatment-naïve patients: Phase 2 Study

The Phase 2 study enrolled untreated patients with the highest disease burden among the 3 studies. The majority of patients (16/26, 62%) were EMs who received eliglustat tartrate 100 mg BID over the 4-year treatment period and approximately half of these had mean Genz-99067 Ctrough <5 ng/mL (n=7) or ≥5 ng/mL (n=9). Despite the low Ctrough values in some patients, no patients changed dose from 100 mg BID to 150 mg BID during the first 4 years of treatment in this study, even though the opportunity to dose increase was made available after the first year.

After 4 years, only one patient underwent a dose increase to 150 mg BID. Site investigators were satisfied with the treatment responses (including the platelet counts) and did not increase the dose further.

The treatment responses in the 2 groups (<5 ng/mL and ≥5 ng/mL group) were compared by evaluating their mean changes over time and final disease parameter values after 4 years of treatment. It should be noted that at baseline, the <5 ng/mL group had less disease burden (and therefore less room for changes towards maximal efficacy) than the ≥5 ng/mL group, as shown by the higher mean hemoglobin level (11.9 g/dL vs. 11.2 g/dL) and platelet count (72 x10 9 /L vs. 64 x10 9 /L), and the smaller mean spleen volume (11.6 MN vs. 19.1 MN) and liver volume (1.4 MN vs. 1.8 MN). Results after 1 and 4 years of treatment are shown below.

Both groups showed clinically meaningful treatment responses that were appropriate for their baseline severities of the 4 disease parameters.

Table 23 - Mean Changes from Baseline in the Phase 2 Study, by Average Plasma Steady State Trough Concentration Levels, for CYP2D6 Extensive Metabolizers Receiving 100 mg BID

	Week 52 / Month 12		Week 208 / Month 48	
	<5 ng/mL (n=7) Mean (SD)	≥5 ng/mL (n=9) Mean (SD)	<5 ng/mL (n=7) Mean (SD)	≥5 ng/mL (n=9) Mean (SD)
Percentage Change in Spleen Volume MN (%)	-37.457 (9.4509)	-39.533 (9.4783)	-55.100 (7.6861)	-63.411 (10.0088)
Absolute Change in Hemoglobin Level (g/dL)	1.436 (0.6951)	2.061 (1.3858)	1.664 (1.5897)	2.372 (1.4252)
Percentage Change in Liver Volume MN (%)	-11.657 (9.1668)	-20.833 (11.4156)	-19.233 (10.6714)	-30.656 (14.6901)
Percentage Change in Platelet Count (%)	39.171 (30.3759)	53.689 (37.4197)	40.686 (33.6417)	116.833 (94.2473)

Reference: Month 48 Average Trough Plasma Value is the average of the pre-dose records from the following visits: Day 30, Week 13, Week 26, Week 39, Week 52, Week 65, Week 78, Week 91, Week 104, Month 36, Month 39 and Month 48. (Reference: Module 2.7.3, Table 37)

Overall, the apparently smaller relative changes observed in the <5 ng/mL group for all parameters are consistent with their less severe disease status, as baseline values that are closer to normal range at the start of treatment may limit the magnitude of improvement. Although the relative difference between the <5 ng/mL and ≥5 ng/mL groups increased for platelet count at 4 years (to 41% vs. 117%), the small difference in mean platelet counts after 4 years of treatment is not clinically meaningful (103 x10 9 /L vs. 125 x10 9 /L). Of note, the mean platelet count in the <5 ng/mL group fluctuated over time, reaching a high of 122 x 10 9 /L after 2 years. Furthermore, when the endpoint changes were adjusted for baseline differences between the two groups, none of the differences in efficacy results after 4 years of treatment were statistically significant by ANCOVA.

Despite different baseline values, the mean values for each of the 4 disease parameters in the <5 ng/mL and ≥5 ng/mL groups converged over time (Figure 3 to Figure 6). After 4 years of treatment, both groups reached similar mean values for hemoglobin level (13.6 g/dL vs. 13.6 g/dL), platelet count (103 x10 9 /L vs. 125 x109/L), spleen volume (5.5 MN vs. 6.8 MN), and liver volume (1.2 MN vs. 1.2 MN).

Figure 4 - Mean (+/-SD) Hemoglobin Over Time by Average Steady-State Ctrough for CYP2D6 Extensive Metabolizers Receiving 100 mg BID for the First 48 Months of Eliglustat treatment (Phase 2 Study)

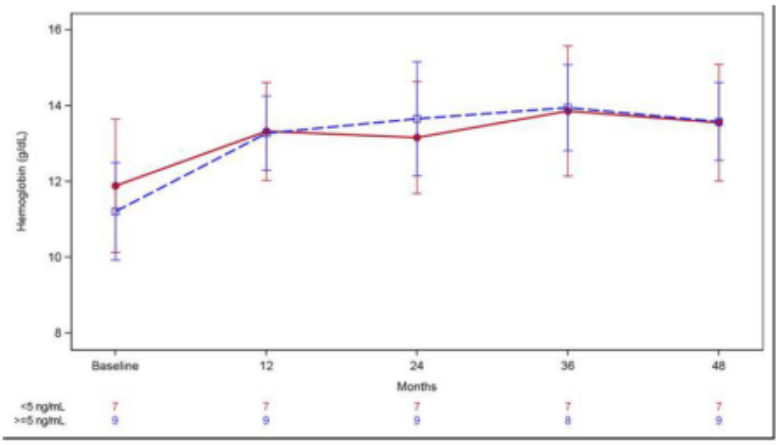


Figure 5 - Mean (+/-SD) Platelet Count Over Time by Average Steady-State Ctrough for CYP2D6 for Extensive Metabolizers Receiving 100 mg BID for the First 48 Months of Eliglustat Treatment (Phase 2 Study)

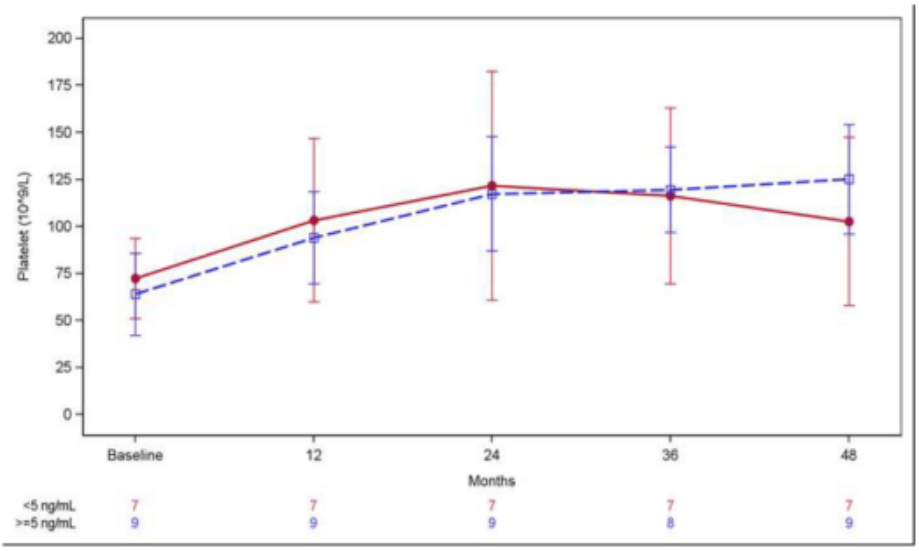


Figure 6 - Mean (+/-SD) Spleen Volume Assessment Over Time by Average Steady-State Ctrough for CYP2D6 Extensive Metabolizers Receiving 100 mg BID for the First 48 Months of Eliglustat Treatment (Phase 2 Study)

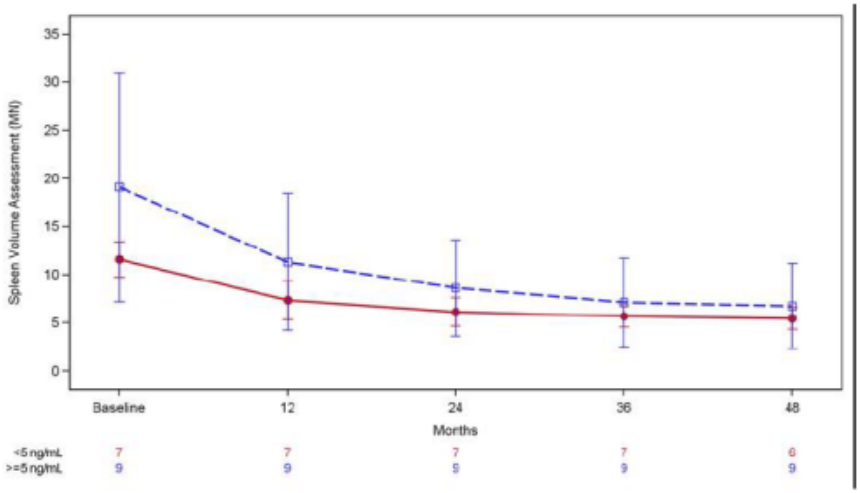
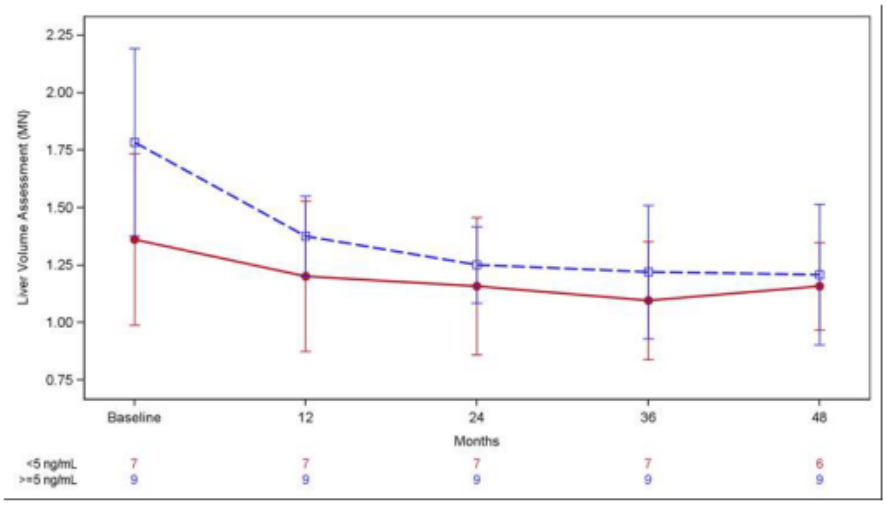


Figure 7 - Mean (+/-SD) Liver Volume Assessment Over Time by Average Steady-State Ctrough for CYP2D6 Extensive Metabolizers Receiving 100 mg BID for the First 48 Months of Eliglustat Treatment (Phase 2 Study)



These results demonstrate that the 100 mg BID dose is appropriate for EM patients and that this is independent of a patient's ability to achieve a 5 ng/mL Ctrough threshold. A clinically meaningful response was observed during the first year of treatment, and there was continued improvement in clinical status through 4 years at the 100 mg BID dose, both in patients with Ctrough <5 ng/mL and ≥5 ng/mL . On average, patients in both groups reached 3 to 4 therapeutic goals (as defined in Pastores, 2004) by 1 year, and maintained their clinical status through 4 years. These results also demonstrate that the 100 mg BID dose is adequate not only for de-bulking of substrate, but also maintaining for patients as they reached therapeutic goals.

