NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dinutuximab beta for treating high-risk neuroblastoma [ID910]

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - EUSA Pharma

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Juliet Gray – clinical expert, nominated by National Institute for Health Research and Children's Cancer and Leukaemia Group
   - Nick Bird – patient expert, nominated by Solving Kids Cancer

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Additional evidence submitted** by EUSA Pharma

6. **Decision Support Unit critique** of company's additional evidence

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

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Dinutuximab beta for treating high-risk neuroblastoma [ID910]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD 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 appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	EUSA Pharma	EUSA Pharma would like to thank the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal and to provide further clarifications for consideration. We are concerned that if the current recommendation were to stand, children and adolescents suffering from high-risk neuroblastoma would be denied the option of treatment with dinutuximab beta. We consider it is important for patients to have the opportunity to receive dinutuximab beta because 6.8 years of data shows that, compared to historical treatment, dinutuximab beta increases long-term survival for children and adolescents in this rare, debilitating and life-threatening disease (1). It is important to note that since 2009, immunotherapy with dinutuximab has been considered standard of care world-wide for high-risk neuroblastoma patients, so much so that clinicians felt it was unethical to include a comparator arm including the retinoic acid in APN311-302 (1). Indeed, the European Medical Agency granted marketing authorisation under exceptional circumstances because, amongst others, it was not considered feasible to generate comprehensive data on dinutuximab beta as neither clinicians nor patients would be prepared to participate in a placebo-controlled trial (1). Additionally, dinutuximab beta is now fully reimbursed in Germany and final discussion on the reimbursement conditions in France and Italy are underway. EUSA Pharma believes that patients in the UK should have the opportunity to receive the same standard of care as in the rest of Europe. We are committed to working with NICE in order to address the Committee's key uncertainties as outlined in the ACD and we hope NICE can work with us to find a solution that will enable patients with high-risk neuroblastoma to access dinutuximab beta. There is significant unmet need to provide an effective treatment option for high-risk neuroblastoma patient. This need was expressed by patients and clinical experts at the NICE committee meetings, and recognised by the NICE committee (ACD document). EUSA Pharma accepts the NICE committee's position that the most recent (2014) data for isotretinoin is the most appropriate to use in the model. We have in good faith based our initial	Comments noted. Please note that dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See final appraisal document (FAD) section 1.1. Please see detailed response to each point below.

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			analysis on the 2010 data, because we believed that this is the most robust data for the base case. For the same reason we continued to use the 2010 dataset during the clarification stage when we were asked to provide additional information and analyses. It was only in March 2018 that we were asked to include the 2014 data in our analyses, which we did. Although we continue to believe the 2010 data is robust, we acknowledge that it is in the best interest of the appraisal to use the 2014 data. EUSA Pharma would also like to acknowledge that the Committee has considered a large amount of evidence in the previous appraisal for Unituxin and in this appraisal for dinutuximab beta. We do however believe that there may be some evidence that could be explored further. We would also like to raise additional points that we believe are relevant to the next Appraisal Committee Meeting. We present a summary of factual inaccuracies and further clarifications for consideration at the end, and an additional scenario in Appendix. EUSA Pharma has submitted a Patient Access Scheme (PAS) to Patient Access Scheme Liaison Unit and this is currently awaiting approval. We hope that discussions will be concluded promptly and will advise NICE when they are completed. Reference: (1) EMA. Dinutuximab beta (Qarziba): European Public Assessment Report (EPAR). 2017.	
2	Consultee	EUSA Pharma	*I. Has all of the relevant evidence been taken into account?* **EUSA Pharma believe that there is some evidence that should be taken into account at the next appraisal meeting. We present these below** **1. EUSA Pharma agree with the Committee that the spline models for EFS dinutuximab beta are relevant however we request that the NICE Committee also consider the Gompertz model as a clinically plausible scenario** EUSA Pharma would suggest the Committee also consider the Gompertz models for EFS dinutuximab beta as this curve fitted well the clinical data (goodness-of-fit see figure 1 *[provided but not reproduced here]*) and the plateau expected by clinical experts from 5 years onwards with dinutuximab beta (clinical expert statement in the ACD document, page 14, section 3.13; figure 2 from the Decision Support Unit (DSU) report). Statistical fits for all model distributions were presented in Table 7 of DSU report and the DSU considers that the spline model with k=1 and scale=odds, as it has the lowest akaike information criterion and bayesian information criterion. The DSU considers the Generalised gamma as a	Comments noted. The NICE appraisal committee considered the Gompertz model as a clinically plausible alternative for modelling EFS. Please see section 3.14 in the FAD.

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			scenario analysis. While the Gompertz was ranked 8th in terms of statistical fit based on the akaike information criterion, its goodness-of-fit was not materially worse than that of the 1st-ranked or 4th-ranked distribution (Figure 1 *[provided but not reproduced here]*). Incorporating the event-free Gompertz extrapolation and the overall survival extrapolation for dinutuximab beta which the committee considered most plausible (section 3.13, Gompertz or spline for overall survival) in the DSU model, produced an incremental cost-effectiveness ratio of £62,886 per quality-adjusted life year gained using Gompertz for overall survival and £70,757 per quality-adjusted life year gained using 2-knot spline. Using a plausible cure-threshold at 5 years will reduce the incremental cost-effectiveness ratio to £58,651 per quality-adjusted life year gained.	
3	Consultee	EUSA Pharma	**2. The cost of 5 cycles of dinutuximab beta at full dose has been included in the cost-effectiveness estimates, but may be lower in clinical practice** EUSA Pharma believes the current incremental cost-effectiveness ratio (ICER) range may be lower if it is taken into consideration that dose reduction and permanent discontinuation of dinutuximab beta may occur in the presence of certain toxicities, as recommended in the Summary of Product Characteristics (SPC). EUSA Pharma chose to be conservative and did not model any treatment discontinuation due to toxicity or tolerability ([redacted]). Whilst EUSA Pharma understands that the ICERs should reflect the SPC recommendations, the clinical benefits included in the model reflect the interim analysis results of study APN311-302 but the cost reflects the full treatment schedule. In clinical practice, should the full dose and number of cycles be administered, then the clinical benefits may be better than that seen in the clinical studies. EUSA Pharma would therefore ask the Committee to consider that in actual clinical practice, the ICER may be lower than that indicated by the model. In the Appendix, EUSA Pharma has presented a new scenario analysis on the DSU cost-effectiveness model that incorporates the effect of the discontinuation, the incremental cost-effectiveness ratio was at £59,491-60,128 per quality-adjusted life year gained using Gompertz models for overall survival and event-free survival (see details in Appendix).	Comments noted. The NICE appraisal committee considered the application of a discontinuation rate appropriate in the economic model. Please see section 3.19 of the FAD.
4	Consultee	EUSA Pharma	**3. End of life costs should be considered in the appraisal and could decrease the ICER estimates**	Comments noted. The NICE appraisal committee considered end of life costs and

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			EUSA Pharma notes that clinical experts advised the DSU that in the case of uncontrolled disease, patients may receive more intensive palliative care for a short period of time but that the DSU response was that "Since all patients would receive palliative care shortly before dying and all modelled patients die, the only impact this cost would have on the results would be due to discounting – which, at 1.5% per annum would be negligible." It is true that that all modelled patients die, but not all patients would die due to the disease (i.e. not all patients would require intensive palliative treatment for high-risk neuroblastoma). EUSA Pharma is aware that the average cost of treating <18 year olds with life limiting conditions according to the NICE guideline NG61 can be estimated as £8,800 in England (£9,116 if inflated to 2017 costs) (2). Including this cost in the model would further decrease the ICER, particularly if applied to only those patients who die due to the disease, and EUSA Pharma asks that the Committee takes this into consideration in their final decision. Reference: (2) NICE. End of life care for infants, children and young people with life-limiting conditions: planning and management; NICE guideline [NG61]. NICE guideline. 2016.	the impact of these on the cost-effectiveness estimates. Please see the committee presentation slides available on the NICE website.
5	Consultee	EUSA Pharma	*II. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* **4. EUSA Pharma suggest that the Committee may not have fully taken into consideration the difficulties of conducting clinical trials in an orphan disease area.** Section 3.4 states that the APN311-302 is not in line with the scope. Whilst this may be true, EUSA Pharma would like to remind the Committee that the clinical trials were designed and executed by clinicians to inform clinical practice. Additionally, being an orphan disease, patient numbers in such studies will always be small and as such, statements around statistical significance may be misleading. In the interest of making the treatment available to patients as soon as possible, immature data had to be used in the appraisal. The evidence that was presented to the Committee was provided on the basis that this is the best available and it should be taken into consideration that it may be more reflective of clinical practice than a strictly controlled randomised trial. Section 3.12 states that the long-term benefit is the main source of uncertainty and a key driver of the cost-effectiveness analysis. EUSA Pharma would like to remind the Committee that the length of data for dinutuximab beta is considerable and this has not been acknowledged in the ACD document. As outlined above, in the interest of informing clinical practice and making the treatment accessible to patients, waiting for certainty on long-term outcomes is not realistic.	Comments noted. The NICE appraisal committee took into consideration that neuroblastoma is a rare disease. Please see section 3.27 of the FAD. Please also note that wording has been amended in section 3.4 of the FAD, and section 3.25 discusses the limited feasibility of data collection on long-term outcomes.

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6	Consultee	EUSA Pharma	*III. Are the recommendations sound and a suitable basis for guidance to the NHS?* **EUSA Pharma respectfully disagrees with the conclusion that the ICER range presented by the DSU is not a cost-effective use of NHS resources. We present our key concerns below** **5. The Single Technology Appraisal (STA) route does not allow for incorporating uncertainties inherent to paediatric and orphan disease treatments** Although it is true that the plausible incremental cost-effectiveness ratio estimates of £62,300 to £79,900 (see factual inaccuracies regarding these values) is much higher than what NICE would normally consider a cost-effective use of NHS resources, exceptions exist as part of the Highly Specialised Technology (HST) Programme where the ICER threshold is £100,000 - £300,000/QALY. EUSA Pharma understands that the Institute took a decision some time ago that the dinutuximab beta should be appraised via the STA route, but the company believes that the challenges for valuing potentially curative treatments for very rare disease in a paediatric population are not fully explored and considered within the STA framework and decision-making process. Many of the patients that develop neuroblastoma are young children who will require extensive care by family members. The patients' young age makes it difficult to obtain and fully understand the treatment's impact on their health-related quality of life (HRQoL). As such it may be that the value of the drug in this very young population is not entirely captured using the cost per quality adjusted life year approach. This approach also does not incorporate the impact on carers' HRQoL and work productivity, and the wider societal benefit such as cost outside of the NHS. EUSA is disappointed that the Institute cannot be more flexible in their considerations of what they considered cost-effective treatments for rare, paediatric diseases outside of the HST programme and ask that the Committee consider this point in their final decision.	Comments noted. The NICE appraisal committee took into consideration that dinutuximab beta had not met the criteria for consideration through the highly specialised technologies programme despite being an orphan medicine. Please see section 3.27 of the FAD.
7	Consultee	EUSA Pharma	**6. The ACD does not recommend dinutuximab beta for treating relapsed or refractory neuroblastoma, with or without residual disease, but contains contradictory statements on the relevance of this population group to the appraisal.** Reading the ACD it is difficult to understand the Committee's position on relapsed and refractory patients and what informed their recommendations and statements in the ACD relating to this population group.	Comments noted. Please note that the wording in relation to the relapsed/refractory population has been clarified in the FAD (see sections 3.3 and 3.5). The wording in

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			On p3 the ACD states that dinutuximab beta is " …not recommended for treating relapsed or refractory neuroblastoma, with or without residual disease", but on p4 the ACD states "…this population is not relevant to current NHS practice, and therefore evidence was not considered in this population." Yet on p7 the ACD states that "Patients with relapsed or refractory neuroblastoma have already had dinutuximab beta in clinical practice". EUSA Pharma would like to ask for clarification on statements in Section 3.3 "the committee concluded that **almost** all patients having treatment for relapsed or refractory neuroblastoma in clinical practice have had dinutuximab beta as a prior treatment in the clinical trial (APN311-302)" and Section 3.5 "…people in the NHS who have relapsed disease are **likely** to have had dinutuximab beta as part of their multi-agent, multimodal first-line therapy". [EUSA Pharma emphasis in bold]. From these sentences, we should understand that not all patients will get dinutuximab beta as part of clinical trial, and thus could be eligible after relapse. Also, to avoid any confusion, please consider adding clarity on why APN311-302 is not in line with NICE scope. The statements in the full paragraph is misleading because it could be interpreted that it was possible to do a head-to-head comparison. After the publication of the positive clinical results of the US Children's Oncology Group (COG) ANBL0032 trial by Yu et al. in 2010 regarding the clinical efficacy and safety of dinutuximab (Unituxin) in addition to GM-CSF, IL-2 and isotretinoin compared to isotretinoin alone, it was deemed unethical to treat patients without immunotherapy, considered at that time to be the "standard of care" (SIOPEN clinical decision), thus the planned randomised trial APN311-301 was stopped and re-designed as APN311-302 (immunotherapy + isotretinoin +/- IL-2). Further seemingly contradictory statements are discussed separately below and EUSA Pharma would welcome further discussion and clarification on the Committee's view on relapsed and refractory patients having access to dinutuximab beta**.**	section 3.4 has also been amended to clarify why there was no head-to-head comparison.
8	Consultee	EUSA Pharma	**7. Patients with relapsed or refractory neuroblastoma DO NOT currently receive dinutuximab beta in clinical practice.** The conclusion on p7 (Section 3.3) that almost all patients having treatment for relapsed or refractory neuroblastoma **in clinical practice** have had dinutuximab beta as prior treatment in the clinical trial APN311-302 cannot be correct in light of the statement on p6 in relation to study APN311-302 that "The committee agreed that dinutuximab beta **cannot be considered established NHS clinical practice** because it is only used in research as part of a clinical trial and	Comments noted. Please note that the wording in relation to the relapsed/refractory population has been clarified in the FAD (see sections 3.3 and 3.5).

