NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Dinutuximab for treating high-risk neuroblastoma [ID799]

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:
   - United Therapeutics Corporation
   - Neuroblastoma UK
   - Solving Kids Cancer

   'No comments' responses were submitted by the Royal College of Nursing, Department of Health and Roche.

3. **Comments on the Appraisal Consultation Document from experts:**
   - *Joint response from* Dr Martin Elliott - clinical expert, nominated by National Cancer Research Institute (NCRI) and Dr Juliet Gray – clinical expert, nominated by National Cancer Research Institute (NCRI)
   - Mr Nick Bird – patient expert, nominated by Neuroblastoma Children's Cancer Alliance UK

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

5. **Additional evidence provided by the company,** United Therapeutics Corporation

6. **Evidence Review Group critique of additional evidence** from Centre for Reviews and Dissemination and Centre for Health Economics - York

7. **Patient access scheme (PAS) and additional evidence submitted by the company, United Therapeutics**

8. **ERG review of the PAS and additional evidence, prepared by Centre for Reviews and Dissemination and Centre for Health Economics – York**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Dinutuximab for treating high-risk neuroblastoma

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
United Therapeutics	In response to the ACD issued in October 2015, United Therapeutics (the Company) wishes to provide comments on aspects of the preliminary NICE Appraisal. Of particular note are: the tendency to make highly unfavourable assumptions unsupported by convincing evidence when addressing issues of uncertainty, applying inconsistent standards with regards to discounting of future quality-of-life benefits, and, most importantly, undervaluing the proven overall survival advantages in a devastating, ultra-orphan, paediatric oncology indication. The Company contends that NICE has routinely taken unsupported and pessimistic views regarding cure, relapse rates, and administration costs. With regards to discounting future health benefits, the Company believes an inconsistent standard is being applied as compared to the precedent of mifamurtide for the treatment of osteosarcoma (TA235). In addition, the Company asserts that NICE is undervaluing the overall survival advantage of dinutuximab despite evidence from 226 patients spanning 8 years. The Company urges the NICE Appraisal Committee (the Committee) to reconsider the provisional decision to 'not recommend' dinutuximab, based on: 1. The innovative nature of dinutuximab in an ultra-orphan paediatric oncology indication with no European Medicines Agency (EMA)-approved therapeutic alternatives; 2. The unreasonable interpretation of the clinical and cost-effectiveness evidence submitted; and 3. The inconsistency with previous decision-making in the technology appraisal of mifamurtide for the treatment of osteosarcoma (TA235). This document outlines specific points that the Company would ask the Committee to reconsider. *Dinutuximab as an Innovative Treatment Option with No EMA-Approved Therapeutic Alternatives*	The committee has based its assumptions on the evidence presented to it by the company. With respect to the cure point used in the model, the committee noted that the longer term data from the 2014 analysis of ANBL0032 showed that events continued to occur in the dinutuximab arm beyond year 5. Therefore, the committee concluded that the 10 year cure point was more appropriate than the 5 year cure point. Section 4.9 of the FAD The committee noted that the results showed a statistically significant difference in overall survival between people having dinutuximab and people having isotretinoin. The committee concluded that the dinutuximab regimen appears to prevent relapse in a small proportion of patients and may be associated with an overall survival benefit, although the size of these benefits is uncertain. Comment noted. The committee noted that the company was not involved in the development of dinutuximab and became involved at a relatively

Consultee	Comment [sic]	Response
	NICE concluded in the ACD that "the dinutuximab regimen represents a novel approach as a maintenance therapy for treating high-risk neuroblastoma, but the evidence of the health gains specifically from dinutuximab remains uncertain." While the contribution of each component of the dinutuximab regimen is difficult to appreciate, many clinicians consider the health gains associated with the regimen to be robust. In response to NICE's preliminary decision, several clinicians (who were involved in the Children's Oncology Group [COG] trial for dinutuximab and who have first-hand experience treating patients with high-risk neuroblastoma with dinutuximab) have reached out directly to the Company to emphasize dinutuximab's role as standard of care, the ethical decision to halt the clinical trial, the belief that patients will not relapse if they have not relapsed in the first 5 years after treatment with dinutuximab, and the quality-of-life associated with children receiving dinutuximab and post-dinutuximab treatment. Quotes from many of these clinicians are included below: • *"For several years now we have considered this agent as standard of care for neuroblastoma patients in first response. This has revolutionized our approach to this deadly disease, and the neuroblastoma parent community has embraced the concept of a novel mechanism designed to prevent relapse, as relapse of high-risk neuroblastoma after standard intensive chemotherapy is not currently curable. Dinutuximab therapy makes sense scientifically, and in this ultra-rare indication we think that there is outstanding clinical support for the routine use of this agent in the care of high-risk neuroblastoma patients."* – John M Maris, MD; Children's Hospital of Philadelphia • *I am confident that dinutuximab improves the survival for children with [high-risk] neuroblastoma whose disease has been responsive to upfront induction and consolidation chemotherapy. For this reason, I consider dinutuximab to be standard of care for this cohort of children and it would be deemed unethical to deny them the opportunity to receive such therapy. Both treating physicians and families understand that the administration of dinutuximab has acute toxicity. However, it is remarkable that patients are able to resume their normal life activities in between treatment courses and following completion of therapy. Based on my interaction with numerous families and patients, I am confident that they believe this therapy has markedly less impact to their lives compared to standard chemotherapy they had previously received as treatment for their high-risk neuroblastoma.*	late stage in the marketing of the product after completion of ANBL0032. It concluded that most of the innovation and development was done by the Children's Oncology Group before the company became involved in the marketing of dinutuximab.

Consultee	Comment [sic]	Response
	Finally, the vast majority of children with high-risk neuroblastoma will not experience recurrence after 5 years from completion of this therapy and now have the opportunity to embark on a developmentally appropriate life." – Julie R. Park, MD; Seattle Children's Hospital • *"Dinutuximab for many years has been standard of care for the treatment of patients with [high-risk] neuroblastoma. It has indeed revolutionized the therapy of these children and we have first-hand seen patients with disease resistant to known therapy clear resistant disease while undergoing treatment with it. Furthermore, it has significantly affected the overall survival of our patients with this deadly disease. Although the therapy administration is intensive, patients and families have not only embraced the therapy but appreciate the opportunity to be able to use a targeted agent for their tumor. In fact, many of my patients are able to go to school in between cycles of therapy, something impossible for chemotherapy agents. Their lives are nearly normal during the therapy and become very normal very quickly after its completion. It is truly a pleasure to be able to not only have disease response but have more normalcy because of the use of this agent. When I see my patients in clinic who have not relapsed after 5 years from end of therapy, I can be rest assured that their chance of relapse decreases to almost nothing and I can reassure the families that they can concentrate on the future, rather than concern about a relapse at that time. In summary, dinutuximab is a drug that has shown in all arenas to be the agent with significant impact and changed the lives of the children and families in a positive manner. I look forward to using this drug for many years to come and explore ways to improve its efficacy over the years to come."* – Araz Marachelian, MD; Children's Hospital Los Angeles Furthermore, due to the very limited size of the patient population and dinutuximab's specific indication, the overall budget impact for dinutuximab in England is very small, representing a cost of <£2.5 million annually. *Unreasonable Interpretation of the Clinical and Cost-Effectiveness Evidence Submitted* In the ACD, NICE did not recommend dinutuximab based on a number of factors that contributed to a higher base case ICER than was estimated in the Company's submission and in the Evidence Review Group's (ERG) report. The assumptions	Section 6.2.14 of the guide to the methods of technology appraisal 2013 states that the potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision.