Treatment-naïve patients: Phase 3 ENGAGE– Primary Analysis Period

The ENGAGE study also enrolled untreated patients with high disease burden. As in the Phase 2 study, the majority of patients receiving eliglustat during the 39-week double-blind placebo-controlled period were EMs that received 100 mg BID (80%, 16/20), and of these, half had

Ctrough <5 ng/mL (8/16) and half ≥5 ng/mL (8/16). One EM patient in the ≥5 ng/mL group had missing data at Week 39. The 2 groups had similar disease characteristics at baseline, respectively, with mean hemoglobin levels, 11.6 g/dL vs. 12.0 g/dL; platelet counts, 75 x10 9 /L vs. 73 x10 9 /L; spleen volumes, 14.1 MN vs. 14.7 MN; and the same liver volumes (1.5 MN). Results after 39 weeks of treatment are shown in Table 5.

Table 24 - Mean Changes from Baseline in ENGAGE Over 39 Weeks, by Average Plasma Steady Stat Trough Concentration Levels, for Extensive CYP2D6 Metabolizers Receiving 100 mg BID

	<5 ng/mL (n=8) Mean (SD)	≥5 ng/mL (n=8) Mean (SD)
Percentage Change in Spleen Volume MN (%)	-24.504 (10.6414)	-31.524 (6.3883)
Absolute Change in Hemoglobin Level (g/dL)	0.463 (1.0049)	1.286 (0.9045)
Percentage Change in Liver Volume MN (%)	-6.025 (7.7120)	-7.659 (5.0182)
Percentage Change in Platelet Count (%)	32.629 (36.7273)	33.244 (31.7866)

Reference: Module 2.7.3, Table 38

Both Ctrough level groups showed clinically meaningful treatment responses. After 39 weeks of treatment, the <5 ng/mL group appeared to show slightly smaller mean changes than the ≥5 ng/mL group, although none of the differences was statistically significant by ANCOVA (Appendix 3-5 Table 13.2). In the <5 ng/mL group, more than half of the patients (5/8, 63%) showed a clinically meaningful (≥20%) reduction in spleen volume after 39 weeks, the treatment effect for which the study was powered. Two of the 3 remaining patients in the <5 ng/mL group came close to achieving a clinically meaningful reduction in spleen volume (both -18%). After 39 weeks of treatment, the <5 ng/mL and ≥5 ng/mL groups showed similar mean values for hemoglobin level (12.1 g/dL vs. 13.2 g/dL), platelet count (101 x109/L vs. 92 x109/L), spleen volume (10.3 MN vs. 9.4 MN), and liver volume (1.4 MN vs. 1.4 MN).
This second study in treatment-naïve patients provides additional support that dose titration based on Ctrough is not necessary, and the 100 mg BID dose is appropriate for EMs. As in the Phase 2 study, a clinically meaningful response was observed within the first 9 months of treatment, both in patients with Ctrough <5 ng/mL and ≥5 ng/mL. On average, patients in both groups achieved 2 to 3 therapeutic goals by Week 39.

Patients with stable disease: Phase 3 ENCORE

The ENCORE study enrolled patients who had received ERT for >3 years, and consequently, these patients had low disease burden at the time of initiation of eliglustat treatment and were considered clinically stable by virtue of meeting pre-specified therapeutic goals.
Of the 29 EMs who received eliglustat tartrate 100 mg BID, 8 were in the <5 ng/mL group and 21 were in the ≥5 ng/mL group. Results after 52 weeks of treatment are shown below.

Table 25 - Mean Changes from Baseline in ENCORE Over 52 Weeks, by Average Plasma Steady State Trough Concentration Levels, for CYP2D6 Extensive Metabolizers Receiving 100 mg BID

	<5 ng/mL (n=8) Mean (SD)	≥5 ng/mL (n=21) Mean (SD)
Percentage Change in Spleen Volume MN (%)	-6.060 (15.5715)	-6.017 (12.0629)
Absolute Change in Hemoglobin Level (g/dL)	-0.125 (0.8763)	-0.198 (0.7097)
Percentage Change in Liver Volume MN (%)	9.638 (9.2333)	0.452 (7.3309)
Percentage Change in Platelet Count (%)	0.100 (19.1365)	5.067 (14.9037)

The between-group changes after 1 year revealed little difference in the mean hemoglobin level, platelet count, spleen volume, and liver volume. These small changes and between-group differences are not clinically meaningful given the essentially normal baseline values along with the variability of the assessments. For example, the mean 9.6% increase in liver volume observed in the <5 ng/mL group represents an increase from 0.9 MN to 1.0 MN, which is well within the therapeutic goal (liver volume <1.5 MN). These small between-group differences are further illustrated for the four endpoints in Table 7.

Table 26 – Mean Baseline and Week 52 Results in ENCORE, by Average Plasma Steady State Trough Concentration Levels, for CYP2D6 Extensive Metabolizers Receiving 100 mg BID

Table 7: Mean Baseline and Week 52 Results in ENCORE, by Average Plasma Steady State Trough Concentration Levels, for CYP2D6 Extensive Metabolizers Receiving 100 mg BID				
	<5 ng/mL (n=8) Mean (SD)		≥5 ng/mL (n=21) Mean (SD)	
	Baseline	Week 52	Baseline	Week 52
Spleen Volume (MN)	3.774 (2.3698)	3.530 (2.3572)	3.158 (1.4770)	3.048 (1.5209)
Hemoglobin Level (g/dL)	12.850 (1.1430)	12.725 (1.1254)	13.802 (1.3166)	13.605 (1.1941)
Liver Volume (MN)	0.928 (0.1306)	1.019 (0.1143)	0.955 (0.2090)	0.961 (0.2192)
Platelet Count (x 10^9/L)	204.375 (69.5731)	200.438 (60.8678)	247.405 (110.3006)	259.929 (110.3701)

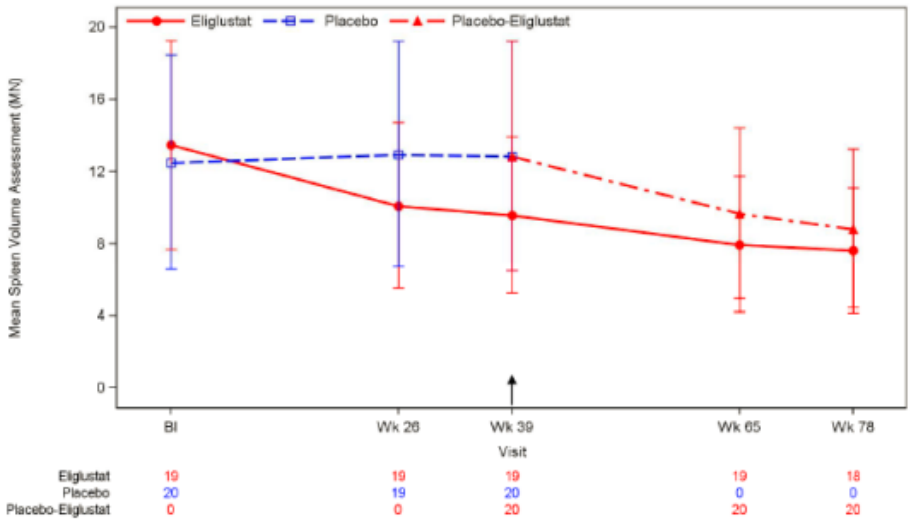
A high percentage of patients met the composite endpoint in the ENCORE study in both the <5 ng/mL (6/8, 75%) and the ≥5 ng/mL (19/21, 90.5%) groups, with substantial overlap in their exact 95% CI. There was a high percentage of stable patients for each of the 4 components of the composite endpoint in both groups (<5 ng/mL vs. ≥5 ng/mL, respectively): hemoglobin, 100% vs. 95.2%; platelet count, 87.5% vs. 95.2%; spleen volume 100% vs. 100%; and liver volume, 87.5% vs. 100%.

Use of 150 mg in Phase 3 ENGAGE Extension Period Supports the Sufficiency of a 100 mg Dose for IMs and Ems

In the ENGAGE open-label extension period, patients originally treated with eliglustat tartrate 50 or 100 mg BID in the PAP received treatment for an additional 39 weeks at doses of 50, 100, or 150 mg BID (patients' doses were re-titrated at the start of the extension period up to a new maximum of 150 mg BID based on Ctrough levels). In addition, patients who were originally randomized to placebo in the PAP were switched to eliglustat treatment at Week 39 and received doses of 50, 100, or 150 mg BID. As of Week 78, ENGAGE patients receiving eliglustat during the PAP had a total of 78 weeks of eliglustat treatment, and patients originally randomized to placebo had received eliglustat for 39 weeks.

Figure 8 shows the percentage change from baseline in spleen volume in both patient groups over 78 weeks in ENGAGE.

Figure 8 - Percentage change from baseline in spleen volume in both patient groups over 78 weeks in ENGAGE



Source: 78-Week Results Memo Report, Figure 14.2.1.1.1
MN = multiples of normal; SD = standard deviation; Arrow (↑) indicates the start of extension (Long-term Treatment Period) Note: Only patients with data in the long term treatment period, i.e beyond the 39-week double-blind Primary Analysis Period (PAP), are included; Patients randomized to placebo in the 39-week PAP switched to Eliglustat after 39 weeks; The average of all values at Weeks 26, 39, 65 and 78 for each patient is used in this figure; Baseline (BI) refers to last assessment prior to Day 1 dose for all patients; Error bars presented are the standard deviation.
Reference: Module 2.7.3, Figure 20

As shown in Figure 8, the rate of mean spleen volume reduction did not change over time in the patients originally randomized to eliglustat in the PAP, despite the fact that 6 EM patients who received 100 mg BID during the PAP transitioned to a higher dose of 150 mg BID in the extension period, after Week 39. This suggests that the additional eliglustat exposure offered by the 150 mg dose does not produce an increased rate of spleen volume reduction, confirming the Phase 2 study findings that EM patients will see an equal clinical benefit over time at 100 mg BID.