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			is not routinely commissioned". It appears contradictory to state on p7 that relapsed or refractory patients would have received **it in clinical practice**, as dinutuximab beta is currently only available **as part of a clinical trial.** [EUSA emphasis on key text in bold]. To the previous point, further discussion and clarification on the Committee's view on relapsed and refractory patients having access to dinutuximab beta **outside of clinical trials and in future clinical practice** would be welcome.	
9	Consultee	EUSA Pharma	**8. The clinical effectiveness evidence for the population with relapsed and or refractory disease IS relevant to clinical practice** EUSA Pharma disagrees with the conclusion that the populations in APN311-202 and APN311-303 do not represent the population with relapsed or refractory disease who would have dinutuximab beta in NHS clinical practice. As outlined above, patients in England are currently receiving dinutuximab beta as part of a clinical trial, which cannot be considered to be established NHS clinical practice (as acknowledge by the Committee and stated in the ACD, p7). So, whilst it is true that the **current** patients in England have had dinutuximab beta, this has only been possible through a clinical trial setting. Outside of a clinical trial setting patient will not have access to dinutuximab beta. Thus, for these future patients, studies APN311-202 and APN311-303 will be relevant to future clinical practice. Again, EUSA Pharma urges that the Committee further discuss and clarify their view on relapsed and refractory patients having access to dinutuximab beta **outside of clinical trials and in future clinical practice**.	Comments noted. Please note that the wording in relation to the relapsed/refractory population has been clarified in the FAD (see sections 3.3 and 3.5).
10	Consultee	EUSA Pharma	*IV. 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?* **EUSA Pharma believes that because neuroblastoma is a rare disease that affects predominantly a paediatric population, the current evaluation framework does not fully allow for the uncertainties and therefore children with rare diseases will be discriminated against. We outline our concerns below**	Comments noted. The NICE appraisal committee was fully aware of the patient population in this appraisal being young children and therefore carefully considered this aspect in its

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			9. End of Life criteria used by the Institute are based on data from adults, and consequently does not apply *as is*, to evaluations in paediatric populations EUSA Pharma considers that the Committee failed to consider the special needs of children and applied NICE's standard end-of-life and clinical effectiveness criteria to dinutuximab beta. NICE's 2-year life-expectancy threshold for its end-of-life criteria is arbitrary, unreasonable and biased against children, as this vulnerable population typically live longer than adults with cancer. Further, the appraisal of dinutuximab beta through the STA process, applying NICE's standard clinical effectiveness criteria, was always likely to produce a negative recommendation for the orphan drug and likely amounts to a breach of a child's right of access to the highest attainable standard of health and facilities for the treatment of illness.	deliberations. Please see sections 3.26 and 3.28 of the FAD.
11	Consultee	EUSA Pharma	**10. HRQoL in children may not be the same as in adults, thus the cost per QALY framework may not provide a complete picture of the impact and value of dinutuximab beta on children's lives** EUSA Pharma would like to point out that many of the patients that develop neuroblastoma are young children (90% < 10 years old). It is known that HRQoL assessments are challenging in children and young people and that there is a lack of well validated measurement instruments for them (3-6). One challenge for accurately valuing HRQoL in children relate to the factors that contribute to a child's HRQoL as these are likely to be different to that of an adult's (8). Additionally, due to their age, young children may find it difficult to articulate how much the disease is bothering them (7). This makes it difficult to fully understand the impact of the treatment these patients' HRQoL and consequently it may be that the value of the drug in this young population is not fully captured. *References:* (3) Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of Health-Related Quality of Life in Children: A Review of Conceptual, Methodological, and Regulatory Issues. Value Heal. 2004;7(1):79–92 (4) Gerharz EW, Eiser C, Woodhouse CRJ. Current approaches to assessing the quality of life in children and adolescents. Br J Urol. 2003;91(2):150–159 (5) Thorrington D, Eames K. Measuring health utilities in children and adolescents: A systematic review of the literature. PLoS One. 2015;10(8):1–21. (6) Coombes LH, Wiseman T, Lucas G, Sangha A, Murtagh FE. Health-related quality-of-life outcome measures in paediatric palliative care: A systematic review of psychometric properties and	Comments noted. The NICE appraisal committee was fully aware of the patient population in this appraisal being young children and therefore carefully considered this aspect in its deliberations. Please see sections 3.26 and 3.28 of the FAD.

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			feasibility of use. Palliat Med. 2016;30(10):935–49. (7) Duarte A, Mebrahtu T, Goncalves P, Harden M, Murphy R, Palmer S, et al. Assessment Group's Report: Adlimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people. 2017.	
12	Consultee	EUSA Pharma	**11. Wider societal benefits such as the impact of children's carers should be included in the consideration of the final ICER** The nature of the young population affected by neuroblastoma means that a higher burden is placed on the parents in relation to caregiving, family relations and emotional impact than it would in an adult population. This in turn affects their ability to work and ultimately places a burden on wider society. Again, the QALY and the STA framework may not be appropriate for evaluating treatments in paediatric patients.	Comments noted. The NICE appraisal committee took into consideration potential uncaptured benefits (please see section 3.26 of the FAD).
13	Consultee	EUSA Pharma	*I. Factual inaccuracies* - Section 1.1, page 3. In the indication, EUSA Pharma suggests removing "autologous" from the sentence, because the EMA label is referring to "Treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and **stem cell transplantation**, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease." Using the word "autologous" will restrict the population and not consider the patients having haplo-identical stem cell transplantation. - Section 3.10, page 12. In the last sentence, "the committee noted that the company had produced a scenario analysis on request, using the 2014 data, but that it had continued to extrapolate the isotretinoin arm beyond 70 months rather than use the actual trial data". This sentence is not correct, EUSA Pharma has provided the scenario analysis including data until 82 months (i.e. approximately 6.8 years) like for dinutuximab beta arm and then extrapolated until 10 years. The dataset used (I.e. EFS and OS until 82 months) was submitted in Appendix 2 (tables 1 and 2), on the 16th March 2018. - Section 3.20, page 19. The different ICERs presented (probabilistic or deterministic) are not found either in the committee slides or in the DSU report, and thus are difficult to evluate for factual inaccuracies. The different sentences for amendment: - "The committee noted that using the 2014 data for isotretinoin in the model, as the DSU had done, increased the probabilistic ICER to **£78,162** per QALY gained". We could use this sentence referencing the numbers in the DSU report (Table 6) or the Committee meeting slides (slide 30): "The committee noted that using the 2014 data for isotretinoin in	Comments noted. Please see section 1.1 of the FAD where this wording has been corrected. This section of text has now been removed because it is no longer relevant. We apologise for this procedural error. The incremental cost-effectiveness ratios (ICERs) reported in the appraisal consultation document (ACD) are

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			the model, as the DSU had done, increased the **ICER to £79,811** per QALY gained". - "Incorporating the event-free and overall survival extrapolation for dinutuximab beta that the committee considered most plausible (see section 3.13) produced an ICER of £79,493 per QALY gained using Gompertz for overall survival, and £79,935 per QALY gained using the 2-knot spline. The committee recognised that other cure thresholds could be plausible (see section 3.14), and was aware that this could reduce the ICER to £62,309 per QALY gained". With the numbers in the DSU report (table 12 and table 15) and the committee meeting slides (slide 31-32), the sentence should be written "…produced an ICER of **£75,831** per QALY gained using Gompertz for overall survival, and **£87,164** per QALY gained using the 2-knot spline. The committee recognised that other cure thresholds could be plausible (see section 3.14), and was aware that this could reduce the ICER to **£60,824** per QALY gained". - Section 3.23, page 21: PASS stands for post authorisation safety study (registry) which is called Safary in the ACD.	the probabilistic ICERs that were requested from the decision support unit (DSU) after the committee meeting, in order to consistently report probabilistic ICERs in this section. This section of text has now been amended (please see section 3.25 of the FAD).
14	Consultee	EUSA Pharma	*I. Additional amendment to texts:* - Section 1.2, page 3. "Dinutuximab beta is an important **new** option for maintenance treatment of the disease". Since 2009, immunotherapy with dinutuximab has been considered standard of care world-wide for high-risk neuroblastoma patients, so much so that clinicians felt it was unethical to include a comparator arm in the high-risk clinical trial. Knowing the history of dinutuximab beta, EUSA Pharma believes that the term "new" is not appropriate. - Section 3.11, page 13. ACD notes that "actual data from the 2014 analysis of ANBL0032 showed that there were no events after approximately 7 years for people having isotretinoin". However, given the uncertainty of isotretinoin survival curves after 7 years (i.e. the proportion of patients becomes small, perhaps when only 15% of the original sample (3)) it should be stated that there is uncertainty and possible that there are events after 7 years for people having isotretinoin. Considering this uncertainty, the extrapolation for EFS and OS data for the isotretinoin arm provided by EUSA Pharma is clinically plausible. - Section 3.10, page 13. The ACD document states that "It was aware that the 2014 analysis was not published but had been considered by the European Medicines Agency in its regulatory assessment of dinutuximab alpha". The sentence should be clarified as only OS of the 2014 analysis has been considered by the European Medicines Agency and not for EFS.	Comments noted. This section of text has now been amended. Please see section 1 of the FAD. The section of text discussing the extrapolation of isotretinoin data has now been removed because it is no longer relevant. This section of text has now been amended. Please see section 3.11 of the FAD.

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			- Section 3.13, page 21 "…including collecting data on biomarkers that could potentially identify subgroups more likely to benefit from treatment". The biomarkers (e.g. Fc Receptor polymorphisms and KIR/KIR-Ligand mismatch analysis) are not being collected by EUSA Pharma currently, thus we will suggest removing this sentence. - In the ACD document, the high-risk and relapsed or refractory population should be clarified. Patients classified with high-risk neuroblastoma may come from two different patient groups: either they are identified during their initial diagnosis as high-risk (first-line), or they are patients who were originally identified with low- or intermediate-risk forms of disease, but following disease relapse or refractory response to initial therapy, become re-evaluated as high-risk and follow individualized treatment plans. Furthermore, when referencing to relapsed or refractory patients who would have dinutuximab beta in NHS clinical practice, the terminology of relapsed or refractory neuroblastoma (previous high-risk) patients should be preferred.	This section of text has now been amended. Please see section 3.25 of the FAD. This section of text has now been amended and references to the relapsed/refractory population clarified. Please see sections 3.3 and 3.5 of the FAD.
15	Consultee	EUSA Pharma	*I. Other minor text clarifications we suggest are as follows:* - Page 9 of the ACD document, the title is not specific to NHS clinical practice whereas the last sentences of the section 3.5 does. We suggest the title be changed to: "The clinical effectiveness evidence for the population with relapsed or refractory disease is not relevant to **NHS** clinical practice" - Section 3.8, page 11. To add clarity regarding why there is no direct evidence comparing dinutuximab beta with isotretinoin, we suggest the first sentence of this section be changed to:" **Due to ethical reason (see section 3.4)**, there was no direct evidence comparing dinutuximab beta with isotretinoin."	This section of text has now been amended. Please see section 3.5 of the FAD. This section of text has now been amended. Please see section 3.8 of the FAD.
16	Commentator	Dr Juliet Gray	i) The consultation documentation states that 'the committee agreed that dinutuximab beta cannot be considered established NHS clinical practice'. However is should be acknowledged that some form of anti-GD2 therpay (dinituximab beta or dinutuximab) has been considered a standard of care for children with high risk neuroblastoma in Europe, the US and Australia since 2009.	Comments noted. The NICE appraisal committee acknowledged this; please see section 3.28 of the FAD.
17	Commentator	Dr Juliet Gray	ii) The consultation document comments that there is 'substantial uncertainty' about the long term benefit of dinutuximab beta. This may be true, but the consultation document should also acknowledge the substantial challenges of obtaining robust data in this very rare population of children. In 2009, a decision was made my the European neuroblastoma research group (SIOPEN) not to include a randomisation with a control (no antibody) arm, as this was considered	Comments noted. The NICE appraisal committee acknowledged this; please see sections

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			unacceptable – due to the significant benefit seen in the COG ABL0032 study of the closely related antibody, Dinutuximab. Some form of anti-GD2 immunotherapy is now considered a standard of care for high risk neuroblastoma in the US, Europe and Australia, and it would not be feasible to run a further randomised study to assess efficacy / long term benefits. All assessment of efficacy will therefore be, by necessity, based on comparison with historical controls.	3.8, 3.25 and 3.28 of the FAD.
18	Commentator	Dr Juliet Gray	iii) The comments related to relapsed/ refractory patients are based on the assumption that the vast majority of children with high risk neuroblastoma will receive anti-GD2 therapy as part of their first line therapy, and that evidence for re-treatment with anti-GD2 at relapse is lacking. This would not be the case if NHS funding is not available to treat patients with this immunotherapy as part of the first line therapy. That being the case, the majority of patients will ultimately relapse, and would be antibody-naïve at relapse. In these children the 'end of life' criteria would probably apply. The consultation document states (Page 9) that "comments from clinical experts that patients who disease has relapsed after dinutuximab beta have not been eligible for further dinutuximab beta within any clinical trial' is incorrect. Our clinical expert opinion was that patients who have previously received anti-GD2 antibody should only receive further anti-GD2 as part of a clinical trial. There are currently 2 clinical trials in the UK, one open and one in set-up, which offer dinutuximab beta in this situation for relapsed / refractory patients.	Comments noted. Please note that the wording in relation to the relapsed/refractory population has been clarified in the FAD (see sections 3.3 and 3.5).
19	Commentator	Dr Juliet Gray	The consultation documentation should acknowledge the orphan nature of this disease and the small number of patients per year who would require treatment. Although the cost per patient is high, the total NHSE cost is relatively low because of the small number of patients.	Comments noted. Please see section 3.27 of the FAD.
20	Commentator	Dr Juliet Gray	v) The consultation document should acknowledge to disparities in health care which would arise if this treatment can not be provided with NHS funding, as those families who can will seek to fund treatment privately or with charitable funding.	Comments noted. Please note that dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See section 1.1 of the FAD.
21	Commentator	Nick Bird	The use of the isotretinoin arm of the ANBL0032 study by Yu. et. al. does not represent the most appropriate 'control arm' for assessing clinical efficacy of dinutuximab beta. The company's initial submission used a comparator arm comprised of data from the SIOPEN HR-NBL1 high-risk neuroblastoma trial. The Committee, rightly and appropriately, questioned the use of this dataset as it contained patients who had received both BuMel and (the inferior) CEM conditioning regimens during PBSCT. The vast majority of patients who received dinutuximab beta (with or without IL2) would have received BuMel as it was declared the winner of the R1 randomisation of HR-NBL1.	Comments noted. Please see section 3.9 of the FAD and note that dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See section 1.1 of the FAD

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			The Committee directed the Company to use the data they had previously viewed during the Appraisal for dinutuximab (Unituxin) – ID799. Specifically, the standard arm of isotretinoin from the Children's Oncology Group (COG) ANBL0032 randomised control trial. Moreover, when the Company undertook comparative analysis using 2010 data published by Yu et. al. in the New England Journal of Medicine, the Committee directed them to use the most recent dataset from March 2014, available only within the NICE Appraisal documentation for ID799. The flaw in all this is that whilst the general treatment approach is the same between SIOPEN and COG, the specific components are completely different. Induction chemotherapy uses different agents, in different combinations, with a different administration schedule. Stem cell collection is performed at a different time-point. Surgery is conducted at a different time-point. The conditioning regimen used by COG in ANBL0032 would have been CEM not BuMel [1], or potentially even tandem transplant with thiotepa–cyclophosphamide followed by modified CEM [2]. Patients could enrol on any protocol prior to ANBL0032, the only eligibility requirement being prior PBSCT. All of these elements may be confounding factors when using the data in a completely unbalanced way such as a comparator arm for this Appraisal. A far superior comparator would actually be the BuMel arm of the SIOPEN R1 randomisation (BuMel vs CEM), the results of which have been published with up to 5 years of follow-up in the Lancet Oncology by Ladenstein et. al [3]. In this study 29 of 296 patients on the BuMel arm received dinutuximab beta, the remainder received isotretinoin alone. All patients received Rapid COJEC, surgery, radiotherapy, myeloablative therapy using Busulfan and Melphalan followed by autologous stem cell rescue. They are the best representative control set of patients for assessing the relative efficacy of the addition of dinutuximab beta. I accept that it is for the Company to provide the evidence that it wishes the Committee to consider. However, I also feel that the previous Appraisal ID799 has muddied the waters and led everybody down a path where we are now not using the best available comparator / historic control arm. The focus of everybody and everything quickly moved on and was elsewhere, rather than on this fundamental point. I would like the Company, Appraisal Committee, and DSU to reflect on this and decide/agree what truly represents the most appropriate comparator. This will influence not only the current decision, but any subsequent future assessment of clinical effectiveness and cost-effectiveness should the drug be included in the Cancer Drugs Fund for a period of time. [1] Whilst CEM was deemed inferior to BuMel in the SIOPEN R1 study, this was only in the context of the Rapid COJEC induction regimen. BuMel has not been adopted by COG as standard of care	

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			because of that finding. During subsequent discussions it was hypothesised that the efficacy of CEM as a conditioning regimen in the SIOPEN settings may have been adversely impacted by the high platinum content in the Rapid COJEC induction regimen, leading to a problem of platinum-resistance in patients. Something that would not occur with the COG induction regimen https://am.asco.org/2011-plenary-retrospective-new-standard-care-high-risk-neuroblastoma-europe. [2] For High-Risk Neuroblastoma, Two Transplants May Be Better Than One. http://www.ascopost.com/issues/june-25-2016/for-high-risk-neuroblastoma-two-transplants-may-be-better-than-one/ [3] Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol 2017; 18: 500–14 Published Online March 1, 2017 http://dx.doi.org/10.1016/ S1470-2045(17)30070-0. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30070-0/fulltext?code=lancet-site	
22	Web comment	Carer	Thank you for the time spent considering recommendation for NHS funding for Immunotherapy for children with High risk Neuroblastoma. I urge you to recommend funding for this treatment It is standard care in Europe and North America. Denial of access for NHS patients will have significant implications for the treatment of young children with this disease. Children in the UK should not be disadvantaged. My [redacted] month old [redacted] was diagnosed last October 2017 with High risk Neuroblastoma and will probably need Immunotherapy. Many other parents and grandparents on [redacted] Ward in [redacted] are facing similar uncertainties. This has taken over our lives. Surely the sign of a civilized society is the way in which we treat those less fortunate than ourselves. Please I urge you to recommend funding for this treatment. Thank you. [redacted]	Comments noted. Dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See section 1.1 of the FAD.
23	Web comment	NHS Professional	Dinituximab beta (DB) is a subtly different agent to dinutiximab, now withdrawn from the European market. Published evidence of antibody functionality indicates some differences and specifically evidence of enhanced cancer cell killing function of DB. A previous randomised trial of Dinituximab versus no immunotherapy in North America was stopped at a very early stage so great was the advantage in 2 year EFS and OS in the Dinituximab group. As a result within Europe SIOPEN network it was realised that it would be unacceptable to perform a randomised study and DB effectively became standard of care throughout Europe. The survival of DB treated patients compared with the best possible historical control is significantly enhanced. my experience of treating countless children with this antibody at the UK's largest	Comments noted. Dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See section 1.1 of the FAD.