Consultee	Comment [sic]	Response
	with the most significant impact on the ICER for dinutuximab are the Committee's assertions that "for both the event-free and overall survival data, the curves converge between 6.5 and 11 years" and "the dinutuximab regimen delayed but did not prevent cancer-related events." The Company does not believe these to be fair or scientifically-credible interpretations of the data provided to the Committee. The event-free survival (EFS) and overall survival (OS) curves do not converge, as seen in the Kaplan-Meier curves in the Company submission. Also, as stated in the Company submission, the ANBL0032 trial was not powered (and not intended to be powered) to test a difference beyond 3 years. The ANBL0032 trial was powered and the sample size estimated to evaluate differences in EFS at 3 years; any analyses of EFS after this time point are considered statistically under-powered and ad-hoc in nature. Randomisation in the ANBL0032 trial was stopped early based on the efficacy demonstrated by immunotherapy after the sixth pre-specified interim analysis at the recommendation of the safety monitoring committee that it would be unethical to continue randomising patients to standard therapy at that point. All interim analyses were pre-specified and utilized an efficacy monitoring scheme based on the Lan-DeMets approach with spending function $\alpha^{*}t^{2}$, which controlled the overall Type I error rate across the planned interim analyses. NICE stated that "the trial should not have been stopped because the stopping criteria had not been reached". Despite the sixth and final interim analysis not reaching the full monitoring boundary (observed p-value = 0.0115 vs. boundary p-value determined *a priori* = 0.0108), the safety monitoring committee, with agreement from the COG Group Chair, felt the lack of significance at the hundredths place of the p-value was still sufficient evidence to conclude efficacy and warrant the ethical halting of randomisation into this trial. The safety monitoring committee regarded the efficacy as "on the boundary" at the 0.01 level. The safety monitoring committee had previously conducted five interim analyses, all of which demonstrated a trend towards the efficacy of immunotherapy, which further provided confidence in this therapy's effect. Upon learning of these NICE assumptions, Julie R. Park, MD of Seattle Children's Hospital, reached out to the Company to reiterate that the trial was halted when it was considered to have reached the appropriate point at which to stop randomisation, so children with neuroblastoma were able to receive an improved, life-saving therapy: *"As chair of the [Children's Oncology Group] COG Neuroblastoma Scientific Committee, I have had the opportunity to continually review our progress for treating high-risk neuroblastoma. The ANBL0032 trial has been pivotal in our understanding of therapy for children with high-risk neuroblastoma and*	Comment noted. The FAD has been amended to reflect that the committee concluded that the dinutuximab regimen appears to prevent relapse in a small proportion of patients and may be associated with an overall survival benefit, although the size of these benefits is uncertain.

Consultee	Comment [sic]	Response
	represents a seminal clinical development in improving survival for these children that does not include further dose escalation of conventional chemotherapy known to have extreme long term toxicities for developing children. As you are aware, high-risk neuroblastoma is an orphan disease, representing less than 500 children per year in all of North America and thereby a very difficult disease to study. It has been our priority to perform randomized clinical trials for this disease, but unlike malignancies occurring in adults, we do not have the patient numbers to quickly or easily conduct a large randomized trial. Furthermore, our improvement in outcome has been slow and incremental; thus close monitoring and early stopping of a trial are required so that we do not delay the ability to offer improved therapy to children. The ANBL0032 was conducted through COG with oversight by the [National Cancer Institute Cancer Therapy Evaluation Program] NCI CTEP. Based on close monitoring of an independent DSMB, the study was stopped and while this allowed more children to have the benefit of this life saving therapy, we are left with limited numbers of patients to provide more extensive statistical analyses." The Company therefore asserts that the clinical and cost-effectiveness assumptions by NICE are not reasonable interpretations of the evidence, as they place a greater weight on statistically underpowered, ad-hoc analyses of inadequate sample size rather than the adequately powered analyses which provided the basis for EMA marketing authorisation of dinutuximab throughout the European Union. The Company acknowledges that there are long term data available for NICE to consider; however, the Company strongly feels that these long term data have been over-interpreted by NICE when considering the benefit of dinutuximab to patients with high-risk neuroblastoma. Additionally it is important to note that the Kaplan-Meier curves for EFS and OS never converge or overlap, with dinutuximab always favoured over isotretinoin alone. This lack of convergence supports the conclusion that dinutuximab does cure many patients and provides a long-term health benefit for patients with high-risk neuroblastoma. Furthermore, NICE's clinical and patient experts, as well as the Company's clinical experts, all indicated that relapses after 5 years are extremely rare, supporting the base case economic model assumptions in the Company's submission. NICE acknowledged in the ACD that the clinical experts who participated in the First Appraisal meeting "stated that relapse after 5 years appears to be increasing", but this statement is not universally agreed upon and is based on anecdotal observation from only two clinicians who have limited to no experience using dinutuximab, and who are applying clinical opinion of a different therapy to this	Comment noted. The committee was concerned that when the data from ANBL0032 were analysed in 2009, it became clear that the pre-defined criteria had not been met. The committee was aware that stopping a trial for benefit before it has met its primary end point can lead to overestimation of the treatment effect. The committee also noted that there were data errors and differences between the data sets of January and June 2009, although the company's analysis showed similar improvements in event-free survival. The committee noted that for these reasons, the European Medicines Agency considered that the event-free survival results from ANBL0032 should be interpreted with caution and that the overall survival results were critical to determining the treatment benefit of dinutuximab.

Consultee	Comment [sic]	Response
	appraisal. The Company also believes the Committee did not provide adequate weight to the substantial OS benefit associated with dinutuximab. The logrank p-value = 0.0301 for OS in the ANBL0032 trial (March 2014 data), represents a significant difference in OS for immunotherapy vs. isotretinoin alone. Despite this, the Committee states "the dinutuximab regimen does not cure neuroblastoma, but rather prevents relapse of the disease". The Company and clinical experts disagree with this assertion, and consider the results beyond 5 years to reinforce that many patients experience cure with dinutuximab treatment, providing an impactful long-term health benefit in an ultra-orphan disease that affects children and that has no other EMA-approved alternatives for treatment. For this reason, the Company provided a scenario utilising a 1.5% discount rate, the precedent for which was set in the NICE appraisal of mifamurtide in osteosarcoma in a paediatric population (TA235). As was highlighted in the Company's submission and by members of NICE at the NICE First Appraisal meeting on October 6th 2015, the Company believes the mifamurtide technology appraisal to be very relevant to the dinutuximab technology appraisal in light of the long-term health benefits associated with immunotherapy treatment. TA235 and the 'Guide to the methods of technology appraisal' issued by the Board of NICE states: *"Where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs"* In the mifamurtide technology appraisal, it was noted that treatment improved OS from 71% to 78% at 8 years compared with chemotherapy alone and that patients treated with mifamurtide who are cured are expected to have a long and sustained benefit and regain normal life expectancy. As such, for the mifamurtide technology appraisal, the Committee concluded that both criteria were met and a discount rate of 1.5% should be used for health effects. For mifamurtide, the analysis of disease-free survival was not statistically significant at interim analysis or at 8 years. Despite this, no concern was cited by NICE that mifamurtide did not provide a cure, but rather prevented relapse. Dinutuximab treatment statistically significantly improved OS (p=0.02), demonstrating OS rates of 75% and 86% in the isotretinoin and dinutuximab arms, respectively, at 2 years in the data analysis from January 2009 (Yu 2010). Likewise, in the March 2014 data analysis, dinutuximab statistically significantly improved OS (p=0.03), demonstrating OS rates of 59% and 74% in the	The committee noted that the Children's Oncology Group and National Cancer Institute did not consider the 2009 overall survival data to be mature enough and that the protocol was amended to include a later analysis for both event-free and overall survival 2-years after the end of randomisation. The committee noted that follow-up data analyses (June 2012 and March 2014) were available and the company confirmed that the overall survival efficacy analysis of the March 2014 data was requested by the European Medicines Agency. The committee stated that it preferred longer term data that provides additional information on outcomes, particularly when patients with the disease have a life expectancy of more than several years. In response, the company stated that ANBL0032 was not powered to detect events beyond the 3 years planned in the protocol. The committee was aware that the statistical power of a trial was determined based on the number of events, therefore, so long as the required number of events have occurred, it is sufficiently powered to detect a treatment effect even when more events occur on follow-up. The committee concluded that the longer term data and the most recent analysis (March 2014) were the most robust data available on which to determine the clinical efficacy of dinutuximab. Comment noted. The committee concluded that the non-reference case discount rate could apply because the 2014 analysis showed that the dinutuximab regimen could be considered to cure neuroblastoma in a small proportion of patients. It also concluded that this discount rate should be applied to both costs and outcomes in line with the current methods guide (see section 4.17 of the