ENGAGE patients originally randomized to placebo in the PAP who crossed-over to eliglustat tartrate 50, 100, or 150 mg BID at Week 39 through Week 78 showed a rate and degree of spleen volume reduction similar to that observed in the eliglustat-randomized patients treated at a maximum of 100 mg BID during the 39 week PAP (see Table 8), despite the fact that 7 of these EM patients received 150 mg BID in the extension period. This again confirms that a dose above 100 mg BID in treatment-naïve EM patients does not lead to a further meaningful clinical outcome.

The pattern of improvements in the other three clinical parameters (liver volume reduction and increase in hemoglobin levels and platelet counts) for the eliglustat and placebo randomized groups was similar to that seen with spleen volume reduction.

Table 27 - Mean Changes from Baseline in ENGAGE following treatment with eliglustat for 39 weeks: Randomized period (from Day 0 to Week 39) vs. Extension period for placebo-randomised patients switched to eliglustat (from Week 39 to Week 78): Full Analysis Set

	Week 39 Eliglustat (n=19) Mean (SD)	Week 78 Placebo to Eliglustat[a] (n=20) Mean (SD)
Percentage change in spleen volume, MN	-29.03 (11.085)	-31.31 (10.125)
Percentage change in liver volume, MN	-5.66 (7.002)	-7.31 (9.974)
Absolute change in haemoglobin level, g/dL	0.76 (1.114)	0.79 (0.818)
Percentage change in platelet count	32.55 (32.443)	39.82 (37.367)

a. change from week 0 to week 78
Abbreviations: MN=multiples of normal; SD=standard deviation.
Source: 78-Week Results Memo Report, Tables 5-8
Reference: Module 2.7.3 Table 32

These results from treatment-naïve patients support the conclusion that increasing the dose above 100 mg BID in EM patients for the purpose of increasing exposure does not translate to increased or optimized efficacy.

ENCORE Non-inferiority Conclusions are Still Valid in the Context of 100 mg BID Commercial Dosing Regimen for IMs and EMs

Sanofi Genzyme's modelling show that selecting a 100 mg BID dose for the IM and EM population will allow for safe and efficacious exposure of this target population, in the same range as observed in our positive clinical trials and without the need for plasma monitoring. A PK/PD-efficacy modelling approach was used to show that the exposures predicted in a CYP2D6 phenotype-based dosing scenario would achieve the same range that has been shown to be safe and efficacious in the pivotal studies.

These analyses were particularly important in the case of ENCORE. As noted by NICE, almost half of the patients in ENCORE received a dose of 150 mg. Therefore, it was necessary to confirm that the ENCORE study population would still achieve comparable efficacy under a phenotype-based dosing regimen with a top dose of 100 mg BID for IMs and EMs.

The ENCORE primary efficacy composite endpoint and its four individual components were evaluated for exposure-response relationships. The four components of the primary endpoint in ENCORE were evaluated for exposure-response relationships. There was no significant exposure-response relationship observed for absolute change in heemoglobin level, percent change in platelet count, or percent change in liver volume. The only parameter that showed a significant exposure-response relationship was % change in spleen volume. Given the limited range of exposure and the success of the trial in maintaining disease stability, it is not unexpected that most of the components of the primary composite endpoint did not show appreciable changes from baseline (when those values were already normal or near-normal). For exposure estimates in this modelling approach, PopPK-predicted PK parameters were used instead of observed PK parameters since the latter were confounded by the fact that dose was adjusted based on Ctrough during Phase 2 and 3.

Using the PK/PD model, percent changes in spleen volume (MN) from Baseline to Week 52 at the study level were predicted using PopPK-predicted exposures. This allowed Sanofi Genzyme to compare the observed study results from the ENCORE trial to the predicted study results if IM and EM patients were to receive 100 mg BID (as proposed in the commercial dosing). PK/PD

analyses predicted that spleen volume treatment responses for IM and EM patients dosed at a fixed dose of 100 mg BID that would be similar to the observed spleen volume treatment effects in the study. The estimated treatment difference from Cerezyme using the simulations and the same Cerezyme data (observed) was also similar to the observed treatment difference in the study.

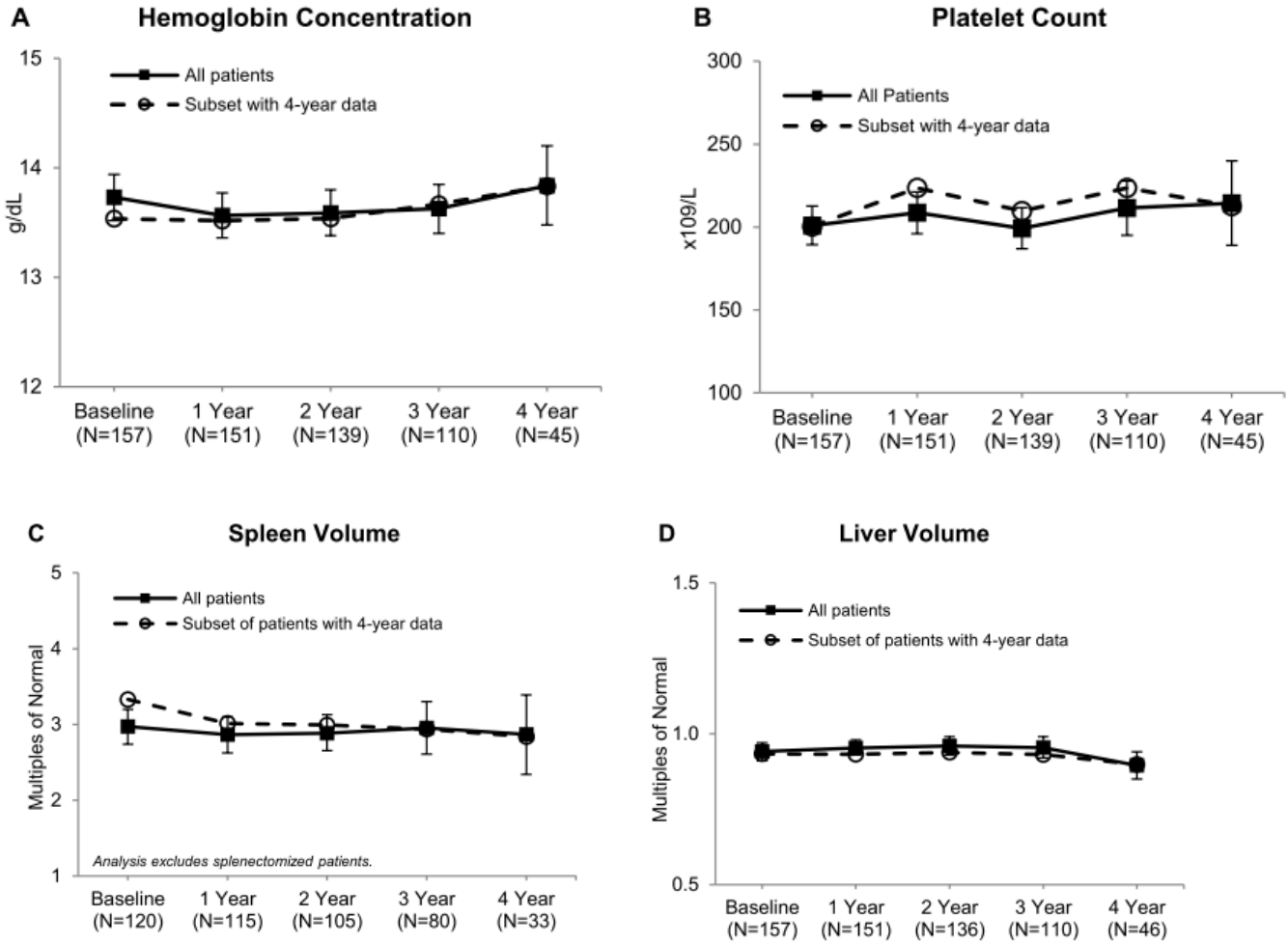
To further confirm that the proposed phenotype-based dosing regimen would not impact the efficacy results of those IM and EM patients actually dosed 150 mg BID and who would be administered the lower dose of 100 mg BID, patient exposure projections were applied to the established PK/PD model with observed percent change in spleen volume to obtain projected percent change in spleen volume values for IM and EM patients when dosed at 100 mg BID. The maximum increase between the observed and projected values for spleen volume at Week 52, due to the reduction in dose from 150 mg BID to 100 mg BID, would be 4% (see Module 2.7.3 Section 4.2.2.1 for a detailed discussion). 4% is a small change relative to the patients' essentially normal spleen volume (therapeutic goal for spleen volume is ≤2 to 8MN) and is comparable to the test-test variability of organ volume measurement by MRI determined during the ENGAGE study using the same methodology, and less than the 12% variability reported in the literature (Barton, 1991, New Engl J Med). Such a small change in patients with little or no splenomegaly would not be clinically or medically noticeable. Thus, 100 mg BID is an effective dose for IM and EM patients receiving chronic therapy aimed at maintaining stability of disease, and the added exposure from a 150 mg BID dose is not expected to provide any further meaningful clinical benefit.

When considering the sufficiency of a 100 mg BID dose for the ENCORE patient population (clinical stable patients switching from ERT), it is important again to consider the efficacy demonstrated in treatment-naïve patients. The Phase 2 and ENGAGE trial, which treated patients with the highest disease burden (the treatment-naïve), have demonstrated the efficacy of the 100 mg BID dose in the most difficult to treat patient population. The ENCORE study enrolled patients who had received enzyme replacement therapy for >3 years, and consequently, these patients had low disease burden at the time of initiation of eliglustat treatment and were considered clinically stable by virtue of meeting pre-specified therapeutic goals. The 100 mg BID dose is therefore expected to also be effective in the patients with lower disease burden (ERT-stabilized patients).

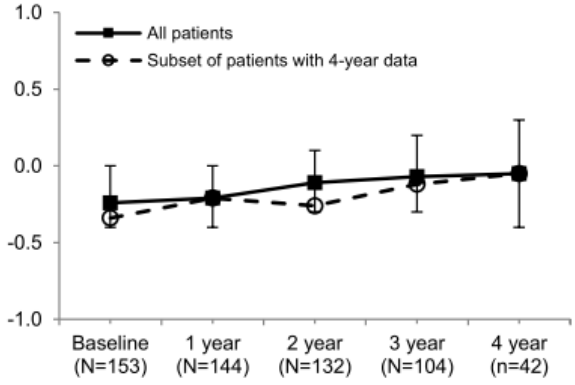
In conclusion, the analyses performed by Sanofi Genzyme not only support the proposed CYP2D6 phenotype-based dosing, but also demonstrate the continued validity of the ENCORE conclusions (non-inferiority to imiglucerase) even with a top dose of 100 mg BID for IMs and EMs.