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			treatment centre for the disease is that is it very well tolerated. Since the age of the patients is so young, the potential gain in terms of young lives saved is high. This must be taken into special consideration.	
24	Web comment	Carer	I am the father of a [redacted] diagnosed with high-risk stage 4 neuroblastoma in [redacted] 2017. She is now taking a course of dinutuximab beta funded by EUSA Pharma. She and some other children needed the drugs after the clinical trial had ended but before the NICE decision had been taken. If NICE's preliminary decision stands, this small cohort will be the last to receive dinutuximab beta in the UK without having to raise finance privately to pay for it. My experience as a parent of a child with this difficult disease leads me to believe that this would be the wrong result. My understanding of the preliminary decision is that the question has now reduced to a financial negotiation between NICE and EUSA, with most of the pressure being on EUSA to lower the price it will charge the NHS so that NICE can recommend the drug for funding via Individual Funding Requests from the Cancer Drugs Fund. If such a compromise can be reached, then there is little more for someone like me to add. However, the fear is that somehow a deal remains out of reach. The purpose of this submission is to urge both sides to take extra steps if such an impasse looks likely. There are good practical, political and moral reasons to ensure that a mutually acceptable arrangement is concluded. Practically, even if dinutuximab beta only extends a child's life by a few years, the proportional benefit is huge compared to adding a few years to the life of someone much older. Added to which, with another five years of data the drug may prove more effective than that. Five years is enough time for a child to to be born, be diagnosed and die from this disease. Every child's life that is saved is another person who will be able to play their part in society perhaps for decades to come. Additionally, there is a practical reason to ensure that companies such as EUSA remain incentivised to develop and produce treatments for rare childhood diseases. When only a small number of patients require a treatment, inevitably it will be more expensive. If treatments like dinutuximab beta are evaluated according to the same criteria as those for chronic adult diseases, they will frequently fail. By default this becomes a policy decision that treatment of diseases like high-risk neuroblastoma will not and may never be fully covered by the NHS. If such a hard decision is necessary, it should not be made as the accidental side-effect of a regulatory process, but deliberately and following proper consideration. If EUSA and NICE fail to fix an acceptable price for this treatment here in the UK, this will disadvantage British children compared to those in many other European countries whose	Comments noted. Dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See section 1.1 of the FAD.

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			governments are prepared to fund IFRs. This is politically uncomfortable, but also raises an important moral question. The clinical investigations which NICE agrees are necessary to establish the long-term benefits of dinutuximab beta will continue elsewhere. It will be unfortunate and a hindrance that the high level of expertise in UK hospitals will be cut off from this work. In a few years' time, it will become clearer whether the treatment prevents or merely delays relapse and most likely improved methods of administration or completely new treatments will have been developed as a result. What will the UK do then? The NHS will surely seek to benefit from these advances. However, in doing so it will, as an advanced and relatively well-resourced health system, be free-riding on the greater willingness of other economically comparably countries to support the development of this drug. For all these reasons, in the event that a deal appears out of reach, I urge EUSA Pharma to be as transparent as possible in laying out the basis on which it has developed its pricing to show it is offering the drug as cheaply as possible while meeting its obligations to shareholders. Equally, I urge NICE to show flexibility to avoid the many negative consequences of not funding this drug.	
25	Web comment	Carer	My son has recently been diagnosed with high risk neuroblastoma and to learnt that he will not reveive a treatment which may save his life is heartbreaking. I won't comment on specifics or science but NICE acknowledges that this treatment works and improves survival rates. To remove this drug from the NHS treatment will make a tiny difference to overall NHS budgets. We are taking about 50 very young children per year and to withdraw the when billions is spent on smoking, alcohol and obesity related illness in adults is shameful. I would urge NICE to work with all stakeholders so that my son and others can access the drugs that can save their lives. Thank you for reading my comments. [redacted], father of [redacted]	Comments noted. Dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See section 1.1 of the FAD.
26	Web comment	NHS Professional	Dear NICE appraisers, I have read the consultation document on the use of Dinituximab beta for upfront treatment for high risk neuroblastoma for patients who have achieved at least a partial response and proceeded through standard therapy for high risk NB.	Comments noted. Dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See

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			I agree with the decision by NICE to focus on upfront treatment without concomitant IL-2 and not to consider relapsed or refractory patients where the evidence is weaker. I note the outcome of the NICE decision that in view of the cost proposed by EusaPharma for diniutuximab beta (£7,610 exc VAT/vial approximately £150,000/ cycle) leads to calculation of an ICER (Incremental cost effectiveness ratio) well above that considered by NICE to recommend a new technology on the NHS. I agree that there were errors in the Eusa documentation regarding risk of relapse after 5 years and that available evidence does exist on long term use of 13 cis retinoic acid alone which could be used rather than relying on modelling. However I think that developing a new drug for an orphan indication such as high risk NB is never going to be profitable for a pharmaceutical company, particularly a relatively small one like EusaPharma unless it is priced above what NICE would normally consider cost-effective. It could also be argued that if we restrict the indication of dinituximab beta to upfront treatment of high risk NB we are looking at around 35-40 patients/year in the UK (fewer if we consider England alone) on the basis that there are approx., 50 new case of high risk NB/year and sadly some will relapse before reaching the phase of minimal residual disease therapy when dinituximab beta will be given (or relapse during this phase and not complete 5 cycles). Does this very small number of patients each year who might benefit from this therapy make it possible for NICE to re-consider an ICER outside the normal range that it would usually consider cost effective for a new treatment, particularly if Eusa were to lower their price/vial ? As a practicing paediatric oncologist I urge NICE and Eusa to negotiate a price so that dinituximab can be adopted by the Cancer Drugs Fund for the next 2-3 years for upfront treatment of children with high risk NB whilst awaiting the additional data needed to provide cost effectiveness and particularly the results of biomarker studies from the recent Phase IIII trial to show which groups of children are most likely to benefit. Many thanks for your help with this matter. Yours sincerely, [redacted]	section 1.1 of the FAD.
27	Web	Carer	Dear Sir,	Comments noted.

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	comment		Please I urge you to work collaboratively to enable any appropriate drugs to be made available on the NHS for children with high risk neuroblastoma. This tragic disease has turned my family's lives upside down. Our [redacted] month old [redacted] was diagnosed last [redacted]2017 and may soon need Immunotherapy. Yours sincerely, [redacted]	Dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See section 1.1 of the FAD.
28	Web comment	NHS Professional	Thank you very much for this opportunity to comment on the NICE appraisal of Dinutuximab Beta for High-Risk Neuroblastoma. While I accept that the evidence base for this treatment is less than perfect, I feel very strongly that this drug should be made available for children with neuroblastoma for the following reasons. Since the data on the American trial of Dinutuximab with IL2 and GM-CSF became available in 2010, some form of treatment with an Anti-GD2 monoclonal antibody has been accepted as the standard of care by paediatric oncologists in both the USA and Europe. At that time, the European Group had started a randomised trial comparing Dinutuximab Beta with no Anti GD2, but it was considered unethical to continue it, as the American data indicated a substantial benefit for this type of treatment. An amendment was introduced to the trial so that all patients received Dinutuximab Beta, with or without IL2. The concept of a further randomised trial in which some patients would not receive this treatment would nowadays be considered completely unacceptable. Failure to provide Dinutuximab Beta in UK on the NHS will be a retrograde step for paediatric oncology in the UK, and meaning that we deliver inferior treatment to the rest of the developed world. It would also result in great inequity for children with Neuroblastoma, as many parents would seek to fund this treatment through private fundraising, but others might not be able to do so. The method of assessment of the value of this drug selected by NICE was probably wrong. Had it been assessed by the HST committee it would have been within the limits of funding considered cost effective. Recognition of the difficulty of undertaking clinical research in very rare diseases needs to be taken into account. In breast and lung cancer where there are many tens of thousands of patients	Comments noted. Dinutuximab beta is now recommended as a treatment option for patients with high-risk neuroblastoma. See section 1.1 of the FAD.

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			diagnosed annually in the UK, very highly powered trials are possible. With an annual incidence of only about 100 neuroblastoma patients (about 60 with high-risk disease), such trials even when conducted on a Europe wide population base take longer to accrue and have broader confidence limits. Despite this, it is clear that survival of children with high-risk neuroblastoma is significantly better in the era of universal access to Dinutuximab Beta than it was previously. We must not lose this therapeutic advantage. While I understand that NICE has a statutory responsibility to ensure that the NHS gets value for money from the pharmaceutical industry, it must be remembered that drug development is never cheap. The costs can be recouped with relatively narrow profit margin if a drug has a market of tens of thousands of patients. If companies are squeezed too hard, then they will be disincentivised from researching drugs for rare conditions like neuroblastoma. I strongly urge NICE to look favourably upon this orphan drug. [redacted] 4 June 2018	

NICE National Institute for Health and Care Excellence

Dinutuximab beta for treating high-risk neuroblastoma [ID910]

Consultation on the appraisal consultation document – deadline for comments 5pm on 29 May 2018 through NICE Docs

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**EUSA Pharma**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Natasa Zibelnik

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NICE National Institute for Health and Care Excellence

Dinutuximab beta for treating high-risk neuroblastoma [ID910]

Consultation on the appraisal consultation document – deadline for comments 5pm on 29 May 2018 through NICE Docs

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	EUSA Pharma would like to thank the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal and to provide further clarifications for consideration. We are concerned that if the current recommendation were to stand, children and adolescents suffering from high-risk neuroblastoma would be denied the option of treatment with dinutuximab beta. We consider it is important for patients to have the opportunity to receive dinutuximab beta because 6.8 years of data shows that, compared to historical treatment, dinutuximab beta increases long-term survival for children and adolescents in this rare, debilitating and life-threatening disease (1). It is important to note that since 2009, immunotherapy with dinutuximab has been considered standard of care world-wide for high-risk neuroblastoma patients, so much so that clinicians felt it was unethical to include a comparator arm including the retinoic acid in APN311-302 (1). Indeed, the European Medical Agency granted marketing authorisation under exceptional circumstances because, amongst others, it was not considered feasible to generate comprehensive data on dinutuximab beta as neither clinicians nor patients would be prepared to participate in a placebo-controlled trial (1). Additionally, dinutuximab beta is now fully reimbursed in Germany and final discussion on the reimbursement conditions in France and Italy are underway. EUSA Pharma believes that patients in the UK should have the opportunity to receive the same standard of care as in the rest of Europe. We are committed to working with NICE in order to address the Committee's key uncertainties as outlined in the ACD and we hope NICE can work with us to find a solution that will enable patients with high-risk neuroblastoma to access dinutuximab beta. There is significant unmet need to provide an effective treatment option for high-risk neuroblastoma patient. This need was expressed by patients and clinical experts at the NICE committee meetings, and recognised by the NICE committee (ACD document). EUSA Pharma accepts the NICE committee's position that the most recent (2014) data for isotretinoin is the most appropriate to use in the model. We have in good faith based our initial analysis on the 2010 data, because we believed that this is the most robust data for the base case. For the same reason we continued to use the 2010 dataset during the clarification stage when we were asked to provide additional information and analyses. It was only in March 2018 that we were asked to include the 2014 data in our analyses, which we did. Although we continue to believe the 2010 data is robust, we acknowledge that it is in the best interest of the appraisal to use the 2014 data. EUSA Pharma would also like to acknowledge that the Committee has considered a large amount of evidence in the previous appraisal for Unituxin and in this appraisal for dinutuximab beta. We do however believe that there may be some evidence that could be explored further. We would also like to raise additional points that we believe are relevant to the next Appraisal Committee Meeting. We present a summary of factual inaccuracies and further clarifications for consideration at the end, and an additional scenario in Appendix. EUSA Pharma has submitted a Patient Access Scheme (PAS) to Patient Access Scheme Liaison

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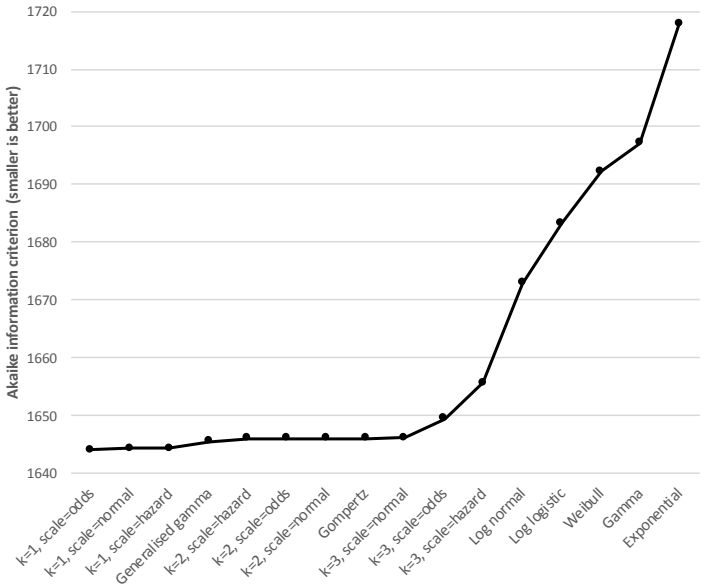
	Unit and this is currently awaiting approval. We hope that discussions will be concluded promptly and will advise NICE when they are completed. Reference: (1) EMA. Dinutuximab beta (Qarziba): European Public Assessment Report (EPAR). 2017.
2	*I. Has all of the relevant evidence been taken into account?* **EUSA Pharma believe that there is some evidence that should be taken into account at the next appraisal meeting. We present these below** **1. EUSA Pharma agree with the Committee that the spline models for EFS dinutuximab beta are relevant however we request that the NICE Committee also consider the Gompertz model as a clinically plausible scenario** EUSA Pharma would suggest the Committee also consider the Gompertz models for EFS dinutuximab beta as this curve fitted well the clinical data (goodness-of-fit see figure 1) and the plateau expected by clinical experts from 5 years onwards with dinutuximab beta (clinical expert statement in the ACD document, page 14, section 3.13; figure 2 from the Decision Support Unit (DSU) report). Statistical fits for all model distributions were presented in Table 7 of DSU report and the DSU considers that the spline model with k=1 and scale=odds, as it has the lowest akaike information criterion and bayesian information criterion. The DSU considers the Generalised gamma as a scenario analysis. While the Gompertz was ranked 8th in terms of statistical fit based on the akaike information criterion, its goodness-of-fit was not materially worse than that of the 1st-ranked or 4th-ranked distribution (Figure 1). **Figure 1: Fit statistics for event-free survival of dinutuximab beta (figure using the Table 7 of DSU report)**  **Figure 2: Event-free survival Kaplan-Meier curve vs fitted models (figure 9 from the DSU**