Consultee	Comment [sic]	Response
	isotretinoin and dinutuximab arms, respectively, at 4 years (Yu 2014). Relapses after 5 years are considered to be extremely rare, and patients who survive neuroblastoma are expected to have normal or near-normal life expectancy. The OS benefit associated with dinutuximab is larger than that of mifamurtide; therefore, it would be clearly inconsistent with the precedent set in TA235 if a 1.5% discount rate is not applied for dinutuximab. The Company strongly believes that a 1.5% discount rate for outcomes must be applied in the case of dinutuximab, to be consistent with the assumptions made in the mifamurtide NICE appraisal. **Administration costs:** The ERG calculated administration costs in their base case using the average number of hospital days from the ANBL0032 trial and the cost of an elective inpatient stay for treating brain tumours or cerebral cysts with the highest complication and comorbidity level and NHS reference costs for the delivery of complex chemotherapy (ERG base case analysis). The ERG also calculated alternative administration costs using the average number of hospital days from the ANBL0032 trial and the costs for the delivery of complex chemotherapy and the mean costs of hospitalisation for an elective inpatient stay for the treatment of paediatric brain tumours (ERG scenario analysis). The ERG scenario analysis, using the alternative administrations costs, resulted in much higher administration costs for dinutuximab compared to the ERG base case analysis. Clinicians at the dinutuximab NICE First Appraisal meeting, who have **not** used dinutuximab for the treatment of high-risk neuroblastoma, provided feedback that "using the average number of hospital days from the ANBL0032 study (69 days) may have underestimated the number of days a patient with neuroblastoma would be hospitalised when having treatment with the dinutuximab regimen". The Company believes this clinician sentiment is a subjective observation based on experience with a different, non-interchangeable immunotherapy (Aperion Biologic's CHO.14.18 per the SIOPEN clinical trial program) rather than on data for dinutuximab and that the clinician's opinion swayed the Committee to decide to inappropriately increase the administration costs associated with dinutuximab in their model: "However, considering the clinical experts' concern that average number of hospital days from the ANBL0032 study seemed to underestimate the number of days a patient with high-risk neuroblastoma would be hospitalised, the Committee concluded that the costs used in the ERG's scenario analysis may still underestimate the administration costs of the dinutuximab regimen". Additionally, although the Committee noted there was no specific code available for	FAD). Comments noted. The committee considered that the estimate from ANBL00931 could be reasonable, but the committee was not comfortable making this conclusion because it had not been presented with the correctly analysed data for ANBL0032 (see section 4.13 of the FAD). The committee noted that in its revised analysis, the company chose the lower cost for an elective inpatient stay for the treatment of brain tumours or cerebral cysts, which it had previously presented in response to clarification. However, the committee did not consider this code appropriate because it is not specific to a paediatric population. The committee was aware that paediatric treatment was generally more costly than adult treatment. The committee concluded that the cost associated with administering dinutuximab was uncertain and the committee would have liked the company to have explored this further by identifying an appropriate paediatric NHS reference cost code to use in its analysis.

Consultee	Comment [sic]	Response
	the maintenance treatment of high-risk neuroblastoma - ("The Committee accepted that without a specific code, the cost of an elective inpatient stay for treating paediatric brain tumours could be considered the most applicable for patients having dinutuximab.") - they elected to use the higher administration costs presented in the ERG scenario analysis. The Company feels this is another example of the Committee electing to choose a highly unfavourable assumption based on anecdotal data against dinutuximab. To better inform the Committee of the number of hospital days, the Company is providing data from study ANBL0931, a phase 3 open-label safety study of dinutuximab, and is requesting approval from NICE for the additional evidence to be considered. These additional data are included in an appendix to this document (APPENDIX A). These data provide evidence that, contrary to the conclusion made by the Committee, the ERG scenario analysis, using the alternative administration costs, likely overestimates, rather than underestimates the administration costs of the dinutuximab regimen. As such, the Company believes that the base case administration costs adopted by the Committee represent an inappropriately high estimate for the cost of administration of dinutuximab, and not the most likely clinical scenario. The cost of administration is an important factor in the economic analysis of dinutuximab. Based on NICE's base case assumptions, if dinutuximab were priced at £0, the product would still have an ICER greater than £50,000 per QALY, which is above the NICE cost-effectiveness threshold. Under the base case assumptions proposed by NICE, an innovative and beneficial treatment for neuroblastoma, an ultra-orphan disease, in a paediatric population administered in an inpatient setting would be unable to demonstrate cost-effectiveness at any price, due to the health system and associated administration costs. **Use of a weighted average dose:** NICE's base case assumptions used a weighted average dose to determine the total cost of drug when determining the ICER for dinutuximab. The Company agrees that a weighted average approach is reasonable to determine the total cost of drug. In patients with a body surface area (BSA) greater than 1 m^2, more than 4 vials may be required to achieve the recommended dose for dinutuximab. While a higher BSA does result in a greater drug cost for dinutuximab, very few patients are likely to have a BSA requiring more than 4 vials. In the dinutuximab clinical trial ANBL0032, only 4.8% of patients had a BSA greater	Comment noted. See sections 4.15 and 4.24 of the FAD. The committee's preferred assumptions included a weighted average of 4.2 dinutuximab vials per treatment course.

Consultee	Comment [sic]	Response
	than 1 m^2. Based on this assumption, the weighted average dose per cycle for patients receiving dinutuximab would be 4.2 vials. The Company would like to confirm that NICE's base case model uses this same weighted average dose per cycle. *Health-related Benefits which are not captured in the Economic Analysis* In addition to the issues with the economic analysis assumptions described above, there exist substantial health-related benefits which are not captured in the economic analysis. While NICE recognized in the ACD there were benefits not captured in the economic analysis (eg, neuroblastoma is a devastating disease affecting children), it could not form an opinion of the extent of benefit. Health-related quality-of-life benefits extend beyond those which are captured in the economic analysis for dinutuximab. Benefits extend not only to patients (whom in this case, are often young children), but to parents, siblings, and other caregivers as well. These quality-of-life benefits are difficult, if not impossible to comprehensively quantify in the context of an economic model, and include parental anxiety and mental health, strain on family relationships, and the time required of parents or other family members providing care for a child with high-risk neuroblastoma. There are health-related quality-of-life reductions due to toxicity related to immunotherapy. However, physicians with experience using dinutuximab in the US express confidence that immunotherapy has markedly less negative impact on health-related quality-of-life compared to standard chemotherapy that patients had previously received as induction and consolidation therapy for their high-risk neuroblastoma. Physicians have indicated that the lives of patients undergoing treatment with dinutuximab are nearly normal during the therapy and that patients resume normal quality-of-life quickly after completing therapy. As noted above, several physicians in the US with experience using dinutuximab, reached out to the Company upon learning of the preliminary decision by NICE to not recommend dinutuximab. Many of the statements from these physicians related to the quality-of-life of patients with high-risk neuroblastoma who have been treated with dinutuximab are noted above. As noted above, John M Maris, MD, Giulio D'Angio endowed professor of paediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania has indicated that based on the preclinical and clinical data as well as first-hand experience, dinutuximab is considered the standard of care in patients with high-risk	Comments noted. The committee also acknowledged the severity of the disease and the importance of generating health benefits for this patient population. It was prepared to consider accepting a higher ICER for a patient population of children and young adults, as well as any other uncaptured health-related benefits that the dinutuximab regimen might offer patients with high-risk neuroblastoma and their families. However, it was not presented with any data to show distinct and substantial uncaptured health-related benefits. The committee discussed whether it would be feasible to quantify these additional benefits and incorporate them in the company's model. The committee was aware that some cost-effectiveness studies have attempted to account for uncaptured quality of life benefits in economic analyses. The committee also recognised the high unmet clinical need for effective new treatments to treat minimal residual disease and prevent relapse of neuroblastoma. It was confident that there were health-related benefits that were not captured in the company's model, but because it had not been presented with any data, it could not form an opinion about the extent of the impact those data might have on the cost-effectiveness estimates (see section 4.19 of the FAD).