Appendix 2

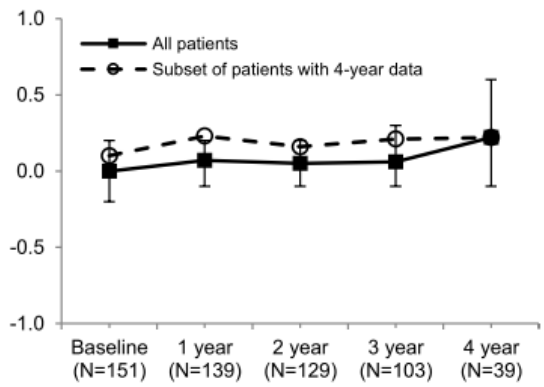
Figure 3 Mean for hematologic, visceral, and bone parameters over four years of eliglustat treatment. Error bars denote upper and lower 95% confidence intervals.



E **Lumbar Spine Z-score**



F **Femur Z-score**



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Date Submitted: 31st March 2017

Gauchers Association – Response to NICE's Evaluation consultation document Eliglustat for treating Type 1 Gaucher disease

As a patient expert representing the Gauchers Association, we challenge NICE's decision NOT to recommend Eliglustat within its marketing authorisation for treating type 1 Gaucher disease, and raise the following points:

1.1: Eliglustat is not recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers.

Our Response:

As part of our preparation for this appraisal we conducted a survey amongst our Members who were concerned and anxious about ongoing difficulties and the burden of venous access after in some cases 23 years on fortnightly (in the early days weekly) infusions. Yes, NICE outlines in para 5.2 'that patient experts highlighted that they were administered intravenously and that this could be burdensome for patients' but this does not recognise the fact that for some patient's venous access is a real challenge, which in the long term may result in not being able to continue on ERT with potentially severe consequences.

It is well documented in the literature that there are sanctuary sites where ERT is not effective, even at high doses and in England, we have a few patients receiving eliglustat for lung involvement and mesenteric lymph nodes. Although the data to demonstrate the benefits of this combination therapy is very limited, due to the small numbers, does eliglustat not offer a treatment for unmet needs in these patients that ERT is not meeting, for those patients currently receiving it for this purpose and for those patients where there is a clinical need in the future.

We must also consider that **new patients** will be diagnosed and may not be clinically suitable for ERT and if eliglustat is not available they will either not receive a treatment and quoting NICE in para 5.1 "The committee concluded that type 1 Gaucher disease is a debilitating condition that has a significant impact on quality of life" and therefore be condemning these patients to a poor quality of life impacting on their ability to work, be

independent and in some cases early death. OR they will have to take Miglustat, which quoting NICE para 4.3 “The clinical and patient experts noted that people with type 1 Gaucher disease choose ERT whenever possible because Miglustat is associated with tolerability and safety issues, and modest efficacy” which is unethical when Eliglustat is a licensed treatment available for these patients.

NHS England Resources – Impact:

In para 5.19, it says “the committee heard from the clinical experts that the availability of eliglustat will reduce the need for the nursing support that is often needed for home infusions of ERT. The committee concluded that the impact of eliglustat on the delivery of specialised services is likely to be relatively negligible.”

Our Response:

What this does not address is the enormous burden the impact of the homecare service has on in particular the Clinical Nurse Specialists and Pharmacists at the 8 Centres who have to monitor the Homecare service and deal with the day to day issues experienced by the patients and families, thus taking their time away from actually dealing with the clinical needs of the patient community. This has not been quantified and taken into consideration in the impact.

Value for Money:

In para 5.7, its says “The committee noted the statement from NHS England that the risks around value for money offered by ERT were lower for Gaucher disease compared with the risks for conditions such as Fabry disease. This is because it is believed, in Gaucher disease, the effectiveness of ERT is well established and because the dose of ERT can be titrated to the lowest effective dose and the number of patients is lower. However, the committee was mindful that the benefits and value for money of ERT has not been formally considered. The committee concluded that this would add to any uncertainty around the value for money of eliglustat.”

Our Response:
The Association would like to emphasise that unlike the Scottish Medicines Commission, ERT for Gaucher Disease has not been formally considered by NICE in England, however in 2007 a NIHR Health Technology Assessment programme was commissioned ‘The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: a longitudinal cohort study of people with lysosomal storage disorders’ which concluded:

Summary of Gaucher disease results
These data provide strong evidence for an association between time on ERT and a clinically significant improvement in platelet count and Hb in adults, irrespective of whether or not they have undergone splenectomy, and in children. There is also a strong, statistically significant association between time on ERT and a clinically important decrease in the likelihood of having an enlarged spleen or liver based on estimated spleen volumes from scans or on palpation. In all of these analyses the data appear to suggest very substantial

*improvements over the first years of treatment (lasting perhaps 5–10 years) and then a plateauing of the effect. (*J Inherit Metab Dis. 2014 Nov; Epub: 2014 Feb 11).

1.2: For those patients, whose treatment with eliglustat was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

Our Response:

It is crucial to point out that the patients currently receiving eliglustat are receiving this treatment through the company's compassionate programme and that it is not being funded by NHS England. These patients have been prescribed Eliglustat for clinical reasons by their treating clinicians at one of the 8 Expert Centres in England, and fall into the following categories:

1. They are unable to take ERT
2. Their Gaucher disease was not responding to ERT
3. They have poor venous access
4. They are receiving eliglustat in addition to ERT to manage untreated symptoms of their Gaucher disease not addressed by ERT.

If NICE refuse to fund eliglustat for these patients, they will either not receive a treatment and quoting NICE in para 5.1 "The committee concluded that type 1 Gaucher disease is a debilitating condition that has a significant impact on quality of life" and therefore be condemning these patients to a poor quality of life impacting on their ability to work, be independent and in some cases early death. OR they will have to take Miglustat, which quoting NICE para 4.3 "The clinical and patient experts noted that people with type 1 Gaucher disease choose ERT whenever possible because Miglustat is associated with tolerability and safety issues, and modest efficacy" which is unethical when Eliglustat is a licensed treatment available for these patients.

In Summary:
In NICE's recent approval of Migalastat for Fabry disease, it says "NHS England and treatment centres to collect more evidence, particularly on the longer-term benefits of migalastat and ERT for treating Fabry disease, which should inform a future evaluation of the costs and benefits of all treatment options for Fabry disease". We would ask NICE to consider recommending eliglustat along the same lines and then implement a Managed Access Scheme for all treatments for Gaucher disease to collect the evidence needed for future evaluations and be proactive rather than reactive.

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30/03/2017

Dr. Peter Jackson,

Chair,

Highly Specialised Evaluation Committee,

National Institute for Health and Care Excellence,

10 Spring Gardens,

London, SW1A 2BU.

Dear Dr. Jackson,

Shire consultation comments for NICE evaluation of eliglustat for treating type 1 Gaucher disease

Shire would like to thank NICE for the opportunity to comment on the draft advice for eliglustat.

1. We note the Committee's consideration of the uncertainties in the clinical trials and wish to express our agreement with the points highlighted in the ECD.
2. We note the Committee's consideration that adverse effects associated with eliglustat would be acceptable to patients, especially in the context of the advantages of oral administration. It is likely that the adverse effects of eliglustat may have a negative impact on adherence rates and subsequently, on health outcomes. As such, in the long run, oral intake may not be advantageous to some patients.
3. Section 4.16 states that 83% of patients who switched from ERT to eliglustat expressed preference for oral therapy. However, it is well documented that adherence to oral therapies is inconsistent; therefore presenting a risk in achieving full benefits for patients.

Thank you for your time and consideration.

Sincerely,

[redacted]

NICE QUESTIONS – [redacted] - keyed responses (in red)

Has all of the relevant evidence been taken into account?

• Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?

4.13 I have reservations about the continued cynicism expressed about the scientific basis for the non-inferiority margin in the ENCORE trial. Justification of these parameters is clearly set out in all the documentation and was accepted in full dialogue with FDA and EMA. It was further clarified at the first session of NICE. The statistical confidence margin was based on 'real-life' data, objectively and independently obtained in the clinical study of enzyme therapy given either every two weeks or monthly (Kishnani PS, Di Rocco M, Kaplan P, Mehta A, Pastores GM, Smith SE, Puga AC, Lemay RM, Weinreb NJ. (2019) Mol Genet Metab. 96:164-70). The parameters chosen and agreed by the regulatory authorities took account of variation in haematological and visceral volumetrics determined by MRi in the baseline stability population enrolled in this clinical trial.

4.21 The suggestion that the (inescapable) open-label nature of the ENCORE trial led to subjective evaluations of therapeutic responses appears to me to be officious: the responses were based on haemoglobin concentrations; platelet counts; and spleen and liver volumes, and in secondary measures by DEXA scintigraphy determined by a blinded set of off-site radiologists who analysed serial data. In the context of clinical trial regulation and monitoring I cannot conceive of how the evaluations of the primary individual and composite endpoint primary endpoint data could be rendered more objective.

4.22 It is disingenuous to claim that there was no explanation for the four-year ENCORE follow-up data involving 46/7 patients. At the first meeting in NICE this matter was set out clearly. It is also further explained in detail in the recent publications. Again: Time on the drug within the conditions of the ENCORE trial was determined by the date of enrolment (which in the many participating centres worldwide spanned 2 years, from September 2009 until November 2011), the initial treatment group to which patients were randomly assigned, and their country of residence. After approval of the drug by the FDA in the Autumn of 2014, US trial participants left the study and received commercial eliglustat; it has been reimbursed in the US and elsewhere for 2½ years. Long-term safety and efficacy with respect to years of exposure for all 157 eliglustat-treated patients in ENCORE is available; in 46 of these, trial data are reported for a period of 4 years. (see Cox TM, Drelichman G, Cravo R, Balwani M, Burrow TA, Martins AM et al (2017). Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy. Blood. Feb 6. pii: blood-2016-12-758409).

In this publication, of ENCOREdata at four years, outcomes are carefully depicted for the whole cohort and also for those in the subset for whom only four year data were available: no material difference was found (see Figure 2, Cox TM et al (2017).