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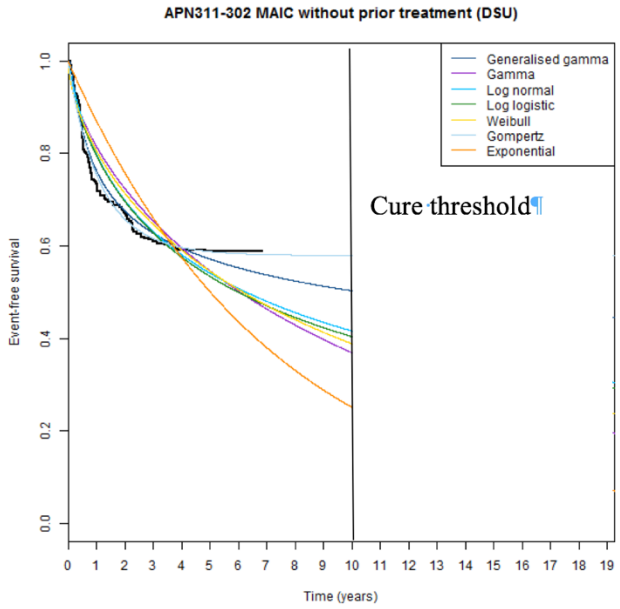
	report)  Incorporating the event-free Gompertz extrapolation and the overall survival extrapolation for dinutuximab beta which the committee considered most plausible (section 3.13, Gompertz or spline for overall survival) in the DSU model, produced an incremental cost-effectiveness ratio of £62,886 per quality-adjusted life year gained using Gompertz for overall survival and £70,757 per quality-adjusted life year gained using 2-knot spline. Using a plausible cure-threshold at 5 years will reduce the incremental cost-effectiveness ratio to £58,651 per quality-adjusted life year gained.
3	**2. The cost of 5 cycles of dinutuximab beta at full dose has been included in the cost-effectiveness estimates, but may be lower in clinical practice** EUSA Pharma believes the current incremental cost-effectiveness ratio (ICER) range may be lower if it is taken into consideration that dose reduction and permanent discontinuation of dinutuximab beta may occur in the presence of certain toxicities, as recommended in the Summary of Product Characteristics (SPC). EUSA Pharma chose to be conservative and did not model any treatment discontinuation due to toxicity or tolerability ([redacted]). Whilst EUSA Pharma understands that the ICERs should reflect the SPC recommendations, the clinical benefits included in the model reflect the interim analysis results of study APN311-302 but the cost reflects the full treatment schedule. In clinical practice, should the full dose and number of cycles be administered, then the clinical benefits may be better than that seen in the clinical studies. EUSA Pharma would therefore ask the Committee to consider that in actual clinical practice, the ICER may be lower than that indicated by the model. In the Appendix, EUSA Pharma has presented a new scenario analysis on the DSU cost-effectiveness model that incorporates the effect of the discontinuation, the incremental cost-effectiveness ratio was at £59,491-60,128 per quality-adjusted life year gained using Gompertz models for overall survival and event-free survival (see details in Appendix).

NICE National Institute for Health and Care Excellence

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4	**3. End of life costs should be considered in the appraisal and could decrease the ICER estimates** EUSA Pharma notes that clinical experts advised the DSU that in the case of uncontrolled disease, patients may receive more intensive palliative care for a short period of time but that the DSU response was that "Since all patients would receive palliative care shortly before dying and all modelled patients die, the only impact this cost would have on the results would be due to discounting – which, at 1.5% per annum would be negligible." It is true that that all modelled patients die, but not all patients would die due to the disease (i.e. not all patients would require intensive palliative treatment for high-risk neuroblastoma). EUSA Pharma is aware that the average cost of treating <18 year olds with life limiting conditions according to the NICE guideline NG61 can be estimated as £8,800 in England (£9,116 if inflated to 2017 costs) (2). Including this cost in the model would further decrease the ICER, particularly if applied to only those patients who die due to the disease, and EUSA Pharma asks that the Committee takes this into consideration in their final decision. Reference: (2) NICE. End of life care for infants, children and young people with life-limiting conditions: planning and management; NICE guideline [NG61]. NICE guideline. 2016.
5	*II. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* **4. EUSA Pharma suggest that the Committee may not have fully taken into consideration the difficulties of conducting clinical trials in an orphan disease area.** Section 3.4 states that the APN311-302 is not in line with the scope. Whilst this may be true, EUSA Pharma would like to remind the Committee that the clinical trials were designed and executed by clinicians to inform clinical practice. Additionally, being an orphan disease, patient numbers in such studies will always be small and as such, statements around statistical significance may be misleading. In the interest of making the treatment available to patients as soon as possible, immature data had to be used in the appraisal. The evidence that was presented to the Committee was provided on the basis that this is the best available and it should be taken into consideration that it may be more reflective of clinical practice than a strictly controlled randomised trial. Section 3.12 states that the long-term benefit is the main source of uncertainty and a key driver of the cost-effectiveness analysis. EUSA Pharma would like to remind the Committee that the length of data for dinutuximab beta is considerable and this has not been acknowledged in the ACD document. As outlined above, in the interest of informing clinical practice and making the treatment accessible to patients, waiting for certainty on long-term outcomes is not realistic.
6	*III. Are the recommendations sound and a suitable basis for guidance to the NHS?* **EUSA Pharma respectfully disagrees with the conclusion that the ICER range presented by the DSU is not a cost-effective use of NHS resources. We present our key concerns below** **5. The Single Technology Appraisal (STA) route does not allow for incorporating uncertainties inherent to paediatric and orphan disease treatments**

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	Although it is true that the plausible incremental cost-effectiveness ratio estimates of £62,300 to £79,900 (see factual inaccuracies regarding these values) is much higher than what NICE would normally consider a cost-effective use of NHS resources, exceptions exist as part of the Highly Specialised Technology (HST) Programme where the ICER threshold is £100,000 - £300,000/QALY. EUSA Pharma understands that the Institute took a decision some time ago that the dinutuximab beta should be appraised via the STA route, but the company believes that the challenges for valuing potentially curative treatments for very rare disease in a paediatric population are not fully explored and considered within the STA framework and decision-making process. Many of the patients that develop neuroblastoma are young children who will require extensive care by family members. The patients' young age makes it difficult to obtain and fully understand the treatment's impact on their health-related quality of life (HRQoL). As such it may be that the value of the drug in this very young population is not entirely captured using the cost per quality adjusted life year approach. This approach also does not incorporate the impact on carers' HRQoL and work productivity, and the wider societal benefit such as cost outside of the NHS. EUSA is disappointed that the Institute cannot be more flexible in their considerations of what they considered cost-effective treatments for rare, paediatric diseases outside of the HST programme and ask that the Committee consider this point in their final decision.
7	**6. The ACD does not recommend dinutuximab beta for treating relapsed or refractory neuroblastoma, with or without residual disease, but contains contradictory statements on the relevance of this population group to the appraisal.** Reading the ACD it is difficult to understand the Committee's position on relapsed and refractory patients and what informed their recommendations and statements in the ACD relating to this population group. On p3 the ACD states that dinutuximab beta is " …not recommended for treating relapsed or refractory neuroblastoma, with or without residual disease", but on p4 the ACD states "…this population is not relevant to current NHS practice, and therefore evidence was not considered in this population." Yet on p7 the ACD states that "Patients with relapsed or refractory neuroblastoma have already had dinutuximab beta in clinical practice". EUSA Pharma would like to ask for clarification on statements in Section 3.3 "the committee concluded that **almost** all patients having treatment for relapsed or refractory neuroblastoma in clinical practice have had dinutuximab beta as a prior treatment in the clinical trial (APN311-302)" and Section 3.5 "…people in the NHS who have relapsed disease are **likely** to have had dinutuximab beta as part of their multi-agent, multimodal first-line therapy". [EUSA Pharma emphasis in bold]. From these sentences, we should understand that not all patients will get dinutuximab beta as part of clinical trial, and thus could be eligible after relapse. Also, to avoid any confusion, please consider adding clarity on why APN311-302 is not in line with NICE scope. The statements in the full paragraph is misleading because it could be interpreted that it was possible to do a head-to-head comparison. After the publication of the positive clinical results of the US Children's Oncology Group (COG) ANBL0032 trial by Yu et al. in 2010 regarding the clinical efficacy and safety of dinutuximab (Unituxin) in addition to GM-CSF, IL-2 and isotretinoin compared to isotretinoin alone, it was deemed unethical to treat patients without immunotherapy, considered at that time to be the "standard of care" (SIOPEN clinical decision), thus the planned randomised trial APN311-301 was stopped and re-designed as APN311-302 (immunotherapy + isotretinoin +/- IL-2).

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	Further seemingly contradictory statements are discussed separately below and EUSA Pharma would welcome further discussion and clarification on the Committee's view on relapsed and refractory patients having access to dinutuximab beta**.**
8	**7. Patients with relapsed or refractory neuroblastoma DO NOT currently receive dinutuximab beta in clinical practice.** The conclusion on p7 (Section 3.3) that almost all patients having treatment for relapsed or refractory neuroblastoma **in clinical practice** have had dinutuximab beta as prior treatment in the clinical trial APN311-302 cannot be correct in light of the statement on p6 in relation to study APN311-302 that "The committee agreed that dinutuximab beta **cannot be considered established NHS clinical practice** because it is only used in research as part of a clinical trial and is not routinely commissioned". It appears contradictory to state on p7 that relapsed or refractory patients would have received **it in clinical practice**, as dinutuximab beta is currently only available **as part of a clinical trial.** [EUSA emphasis on key text in bold]. To the previous point, further discussion and clarification on the Committee's view on relapsed and refractory patients having access to dinutuximab beta **outside of clinical trials and in future clinical practice** would be welcome.
9	**8. The clinical effectiveness evidence for the population with relapsed and or refractory disease IS relevant to clinical practice** EUSA Pharma disagrees with the conclusion that the populations in APN311-202 and APN311-303 do not represent the population with relapsed or refractory disease who would have dinutuximab beta in NHS clinical practice. As outlined above, patients in England are currently receiving dinutuximab beta as part of a clinical trial, which cannot be considered to be established NHS clinical practice (as acknowledge by the Committee and stated in the ACD, p7). So, whilst it is true that the **current** patients in England have had dinutuximab beta, this has only been possible through a clinical trial setting. Outside of a clinical trial setting patient will not have access to dinutuximab beta. Thus, for these future patients, studies APN311-202 and APN311-303 will be relevant to future clinical practice. Again, EUSA Pharma urges that the Committee further discuss and clarify their view on relapsed and refractory patients having access to dinutuximab beta **outside of clinical trials and in future clinical practice**.
10	*IV. 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?* **EUSA Pharma believes that because neuroblastoma is a rare disease that affects predominantly a paediatric population, the current evaluation framework does not fully allow for the uncertainties and therefore children with rare diseases will be discriminated against. We outline our concerns below**

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	9. End of Life criteria used by the Institute are based on data from adults, and consequently does not apply *as is*, to evaluations in paediatric populations EUSA Pharma considers that the Committee failed to consider the special needs of children and applied NICE's standard end-of-life and clinical effectiveness criteria to dinutuximab beta. NICE's 2-year life-expectancy threshold for its end-of-life criteria is arbitrary, unreasonable and biased against children, as this vulnerable population typically live longer than adults with cancer. Further, the appraisal of dinutuximab beta through the STA process, applying NICE's standard clinical effectiveness criteria, was always likely to produce a negative recommendation for the orphan drug and likely amounts to a breach of a child's right of access to the highest attainable standard of health and facilities for the treatment of illness.
11	**10. HRQoL in children may not be the same as in adults, thus the cost per QALY framework may not provide a complete picture of the impact and value of dinutuximab beta on children's lives** EUSA Pharma would like to point out that many of the patients that develop neuroblastoma are young children (90% < 10 years old). It is known that HRQoL assessments are challenging in children and young people and that there is a lack of well validated measurement instruments for them (3-6). One challenge for accurately valuing HRQoL in children relate to the factors that contribute to a child's HRQoL as these are likely to be different to that of an adult's (8). Additionally, due to their age, young children may find it difficult to articulate how much the disease is bothering them (7). This makes it difficult to fully understand the impact of the treatment these patients' HRQoL and consequently it may be that the value of the drug in this young population is not fully captured. *References:* (3) Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of Health-Related Quality of Life in Children: A Review of Conceptual, Methodological, and Regulatory Issues. Value Heal. 2004;7(1):79–92 (4) Gerharz EW, Eiser C, Woodhouse CRJ. Current approaches to assessing the quality of life in children and adolescents. Br J Urol. 2003;91(2):150–159 (5) Thorrington D, Eames K. Measuring health utilities in children and adolescents: A systematic review of the literature. PLoS One. 2015;10(8):1–21. (6) Coombes LH, Wiseman T, Lucas G, Sangha A, Murtagh FE. Health-related quality-of-life outcome measures in paediatric palliative care: A systematic review of psychometric properties and feasibility of use. Palliat Med. 2016;30(10):935–49. (7) Duarte A, Mebrahtu T, Goncalves P, Harden M, Murphy R, Palmer S, et al. Assessment Group's Report: Adlimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people. 2017.
12	**11. Wider societal benefits such as the impact of children's carers should be included in the consideration of the final ICER** The nature of the young population affected by neuroblastoma means that a higher burden is placed on the parents in relation to caregiving, family relations and emotional impact than it would in an adult population. This in turn affects their ability to work and ultimately places a burden on wider society. Again, the QALY and the STA framework may not be appropriate for evaluating treatments in paediatric patients.

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13	*V. Factual inaccuracies* - Section 1.1, page 3. In the indication, EUSA Pharma suggests removing "autologous" from the sentence, because the EMA label is referring to "Treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and **stem cell transplantation**, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease." Using the word "autologous" will restrict the population and not consider the patients having haplo-identical stem cell transplantation. - Section 3.10, page 12. In the last sentence, "the committee noted that the company had produced a scenario analysis on request, using the 2014 data, but that it had continued to extrapolate the isotretinoin arm beyond 70 months rather than use the actual trial data". This sentence is not correct, EUSA Pharma has provided the scenario analysis including data until 82 months (i.e. approximately 6.8 years) like for dinutuximab beta arm and then extrapolated until 10 years. The dataset used (I.e. EFS and OS until 82 months) was submitted in Appendix 2 (tables 1 and 2), on the 16th March 2018. - Section 3.20, page 19. The different ICERs presented (probabilistic or deterministic) are not found either in the committee slides or in the DSU report, and thus are difficult to evluate for factual inaccuracies. The different sentences for amendment: - "The committee noted that using the 2014 data for isotretinoin in the model, as the DSU had done, increased the probabilistic ICER to **£78,162** per QALY gained". We could use this sentence referencing the numbers in the DSU report (Table 6) or the Committee meeting slides (slide 30): "The committee noted that using the 2014 data for isotretinoin in the model, as the DSU had done, increased the **ICER to £79,811** per QALY gained". - "Incorporating the event-free and overall survival extrapolation for dinutuximab beta that the committee considered most plausible (see section 3.13) produced an ICER of £79,493 per QALY gained using Gompertz for overall survival, and £79,935 per QALY gained using the 2-knot spline. The committee recognised that other cure thresholds could be plausible (see section 3.14), and was aware that this could reduce the ICER to £62,309 per QALY gained". With the numbers in the DSU report (table 12 and table 15) and the committee meeting slides (slide 31-32), the sentence should be written "…produced an ICER of **£75,831** per QALY gained using Gompertz for overall survival, and **£87,164** per QALY gained using the 2-knot spline. The committee recognised that other cure thresholds could be plausible (see section 3.14), and was aware that this could reduce the ICER to **£60,824** per QALY gained". - Section 3.23, page 21: PASS stands for post authorisation safety study (registry) which is called Safary in the ACD.
14	*VI. Additional amendment to texts:* - Section 1.2, page 3. "Dinutuximab beta is an important **new** option for maintenance treatment of the disease". Since 2009, immunotherapy with dinutuximab has been considered standard of care world-wide for high-risk neuroblastoma patients, so much so that clinicians felt it was unethical to include a comparator arm in the high-risk clinical trial. Knowing the history of dinutuximab beta, EUSA Pharma believes that the term "new" is not appropriate. - Section 3.11, page 13. ACD notes that "actual data from the 2014 analysis of ANBL0032 showed that there were no events after approximately 7 years for people having isotretinoin". However, given the uncertainty of isotretinoin survival curves after 7 years (i.e. the proportion of patients becomes small, perhaps when only 15% of the original sample (3)) it should be stated that there is uncertainty