Consultee	Comment [sic]	Response
	neuroblastoma and has revolutionized the approach to treating high-risk neuroblastoma. Additionally, the Committee acknowledged the severity of the disease and the importance of generating health benefits for this patient population, but could not form an opinion about the extent of the impact of health-related benefits not captured in the model. While there is no published evidence detailing the burden of neuroblastoma affecting children, young adults, and their families, Gavin and Wendy Lindberg (Co-Founders of The EVAN Foundation and parents of Evan Lindberg, who was diagnosed with neuroblastoma) provided insight to their journey throughout Evan's treatment: *"High-risk neuroblastoma is one of the most devastating diagnoses a family can receive. To learn that your young child has less than a 30% chance of long-term survival is beyond heartbreaking. Our son Evan was diagnosed with Stage IV, n-myc amplified neuroblastoma in 2006 at the age of three. He fought with incredible courage and grace for four years before succumbing to this insidious disease in 2010. Evan was just seven years-old when he passed. He was our only child.* *Throughout Evan's treatment, we leaned on two things; the promise of treatment advances in neuroblastoma, and the hope that somehow our son would beat the odds. Both were essential in caring for a child with neuroblastoma. A snapshot of what Evan was forced to endure is below:* • *1,430 days as a patient – not one without treatment or recovery.* • *6 weeks of high dose chemotherapy and neutropenic recovery.* • *100+ nights in the hospital [for induction, consolidation, and maintenance treatments].* • *75+ nights in Ronald McDonald Houses away from home* • *4 relapses and 4 Phase I clinical trials* • *7 surgeries, 4 of which were brain surgeries (1 emergency surgery)* • *35+ week-long rounds of "low-dose" intravenous chemotherapy.* • *25 excruciatingly painful days of immunotherapy (3F8) and recovery.* • *Weeks of radiation to brain, spine, abdomen and hip.* • *A constant stream of CTs, MRIs, MIBG's, bone marrow pulls, blood draws, shots, physical therapy and other procedures.* • *Pain, nausea and discomfort as constant companions.* *The same week in 2010 that we took Evan home from the hospital for the*	

Consultee	Comment [sic]	Response
	last time to begin hospice care, the results of the Phase III, ch14.18 trial were published. Although this was ground-breaking news in the world of neuroblastoma, it left us with a hollow feeling. We did not enroll Evan in the ch14.18 trial. We opted for another immunotherapy option at Memorial Sloan Kettering Cancer Center in New York. To learn that the trial was stopped early after two years because of the difference in survival between ch14.18 and isotretinoin was remarkable. While there would have been value from a statistical standpoint in seeing data beyond two-years, we agree with the Children's Oncology Group [COG] that it would have been unethical to continue the trial given the difference in survival rates. *We will never know if Unituxin would have made a difference for our son. However, we take some comfort in knowing that the option was available to us. Options equal hope and Unituxin is an important therapeutic option. It is the first therapy approved to treat children with high-risk neuroblastoma. It has more clinical data associated with it than any other neuroblastoma treatment. It answered the longstanding question whether immunotherapy contributes to the long-term survival of high-risk patients. It is the standard of care for children in the United States.* *We understand that there is a SIOPEN clinical trial open to eligible neuroblastoma patients in the UK that provides an immunotherapy treatment option. What happens to those children who do not meet the eligibility criteria for the trial? Are they relegated to treatment with isotretinoin with no opportunity to benefit from immunotherapy unless they travel to the U.S.? Throughout Evan's treatment, we met families from England who uprooted their lives to come to the U.S. to enroll in the COG ch14.18 trial. What an incredible hardship to endure on top of the devastation of dealing with a neuroblastoma diagnosis.* *We appreciate the cost considerations that NICE takes into account when making determinations about coverage. We don't envy the challenging position you are in or the difficult decisions you have to make. In our view, however, the one segment of the population that deserves every consideration when it comes to the expenditure of healthcare resources aimed at prolonging life is children. Even if Unituxin is not curative for some patients and might only prolong life for one or two years, that is priceless time for a child and their family.* *Given that Unituxin is the only EMA-approved therapy for high-risk neuroblastoma, we encourage you to find a way to make the treatment*	

Consultee	Comment [sic]	Response
	available to patients in England and Wales. Families seeking every opportunity to give their child the best chance at the longest possible life will be forever grateful. Thank you in advance for your consideration of our views." *Revised Economic Analysis* As outlined above, the Company recommends the following changes to the Committee's base case analysis: • Utilizing a 1.5% discount rate for outcomes, due to the long term health benefits associated with dinutuximab treatment and precedent set by the mifamurtide for the treatment of osteosarcoma (TA235) decision • Utilizing a 5 year cure point, given the significant uncertainty associated with the survival analysis data • Utilizing the ERG base case analysis cost per hospital day as opposed to the Committee's higher estimates (utilizing the ERG scenario analysis) • Utilizing a weighted average of 4.2 dinutuximab vials per treatment course, to ensure that the product utilization is not over-estimated With these modifications to the model, the base case ICER is reduced to £50,329 per QALY. The Company believes that dinutuximab represents a significant and innovative therapeutic advance for a rare paediatric disease with severe health consequences. As such, dinutuximab is now considered the standard of care for patients with high-risk neuroblastoma in the US. The treatment delays disease progression, improves overall survival, and offers a potential cure to neuroblastoma patients. The Company believes that these and other health-related quality-of-life benefits may not have been adequately and fully captured in the preliminary ACD economic analysis presented by the NICE Appraisal Committee. The Company believes the revisions contained herein represent a fair assessment of the evidence and result in dinutuximab representing a good therapeutic value for money for patients with a devastating ultra-orphan paediatric condition. The Company would like to work with the NICE Committee to ensure access to dinutuximab for this patient population.	Comments noted. Using the committee's preferred assumption based on the evidence presented (section 4.24 of the FAD), the committee considered that the ICER for dinutuximab compared with isotretinoin was £98,800 per QALY gained (see section 4.24 of the FAD). The committee acknowledge that the ICER could be lower if the committee had been presented with the correct number of hospital days from ANBL0032 and an appropriate paediatric hospital cost were used to calculate the ICER, but concluded that the most plausible ICER would likely still be considerably higher than £30,000 per QALY gained. It also considered that there may be a case for accepting a higher ICER for a patient population of children and young adults to account for the uncaptured health-related benefits of treatment. However, the ICER was too high to allow it to recommend the dinutuximab regimen, even when taking into account other aspects of health-related quality of life not adequately captured in the QALY. The committee concluded that dinutuximab does not represent a cost-effective use of NHS resources and that it should not be recommended for treating high-risk neuroblastoma in patients of 1-17 years, whose disease has at least partially responded to induction chemotherapy, myeloablative therapy and autologous stem cell transplant.