4.22 Efficacy:

In ENCORE, clinical stability was maintained with respect to haemoglobin concentration, platelet count, liver and spleen volume, bone mineralization density and widely accepted Gaucher biomarkers

for up to 4 years - well beyond the interval that might be attributed to residual effects of prior long-term enzyme therapy.

By its nature, since active bone disease was an exclusion criterion in the stable population, this trial cannot comprehensively address the capacity of the drug to reverse bone disease, but as cited in the NICE report there are indications of a strong primary effect of the drug over all aspects of the phase 2 and phase 3 trial outcomes.

A further important point set out in Table 2 of this publication relates to the demonstration of efficacy in the ENCORE trial: which sets out changes from baseline in haematological, visceral, and bone parameters over each year on the study drug. Using the appropriate analysis in the repeated measures mixed model of least-square mean changes from baseline in these efficacy parameters, attained after a mean of 10 years of enzyme therapy, mean values for haemoglobin concentration, platelet count, spleen and liver volumes in the subset of patients who had 4-year data (Figure 2, A-D), there were small but statistically significant reductions in least-square mean liver (3%, P=0.02) and spleen volumes (13%, P<0.001) after 4 years of eliglustat treatment (Table 2). Also after treatment with eliglustat, lumbar spine least-square mean Z scores of BMD increased by 0.29 (significantly).

• Are the provisional recommendations sound and a suitable basis for guidance on the use of eliglustat in the context of national commissioning by NHS England?

4.51

• Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The committee and NICE is impressive for its general willingness to make its decisions partly on behalf of patients and in relation to those at the centre of the illness and its possible treatments. However, on this occasion, I have strong reservations about the procedure adopted. The committee fixed the dates firmly for the two hearings but then changed the date of the second hearing at short notice and at a time when none of the experts nor patient representatives could attend. It is thus appears counter to usual practice that the committee has in effect met and apparently decided upon several weighty matters related to this drug in camera. Despite being immediately informed about this matter by several advisors, the committee went ahead. I contend that full appreciation of the patients' concerns and experiences with the different agents could not have been fully taken in at one brief session.

'Eliglustat is not recommended within its marketing authorisation for treating type 1 Gaucher disease, that is, for long-term treatment in adults who are cytochrome P450 2D6 poor, intermediate or extensive metabolisers'.

In view of this negative recommendation, there is a feeling that something went wrong with the evaluation process – at least so far. The patients' voice has been inadequately heard in relation to the take up and attractiveness of an oral therapy - specifically in terms of cost, labour, efficiency, practical advantage and acceptability.

As an (unpaid) international investigator in the clinical phase 3 programme and earlier a participant in the international safety monitoring committee, I can report that with continuing evidence of safety, tolerability and efficacy, the international take-up of eliglustat has exceeded expectations. The international Phase II and Phase III clinical studies undertaken with eliglustat over more than a decade represent the largest programme of therapeutic investigation ever conducted in any ultra-orphan disease (as defined by Sir Michael Rawlins a disease that affects less - much fewer - than 500 patients

in the UK). Hitherto, data from 1400 patient years of exposure are available with comprehensive studies of 225 patients for up to 12 years. It is salutary also to note that the agent is the first ever of six therapies accepted for Gaucher disease to be investigated in the formal setting of a randomized controlled double-blind, placebo-controlled and cross-over clinical trial.

While one understands that the report from the NICE Evaluation Committee is, to date, a preliminary recommendation, recent approvals by the Institute in relation to ultra-orphan diseases seem to have adopted very different standards for acceptance on grounds that do not seem to have been subject to equally rigorous scientific consideration. Given some inaccuracies in the assumptions (from the first meeting) and the unprecedented depth and quality of the clinical trial findings obtained with the enrolment of British patients suffering from Gaucher disease over many years, it appears likely that matters of cost must have taken priority in the decision-making so far.

After approval by the FDA in August 2014 and EMSA in early 2015, eliglustat is approved or about to be recommended for reimbursement in most eligible countries. Given the weight of evidence for its tolerability, safety and efficacy and the huge advantage for most patients of a first-line oral agent, I can only comment from experience, that the case for its acceptance for NHS reimbursement is incredibly strong. Without wishing to overreach the limits of expert opinion, I personally take the view that, subject to reasonable cost negotiations, it would be an injustice and disservice to UK patients were the drug to be denied them in the NHS specialist centres or elsewhere.

Xxxxxxx x xxx xx xxxx xxxxxxx

Xxxxxxxxxx xx

2 April 2017

[redacted] – In response to NICE's ECD on Eliglustat for Type 1 Gaucher disease – 4th April 2017

I was diagnosed with Gaucher aged 17, and there was no cure or even treatment, but a whisper of a new treatment in the USA gave my parents & myself fresh hope.

Eventually in 1991, I started taking the Ceredase twice a week -this was infusions and involved two days a week in hospital, my Mother had to give up work and our lives pretty much revolved around hospital visits & stays.
Two infusions a week with poor intravenous access, eventually took its toll and after endless failed attempts at access and every option exhausted including between my fingers & toes, wrists & neck used for infusions. Due to the constant trauma, I ended up with acute needle phobia and with no more places to gain access I was given a portacath., still requiring a needle, but in a designated spot and guaranteed access every time. Though still very unpleasant and somewhat uncomfortable I managed to get 18 years use from the port until it blocked and became unusable.

At this point Zavesca (Miglustat) was available, my relief was indescribable, a tablet! The side effects of Zavesca were not pleasant. Unfortunately, after taking Zavesca for 5 years I noticed tingling & loss of feeling in my fingers & toes … I was instructed to stop taking the tablet with immediate effect - the tablet had caused peripheral neuropathy - I was devastated and terrified about having to start having infusions again.

[redacted] told me he was trying to get Eliglustat for me on compassionate grounds, this was major news and the feeling of relief was overwhelming. He pulled out of all the stops to get the drug for me on the compassionate basis of I'd been without treatment for 9 months and fearing my markers were not looking good but eventually after another fight for treatment I got the Eliglustat, a far superior drug to Zavesca in every way from the efficiency of treating Gaucher to the dreaded side effects. The relief was overwhelming, I started the tablets in March 2015, the results have been brilliant, much better than when I was on Zavesca, my health has improved, there are no side effects and again I have the promise of normality! To find out that I might now lose this treatment is devastating - for me there is no other option for treatment.

Eliglustat is my only option, to find that I may now lose this is terrifying, it's taking away my health, my fear of this is impalpable - when the treatment is there and WORKS.

For me as a patient there is no other treatment for me to take to treat my Gaucher disease, to take this away from me is condemning me to a future of uncertainty and without doubt major deterioration health wise.

On Eliglustat, my illness is managed easily and effectively, with a safe, stable & reliable drug. My biomarkers have dropped, as much as 30% in just one year! To take this away from me would feel like a death sentence. Which is why I urge that you reconsider your decision on this drug. It is not a miracle cure per se but for myself (and hopefully other Gaucher patients) it is a miracle treatment.

'Private and Confidential'

Personal Statement of Patient Expert for Eiglustat- [redacted]

As a patient Expert for Eiglustat, I would like to register my disappointment with NICE's decision not to fund Eiglustat on the NHS on the following grounds:

As a Gauchers Disease Type I patient , I was put on ERT for a number of years where I experienced a number of side effects including constant diarrhoea and vanishing veins. My quality of life and mental wellbeing was suffering compared to normal person. I was than taken off ERT and put on Miglustat to improve my quality of life. Being on miglustat for the past 4 years has been a horrendous experience as it has permanently damaged 25% of my kidneys, having normal kidneys before being put on Miglustat.

On compassionate grounds, I was put on Eiglustat funded by the company (not the NHS). This improved my quality of life and mental wellbeing by taking one tablet a day and preserving the rest of my kidneys. To be told by NICE that NHS will not fund this medicine is a severe blow not only to my quality of life but also for my mental wellbeing. Taking a tablet a day has enabled me to carry on with my life as a normal person. I hope and believe that NICE will re-consider its decision in light of the above said.

Eliglustat for treating type 1 Gaucher Disease

ERG appraisal of the updated patient access scheme and additional evidence provided following the ECD

Produced by Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE)

Date 13/04/17

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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Section 1: Introduction

The ERG was requested by NICE to provide validity checks on the application of a patient access scheme (PAS) and additional evidence submitted by the company following the most recent committee meeting. Due to the limited resource available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission.

Following the latest committee meeting the company provided the following:

1. Details of a revised PAS submission, and cost-effectiveness results for the company's and ERG's base-case, incorporating the PAS discount and estimated commercial arrangements for the enzyme replacement therapies;
2. Long-term clinical data from the ENCORE trial four year extension period;
3. Responses to comments made by the company relating to the ECD.

The company did not provide an updated executable model. Therefore, the ERG applied the stated revisions to the model in the executable model provided at the points for clarification stage consistent with the ERG's response to the company's previous PAS/revised list price submission. This model is one agreed by the company to represent their original base-case and produces results identical to those presented in the company's original submission assuming the original base-case assumptions and the original list price. In addition, the company presented results using estimations of the commercial arrangements for imiglucerase and velaglucerase but did not explicitly state what percentage discounts were applied to the prices of the ERT's. This meant that the ERG was unable to validate these results that were presented by the company.

Section 2: Response to ECD Comments

In their response, the company highlighted numerous issues with the content of the ECD. It was requested that the ERG provide comment on several of the responses in order to assist NICE in their decision making process. Therefore Table 1 presents the relevant company ECD comments and the ERG's subsequent responses.