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	and possible that there are events after 7 years for people having isotretinoin. Considering this uncertainty, the extrapolation for EFS and OS data for the isotretinoin arm provided by EUSA Pharma is clinically plausible. - Section 3.10, page 13. The ACD document states that "It was aware that the 2014 analysis was not published but had been considered by the European Medicines Agency in its regulatory assessment of dinutuximab alpha". The sentence should be clarified as only OS of the 2014 analysis has been considered by the European Medicines Agency and not for EFS. - Section 3.13, page 21 "…including collecting data on biomarkers that could potentially identify subgroups more likely to benefit from treatment". The biomarkers (e.g. Fc Receptor polymorphisms and KIR/KIR-Ligand mismatch analysis) are not being collected by EUSA Pharma currently, thus we will suggest removing this sentence. - In the ACD document, the high-risk and relapsed or refractory population should be clarified. Patients classified with high-risk neuroblastoma may come from two different patient groups: either they are identified during their initial diagnosis as high-risk (first-line), or they are patients who were originally identified with low- or intermediate-risk forms of disease, but following disease relapse or refractory response to initial therapy, become re-evaluated as high-risk and follow individualized treatment plans. Furthermore, when referencing to relapsed or refractory patients who would have dinutuximab beta in NHS clinical practice, the terminology of relapsed or refractory neuroblastoma (previous high-risk) patients should be preferred.
15	*VII. Other minor text clarifications we suggest are as follows:* - Page 9 of the ACD document, the title is not specific to NHS clinical practice whereas the last sentences of the section 3.5 does. We suggest the title be changed to: "The clinical effectiveness evidence for the population with relapsed or refractory disease is not relevant to **NHS** clinical practice" - Section 3.8, page 11. To add clarity regarding why there is no direct evidence comparing dinutuximab beta with isotretinoin, we suggest the first sentence of this section be changed to:" **Due to ethical reason (see section 3.4)**, there was no direct evidence comparing dinutuximab beta with isotretinoin."

Comment on Dinutuximab beta Appraisal Consultation Document - Dr Juliet Gray – Associate Professor and Consultant in Paediatric Oncology, University of Southampton.

i) The consultation documentation states that 'the committee agreed that dinutuximab beta cannot be considered established NHS clinical practice'. However is should be acknowledged that some form of anti-GD2 therpay (dinituximab beta or dinutuximab) has been considered a standard of care for children with high risk neuroblastoma in Europe, the US and Australia since 2009.

ii) The consultation document comments that there is 'substantial uncertainty' about the long term benefit of dinutuximab beta. This may be true, but the consultation document should also acknowledge the substantial challenges of obtaining robust data in this very rare population of children. In 2009, a decision was made my the European neuroblastoma research group (SIOPEN) not to include a randomisation with a control (no antibody) arm, as this was considered unacceptable – due to the significant benefit seen in the COG ABL0032 study of the closely related antibody, Dinutuximab. Some form of anti-GD2 immunotherapy is now considered a standard of care for high risk neuroblastoma in the US, Europe and Australia, and it would not be feasible to run a further randomised study to assess efficacy / long term benefits. All assessment of efficacy will therefore be, by necessity, based on comparison with historical controls.

iii) The comments related to relapsed/ refractory patients are based on the assumption that the vast majority of children with high risk neuroblastoma will receive anti-GD2 therapy as part of their first line therapy, and that evidence for re-treatment with anti-GD2 at relapse is lacking. This would not be the case if NHS funding is not available to treat patients with this immunotherapy as part of the first line therapy. That being the case, the majority of patients will ultimately relapse, and would be antibody-naïve at relapse. In these children the 'end of life' criteria would probably apply. The consultation document states (Page 9) that "comments from clinical experts that patients who disease has relapsed after dinutuximab beta have not been eligible for further dinutuximab beta within any clinical trial' is incorrect. Our clinical expert opinion was that patients who have previously received anti-GD2 antibody **should only** receive further anti-GD2 as part of a clinical trial. There are currently 2 clinical trials in the UK, one open and one in set-up, which offer dinutuximab beta in this situation for relapsed / refractory patients.

iv) The consultation documentation should acknowledge the orphan nature of this disease and the small number of patients per year who would require treatment. Although the cost per patient is high, the total NHSE cost is relatively low because of the small number of patients.

v) The consultation document should acknowledge to disparities in health care which would arise if this treatment can not be provided with NHS funding, as those families who can will seek to fund treatment privately or with charitable funding.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
Name of commentator person completing form:	Nicholas Bird

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The use of the isotretinoin arm of the ANBL0032 study by Yu. et. al. does not represent the most appropriate 'control arm' for assessing clinical efficacy of dinutuximab beta. The company's initial submission used a comparator arm comprised of data from the SIOPEN HR-NBL1 high-risk neuroblastoma trial. The Committee, rightly and appropriately, questioned the use of this dataset as it contained patients who had received both BuMel and (the inferior) CEM conditioning regimens during PBSCT. The vast majority of patients who received dinutuximab beta (with or without IL2) would have received BuMel as it was declared the winner of the R1 randomisation of HR-NBL1. The Committee directed the Company to use the data they had previously viewed during the Appraisal for dinutuximab (Unituxin) – ID799. Specifically, the standard arm of isotretinoin from the Children's Oncology Group (COG) ANBL0032 randomised control trial. Moreover, when the Company undertook comparative analysis using 2010 data published by Yu et. al. in the New England Journal of Medicine, the Committee directed them to use the most recent dataset from March 2014, available only within the NICE Appraisal documentation for ID799. The flaw in all this is that whilst the general treatment approach is the same between SIOPEN and COG, the specific components are completely different. Induction chemotherapy uses different agents, in different combinations, with a different administration schedule. Stem cell collection is performed at a different time-point. Surgery is conducted at a different time-point. The conditioning regimen used by COG in ANBL0032 would have been CEM not BuMel [1], or potentially even tandem transplant with thiotepa–cyclophosphamide followed by modified CEM [2]. Patients could enrol on any protocol prior to ANBL0032, the only eligibility requirement being prior PBSCT. All of these elements may be confounding factors when using the data in a completely unbalanced way such as a comparator arm for this Appraisal. A far superior comparator would actually be the BuMel arm of the SIOPEN R1 randomisation (BuMel vs CEM), the results of which have been published with up to 5 years of follow-up in the Lancet Oncology by Ladenstein et. al [3]. In this study 29 of 296 patients on the BuMel arm received dinutuximab beta, the remainder received isotretinoin alone. All patients received Rapid COJEC, surgery, radiotherapy, myeloablative therapy using Busulfan and Melphalan followed by autologous stem cell rescue. They are the best representative control set of patients for assessing the relative efficacy of the addition of dinutuximab beta. I accept that it is for the Company to provide the evidence that it wishes the Committee to consider. However, I also feel that the previous Appraisal ID799 has muddied the waters and led everybody down a path where we are now not using the best available comparator / historic control arm. The focus of everybody and everything quickly moved on and was elsewhere, rather than on this fundamental point.

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	I would like the Company, Appraisal Committee, and DSU to reflect on this and decide/agree what truly represents the most appropriate comparator. This will influence not only the current decision, but any subsequent future assessment of clinical effectiveness and cost-effectiveness should the drug be included in the Cancer Drugs Fund for a period of time. [1] Whilst CEM was deemed inferior to BuMel in the SIOPEN R1 study, this was only in the context of the Rapid COJEC induction regimen. BuMel has not been adopted by COG as standard of care because of that finding. During subsequent discussions it was hypothesised that the efficacy of CEM as a conditioning regimen in the SIOPEN settings may have been adversely impacted by the high platinum content in the Rapid COJEC induction regimen, leading to a problem of platinum-resistance in patients. Something that would not occur with the COG induction regimen https://am.asco.org/2011-plenary-retrospective-new-standard-care-high-risk-neuroblastoma-europe. [2] For High-Risk Neuroblastoma, Two Transplants May Be Better Than One. http://www.ascopost.com/issues/june-25-2016/for-high-risk-neuroblastoma-two-transplants-may-be-better-than-one/ [3] Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol 2017; 18: 500–14 Published Online March 1, 2017 http://dx.doi.org/10.1016/ S1470-2045(17)30070-0. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30070-0/fulltext?code=lancet-site
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Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without

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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Grandmother /part-time carer of patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on the ACD:	
Thank you for the time spent considering recommendation for NHS funding for Immunotherapy for children with High risk Neuroblastoma. I urge you to recommend funding for this treatment It is standard care in Europe and North America. Denial of access for NHS patients will have significant implications for the treatment of young children with this disease. Children in the UK should not be disadvantaged. My [redacted] month old [redacted] was diagnosed last October 2017 with High risk Neuroblastoma and will probably need Immunotherapy. Many other parents and grandparents on [redacted] Ward in [redacted] are facing similar uncertainties. This has taken over our lives. Surely the sign of a civilized society is the way in which we treat those less fortunate than ourselves. Please I urge you to recommend funding for this treatment. Thank you. [redacted]	

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	UCL Great Ormond Street Institute of Child Health and Great Ormond St Hospital
Location	
Conflict	
Notes	
Comments on the ACD:	
Dinituximab beta (DB) is a subtly different agent to dinutiximab, now withdrawn from the European market. Published evidence of antibody functionality indicates some differences and specifically evidence of enhanced cancer cell killing function of DB. A previous randomised trial of Dinituximab versus no immunotherapy in North America was stopped at a very early stage so great was the advantage in 2 year EFS and OS in the Dinituximab group. As a result within Europe SIOPEN network it was realised that it would be unacceptable to perform a randomised study and DB effectively became standard of care throughout Europe. The survival of DB treated patients compared with the best possible historical control is significantly enhanced. my experience of treating countless children with this antibody at the UK's largest treatment centre for the disease is that is it very well tolerated. Since the age of the patients is so young, the potential gain in terms of young lives saved is high. This must be taken into special consideration.	

Name	[redacted]
Role	Carer
Other role	

Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

I am the father of a [redacted] diagnosed with high-risk stage 4 neuroblastoma in [redacted]2017. She is now taking a course of dinutuximab beta funded by EUSA Pharma. She and some other children needed the drugs after the clinical trial had ended but before the NICE decision had been taken. If NICE's preliminary decision stands, this small cohort will be the last to receive dinutuximab beta in the UK without having to raise finance privately to pay for it.

My experience as a parent of a child with this difficult disease leads me to believe that this would be the wrong result. My understanding of the preliminary decision is that the question has now reduced to a financial negotiation between NICE and EUSA, with most of the pressure being on EUSA to lower the price it will charge the NHS so that NICE can recommend the drug for funding via Individual Funding Requests from the Cancer Drugs Fund.

If such a compromise can be reached, then there is little more for someone like me to add. However, the fear is that somehow a deal remains out of reach. The purpose of this submission is to urge both sides to take extra steps if such an impasse looks likely.

There are good practical, political and moral reasons to ensure that a mutually acceptable arrangement is concluded. Practically, even if dinutuximab beta only extends a child's life by a few years, the proportional benefit is huge compared to adding a few years to the life of someone much older. Added to which, with another five years of data the drug may prove more effective than that. Five years is enough time for a child to to be born, be diagnosed and die from this disease. Every child's life that is saved is another person who will be able to play their part in society perhaps for decades to come.

Additionally, there is a practical reason to ensure that companies such as EUSA remain incentivised to develop and produce treatments for rare childhood diseases. When only a small number of patients require a treatment, inevitably it will be more expensive. If treatments like dinutuximab beta are evaluated according to the same criteria as those for chronic adult diseases, they will frequently fail. By default this becomes a policy decision that treatment of diseases like high-risk neuroblastoma will not and may never be fully covered by the NHS. If such a hard decision is necessary, it should not be made as the accidental side-effect of a regulatory process, but deliberately and following proper consideration.

If EUSA and NICE fail to fix an acceptable price for this treatment here in the UK, this will disadvantage British children compared to those in many other European countries whose governments are prepared to fund IFRs. This is politically uncomfortable, but also raises an important moral question. The clinical investigations which NICE agrees are necessary to establish the long-term benefits of dinutuximab beta will continue elsewhere. It will be unfortunate and a hindrance that the high level of expertise in UK hospitals will be cut off from this work. In a few years' time, it will become clearer whether the treatment prevents or merely delays relapse and most likely improved methods of administration or completely new treatments will have been developed as a result. What will the UK do then?
The NHS will surely seek to benefit from these advances. However, in doing so it will,

as an advanced and relatively well-resourced health system, be free-riding on the greater willingness of other economically comparably countries to support the development of this drug.

For all these reasons, in the event that a deal appears out of reach, I urge EUSA Pharma to be as transparent as possible in laying out the basis on which it has developed its pricing to show it is offering the drug as cheaply as possible while meeting its obligations to shareholders. Equally, I urge NICE to show flexibility to avoid the many negative consequences of not funding this drug.

Name	[redacted]
Role	Oncology parent
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

My son has recently been diagnosed with high risk neuroblastoma and to learnt that he will not reveive a treatment which may save his life is heartbreaking.

I won't comment on specifics or science but NICE acknowledges that this treatment works and improves survival rates.

To remove this drug from the NHS treatment will make a tiny difference to overall NHS budgets.

We are taking about 50 very young children per year and to withdraw the when billions is spent on smoking, alcohol and obesity related illness in adults is shameful.

I would urge NICE to work with all stakeholders so that my son and others can access the drugs that can save their lives.

Thank you for reading my comments.

[redacted], father of [redacted]

Name	[redacted]
Role	
Other role	
Organisation	Wolfson Childhood Cancer Research Centre, Northern Institute for Cancer Research
Location	England
Conflict	
Notes	

Comments on the ACD:

Dear NICE appraisers,

I have read the consultation document on the use of Dinituximab beta for upfront treatment for high risk neuroblastoma for patients who have achieved at least a partial response and proceeded through standard therapy for high risk NB.

I agree with the decision by NICE to focus on upfront treatment without concomitant IL-2 and not to consider relapsed or refractory patients where the evidence is weaker.

I note the outcome of the NICE decision that in view of the cost proposed by EusaPharma for diniutuximab beta (£7,610 exc VAT/vial approximately £150,000/ cycle) leads to calculation of an ICER (Incremental cost effectiveness ratio) well above that considered by NICE to recommend a new technology on the NHS.

I agree that there were errors in the Eusa documentation regarding risk of relapse after 5 years and that available evidence does exist on long term use of 13 cis retinoic acid alone which could be used rather than relying on modelling.

However I think that developing a new drug for an orphan indication such as high risk NB is never going to be profitable for a pharmaceutical company, particularly a relatively small one like EusaPharma unless it is priced above what NICE would normally consider cost-effective.

It could also be argued that if we restrict the indication of dinituximab beta to upfront treatment of high risk NB we are looking at around 35-40 patients/year in the UK (fewer if we consider England alone) on the basis that there are approx., 50 new case of high risk NB/year and sadly some will relapse before reaching the phase of minimal residual disease therapy when dinituximab beta will be given (or relapse during this phase and not complete 5 cycles).

Does this very small number of patients each year who might benefit from this therapy make it possible for NICE to re-consider an ICER outside the normal range that it would usually consider cost effective for a new treatment, particularly if Eusa were to lower their price/vial ?

As a practicing paediatric oncologist I urge NICE and Eusa to negotiate a price so that dinituximab can be adopted by the Cancer Drugs Fund for the next 2-3 years for upfront treatment of children with high risk NB whilst awaiting the additional data needed to provide cost effectiveness and particularly the results of biomarker studies from the recent Phase IIII trial to show which groups of children are most likely to benefit.