Consultee	Comment [sic]	Response
Department of Health	No comments	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Solving Kids Cancer (formerly Neuroblastoma Children's Cancer Alliance UK)	**1. Specific Comments** 1.1 [Section 2.3, Page 4] Considering the development path for dinutuximab, that UTC only came on to the scene at a relatively late stage to commercialize its manufacture, that it has received a Creating Hope Act voucher which it sold for $350M, that it is already able to sell into the U.S. healthcare system, that the administration costs associated with the treatment are high, the amount that the company is seeking to charge per child is too high. That said the potential payback for pharmaceutical companies developing drugs to treat children with cancer, most of which are ultra-rare diseases with very small patient populations, is very limited. It should be recognised that dis-incentivising drugs companies from investing in this area will only result in more difficult climate, and it will ultimately be children with cancer, and by extension their families, who will suffer even more. 1.2 [Section 3.16, Page 11] ANBL0032. The specific and very technical point about the criteria for early stopping having not been met, was highlighted for its significance and used to cast doubts about the validity and integrity of the research that was conducted, and results that were collected. This should be viewed in the context of the trial, and the implications that an ultra-rare disease such as neuroblastoma has for conducting clinical research. Meaningful Phase III clinical trials can only be run through wide-scale collaborative efforts. ANBL0032 was a trial operated by the Children's Oncology Group and was open at institutions across North America and beyond. To put this in context, ANBL0032 is still open at 191 locations across United States, Canada, Australia, and New Zealand; a significant number of which would have been involved in the randomization study.	The committee appreciates there is little incentive for companies to invest in treatments for paediatric cancers because these cancers are rare and the patient population is usually small, however, it noted that the company was not involved in the development of dinutuximab and only became involved at a relatively late stage in the marketing of the product after completion of ANBL0032. The committee concluded that the development and availability of new treatment options is very important to patients with high-risk neuroblastoma and their families and carers, but that most of the innovation and development was done by the Children's Oncology Group before the company become involved in the marketing of dinutuximab (see section 4.18 of the FAD). Although the early termination of ANBL0032 concerned the committee, because stopping a trial for benefit before it has met its primary end point can lead to overestimation of the treatment effect, the committee still concluded that the dinutuximab regimen appears to prevent relapse in a small proportion of patients and may be associated with an overall survival benefit, although the size of these benefits is uncertain (see sections 4.3 and 4.4 of the FAD).

Nominating organisation	Comment [sic]	Response
	The trial opened for enrolment in October 2001 and had been running for 8 years when it was stopped early for efficacy and ethical reasons. Had it continued then it was not expected to complete enrolment until mid-2012. It was conducted using best practise, with a data review committee, and independent data safety monitoring committee (Page 300, Committee Papers Oct 2015). It underwent several revisions to the study design, in consort with the FDA, including amending the alpha in spending function from 0.05 to 0.025. The results from January 2009 were not reproduced in June 2009, this was a different data cut and any such retrospective analysis should be set against the background of how the trial was being conducted in real-time. It's also worth noting that it took more than 7 years to accrue a sufficient number of patients to determine the significant 2-year EFS difference. The trial may have been stopped early, but the process of getting there was slow and arduous. The trial was closed early for efficacy *and* for ethical reasons as the difference between the two arms was large; it was deemed not ethical to enrol more children on a randomized trial and thereby deny them access to anti-GD2 immunotherapy. Indeed, such was the moral and ethical dilemma, that it was decided earlier children who had been enrolled on the control arm would be subsequently offered anti-GD2 immunotherapy on a compassionate basis. When viewed in the appropriate context it should be seen why ANBL0032 was closed early, and why it would be completely impossible to repeat this research. The simple fact is that researchers internationally agree that anti-GD2 immunotherapy is now an important part of high-risk neuroblastoma treatment, and it would be impossible to conduct a randomized trial in which some children did not receive this intervention. Not least because the parent community would be completely up in arms were any such trial to be conducted, even if researchers believed there was merit in doing it. 1.3 [Section 3.17, Page 12] When clinicians discuss outcomes with parents, a time point 5-years of continuous remission is often used as the time at which an individual family can feel more hopeful about long-term survival i.e. it is most appropriate for thinking about an individual child's risk of relapse. Five-year survival is also the benchmark for comparing survival outcomes in	Comment noted. The committee was aware that the longer term data from the 2014 analysis showed that events continued to occur in the dinutuximab arm beyond year 5. However, the committee concluded that the dinutuximab regimen appears to

Nominating organisation	Comment [sic]	Response
	high-risk neuroblastoma. This is a major bone of contention with parents because we recognise that 5-year overall survival does not necessarily mean a child is cured and will live to grow up. However, it is a benchmark that is used for assessing incremental improvements in outcomes due to changes in treatment and care. In assessing improvements in outcomes from clinical trial research in high-risk neuroblastoma is it usual for 2yr or 3yr EFS to be reported, and long-term results (not always published) would tend to look at 5yr OS. The following from Children's Oncology Group regarding another high-profile randomized Phase III trial of Bone Marrow Transplant indicates this point. http://jco.ascopubs.org/content/32/36/4174.full It is my view that 5-year OS from March 2014 should be used. There are still 74 and 53 patients at risk, compared to 10-years out when these numbers have dwindled to 9 and 7 (Figure 13: Kaplan-Meier plot of OS, March 2014, Page 307, Committee Papers Oct 2015). This seems a woefully inadequate number of patients on which to base any kind of worthwhile quantitative comparison. The trial was open from Oct 2001 through January 2009, and using analysis of 10-year survival data from March 2014 surely means that, by definition, only those children who were enrolled before March 2004 would be contributing to the longest time periods in that analysis? In many respects the ANBL0032 is being twice penalized because it accrued so slowly - caused by the limited number of eligible patients available. Not only is this a bad thing itself in terms of being able to answer research questions as quickly as possible, it now becomes a further hindrance because the data is being analysed in this manner. When considering EFS or OS, the paradigm of neuroblastoma relapse being uniformly fatal is now being challenged. The use of salvage chemotherapy, targeted drugs, novel agents, and anti-GD2 immunotherapy in a relapse setting means that long-term survivors of relapsed neuroblastoma are a growing population, and this can reasonably be expected to continue. 1.4 [Section 3.18, Pages 12 - 13] Notwithstanding the above comment, using a modelled cure rate of 47% in both arms is not appropriate. At 10-years the difference is 5.6% in EFS and 7.7% in OS. If 10-year survival data is to be used these are the appropriate numbers. Whilst the data is the data, the horizontal survival curve in the	prevent relapse in a small proportion of patients and may be associated with an overall survival benefit, although the size of these benefits is uncertain (see section 4.4 of FAD). The committee prefers the longer term data from ANBL0032 that provides additional information on outcomes, particularly since patients with neuroblastoma have a life expectancy of more than several years. The committee is aware that the statistical power of a trial is determined based on the number of events, therefore, so long as the required number of events have occurred, it is sufficiently powered to detect a treatment effect even when more events occur on follow-up. The committee concluded that the longer term data and the most recent analysis (March 2014) were the most robust data available on which to determine the clinical efficacy of dinutuximab (see section 4.3 of FAD). The Committee noted that the ERG did not apply a parametric curve on the longer term Kaplan-Meier data and the cure rate which it calculated as scenario was not used in its calculations.