Table 1 The ERGs comments on the company's ECD response

Paragraph number	Comment in ECD	Company response	ERG response
4.22	The ERG noted that, although few patients withdrew from ENCORE because of adverse events, only 44 of the 159 patients who started the trial were in the analysis at 4 years	The company has already provided the information needed to address this issue in response to the ERG report publication in July 206. We reiterate it here: The ENCORE trial ended on a calendar date, not after a pre-specified time on treatment. All enrolled patients had the opportunity to be treated with eliglustat for at least 2 years, but some patients ended up being in the trial for much longer, due to the fact that trial enrolment was spread out over 2 full years. People who enrolled early were in the trial for the longest. In total, 130/157 eliglustat-treated patients (82%) either completed the trial or were switched to commercial therapy when it became available in the United States. The smaller number of patients with 4-year data in ENCORE is due to the timing of their enrolment and/or the group they were in during the primary analysis. ENCORE patients who enrolled very early, were randomized to eliglustat, and did not live in the US, had the opportunity to be on eliglustat for 4 years or longer (one patient had 5-year data). On the other extreme, patients who enrolled very late, were randomized to imiglucerase for the first year, and lived in the US would have had the opportunity to be on eliglustat for	The statement in the ERG report reflected a lack of information in the original submission. The further information provided by the company (based on the publication Cox 2017) clarifies the patient disposition regarding their use of eliglustat therapy in the longer term. It makes it clear that not all of the patients who failed to have a full 4 years of follow-up stopped taking eliglustat due to a lack of efficacy or tolerability: 130/157 (82%) eliglustat-treated patients either completed the trial (i.e. stayed on eliglustat until the calendar date on which the trial stopped) or were switched to commercially available eliglustat. From the publication, of the 111 who did not have a full 4 years of follow-up on trial eliglustat, 51 continued to take eliglustat but as a commercially available product. The analysis of long term follow-up data for the 44 patients who had 4 years of follow-up, indicates that

		only 2.3 years before the trial ended. 36 patients were switched to commercial product, 48 had timed out of the trial and 12 patients withdrew due to adverse events, of these, 4 were withdrawals due to AEs considered related to eliglustat; 10 patients wished to withdraw, 4 patients withdrew due to pregnancy, 2 to noncompliance, and 1 was lost to follow up. Patient disposition is given below.	for patients who continue treatment with eliglustat, almost all patients maintain their pre-specified therapeutic goals. There are no long-term data comparing eliglustat with imiglucerase.
4.44	The ERG stated that assuming long-term equivalence of eliglustat and ERT underpinned the calculation of long-term benefits, and had a considerable impact on estimated incremental QALYs. The ERG considered that this assumption had not been adequately justified in the company's submission. It stated that short-term non-inferiority results in the ENCORE trial did not imply non-inferiority in the long term.	Long term state transition matrices are populated based on the baseline state a patient begins in. Patients begin in the same state distribution and transition based on their treatment-specific transition matrix, the dependency on the baseline state has the effect of making the transition matrices the same for both treatment arms. While there is a difference in a patient's state path because of the treatment effect difference at one year, there is convergence to the same state path since the same transition matrices are applied to both arms. Although the analysis of the data indicated that transition matrices were dependent on the baseline state, this criticism is valid. We have explored alternative analyses and implementation of the long term data to test the impact of basing the long term the long term transitions on where they end up after the trial treatment effect.	The ERG accepts that the wording in the ECD is strong and should instead state that the assumption of clinical equivalence has the 'potential' to have a considerable impact on incremental QALYs. The ERG has been unable to validate the alternative analyses explored by the company as an updated executable model has not been made available. However, the assumption of long-term equivalence in the model is not under-pinned by how the transition probabilities are calculated but by using the same probabilities in the long-term in both the treatment and comparator arm. The short-term non-inferiority data available fails to provide adequate justification for such a strong assumption.
4.49	The ERG identified the Wyatt et al. study (2012), which showed that the mean age at which treatment	The statement in 4.49 is not representative of the data presented in Wyatt 2012. Wyatt conducted an observational study of a UK cohort identified in treatment centres. Their baseline characteristics at enrolment are in	Although the ERG may have made reference to the uncertainty surrounding the age at which patients begin to receive therapy, no changes to age were

	was started was 35.2 years in the treatment-naive population and was 46.4 years in those who were stable on treatment with ERT. The ERG considered that the starting age in the model was underestimated, therefore overestimating lifetime differences. The ERG explored this in its analyses	Tables 12 and 13, with Table 12 only presenting the characteristics for adults. The ERG has used the "age of treatment initiation" as the mean age at which treatment is started among treatment naïve patients with GD1; however, this is likely to be biased as it likely includes patients who began treatment after having GD1 for years prior to the introduction of ERT. The ERG made the mean starting age for the stable on treatment population to be the average age of the study cohort from Wyatt 2012, which are not equivalent statistics. The average age of the cohort in Wyatt is biased for the same reasons listed above for the treatment naïve population, and literature has shown that patients stabilize on ERT within 2-5 years of their initiation, not 10 as indicated by the value used by the ERG (Weinreb 2015; Weinreb 2002). Data from the Ibrahim et al (2016) study reports mean age of treatment initiation being 32-35 years.	made in the ERG base-case analysis or any exploratory analyses in the executable model. In addition, the starting age used in the model makes little difference to the outcomes as long-term equivalence is assumed between the two therapies.
5.4 (a)	It heard from clinical experts that the approach in practice is to titrate the dose of ERT and use the lowest effective dose. It heard that patients generally start on 30 U/kg, followed by close monitoring for the first 12 months, with further	SGZ considers this a more accurate representation of the dose issue in the UK than paragraph 4.52 above.	The ERG report highlighted that there was some uncertainty around whether patients who were stable on treatment would receive the same average dose as those who were treatment naïve as was assumed in the model. There was also uncertainty surrounding whether patients begin with a higher dose in-line with what the SPC and SOP suggest, or whether newly

	dose reductions depending on response. The clinical experts stated that some people with newly diagnosed type Gaucher disease occasionally have very severe disease and may need a higher starting dose.		diagnosed patients start with a lower dose as they are typically less severely affected by the disease, which is what the clinical advisor to the ERG suggested can sometimes occur in practice. However, as we utilise the average dose used in clinical practice in England in the ERG base-case analysis, establishing the true initial dose patients receive is irrelevant for the purposes of the executable model as the initial dose will likely be captured in the average.
5.4 (b)	The committee also heard that there were no differences in the effect of eliglustat in the ENCORE trial when stratified according to ERT dose.	SGZ suggests this is a misinterpretation of the table below to conclude that outcomes seen with a mean of 42.4U/kg would be achieved with a mean dose of 25U/kg. The ENCORE data were analyses by doses ≥35U and <35U. The mean dose in the <35U population was 27U while the mean dose in the ≥35U dose was 51.23U (last dose received, ITT population). The committee have assumed a 'flat dose' of 51U/kg is equal to a 'flat dose' 27U/kg and thereafter 25U/kg without taking into account that does of ERT will be affected by patient weight, baseline characteristics and disease severity. What the <35 and ≥35U data show is that, if patients are well managed on doses are ERT uniquely tailored to their characteristics then ERT leads to maintained stability over 52 weeks. It does not show that if every patient	The ERG accepts that the data does not necessarily show that if every patient in the imiglucerase arm of the ENCORE trial had received a dose of 27U/kg that they would achieve the same outcomes as were observed in the trial. However, the data does provide evidence that patients on lower doses still respond well to treatment and indicates that there is little difference in clinical performance between those on a lower dose and those on a higher dose.

		on the ERT arm of the ENCORE study had received 27U the same outcomes would have been achieved.	
5.10	The company assumed long-term equivalence of eliglustat and ERT, and the ERG highlighted that this had a considerable impact on estimated incremental quality-adjusted life years QALYs).	SGZ requests this analysis is provided to us to be able to validate the veracity of this statement, the information we were able to find from the ERG report dated July 2016 was that, 'The ERG attempted to incorporate differential efficacy into the analysis in order to demonstrate the impact on the results if the assumption of non-inferiority did not hold in the long-term. However, the ERG was unable to explore this scenario as any attempt to remove the assumption of non-inferiority resulted in inconsistent results, and a lack of transparency in the cost-effectiveness model prevented the identification of any errors'. This is quite a different proposition and the company would like to understand the basis for this statement. SGZs exploratory analysis suggests that from a base case of 2.28 QALY gain, a plausible difference would be a 0.01 increase/decrease in QALY gain.	The company is correct to state that the ERG were unable to explore the impact of removing the assumption long-term equivalence between eliglustat and ERT from the model. The ECD should therefore state that the assumption has the 'potential' to have a considerable impact on estimated incremental quality-adjusted life years QALYs).
	The committee agreed with the ERG that non-inferiority was not the same as equivalence, and that non-inferiority in the short term does not imply non-inferiority in the long term.	SGZ agrees with the accuracy of this statement. However, this is not the same as stating the products have clinically meaningful difference in effectiveness. There is an indication of similar outcomes in the study by Ibrahim et al for treatment naïve patients. Considering how eliglustat might be used in ERT stable patients, and	The ERG never claimed in their report that the products have clinically meaningful differences in effectiveness, but instead highlighted the limitations of what we can conclude from the clinical data. The ENCORE trial demonstrates that eliglustat is non-inferior to imiglucerase over a one year period based

		recognising that patients with sub-optimal outcomes would not be maintained on a product, there is likely not to be clinically meaningful difference in outcomes in ERT-stable patients in the long-term. Further the per protocol results for ENCORE at 1 year demonstrate that after 52 weeks of treatment, 92% of patients in the eliglustat group and 94% in the Cerezyme group were stable and "normal" as defined by the composite endpoint.	on a composite endpoint using a wide pre-specified 25% non-inferiority margin. Although in practice patients who experience sub-optimal outcomes on eliglustat could potentially be transferred onto ERT, this is not relevant to our analysis which seeks to establish the impact that offering eliglustat to patients would have on total QALYs and costs.
	The committee considered that there was uncertainty around the assumption of equivalence, especially in the long term	We would again agree with the principle of this statement. Regarding the absence of long-term data in a new product eliglustat is no different to any therapy, which is why NICE has a process option for a 3 year re-review process. Given the strong indication, that in patients who continue to meet well-established therapeutic goals, there is no clinically meaningful difference between ERT and eliglustat. For patients who do not meet these goals, in line with a conversation between patient and clinician, patients would be unlikely to be maintained. Further, there are unknowns with both treatments at the dose of ERT given in the UK and the indication from Dutch/German data that lower doses affect BMB outcomes (de Fost et al 2006) there is a plausible scenario in which eliglustat offers patients better long-term outcomes as the small molecule penetration provides better bone outcomes, the bone outcomes being the most troublesome to the patient and	This statement in the ECD makes no comment to whether eliglustat is an effective therapy. However, it simply highlights that the results of a one year non-inferiority trial which utilises a pre-specified non-inferiority margin of 25% do not show that eliglustat and ERT are clinically equivalent in the short-term, and certainly do not demonstrate non-inferiority or equivalence in the long-term. Therefore, the assumption of long-term equivalence in the model that is made by utilising the same long-term transition probabilities in both arms in the executable model lacks justification, which adds uncertainty to the results.
	The dose of ERT used in the model	It is true that dose is a key driver in the model. Dose is a composite of	The use of 25U/kg as the average dose in the model

	was 42.4 U/kg, every 2 weeks, based on the mean dose of imiglucerase patients had in the ENCORE study. The committee recalled (see section 5.4) that a dose of between 15–30 U/kg was considered most reflective of clinical practice. The committee was aware that the dose of ERT was a key driver of results and that the ERG had explored the impact of including a dose of 25 U/kg. The committee considered that the ERG exploratory analysis that included a dose of 25 U/kg was appropriate	U/kg and weight (kg). Discussion of weight is omitted in the ECD document. The company submitted a base case of the dose/weight/efficacy directly from the ENCORE trial, as an alternative it reported the dose/weight combination reported in the velaglucerase submission to the AWMSG of 32U/kg and 75kg (average UK weight according to most recent, but old ONS data (2010) was 83.6KG for men and 70.2KG for women, a population average of 76.9kg). In response to this ECD the company has sought accurate GD1 patient weight information: **UK data for weight of Gaucher Disease patients** Source / Weight / Total dose @25U / Vials ERG proposition / 67.5kg / 1687.5 / 4 Royal Free Hospital (RFH 2017) / 73.29 / 1832.25 / 5 ICGG (SGZ Data on file_2017a) / 71.8 (last follow up) / 1795 / 5 Pooled UK patients from ENGAGE and ENCORE(SGZ Data on file_2017b) / 73.6 (study end) / 1840 / 5 UK national average / 76.9kg / 1922.5 / 5 Results presented in the base case give a price per unit, rather than per vial, and while the SGZ recognises that the SOP and usual practice is not	was based on prescribing data in England. This data showed that patients received an average dose of [redacted] units per month, and therefore if we were to assume an average patient weight of 67.5kg in-line with the ENCORE trial, that equates to a dose of 25U/kg. Therefore, although the alternative weight values presented by the company have validity, the dose the ERG use in the model was calculated from the average units patients received per month, rather than from the average patient weight. This means that increasing the weight will simply decrease the units per kilogram, and will therefore have no impact on the total dose patients receive and the resulting cost of ERT.