Many thanks for your help with this matter.

Yours sincerely,

[redacted]

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Dear Sir,

Please I urge you to work collaboratively to enable any appropriate drugs to be made available on the NHS for children with high risk neuroblastoma.

This tragic disease has turned my family's lives upside down. Our [redacted] month old [redacted] was diagnosed last [redacted]2017 and may soon need Immunotherapy.

Yours sincerely,
[redacted]

Name	[redacted]
Role	Consultant in Clinical Oncology
Other role	[redacted]
Organisation	University College London Hospitals and Great Ormond Street Hospital for Children NHS Foundation Trusts
Location	250 Euston Road, London, NW1 2PG
Conflict	None to declare.
Notes	Neuroblastoma (high risk) - Dinutuximab beta [ID910]

Comments on the ACD:

Thank you very much for this opportunity to comment on the NICE appraisal of Dinutuximab Beta for High-Risk Neuroblastoma. While I accept that the evidence base for this treatment is less than perfect, I feel very strongly that this drug should be made available for children with neuroblastoma for the following reasons.

Since the data on the American trial of Dinutuximab with IL2 and GM-CSF became available in 2010, some form of treatment with an Anti-GD2 monoclonal antibody has been accepted as the standard of care by paediatric oncologists in both the USA and Europe.

At that time, the European Group had started a randomised trial comparing Dinutuximab Beta with no Anti GD2, but it was considered unethical to continue it, as the American data indicated a substantial benefit for this type of treatment. An amendment was introduced to the trial so that all patients received Dinutuximab Beta, with or without IL2. The concept of a further randomised trial in which some patients would not receive this treatment would nowadays be considered completely unacceptable.

Failure to provide Dinutuximab Beta in UK on the NHS will be a retrograde step for paediatric oncology in the UK, and meaning that we deliver inferior treatment to the rest of the developed world.

It would also result in great inequity for children with Neuroblastoma, as many parents would seek to fund this treatment through private fundraising, but others might not be able to do so.

The method of assessment of the value of this drug selected by NICE was probably wrong. Had it been assessed by the HST committee it would have been within the limits of funding considered cost effective.

Recognition of the difficulty of undertaking clinical research in very rare diseases needs to be taken into account. In breast and lung cancer where there are many tens of thousands of patients diagnosed annually in the UK, very highly powered trials are possible. With an annual incidence of only about 100 neuroblastoma patients (about 60 with high-risk disease), such trials even when conducted on a Europe wide population base take longer to accrue and have broader confidence limits. Despite this, it is clear that survival of children with high-risk neuroblastoma is significantly better in the era of universal access to Dinutuximab Beta than it was previously. We must not lose this therapeutic advantage.

While I understand that NICE has a statutory responsibility to ensure that the NHS gets value for money from the pharmaceutical industry, it must be remembered that drug development is never cheap. The costs can be recouped with relatively narrow profit margin if a drug has a market of tens of thousands of patients. If companies are squeezed too hard, then they will be disincentivised from researching drugs for rare conditions like neuroblastoma.

I strongly urge NICE to look favourably upon this orphan drug.

[redacted]
4 June 2018

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Kate Moore
Project Manager
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Level 1A, City Tower
Piccadilly Plaza
Manchester
M1 4BT
By email

28th May 2018

Re: Neuroblastoma (high-risk) – Dinutuximab beta [ID910] – Appraisal Consultation Document

EUSA Pharma would like to thank the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee for the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal and to provide further clarifications for consideration.

We are concerned that if the current recommendation were to stand, children and adolescents suffering from high-risk neuroblastoma would be denied the option of treatment with dinutuximab beta. We consider it is important for patients to have the opportunity to receive dinutuximab beta because 6.8 years of data shows that, compared to historical treatment, dinutuximab beta increases long-term survival for children and adolescents in this rare, debilitating and life-threatening disease (EPAR Qarziba). It is important to note that since 2009, immunotherapy with dinutuximab has been considered standard of care world-wide for high-risk neuroblastoma patients, so much so that clinicians felt it was unethical to include a comparator arm including the retinoic acid in APN311-302. Indeed, the European Medical Agency granted marketing authorisation under exceptional circumstances because, amongst others, it was not considered feasible to generate comprehensive data on dinutuximab beta as neither clinicians nor patients would be prepared to participate in a placebo-controlled trial (EPAR Qarziba).

Additionally, dinutuximab beta is now fully reimbursed in Germany and final discussion on the reimbursement conditions in France and Italy are underway. EUSA Pharma believes that patients in the UK should have the opportunity to receive the same standard of care as in the rest of Europe.

We are committed to working with NICE in order to address the Committee's key uncertainties as outlined in the ACD and we hope NICE can work with us to find a solution that will enable patients with high-risk neuroblastoma to access dinutuximab beta. There is significant unmet need to provide an effective treatment option for high-

risk neuroblastoma patient. This need was expressed by patients and clinical experts at the NICE committee meetings, and recognised by the NICE committee (ACD document).

EUSA Pharma accepts the NICE committee's position that the most recent (2014) data for isotretinoin is the most appropriate to use in the model. We have in good faith based our initial analysis on the 2010 data, because we believed that this is the most robust data for the base case. For the same reason we continued to use the 2010 dataset during the clarification stage when we were asked to provide additional information and analyses. It was only in March 2018 that we were asked to include the 2014 data in our analyses, which we did. Although we continue to believe the 2010 data is robust, we acknowledge that it is in the best interest of the appraisal to use the 2014 data.

EUSA Pharma would also like to acknowledge that the Committee has considered a large amount of evidence in the previous appraisal for Unituxin and in this appraisal for dinutuximab beta. We do however believe that there may be some evidence that could be explored further. We would also like to raise additional points that we believe are relevant to the next Appraisal Committee Meeting. We present a summary of factual inaccuracies and further clarifications for consideration at the end, and an additional scenario in Appendix.

EUSA Pharma has submitted a Patient Access Scheme (PAS) to Patient Access Scheme Liaison Unit and this is currently awaiting approval. We hope that discussions will be concluded promptly and will advise NICE when they are completed.

We look forward to the Committee's viewpoints on the points raised in our response. If you require clarification on any aspects of our response, please do not hesitate to contact me.

Yours sincerely,

Natasa Zibelnik
European Market Access Director EUSA Pharma

Appendix to the responses to the ACD

This appendix presents the results of an updated analysis based on the discontinuation rates that could be expected in NHS clinical practice. Additional changes made to the DSU model were based on the preferred extrapolation curves by the committee discussed in section 3.13, as well as using the Gompertz EFS extrapolation (see EUSA Pharma comment I.1, in the stakeholder comments). The different cure points are also presented as the NICE Committee recognized that other cure thresholds could be plausible.

Discontinuation

As previously stated, EUSA Pharma chose to be conservative and did not model any treatment discontinuation due to toxicity or tolerability ([redacted]). Whilst EUSA Pharma understands that the ICERs should reflect the SPC recommendations, the clinical benefits included in the model reflect the interim analysis results of study APN311-302 but the cost reflects the full treatment schedule. In clinical practice, should the full dose and number of cycles be administered, then the clinical benefits may be better than that seen in the clinical studies.

According to interim clinical study report for APN311-302, discontinuation due to toxicity is around [redacted] for the dinutuximab beta+isotretinoin arm without IL-2 and [redacted] for the dinutuximab beta+isotretinoin +/- IL-2 arm. A 3.54% (4 patients out of 113) discontinuation rate was applied for the isotretinoin control arm based on the results of Yu et al study (4).

Based on these data, two scenarios were tested: [redacted] of patients in the dinutuximab beta arm were modelled to discontinue treatment throughout cycle 1 to 5 on top of the progressing patients (i.e. EFS).

CEA model scenarios

Table 1 summarizes the scenarios made to the DSU economic model.

Table 1: Scenario analysis in the economic model

	Preferred assumptions from NICE committee (results from the DSU excel model, section V)		Preferred assumptions from EUSA Pharma (section I.1)
	EFS: Spline OS: Gompertz	**EFS: Spline OS: Spline**	**EFS: Gompertz (DSU model extrapolation curve) OS: Gompertz**
Cure points			
10 years	£75,831	£87,164	£62,886
5 years	£60,824	£61,222	£58,651
Discontinuation rate			
[redacted], 10 years cure point	£72,587	£83,450	£60,128
[redacted], 10 years cure point	£71,837	£82,592	£59,491
[redacted], 5 years cure point	£58,227	£57,686	£56,082
[redacted], 5 years cure point	£57,627	£57,096	£55,489

In line with the rational outlined in the original submission (see I.1. of this document), the Gompertz extrapolation was used in the scenario analysis as it was part of the best statistical fits and is a clinically plausible scenario.

The changes to the DSU model has been submitted in addition to this appendix. Changes to include discontinuation rate are done in the excel sheet called “ModelFL”, cells GK-GQ 9-15 (highlighted in yellow) and an option for selecting the different scenarios are provided in the results sheet.

DINUTUXIMAB BETA FOR TREATING HIGH-RISK NEUROBLASTOMA: REVIEW OF COMPANY'S ADDITIONAL EVIDENCE IN RESPONSE TO THE ACD

REPORT BY THE DECISION SUPPORT UNIT

08 June 2018

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by the National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk.

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Acknowledgements

The authors wish to thank Stephen Palmer (University of York) for his review of this document.

EXECUTIVE SUMMARY

In response to the Appraisal Consultation Document for dinutuximab beta for treating high – risk neuroblastoma, the company has submitted additional evidence. This evidence includes cost-effectiveness analyses using the Gompertz model for event-free survival (EFS), a revised approach for modelling discontinuation, and suggestions to include end of life costs for patients dying from neuroblastoma.

The Decision Support Unit (DSU) considers that although goodness of fit statistics suggested the Spline models fit the EFS data better, the Gompertz may be appropriate if it is clinically plausible the monthly risk of progression is below 0.1% after five years.

The DSU believes that the company's revised approach to estimate treatment discontinuation is not accurate and [redacted] the time on treatment, and prefers to use the actual proportion of patients on treatment each cycle reported in the trial.

Depending on the choice of Gompertz or Spline models for EFS and overall survival (OS), the deterministic incremental cost-effectiveness ratio (ICER) for dinutuximab beta compared to isotretinoin ranges from £64,000 to £87,000 per quality-adjusted life year (QALY) using a 10 year cure point. The probabilistic ICERs range from £69,000 to £80,000 per QALY using a 10 year cure point. Using a 5 year cure point, the deterministic ICER ranges from £59,000 to £60,000 per QALY.

Including end of life costs of up to £21,000 for patients who die before the 10 year cure point in the model, the ICERs decrease by less than £1,000 per QALY.

Including a Patient Access Scheme (PAS) discount of [redacted], the deterministic ICER with the 10 year cure point ranges from [redacted] to [redacted] per QALY depending on the choice of Gompertz or Spline models for EFS and OS. The probabilistic ICERs range from [redacted] to [redacted] per QALY using a 10 year cure point with the PAS. With the PAS, the deterministic ICERs with a 5 year cure point range from [redacted] to [redacted] per QALY, and the probabilistic ICERs are all in the region of [redacted] per QALY.

CONTENTS

TABLES

FIGURES

ABBREVIATIONS AND DEFINITIONS

AIC	Akaike information criterion
AD	Aggregate data
ASCT	Autologous stem cell transplant
BIC	Bayesian information criterion
BSA	Body surface area
BuMel	Busulfan and melphalan hydrochloride
CC	Complication and comorbidity
CEM	Carboplatin, etoposide and melphalan
DSU	Decision Support Unit
EFS	Event-free survival
EQ-5D	EuroQol 5 Dimension
ERG	Evidence review group
ICER	Incremental cost-effectiveness ratio
IL-2	Interleukin-2
IPD	Individual patient-level data
INSS	International Neuroblastoma Staging System
KM	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
MYCN	N-myc proto-oncogene protein
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PAS	Patient access scheme
QALY	Quality-adjusted life-year
TSD	Technical Support Document

1. INTRODUCTION

1.1. BACKGROUND

In the Appraisal Consultation Document (ACD), published on 04 May 2018, dinutixumab beta was not recommended within its marketing authorisation for people aged 12 months and over, that is, for treating high-risk neuroblastoma after at least a partial response from induction chemotherapy, followed by myeloablative therapy and autologous stem cell transplant, and for treating relapsed or refractory neuroblastoma, with or without residual disease[1]. In response to the ACD, the company has submitted additional evidence, including new analyses in the cost-effectiveness modelling.

1.2. THIS REVIEW

This document reviews and critiques the evidence and analyses from the company to determine if their revised cost-effectiveness analyses are appropriate. Additionally, this document describes the methods and results of further analyses undertaken by the Decision Support Unit (DSU).

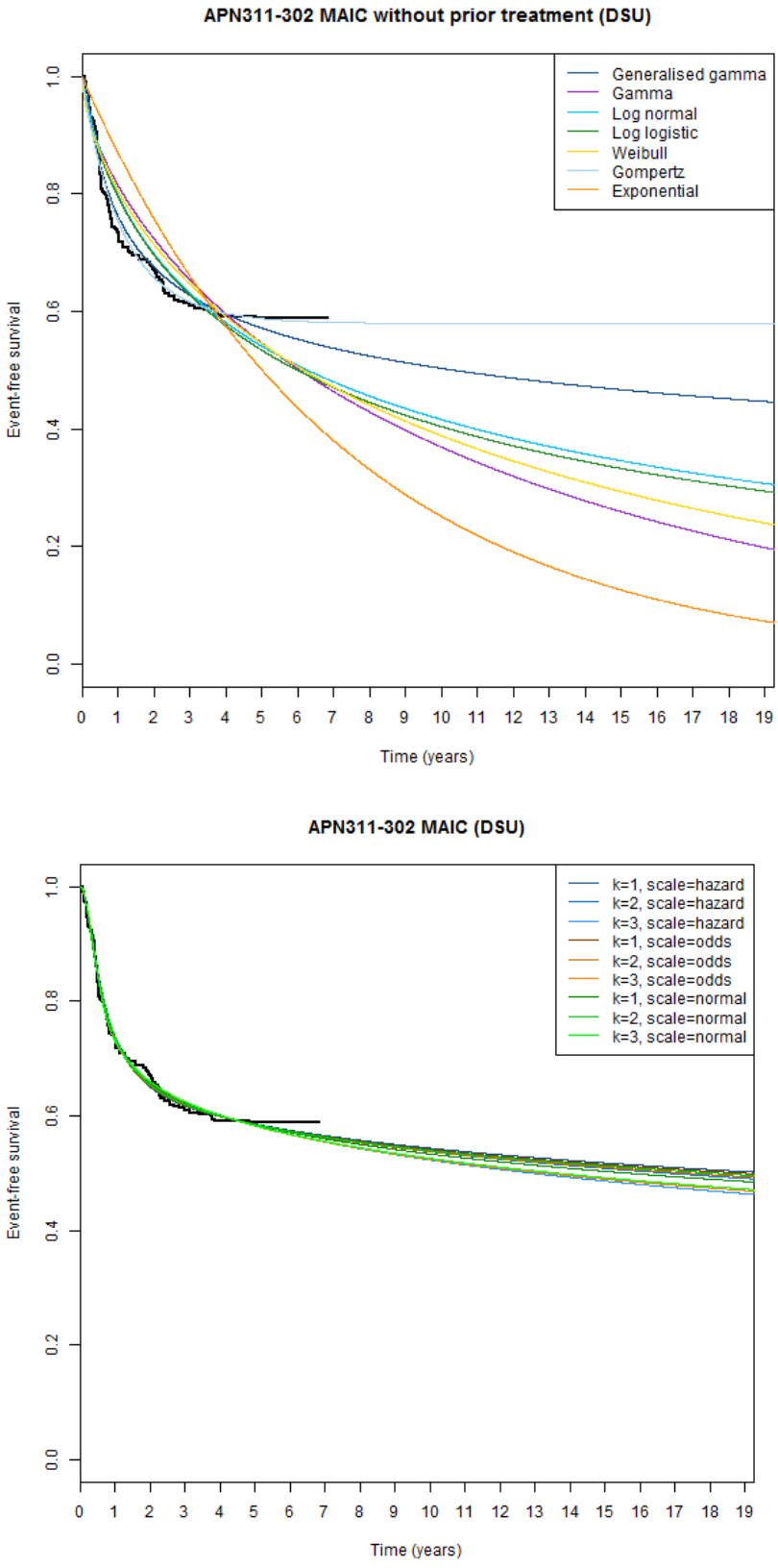
2. REVISED COST-EFFECTIVENESS ANALYSES

The company's revised cost-effectiveness analysis incorporates the Yu et al (2014) isotretinoin data, the Gompertz distribution for dinutuximab beta event-free survival (EFS) and new data on treatment discontinuation. As the Yu et al (2014) data has already been considered most appropriate by the committee[1], it is not discussed further here. The use of the Gompertz distribution for dinutuximab beta EFS and the new treatment discontinuation data are reviewed in turn.