Nominating organisation	Comment [sic]	Response
	standard therapy arm beyond four years, and occurrence of late relapses in the dinutuximab arm, does not mean that it is appropriate to fit a parametric model and therefore close the difference down to zero. The relapse rate is discrete, and should not be modelled in this way. It is unknown what the data will show beyond 10-years, or how the results will look when a larger number of patients have reached 10 years of follow-up. 1.5 [Section 4.16 - 4.17, Pages 30 - 32] It would appear that the decision about whether or not it is appropriate to use a 1.5% outcome discount rate, is highly dependent on the decision regarding which data cut, and follow-up duration, is the most appropriate to use. The decision to use the weakest set of results; 10-years from March 2014 with a model-fitted overlay provides the poorest justification for using a 1.5% outcome rate. Again the committee should reconsider this decision. In particular, it should consider contributions of the international paediatric oncology research community as to what is considered best practise when conducting research in this particular field in order to guide its use of the available data. 1.6 [Section 4.23, Page 34] The median life expectancy for patients with high-risk neuroblastoma was 4 years. "Population-based survival curves created using the most recent data available for patients aged 1 to 14 with neuroblastoma in Great Britain (December 2002 to December 2005) show a median survival of approximately 4 years (Stiller 2012). " (Pages 84-85, Committee Papers) I believe this may be incorrect. The Population-based survival curve from this paper is for children diagnosed with neuroblastoma at age 1-14. This would include the 50% of children diagnosed with low and intermediate risk neuroblastoma, for whom the prognosis is generally excellent. A common cause of misinterpretation (and misuse) or statistics is referring to neuroblastoma as a single disease when the dichotomy of outcomes between high-risk neuroblastoma and other risk groups is extreme. **2. General Comments** 2.1 The amount of time that the participants were given to prepare for	The committee concluded that the non-reference case discount rate could apply because the 2014 analysis showed that the dinutuximab regimen could be considered to cure neuroblastoma in a small proportion of patients. It also concluded that this discount rate should be applied to both costs and outcomes in line with the current methods guide (see sections 4.4 and 4.17 of FAD). Based on the evidence presented, the committee agreed that, dinutuximab did not fulfil the criterion for short life expectancy (see section 4.23 of FAD). Comments noted and your feedback has been shared with our patient and public involvement team.

Nominating organisation	Comment [sic]	Response
	the meeting was insufficient. Receiving a mountain of paperwork on 2nd October (I think?) for a meeting on the 6th did not leave enough time for any careful consideration prior to the meeting itself. Moreover, there was no real guidance as to the most pressing considerations that would ultimately affect the Committee's decision. None of the experts, clinical or patient, had any first-hand experience of how a NICE appraisal meeting works. 2.2 The three drivers to the ICER are; cost of treatment, perceived benefit, and discount rate. The discount rate is strongly linked to perceived benefit which rests entirely upon the interpretation of ANBL0032. During the appraisal meeting the view of the Evidence Review Group regarding this trial was largely accepted without challenge. UTC had no involvement with this clinical trial, neither did the clinical experts. Moreover, there appeared to be no expertise on the Committee regarding paediatric oncology, or of running clinical trials in this kind of patient population. The appraisal ought to be able to accept the views of experts in the field of high-risk neuroblastoma regarding the particular challenges of conducting clinical research in this ultra-rare disease. It ought also to specifically refer directly to the investigators involved in ANBL0032 as to how the trial was designed, conducted, and the results are being interpreted within the international research community. It should use this information to decide which data cut, and outcome duration is the most appropriate to use. UTC were not involved in the research and development of this drug, only coming in at a much later stage during its commercialisation. 2.3 Why are the committee requiring event-free survival data at 10 years after randomization? Why are they assessing effectiveness using cure as the primary determinant? Are these approval criteria the same as those routinely applied in the assessment of adult cancer drugs, and if not why not? It cannot be the case that more stringent criteria are applied when deciding whether or not to approve drugs for children with cancer? Otherwise, how is that fair? And how will drugs for such diseases ever get approved? 2.4 High-risk neuroblastoma is a disease that kills small children. The incidence in the UK is around 50, and fewer than half of those will currently survive with the best available treatments. There was an average of 37	Comment noted. The committee's preferred assumptions were based on the evidence presented to it in the submissions, ERG reports and evidence presented at the committee meetings, including the responses from consultation. Although the clinical experts attending the committee meetings were not involved in the dinutuximab clinical trials, both are consultants in paediatric oncology with involvement in on-going clinical trials in children with high-risk neuroblastoma. NICE encourages all consultees and commentators to nominate clinical experts and patient experts to take part in the first appraisal committee meeting discussion. Views have been sought during consultation from the relevant stakeholder groups in this disease area and fully considered by the committee. The committee are not requiring event-free survival data at 10 years after randomisation, rather the committee preferred longer term data that provides additional information on outcomes, particularly when patients with the disease have a life expectancy of more than several years. Also, the committee noted that the evidence showed further events occurring in ANBL0032 after 5 years, especially in the immunotherapy arm. It also agreed that it was implausible that there would be no events after 5 years, as modelled by the company (see section 4.9 of FAD).

Nominating organisation	Comment [sic]	Response
	deaths per year due to neuroblastoma (SNS cancers) in Great Britain from 1996-2005 (http://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/mortality#heading-One). The disease accounts for around 5% of incidence and 10% of deaths due to cancer in children; around half of the incidence, but the vast majority of deaths, are due to high-risk neuroblastoma. The point being that outcomes are poor, and too many children are being lost to this disease. There is enormous unmet need for better, safer, and less toxic treatments for these children – and indeed for children with cancer in general. Improvements are almost always slow and incremental. And the debate about their true effectiveness often continues even after they've become part of standard therapy; Rapid COJEC induction therapy, Autologous Stem Cell Transplant, Isotretinoin. Some would question the strength of the scientific evidence that resulted in these becoming part of standard treatment over the years. And certainly there has never been any published 10-year EFS follow-up on any of these clinical trials. However, with their introduction long-term survival for children diagnosed with high-risk neuroblastoma has gradually improved. Gradually and incrementally, not dramatically. Ch14.18 was 30-years in the making. It is the first new drug to be approved, anywhere in the world, for use in children with neuroblastoma in decades. There is very poor engagement from pharmaceutical companies as development costs can be high, and the potential payback very limited by the size of the patient population. This provides a hugely challenging environment for researchers to work in, and is an enormous source of frustration for the parents of these children. Poor funding and poor access to new drugs, means limited research, which in turn means stifled progress. These are all important aspects of the treatment of childhood cancer which cannot be captured in a very dry and technical cost-benefit analysis, such as has been undertaken. The appraisal process also does not take into account any of the wider implications that this decision might have on the drug development landscape, and therefore on the ability of researchers to make that next incremental, yet vital, improvement in outcomes. 2.5 How often, comparatively, does NICE appraise a drug for paediatric cancer? Or an ultra-rare disease that affects children?	The committee was aware that there is a limited incentive for companies to invest in treatments for paediatric cancers because these cancers are rare and the patient population is usually small. However, the development of dinutuximab was done by the Children's Oncology Group before the company became involved in the marketing of dinutuximab (see section 4.18 of FAD), The committee agrees that high-risk neuroblastoma places a significant burden on patients and their families and carers. The committee also acknowledged the severity of the disease and the importance of generating health benefits for this patient population. The committee stated that it was prepared to consider accepting a higher ICER for a patient population of children and young adults, as well as any other uncaptured health-related benefits that the dinutuximab regimen might offer patients with high-risk neuroblastoma and their families. However, it was not presented with any data to show distinct and substantial uncaptured health-related benefits (see section 4.19 of FAD). Comments noted. See above.