		to waste ERT, what is clear is that the ERG estimate is the only estimate that is close to 4 vials, all others are close to 5 vials.	
	The company assumed that there are no administration costs associated with eliglustat because it is an oral therapy. The committee considered that the ERG's exploration including a monthly dispensary cost for eliglustat was appropriate, noting that this had a minor impact on the results.	This is a legitimate challenge that the company accepts, except to point out that pre-launch discussions with relevant stakeholders suggest that treatment would be sent out every one, two or three months, therefore frequency of dispensary costs may need to be adjusted. .	Although this point may be valid; due to the uncertainty regarding the frequency of prescribing and the insensitivity of the model to changes in the administration costs, the ERG believe that the frequency should remain unchanged in the executable model.
	The ERG highlighted that the administration costs for ERT were likely to be overestimated in the company's model because they were higher than the costs of hospital administration. The committee agreed that this was implausible and noted that the ERG had explored this assumption.	We accept that a consideration of the cost of homecare and hospital treatment is appropriate. We dispute the ERG's conclusion that that it is 'implausible' for the cost of homecare to be greater than hospital care. Nurse time in the home has no economies of scale and far more limited economies of scope than nurse time in a hospital. As such, whether homecare or hospital care is more expensive is a factor of the perspective of the costing analysis. Consideration of the cost 'per hour of nurse time' and the activities that the nurse can deliver in that time leads to different results to the 'nurse cost per infusion'. Costing differences are also dependent upon the composition of the costs, for example is there a portion of cost ascribed to sunk capital costs, training costs, support staff costs and sundries, in which case a NHS nurse with all the accompanying	The ERG's view that the company's assumption is implausible is based on several studies which have assessed the cost-effectiveness of home vs hospital administration of IV therapies that have consistently shown home administration to be the lower cost option. In addition, data supplied by NICE from the CMU on rates charged by the three different homecare companies also suggest lower costs of home therapy than those used in the company's base-case. Therefore, the ERG believe that their assumption that the costs of home administration and hospital administration are equal still over-estimates

		NHS organisation costs to include is likely to be more expensive in the hospital, and giving care in the home, than a nurse from a smaller, third party homecare organisation. If using the gold standard costing compendium from the PSSRU as the source for unit costs, costs can be consistently applied across resources. However, PSSRU doesn't have a cost for homecare delivered by a third party organisation. Because of this we sought to find a publicly available price for homecare delivery, which we reported. While we accept that cost attributed to home delivery may be a high estimate in the base-case, and the ERGs simplifying approach is reasonable, we suggest there is uncertainty with the ERGs estimated and costs may be higher.	the costs of home therapy, and considers their assumption conservative. The ERG have therefore left this assumption unchanged in their base-case analysis.
	The committee discussed the utility increment used in the company's model for oral therapy, which it understood was the key driver of QALY benefits. It heard from the patient and clinical experts that the availability of an oral treatment would have a huge impact on health-related quality of life compared with an intravenous infusion. The committee took note of several patient testimonies	SGZ recognised that the original value submitted for oral benefit of 0.12 double counted some aspects of the adverse events due to intravenous infusion. Had an ECD been produced after the September committee meeting, SGZ would have shared this information. SGZ accepts the committee's most plausible utility value for QALY benefit of an oral treatment in this therapy area is 0.05. However, we are concerned that oral utility discussions from previous NICE submissions: adverse events and the benefits of other oral therapies estimated in previous NICE submissions may be being inappropriately applied to this HST evaluation. The references in the ERG report used to defend a lower utility value were all being taken from cancers with a poor	The ERG did not describe the value of 0.12 as 'ridiculous' but as implausibly large based on previous NICE submissions, the wider literature and the logical implications of using this value. The utility values are not dependent on time so whether the condition is a short-term or long-term condition should theoretically have a limited effect on the estimation of the value. The long-term quality of life benefits achieved through receiving an oral therapy are captured by patients accruing this benefit over a longer period of time. Even if this argument made by the company did have any validity then the value

	describing the positive impact of an oral treatment and the potential this offered for them to return to a more normal life. The committee heard from the ERG that it agreed that oral therapy would provide a clear quality-of-life benefit but questioned the extent of the benefit assumed by the company, even though this was based on a vignette study. The ERG highlighted that an increment of 0.12 was substantial when compared with the decrements from significant adverse events and the benefits of other oral therapies estimated in previous NICE submissions. The committee was aware that the ERG explored an alternative utility increment of 0.05. The committee concluded that, although the true value was uncertain, the alternative value used by the ERG was more	survival prognosis (Liu et al 1997; Twelves et al 2006; Tabberer et al 2006; and NICE 2007). It is a very different proposition being asked if you prefer an oral therapy or an IV therapy in the last 6 months of life than being asked if you prefer an oral therapy or an IV therapy at the start of a treatment plan that will last for the next 50-60 years. The ERG postulates a scenario in which it states the original utility value submitted (0.12) would suggest people were prepared to trade-off 2.29 years of life in full health for the convenience of an oral therapy [over 50-60 years]. The ERG poses this as a ridiculous assumption. While SGZ would accept 0.12 is too high and therefore 2.29 years is too long, we would challenge that this is a ridiculous assumption and suggest that it is patients that should be making that decision.	used by the ERG in the executable model of 0.05, which is taken from the company's vignette study, is larger than many of the values used in the literature. Therefore, the value of 0.05 may be an over-estimation of the utility benefit. The ERG have therefore made no adjustment to the utility value used in their base-case analysis.

	appropriate.		
	Budget impact model The committee concluded that company's estimates of budget impact were additionally uncertain because: • the model excluded poor metabolisers • the dosage of ERT was assumed to be higher than in clinical practice • of incorporation of mortality and stopping treatment in estimated total costs.	SGZ is surprised by the approach the ERG adopted: 1 patient over 5 years. The advice in the STA User Guide is, 'State the estimated annual budget impact on the NHS in England' (NICE 2015). Reviewing the HST interim methods guide we couldn't see any recommendations to use a different approach (NICE 2013). Given the perspective is NHS-England, it is usual that a budget impact analysis includes an assumption for mortality and, although this varies by therapy area, treatment stopping. The principle being that if a patient dies within the 5 year timeframe of the BI analysis they are no longer costing the NHS money. It may have been fair to question if an annualised mortality rate would have been more appropriate, or some other estimate for the number of patients in the Gaucher Disease population that would die in a 5 year period. Regarding treatment stopping, the same principle applies, if a patients asks for a treatment break for a period of time and the NHS is not funding their treatment then there is no cost and this should be included. However, SGZ accepts that for simplicity this stopping rule can be removed. SGZ agrees that the poor metaboliser population should have been included in the budget impact analysis and agrees that a rate of 4% is	The ERG believes their approach is a more accurate way of representing the true budget impact of eliglustat compared to the company's method of linking the cost-consequence model directly to the budget impact model. Although it may lack some precision we believe it is more accurate to focus on the costs of one patient over five years rather than applying the average cost of treating a patient over a lifetime to each year in a five year period as the company has done. Although there will be some mortality observed over the five years there will also be new incident patients who will begin receiving therapy resulting in the population remaining fairly stable. Regarding discontinuation, the cost-consequence and budget impact models both separately account for the fact that a proportion of patients switch treatments. In order to avoid double counting the ERG set discontinuation to zero in the cost-consequence model to estimate the budget impact. The ERG have therefore left the assumptions used for their base-case budget-impact model unchanged.

		appropriate.	
	using ENCORE effectiveness data in the treatment-naive population during the first cycle.	SGZ strongly refutes this suggestion. Given that patients in the ENCORE trial had to have been on ERT for a minimum of three years, to have documented stability for the last 6 months and to be on a dose ranging from 30U/kg – 130U/kg, and that the mean patient across both of the per protocol arms had been on ERT for a mean of 10 years, we consider the assumption that these patients are equivalent to treatment-naive patients is flawed. The study by Ibrahim et al, and reported in the EPAR appears to demonstrate that very similar outcomes are achieved in the first-year of active treatment with eliglustat or ERT	The ERG never claimed that patients who were stable on treatment are equivalent to those who are treatment-naïve, and accept that this method has limitations. However, using data from the single-arm ENGAGE study to estimate transition probabilities for eliglustat patients, and applying these probabilities to both treatment arms in the first cycle of the model is not justified. This method does not capture any of the potential differences between eliglustat and imiglucerase. Although using data from patients who are stable on ERT in the treatment naïve population is flawed the ERG believes it is an improvement on the company's analysis, and have therefore kept the assumption in the ERG base-case analysis.

Section 3: Application of revised list price and PAS discount

In this section, the ERG presents the following:

- Results of company's original base-case with the updated PAS discount applied;

The documentation provided by the company presents a revision to the PAS. The PAS consists of a simple discount of [redacted] over the original list price and [redacted] over the newest list price. Table 1 presents the original list price per pack, the revised list price per pack and price per pack with the new PAS discount applied.