2.1. GOMPERTZ FOR EFS

In the survival analysis of the dinutuximab beta EFS performed by the DSU, the Gompertz was considered, amongst other parametric and flexible spline models, reproduced in Figure 1. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) indicated that the best fitting models were the spline models, followed by the Generalised Gamma model and then the Gonpertz model.

Figure 1: Event-free survival Kaplan-Meier curve vs. fitted models



DSU: decision support unit, MAIC: matching-adjusted indirect comparison

The company has produced a Figure for the fit statistics for EFS for dinutuximab beta, which they state is based on Table 7 of the DSU report and presents the Akaike Information Criterion on the y-axis. Table 7 of the previous DSU report contains the fit statistics for overall survival (OS), whereas the fit statistics for EFS were presented in Table 11. For clarity, the DSU has produced figures for the goodness of fit statistics for EFS, using the data in Table 11 of the previous report. The AIC is presented in Figure 2 and the BIC in Figure 3. The statistics for the Gompertz are shown in red, and for all other models in blue.

Figure 2: Akaike Information Criterion for event-free survival of dinutuximab

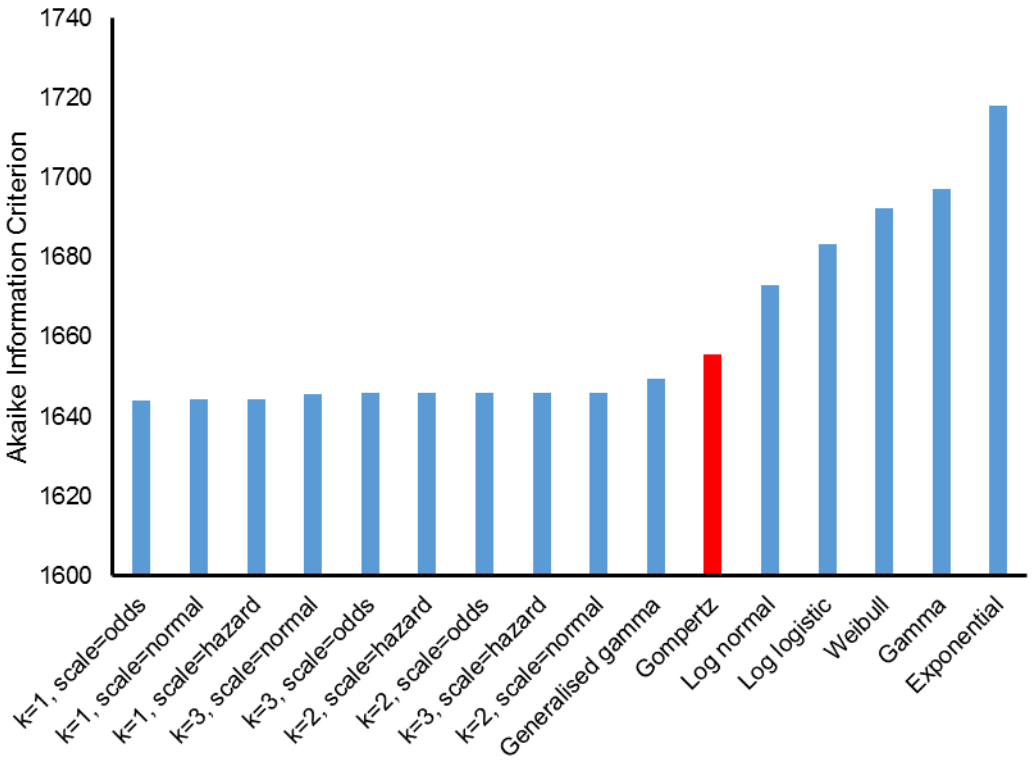
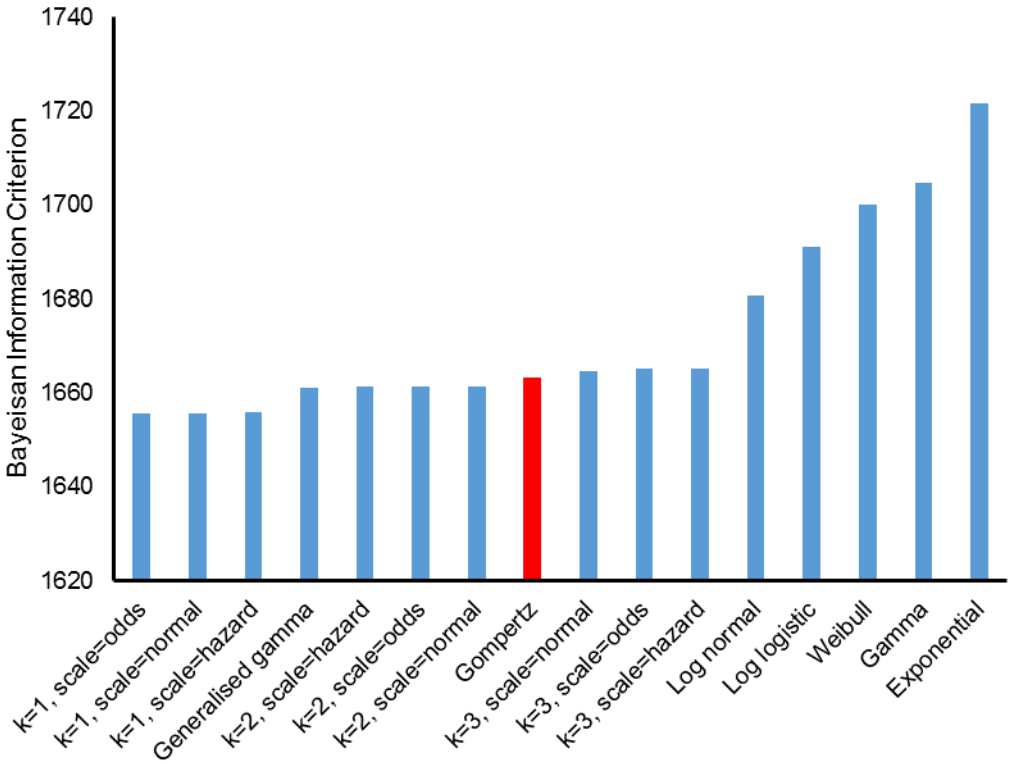


Figure 3: Bayesian Information Criterion for event-free survival of dinutuximab



The company commented that the goodness of fit for the Gompertz was not "materially worse" than the Generalised Gamma or spline models. The AIC for the Gompertz is 11.6 points higher than for the best-fitting spline model (k=1, scale=odds), and the BIC for the Gompertz is 7.78 points higher than for the best-fitting spline model (k=1, scale=odds). As a rule of thumb for nested models, Burnham et al (2003) suggest that a difference of 0-2 points provides substantial support for that model, a difference of 4-7 provides considerably less, and a difference of >10 provides essentially no support for that model[2]. It should be noted that the models considered here are non-nested models, and Burnham et al (2003) suggest that the values may be bigger for non-nested models but do not provide specific values. Overall, it appears that the Gompertz may be a potentially suitable model for EFS based on tests of internal goodness of fit. However, AIC and BIC are not the only elements that should be considered: visual inspection, external data and clinical validity must should be considered[3].

The Gompertz, Generalised Gamma and Spline models for EFS are compared with the dinutuximab beta Kaplan Meier data in Figure 4. The three models are relatively similar to each other and the Kaplan Meier data until month 60, after which point the Generalised Gamma displays the steepest gradient, whereas the Gompertz appears to plateau, and the Spline model lies somewhere in between. Figure 5 shows the hazards (risk) of progression or death for each of the three models. The hazard for the Gompertz decreases to 0.09% at month

60 (year 5) and to below 0.02% after around 89 months (7.4 years), whereas the hazards for Spline and Generalised Gamma models remain above this. Figure 5 shows the hazards (risk) of progression or death for each of the three models and the hazards of death for the Spline and Gompertz models for OS. For both OS models, the hazard of death remains above zero (but very small) – the application of the EFS and OS in the model mean that patients can die at any point, so the risk of death never becomes zero. Using the Gompertz model for EFS effectively means that the monthly risk of progression is less than 0.10% beyond 5 years and less than 0.02% beyond 7.4 years. Using the Spline model for EFS effectively means that the monthly risk of progression is above 0.10% for years 5-10. Which model is most appropriate depends on what risk of progression is most clinically plausible.

Figure 4: Dinutuximab beta EFS and fitted models

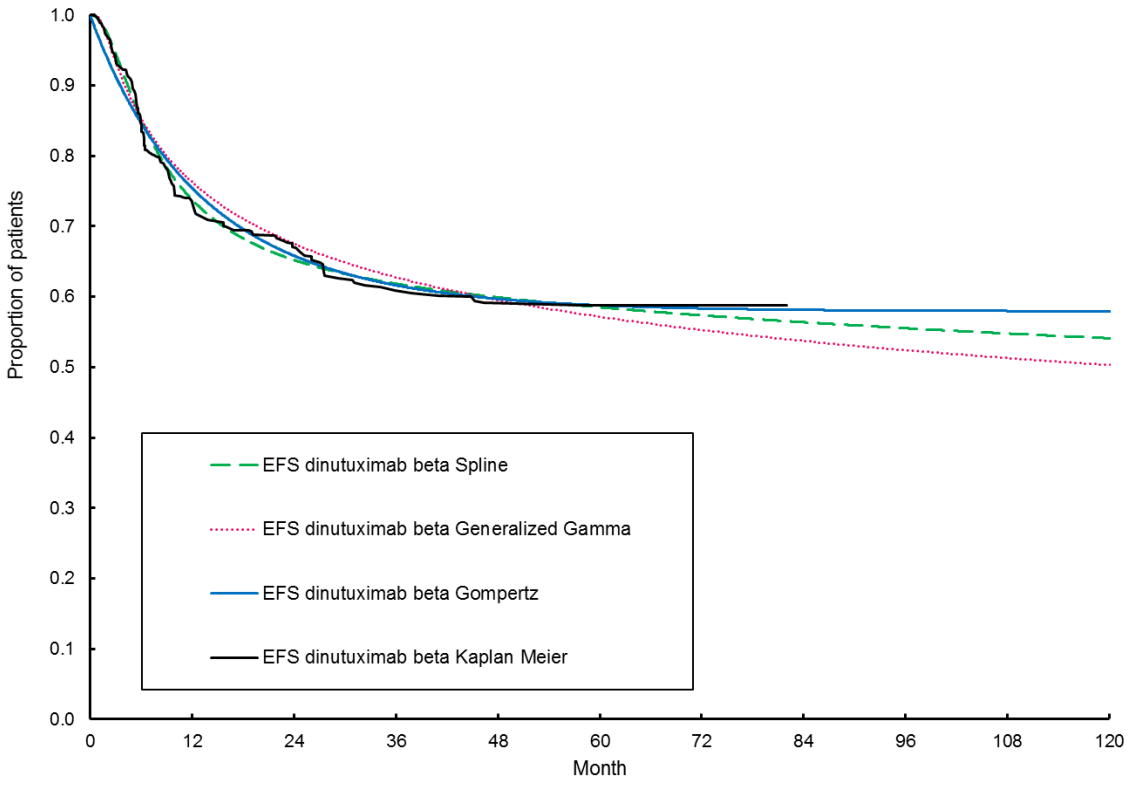


Figure 5: Dinutuximab beta EFS hazards

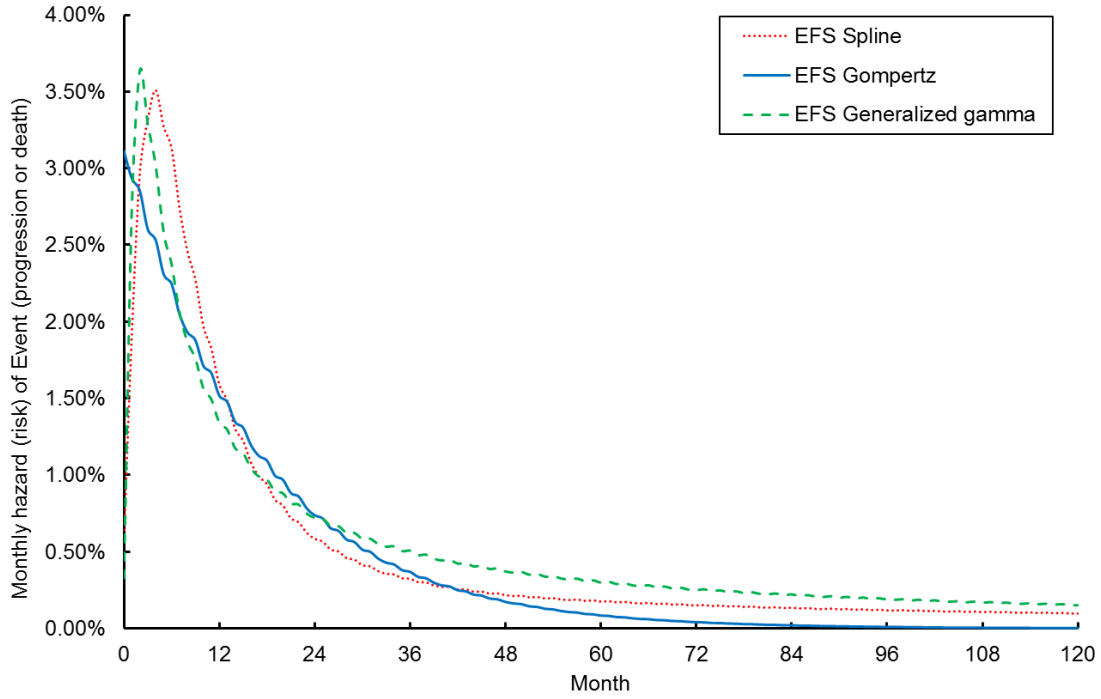
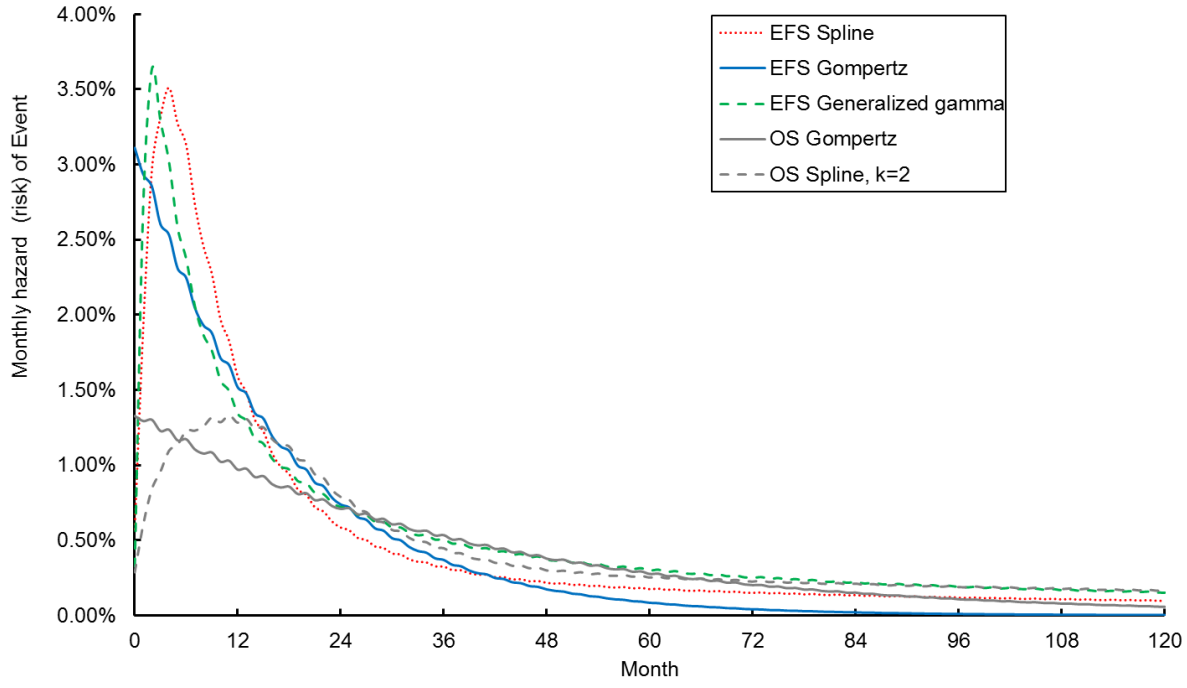


Figure 6: Dinutuximab beta EFS and OS hazards



2.1. DISCONTINUATION

In the previous modelling work, EFS was used to model to proportion of patients on treatment. In their revised analysis, the company has additionally subtracted the proportion of patients who stopped treatment due to toxicity. This assumes that progression and discontinuation due to toxicity are mutually exclusive. In [redacted] A more accurate way of modelling discontinuation would be to use the reported number of patients treated per cycle, which are reported in [redacted].