Nominating organisation	Comment [sic]	Response
	Are the NICE guidelines even adequate when it comes to assessing these kinds of diseases? That are chronically under-funded, in desperate need of better and less toxic therapies, and where even the smallest of children are given drugs developed to treat adults. Although the £/QALY may be significantly higher than the threshold at which approval is usually given, the total numbers of patients is very small, and comprised of a very special sub-set of the population. There needs to be a wider consideration of how the process deals with diseases and patient populations that are 'special' by their rarity, their vulnerability, and their inability to advocate for themselves. The costs of drugs solely for these patients, without having any other adult indication, are bound to be significantly higher. Is it appropriate that the approval process for a drug for a disease that affects a small number of children under five is conducted in exactly the same way as would be a drug for, say, prostate or breast cancer? Or that a disease for which there has never before been an approval request, and for which the number of approval requests will by definition be very small, be subject to the same scrutiny as a disease where there are lots of potential treatments available and perhaps the decision comes down to the fact that not all of them can be funded. Should there not be a mechanism whereby approval requests for diseases like high-risk neuroblastoma are taken offline; where clinical experts are engaged to assess the effectiveness, and approval can be given in principle subject to some kind of agreement on price? This is not to suggest dismissing the scientific evidence, but to question whether the balance is right in this instance. In my experience when childhood cancer and adult cancers are thought of in the same way, childhood cancer always comes off worst. How can that be justified? NICE can approve many drugs for the same adult cancer, for which the	Comment noted. The committee considers that the NICE Board should clarify whether the short life expectancy criterion should apply to children as it is applied to adults (see section 4.21 of FAD). The committee is aware of the patient experts statement that there is limited incentive for

Nominating organisation	Comment [sic]	Response
	cost-benefit number is within range. The drug company can sell it more inexpensively and make money due to the number of units sold. And because of the incidence of the disease, the cost of this drug to the NHS will be large. However, based on a supposed large cost-benefit number NICE cannot approve one single drug for a paediatric cancer for which the absolute cost will still be (comparatively) miniscule. So not only does the whole drug development situation work against children with these ultra-rare diseases, so too does the approval system when assessing those tiny number of drugs that do actually get developed and seen through to approval. Children with this disease deserve to be given every possible chance to grow up. If 37 children die of neuroblastoma per year, and this drug can save only 1 of them, how can that not in itself be sufficient to find a way for it to be approved? 2.6 A negative decision will adversely affect UK families with children suffering from neuroblastoma regarding how they view NHS provision. A treatment that is approved by the FDA and EMA, yet denied to children in the United Kingdom will be seen as an indictment of a second-rate healthcare system that does not care about its country's children. 2.7 A negative decision will be in direct contradiction of the international consensus amongst researchers that anti-GD2 immunotherapy improves outcomes for children with neuroblastoma, and is significant in saving the lives of children who prior to current day therapy had a dismal prognosis. 2.8 A negative decision will leave UK children at the absolute mercy of supply of ch14.18/CHO by APEIRON Biologics (APN), a direct competitor of United Therapeutics (UTC), in order for them to have continued access to anti-GD2 immunotherapy in this country. APEIRON have filed their own approval request in the UK, and clearly, there are commercial considerations already in play here. Should UTC's Unituxin not be approved, it is difficult to see how APN's APN311 could ever gain approval considering the only Phase III randomized study data remains unpublished,	companies to invest in treatments for paediatric cancers because these cancers are rare and the patient population is usually small. The committee noted that in this case the company was not involved in the development of dinutuximab and became involved at a relatively late stage in the marketing of the product after completion of ANBL0032. The committee concluded that the dinutuximab regimen represents a novel approach as a maintenance therapy for treating high-risk neuroblastoma, but the evidence of the health gains specifically from dinutuximab (as opposed to the other drugs included in the regimen) remains uncertain. It also concluded that most of the innovation and development was done by the Children's Oncology Group before the company became involved in the marketing of dinutuximab (see section 4.18 of the FAD). Comment noted. The committee is aware of the significant burden that neuroblastoma places on

Nominating organisation	Comment [sic]	Response
	and comes from the SIOPEN clinical trial which has no standard therapy arm. The reason for this being the consensus that anti-GD2 is an established and accepted part of standard therapy, and to deny any child access to it would be unethical. 2.9 Without approval of Unituxin children in the UK would be solely reliant upon continued access to anti-GD2 immunotherapy through clinical trails, even though it is considered part of standard therapy. Continuous access to APN311 cannot be relied upon, and whilst this is not a case of UTC vs APEIRON, putting APEIRON in a position of such strength regarding access to ch14.18 in the UK would be potentially dangerous. International researchers agree that anti-GD2 immunotherapy is an established part of neuroblastoma treatment. As such, UK children should have the *right* to ch14.18, and their parents the *choice* of whether or not to enrol them on a clinical trial seeking to make further improvements. They should not be forced to enrol on clinical trials to receive what is now considered to be a standard treatment. 2.10 A negative decision raises the prospect that children in the UK could, at some point in the future, be unable to receive anti-GD2 immunotherapy in this country. The prospect of parents having to raise hundreds of thousands of pounds and travel abroad to access a treatment that clinicians agree is part of recognised standard therapy would be completely indefensible. The potential fallout would be enormous, and political. 2.11 The idea that anti-GD2 is not part of standard therapy, and it remains a possibility for children in the UK to go back to receiving isotretinoin alone as a maintenance therapy, as they did before 2009, is incomprehensible. Parents do not care whether UTC or APEIRON, whether ch14.18/SP2/0 or ch14.18/CHO. They don't care whether one, or other, or both, drugs are approved. They want their healthcare system to provide the best available treatment for their children.	patients and their families and carers. The committee also acknowledged the severity of the disease and the importance of generating health benefits for this patient population. It was prepared to consider accepting a higher ICER for a patient population of children and young adults, as well as any other uncaptured health-related benefits that the dinutuximab regimen might offer patients with high-risk neuroblastoma and their families. However, it was not presented with any data to show distinct and substantial uncaptured health-related benefits. But the committee also heard from clinical experts that most patients with high-risk neuroblastoma in the UK are enrolled in the SIOPEN trial that is investigating APN311. However, APN311 is currently not licensed in the UK and therefore cannot be considered established clinical practice in the NHS (see section 4.2 of FAD). Comment noted. Based on the evidence presented, the committee concluded that dinutuximab does not represent a cost-effective use of NHS resources and that it should not be recommended for treating high-risk neuroblastoma in patients of 1-17 years, whose disease has at least partially responded to induction chemotherapy, myeloablative therapy and autologous stem cell transplant (see section 4.24 of FAD). Comment noted. The committee noted that APN311 is not currently licensed for treating neuroblastoma and because its use in a research setting is viewed

Nominating organisation	Comment [sic]	Response
	2.12 Neuroblastoma does not simply affect the lives of children. The effects are felt throughout families, and communities. It is not uncommon for parents to have to give up their careers to care for their children, or simply through being unable to work due to stress. They must live off welfare, disability and carers allowances. The strain on relationships leads to marriage breakdown and divorce, people lose their houses. It really is no exaggeration to say that neuroblastoma ruins lives. How these effects can ever be captured and understood in an economic cost model is hard to envisage.	as use in new and experimental circumstances, the committee agreed that APN311 could not be considered established practice (see section 4.2 of FAD). Comment noted. Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 2).
National Cancer Research Institute Children's Cancer and Leukaemia Clinical Study Group	We would like to make the following comments: *i)* On page 20 of the consultation document, it is stated that *"The Committee considered current clinical practice within the UK for treating high-risk neuroblastoma It is understood that Isotretinoin is the standard of the care for patients in the UK for patients with high risk neuroblastoma who have received induction chemotherapy followed by surgery…"* As stated in the meeting on 6th October 2015, virtually all children in the UK with high risk neuroblastoma have received anti-GD2/CHO based immunotherapy since 2010, as part of the SIOPEN HR-NBL-1 or SIOPEN LTI trials. In view of the results of ANBL0032 study (released in 2009) it was felt unethical and unacceptable to consider Isotretinoin alone as the 'standard' arm in the HR-NBL-1 study and all patients within the study have received ch14.18/CHO. For the very small number of patients that have not been eligible for ch14.18/CHO within one of these SIOPEN trials, we have	Comment noted. The committee noted that APN311 is not currently licensed for treating neuroblastoma and because its use in a research setting is viewed as use in new and experimental circumstances, the committee agreed that APN311 could not be considered established practice (see section 4.2 of FAD).