Table 2 Price of Eliglustat with revised list price and new PAS discount

	Cost per 56-tablet blister pack (excluding VAT)	
	List price	**Discount over original list price**
Original List price	£15,811.04	0%
Revised List price	£19,164.96	-21.21%
Price with PAS applied	[redacted]	[redacted]

The results of the company's original base-case with the updated PAS discount applied are presented in Tables 3-5.

Company's Base-Case (updated PAS discount applied)

Table 3: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	**Incremental Cost**
ERT stable IM/EM	**Total: 2.28**	[redacted]
ERT stable PM	**Total: 2.28**	[redacted]
ERT naïve IM/EM	**Total: 2.43**	[redacted]
ERT naïve PM	**Total: 2.43**	[redacted]

Table 4: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	**Incremental Cost**
ERT stable IM/EM	**Total: 2.28**	[redacted]
ERT stable PM	**Total: 2.28**	[redacted]
ERT naïve IM/EM	**Total: 2.45**	[redacted]
ERT naïve PM	**Total: 2.45**	[redacted]

Table 5: Budget Impact with Updated Eliglustat Uptake Values (ERT Stable IM/EM Patients)

	2017	2018	2019	2020	2021
Total	**-£3,218,028**	**-£6,934,836**	**-£10,387,168**	**-£12,903,992**	**-£15,389,609**
Cumulative Total	**-£3,218,028**	**-£10,152,864**	**-£20,540,032**	**-£33,444,024**	**-£48,833,634**

Section 4: ERG base-case analysis

This section presents the results of the ERG base-case analysis with the updated list price and the new PAS discount in Tables 6-11. In an accompanying confidential appendix the ERG also present the results of this analysis with commercial arrangements for imiglucerase and velaglucerase applied. The ERG base-case analysis remains consistent with the analysis presented in the ERG report and makes the following changes to the company's base-case:

- Alternative assumptions regarding the mortality of Gaucher patients;
- Alternative assumptions regarding the HRQoL benefits associated with oral therapy.
- Alternative assumptions made regarding the administrative costs of eliglustat and ERT;
- Changes to the dose of eliglustat and ERT treatment assumed in the model;
- Alternative assumptions regarding the short-term effectiveness of eliglustat in treatment naïve patients;
- Alternative assumptions regarding the prevalence of Type 1 Gaucher disease in England.

The ERG base-case budget impact analysis also assumes zero discontinuation and mortality consistent with the analysis presented in the ERG report. Additionally, the company presented updated estimates for the projected uptake of eliglustat over the next five years for the budget impact analysis in their previous company PAS/revised list price submission. The ECD states that the committee was satisfied that the company's revised estimates sufficiently reflected the expectations in clinical practice in England. The ERG also previously noted that the budget impact results presented by the company excluded poor metabolisers, and the committee appeared to agree with the ERG in the ECD that this was inappropriate. Therefore, the ERG have included the updated uptake estimates and the impact of poor metabolisers in the ERG's base-case budget impact analysis.

The company in their ECD response claimed that were inconsistencies in using the average UK clinical practice dose of 25U/kg while continuing to use the average patient weight from the ENCORE trial of 67.5kg. The company have therefore presented two alternative estimates of the average weight of gaucher patients which are taken from the International Collaborative Gaucher Group (24 patients and an average weight of 71.8kg) and the Royal Free Hospital (110 patients and an average weight of 73.29kg).

The use of 25U/kg as the average dose in the model was based on prescribing data in England. This data showed that patients received an average dose of [redacted] units per month, and therefore if we were to assume an average patient weight of 67.5kg in-line with the ENCORE trial, that equates to a dose of 25U/kg. Therefore, although the alternative weight values presented by the company have validity, the dose the ERG use in the model was calculated from the average units patients received per month, rather than from the average patient weight. This means that increasing the weight will simply decrease the units per kilogram, and will therefore have no impact on the total dose patients receive and the resulting cost of ERT. However, scenarios are presented below in Tables 12-23 reporting the results of the ERG-base case analysis when these alternative weight values are implemented.

ERG Base-Case Analysis (eliglustat list price)

Table 6: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	**Total: £ 2,638,293**
ERT stable PM	**Total: 1.05**	**Total: -£ 6,825**
ERT naïve IM/EM	**Total: 1.04**	**Total: £ 2,605,712**
ERT naïve PM	**Total: 1.04**	**Total: -£ 49,688**

Table 7: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	**Total: £ 1,849,412**
ERT stable PM	**Total: 1.05**	**Total: -£ 795,706**
ERT naïve IM/EM	**Total: 1.06**	**Total: £ 1,900,060**
ERT naïve PM	**Total: 1.06**	**Total: -£ 755,340**

Table 8: Budget Impact (ERT Stable IM/EM/PM Patients)

	2017	2018	2019	2020	2021
Total	**£2,211,946**	**£4,818,731**	**£7,324,191**	**£9,223,107**	**£11,123,765**
Cumulative Total	**£2,211,946**	**£7,030,676**	**£14,354,867**	**£23,577,974**	**£34,701,739**

ERG Base-Case Analysis (updated PAS discount applied)

Table 9: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	[redacted]
ERT stable PM	**Total: 1.05**	[redacted]
ERT naïve IM/EM	**Total: 1.04**	[redacted]
ERT naïve PM	**Total: 1.04**	[redacted]

Table 10: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	[redacted]
ERT stable PM	**Total: 1.05**	[redacted]
ERT naïve IM/EM	**Total: 1.06**	[redacted]
ERT naïve PM	**Total: 1.06**	[redacted]

Table 11: Budget Impact (ERT Stable IM/EM/PM Patients)

	2017	2018	2019	2020	2021
Total	**-£1,043,654**	**-£2,273,932**	**-£3,458,155**	**-£4,361,633**	**-£5,263,975**
Cumulative Total	**-£1,043,654**	**-£3,317,586**	**-£6,775,741**	**-£11,137,374**	**-£16,401,349**

ERG Base-Case Analysis (eliglustat list price and ICGG patient weight of 71.8 kg)

Table 12: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	**Total: £ 2,479,345**
ERT stable PM	**Total: 1.05**	**Total: -£ 165,773**
ERT naïve IM/EM	**Total: 1.04**	**Total: £ 2,443,398**
ERT naïve PM	**Total: 1.04**	**Total: -£ 212,002**

Table 13: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	**Total: £ 1,640,209**
ERT stable PM	**Total: 1.05**	**Total: -£ 1,004,909**
ERT naïve IM/EM	**Total: 1.06**	**Total: £ 1,692,793**
ERT naïve PM	**Total: 1.06**	**Total: -£ 962,607**

Table 14: Budget Impact (ERT Stable IM/EM/PM Patients)

	2017	2018	2019	2020	2021
Total	**£2,019,716**	**£4,399,939**	**£6,687,538**	**£8,420,984**	**£10,156,138**
Cumulative Total	**£2,019,716**	**£6,419,655**	**£13,107,193**	**£21,528,177**	**£31,684,315**

ERG Base-Case Analysis (updated PAS discount applied and ICGG patient weight of 71.8 kg)

Table 15: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	[redacted]
ERT stable PM	**Total: 1.05**	[redacted]
ERT naïve IM/EM	**Total: 1.04**	[redacted]
ERT naïve PM	**Total: 1.04**	[redacted]

Table 16: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	[redacted]
ERT stable PM	**Total: 1.05**	[redacted]
ERT naïve IM/EM	**Total: 1.06**	[redacted]
ERT naïve PM	**Total: 1.06**	[redacted]

Table 17: Budget Impact (ERT Stable IM/EM/PM Patients)

	2017	2018	2019	2020	2021
Total	**-£1,235,884**	**-£2,692,724**	**-£4,094,807**	**-£5,163,756**	**-£6,231,603**
Cumulative Total	**-£1,235,884**	**-£3,928,608**	**-£8,023,415**	**-£13,187,171**	**-£19,418,774**

ERG Base-Case Analysis (eliglustat list price and RFH patient weight of 73.29 kg)

Table 18: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	**Total: £ 2,424,268**
ERT stable PM	**Total: 1.05**	**Total: -£ 220,850**
ERT naïve IM/EM	**Total: 1.04**	**Total: £ 2,387,154**
ERT naïve PM	**Total: 1.04**	**Total: -£ 268,246**

Table 19: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	**Total: £ 1,567,718**
ERT stable PM	**Total: 1.05**	**Total: -£ 1,077,400**
ERT naïve IM/EM	**Total: 1.06**	**Total: £ 1,620,973**
ERT naïve PM	**Total: 1.06**	**Total: -£ 1,034,427**

Table 20: Budget Impact (ERT Stable IM/EM/PM Patients)

	2017	2018	2019	2020	2021
Total	**£1,953,106**	**£4,254,822**	**£6,466,930**	**£8,143,040**	**£9,820,843**
Cumulative Total	**£1,953,106**	**£6,207,928**	**£12,674,859**	**£20,817,898**	**£30,638,742**

ERG Base-Case Analysis (updated PAS discount applied and RFH weight of 73.29 kg)

Table 21: Incremental QALYs and Costs (Eliglustat vs. Imiglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	[redacted]
ERT stable PM	**Total: 1.05**	[redacted]
ERT naïve IM/EM	**Total: 1.04**	[redacted]
ERT naïve PM	**Total: 1.04**	[redacted]

Table 22: Incremental QALYs and Costs (Eliglustat vs. Velaglucerase)

	Incremental QALYs	Incremental Cost
ERT stable IM/EM	**Total: 1.05**	[redacted]
ERT stable PM	**Total: 1.05**	[redacted]
ERT naïve IM/EM	**Total: 1.06**	[redacted]
ERT naïve PM	**Total: 1.06**	[redacted]

Table 23: Budget Impact (ERT Stable IM/EM/PM Patients)

	2017	2018	2019	2020	2021
Total	**-£1,302,493**	**-£2,837,841**	**-£4,315,415**	**-£5,441,700**	**-£6,566,897**
Cumulative Total	**-£1,302,493**	**-£4,140,334**	**-£8,455,749**	**-£13,897,449**	**-£20,464,346**

Section 6: Conclusions

The introduction of the new PAS discount substantially lowers the acquisition costs associated with eliglustat and reduces the overall budget impact. Interpretation of these results should however, bear in mind that ERT is itself a highly cost-ineffective therapy in of itself and has an estimated ICER of £380,000 to £476,000 per QALY, based on a previous cost-effective analysis carried out as part of the NHS HTA programme.[1] Any consideration of the cost-effectiveness of eliglustat such therefore consider the fact that ERT is currently provided to Gaucher disease patients at a cost to the NHS which would be unacceptable for other more common diseases.

Section 7: References

1. Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, et al. The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review. Health Technol Assess 2006;10:1-136.