The company has presented discontinuation rates for the dinutuximab beta+isotretinoin arm without IL-2 and both arms (with and without IL-2) combined. Discontinuation due to adverse events is [redacted] for both arms combined. Since the model assumes 0% of patients receive IL-2, the DSU considers it more appropriate to use discontinuation data only for the dinutuximab beta+isotretinoin without IL-2 arm.

The proportion of patients on dinutuximab beta using the previous approach to modelling discontinuation (using EFS), the company's revised approach, and the reported number of patients treated per cycles are presented in Table 1. The previous approach using EFS using the Gompertz model [redacted] the proportion of patients on treatment, and using the Spline model [redacted]. The company's revised approach using EFS and discontinuation due to toxicity [redacted] the proportion of patients on treatment. The differences between the previous approach using EFS and the patients treated per cycle are may be due to model-fitting to EFS data, and due to patients discontinuing for reasons other than progression. The differences between the company's revised approach and proportion treated per cycle may be due to patients discontinuing due to toxicity and then progressing, and the revised approach [redacted] these. For accuracy, we consider that using the proportion of patients treated per cycle reported in [redacted] is the most appropriate approach, and use this in our analysis.

Table 1: Comparison of approaches to discontinuation

Cycle	Previous approach: EFS Spline	Previous approach: EFS Gompertz	Company's revised approach: Gompertz	Patients treated per cycle
1	100.0%	100.0%	[redacted]	[redacted]
2	99.4%	96.9%	[redacted]	[redacted]
3	97.5%	94.0%	[redacted]	[redacted]
4	94.6%	91.4%	[redacted]	[redacted]
5	91.5%	89.0%	[redacted]	[redacted]

The company's revised analysis assumes that 4 of 113 isotretinoin patients discontinue due to toxicity. We have been unable to trace this number, and consider that the same issues of using discontinuation due to toxicity on top of EFS may apply to isotretinoin as dinutuximab beta. If the discontinuation Kaplan Meier data were available from Yu et al (2014), this would represent the most accurate approach. However, in absence of this data, we consider it most appropriate to use EFS to model time on treatment for isotretinoin.

3. RESULTS OF THE REVISED COST-EFFECTIVENESS ANALYSIS

3.1. RESULTS WITH THE LIST PRICE FOR DINUTUXIMAB BETA

3.1.1. Company's revised results

The company present revised cost-effectiveness analysis results, reproduced in Table 2.

Table 2: Company's revised cost-effectiveness results (deterministic)

	Preferred assumptions from NICE committee		Preferred assumptions from EUSA Pharma
	EFS: Spline OS: Gompertz	**EFS: Spline OS: Spline**	**EFS: Gompertz OS: Gompertz**
Cure points			
10 years	£75,831	£87,164	£62,886
5 years	£60,824	£61,222	£58,651
Discontinuation rate			
[redacted] 10 years cure point	£72,587	£83,450	£60,128
[redacted] 10 years cure point	£71,837	£82,592	£59,491
[redacted] 5 years cure point	£58,227	£57,686	£56,082
[redacted] 5 years cure point	£57,627	£57,096	£55,489

For completeness, we have produced full results tables using the Spine and Gompertz models for EFS and OS, for the 10 year cure point (Table 3) and 5 year cure point (Table 4).

Table 3: Revised results, 10 year cure point (deterministic)

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£224,234	18.61	35.99	£163,775	2.16	4.40	£75,831
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£224,898	18.34	35.17	£164,439	1.89	3.59	£87,164
OS: Gompertz. EFS: Gompertz							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£220,213	18.99	36.26	£159,753	2.54	4.68	£62,886
*OS: spline k=2, scale=hazards. EFS: Gompertz***							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£220,877	18.72	35.45	£160,417	2.27	3.86	£70,757

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years

*LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

**Not included in company's revised analysis

Table 4: Revised results, 5 year cure point (deterministic)

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	£225,699	19.79	38.63	£164,090	2.70	5.05	£60,824
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	£226,915	19.84	38.76	£165,306	2.74	5.18	£60,239
OS: Gompertz. EFS: Gompertz							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	£221,573	19.82	38.65	£159,964	2.73	5.07	£58,651
*OS: spline k=2, scale=hazards. EFS: Gompertz***							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	£222,789	19.87	38.78	£161,180	2.77	5.20	£58,109

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years
*LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.
**Not included in company's revised analysis

3.1.2. Results with revised discontinuation

We present deterministic results modelling discontinuation using [redacted] using the Spine and Gompertz models for EFS and OS, for the 10 year cure point (Table 5) and 5 year cure point (Table 6). Using this discontinuation data decreases the dinutuximab beta costs and hence the ICERs for the EFS Spline model, and increases the dinutuximab beta costs and hence the ICERs for the EFS Gompertz model, because of the differences seen in Table 1.

Table 5: Revised results with discontinuation from APN311-302, 10 year cure point (deterministic)

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£222,980	18.61	35.99	£162,521	2.16	4.40	£75,251
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£223,644	18.34	35.17	£163,185	1.89	3.59	£86,500
OS: Gompertz. EFS: Gompertz							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£222,828	18.99	36.26	£162,369	2.54	4.68	£63,916
OS: spline k=2, scale=hazards. EFS: Gompertz							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	£223,493	18.72	35.45	£163,033	2.27	3.86	£71,910

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years

*LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

Table 6: Revised results with discontinuation from APN311-302, 5 year cure point (deterministic)

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	£224,445	19.79	38.63	£162,836	2.70	5.05	£60,359
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	£225,661	19.84	38.76	£164,052	2.74	5.18	£59,782
OS: Gompertz. EFS: Gompertz							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	£224,189	19.82	38.65	£162,580	2.73	5.07	£59,611
OS: spline k=2, scale=hazards. EFS: Gompertz							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	£225,404	19.87	38.78	£163,795	2.77	5.20	£59,052

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years
*LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

3.1.3. Probabilistic analysis

Probabilistic results for 10,000 simulations are summarised for EFS and OS using the Spline and Gompertz models, using the discontinuation data from APN311-302 and a 10 year cure point in Table 7. Probabilistic sensitivity analysis incorporates parameter uncertainty and includes non-linearities in the model and therefore may be preferable to deterministic analysis. The probabilistic ICERs are similar to the deterministic ICERs, but are slightly higher where the Gompertz is used for OS and slightly lower where the Spline model is used for EFS.

Table 7: Probabilistic results with 10 year cure point

	EFS: Spline		EFS: Gompertz	
	OS: Gompertz	**OS: Spline**	**OS: Gompertz**	**OS: Spline**
Deterministic ICER	£75,251	£86,500	£63,916	£71,910
Probabilistic mean ICER	£79,640	£79,886	£68,849	£69,736
Probability cost-effective at £20,000/QALY	9%	9%	7%	7%
Probability cost-effective at £30,000/QALY	11%	11%	10%	10%
Probability cost-effective at £50,000/QALY	29%	30%	34%	34%
Probability cost-effective at £100,000/QALY	69%	70%	76%	74%

3.1.4. Scenario analysis including end of life costs

The company states that end of life costs should be considered in the appraisal, but do not include them in their analysis. The company proposes that the cost of intensive palliative treatment should be considered for children who die from neuroblastoma, and provide a cost of £8,800 referenced to the 2016 NICE guideline NG61 End of life care for infants, children and young people with life-limiting conditions. We have been unable to find the cost of £8,800 stated by the company, but note that the full guideline for NG61 provides a cost of £8,699 per child using a day-and-night service, and a cost of £20,625 per child receiving inpatient care on a paediatric ward[4]. Inflating these costs to 2017 using the Hospital and Community Health Services Index[5] gives a cost per child for the day-and-night service of £8,854 and for the inpatient care of £20,993. In scenario analyses, we apply these costs to modelled patients who die before the cure point, assuming that these patients represent those who die from neuroblastoma. The results, shown in Table 8 and Table 9, demonstrate that this makes very little difference to the ICERs, reducing them by less than £1,000. This is because the difference in overall survival at 10 years is less than 10%, so the difference in incremental cost is less than £2,000, which when divided by the incremental QALYs (1.89 to 2.54), is minimal.

Table 8: Revised results with discontinuation from APN311-302, 10 year cure point, day-and-night end of life costs (deterministic)

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£64,555	16.45	31.58				
Dinutuximab beta	£226,363	18.61	35.99	£161,808	2.16	4.40	£74,921
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£64,555	16.45	31.58				
Dinutuximab beta	£227,179	18.34	35.17	£162,623	1.89	3.59	£86,202
OS: Gompertz. EFS: Gompertz							
Isotretinoin	£64,555	16.45	31.58				
Dinutuximab beta	£226,212	18.99	36.26	£161,656	2.54	4.68	£63,635
OS: spline k=2, scale=hazards. EFS: Gompertz							
Isotretinoin	£64,555	16.45	31.58				
Dinutuximab beta	£227,027	18.72	35.45	£162,472	2.27	3.86	£71,663

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years

*LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

Table 9: Revised results with discontinuation from APN311-302, 10 year cure point, inpatient end of life costs (deterministic)

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£70,170	16.45	31.58				
Dinutuximab beta	£231,001	18.61	35.99	£160,831	2.16	4.40	£74,468
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£70,170	16.45	31.58				
Dinutuximab beta	£232,024	18.34	35.17	£161,854	1.89	3.59	£85,794
OS: Gompertz. EFS: Gompertz							
Isotretinoin	£70,170	16.45	31.58				
Dinutuximab beta	£230,850	18.99	36.26	£160,679	2.54	4.68	£63,251
OS: spline k=2, scale=hazards. EFS: Gompertz							
Isotretinoin	£70,170	16.45	31.58				
Dinutuximab beta	£231,872	18.72	35.45	£161,702	2.27	3.86	£71,323

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years
*LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

3.1. RESULTS WITH THE PAS DISCOUNT FOR DINUTUXIMAB BETA

3.1.1. Company's revised results

The company's revised cost-effectiveness analysis results, including a [redacted] PAS discount, are shown in Table 10.

Table 10: Company's revised cost-effectiveness results with PAS (deterministic)

	Preferred assumptions from NICE committee		Preferred assumptions from EUSA Pharma
	EFS: Spline OS: Gompertz	**EFS: Spline OS: Spline**	**EFS: Gompertz OS: Gompertz**
Cure points			
10 years	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]
Discontinuation rate			
[redacted] 10 years cure point	[redacted]	[redacted]	[redacted]
[redacted] 10 years cure point	[redacted]	[redacted]	[redacted]
[redacted] 5 years cure point	[redacted]	[redacted]	[redacted]
[redacted] 5 years cure point	[redacted]	[redacted]	[redacted]

3.1.1. Results with revised discontinuation

We present results modelling discontinuation using [redacted] using the Spine and Gompertz models for EFS and OS, including the [redacted] PAS discount, for the 10 year cure point (Table 11) and 5 year cure point (Table 12Table 6).

Table 11: Revised results with discontinuation from APN311-302, 10 year cure point, with PAS (deterministic)

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	[redacted]	18.61	35.99	[redacted]	2.16	4.40	[redacted]
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	[redacted]	18.34	35.17	[redacted]	1.89	3.59	[redacted]
OS: Gompertz. EFS: Gompertz							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	[redacted]	18.99	36.26	[redacted]	2.54	4.68	[redacted]
OS: spline k=2, scale=hazards. EFS: Gompertz							
Isotretinoin	£60,459	16.45	31.58				
Dinutuximab beta	[redacted]	18.72	35.45	[redacted]	2.27	3.86	[redacted]

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years

*LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

Table 12: Revised results with discontinuation from APN311-302, 5 year cure point, with PAS (deterministic)

	Total			Incremental			ICER
	Cost	**QALYs**	**LYs***	**Cost**	**QALYs**	**LYs***	
OS: Gompertz. EFS: spline k=1, scale=odds							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	[redacted]	19.79	38.63	[redacted]	2.70	5.05	[redacted]
OS: spline k=2, scale=hazards. EFS: spline k=1, scale=odds							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	[redacted]	19.84	38.76	[redacted]	2.74	5.18	[redacted]
OS: Gompertz. EFS: Gompertz							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	[redacted]	19.82	38.65	[redacted]	2.73	5.07	[redacted]
OS: spline k=2, scale=hazards. EFS: Gompertz							
Isotretinoin	£61,609	17.10	33.58				
Dinutuximab beta	[redacted]	19.87	38.78	[redacted]	2.77	5.20	[redacted]

EFS: event-free survival, ICER: incremental cost-effectiveness ratio, LYs: life years, OS: overall survival, QALY: quality adjusted life years
*LYs are undiscounted. Costs and QALYs are discounted at 1.5% per annum.

3.1.1. Probabilistic analysis

Probabilistic results for 10,000 simulations are summarised for EFS and OS using the Spline and Gompertz models, using the discontinuation data from APN311-302 and a 10 year cure point in Table 13.

Table 13: Probabilistic results with 10 year cure point with PAS

	EFS: Spline		EFS: Gompertz	
	OS: Gompertz	OS: Spline	OS: Gompertz	OS: Spline
Deterministic ICER	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic mean ICER	[redacted]	[redacted]	[redacted]	[redacted]
Probability cost-effective at £20,000/QALY	[redacted]	[redacted]	[redacted]	[redacted]
Probability cost-effective at £30,000/QALY	[redacted]	[redacted]	[redacted]	[redacted]
Probability cost-effective at £50,000/QALY	[redacted]	[redacted]	[redacted]	[redacted]
Probability cost-effective at £100,000/QALY	[redacted]	[redacted]	[redacted]	[redacted]

Table 14: Probabilistic results with 5 year cure point with PAS

	EFS: Spline		EFS: Gompertz	
	OS: Gompertz	OS: Spline	OS: Gompertz	OS: Spline
Deterministic ICER	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic mean ICER	[redacted]	[redacted]	[redacted]	[redacted]
Probability cost-effective at £20,000/QALY	[redacted]	[redacted]	[redacted]	[redacted]
Probability cost-effective at £30,000/QALY	[redacted]	[redacted]	[redacted]	[redacted]
Probability cost-effective at £50,000/QALY	[redacted]	[redacted]	[redacted]	[redacted]
Probability cost-effective at £100,000/QALY	[redacted]	[redacted]	[redacted]	[redacted]

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