Nominating organisation	Comment [sic]	Response
	sought to obtain anti-GD2 antibody for the child through another source, e.g. the Idis Managed Accessed Programme. Therefore some form of anti-GD2 antibody therapy, in addition to Isotretinoin, has effectively been considered a standard of care in the UK for these children since 2010.	
	ii) We acknowledge that the differences in overall survival and event free survival between the standard and immunotherapy arm have been lost by 10 years, in part due to the small numbers of patients at the later time points. Whilst in an ideal word a further, larger, randomised study would be conducted (with Isotretinoin as standard arm and Dinutuximab immunotherapy as the experimental arm), it is very unlikely that it will ever be possible to conduct such as study as Isotretinoin alone would be unacceptable to most parents and clinicians.	Comment noted. The committee concluded that the dinutuximab regimen appears to prevent relapse in a small proportion of patients and may be associated with an overall survival benefit, although the size of these benefits is uncertain (see section 4.4 of FAD).
	iii) Within the UK our priority will be to continue to try and ensure that we have clinical trials open to improve the delivery and efficacy of anti-GD2 therapy, and to ensure children have access to this form of immunotherapy, this may not always be possible. We are therefore likely to be faced with children and families seeking to travel abroad for therapy if the treatment is not available through NHS funding.	Comment noted. The committee is aware of the significant burden that neuroblastoma places on patients and their families and carers (see section 4.1 of FAD).
	iv) We feel some consideration to the young age of the patients involved, and the 'value' that parents and society place on extension of an incurable child's life. Extending a 5 year old child's life for e.g. 5 years, even if he or she subsequently dies from their disease, is likely to be viewed as hugely valuable,	Comment noted. Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of

Nominating organisation	Comment [sic]	Response
	providing the quality of extended life is good. In addition, extension of survival, even if only for a few years, offers the hope to parents that an innovative and effective treatment may become available within that time, and change an otherwise poor prognosis to a better one. v) In the consultation meeting, comparison was made with the previous appraisal of Mifamurtide. We would be grateful if clarification could be provided as to the special circumstances that were applied in this appraisal, which may potentially be applicable to Dinutuximab.	NICE guidance', principle 2). However, the committee has considered that the NICE Board should clarify whether the short life expectancy criterion should apply to children as it is applied to adults (see section 4.21 of FAD). In the mifamurtide appraisal, the committee applied a non-reference discount rate of 1.5% for benefits. Later, the NICE's guide to the methods of technology appraisal stated that 'in cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered.' The committee considered dinutuximab and concluded that the non-reference case discount rate of 1.5% could apply because the 2014 analysis showed that the dinutuximab regimen could be considered to cure neuroblastoma in a small proportion of patients. It also concluded that this discount rate should be applied to both costs and outcomes in line with the current methods guide (see section 4.17 of FAD).
Solving Kids' Cancer	In our assessment, the committees report into the evaluation of dinutuximab has several shortcomings. Firstly, the difficulties of conducting a clinical trial in this population did not seem to be fully understood. The high relapse and mortality rate of children	Comment noted. The committee is aware of the significant burden that neuroblastoma places on patients and their families and carers. The committee also acknowledged the severity of the disease and the importance of generating health benefits for this patient population. It was prepared to consider accepting a higher ICER for a patient

Nominating organisation	Comment [sic]	Response
	with high risk neuroblastoma does mean that families will go to extreme ends to make sure their children receive the best possible treatment. If the ANBL0032 trial had not been stopped early because of the clear difference in efficacy, it is not certain that the trial would have continued to accrue patients at the rate suggested. At the time this was an unproven treatment that entailed significant hospital stays and therefore there was the real possibility that families would choose to enrol their children on other clinical trials. In this context, it is an achievement that the trial accrued in the way it did. It should be understood that there are special challenges to conducting a randomised control trial in high risk neuroblastoma patients. The numbers of children who are diagnosed is very small and the numbers available for the trials are even smaller. These are challenges that do not exist in many adult cancers and many other childhood cancers. These extra difficulties do not seem to have been taken into account in the committee's assessment, and if they had been, they would have been more favourable to the ANBL0032 trial. The subsequent analysis of the early results led to the landmark New England Journal of Medicine paper in September 2010, which has contributed to this treatment becoming the standard of care in the US, Canada, Australia and New Zealand. Because NICE is such a respected organisation, the decision to reject the treatment will be a devastating blow for the feasibility of conducting trials into new treatments for this disease. Without the ability to have these trials progress to a reimbursable treatment, the decision is likely to have a negative impact on pharmaceutical interest in the disease. Eurocare studies that have assessed the survival rates of cancer diagnosis	population of children and young adults, as well as any other uncaptured health-related benefits that the dinutuximab regimen might offer patients with high-risk neuroblastoma and their families. However, it was not presented with any data to show distinct and substantial uncaptured health-related benefits (see section 4.19 of FAD). Comment noted. Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 2). However, the committee has considered that the NICE Board should clarify whether the short life expectancy criterion should apply to children as it is applied to adults (see section 4.21 of FAD).

Nominating organisation	Comment [sic]	Response
	across Europe, have in the past identified neuroblastoma as one of the few paediatric cancers that showed a significantly poorer survival rate in Europe compared to North America. Much effort has been expended to close this gap and this decision could reverse the gains made. If this does happen, families may be left with the impression that their children's chance of survival has been directly set by a chiefly financial decision. In this context value for money will only truly make sense when there is an alternative treatment path. In this case there is none, except a place on a trial of an untested drug. Lastly, a key part of the analysis of dinutuximab used an extrapolated and fitted curve to the survival data. We believe that this use was unwarranted because; in the context of neuroblastoma patients there was no presented evidence that the population group would respond in this way and more specifically in this case, the statistical evidence at 4 or more years from the commencement of treatment was too weak. It also does not appear that the committee took into account that the key trial was not run by United Therapeutics and was chiefly designed to test for 2 year event free survival – not 10. While we can be disappointed with the price set by United Therapeutics for dinutuximab, the attempt to use extrapolated ten year data in this population of extremely vulnerable children does not appear appropriate. We urge the committee to reassess the decision and take into account the special circumstances surrounding both the trial that generated the data in question and the patient group the treatment will serve	
Neuroblastoma UK	Neuroblastoma UK (formerly the Neuroblastoma Society) was established as a registered charity in 1982 by parents of children who had died of	

Nominating organisation	Comment [sic]	Response
	neuroblastoma. Since then we have raised and invested millions of pounds to support scientific and clinical research studies, some of which have latterly been in collaboration with other charities. Research grants are made following a robust appraisal process, incorporating peer appraisal by UK and international specialists, and supervised by a Scientific Advisory Board including European experts. Among other outcomes, our research projects typically generate a number of papers in ranking scientific journals. We also work in collaboration with the International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) and the Children's Cancer & Leukaemia Group (CCLG) to support the establishment and conduct of international clinical trials, and organise a biannual UK research symposium attended by up to 200 researchers and clinicians. This preamble demonstrates our commitment to rigorous scientific investigation and an evidence-based approach to evaluating the effectiveness of candidate treatments. We have been associated with immunotherapy treatment for neuroblastoma patients since its first introduction into the treatment strategy in the European (SIOPEN) High Risk Neuroblastoma trial. Hence we have followed closely the spectrum of emerging data and results on immunotherapy in the context of high risk disease. We acknowledge the importance of thorough and rigorous appraisal of available evidence using consistent methodology, as demonstrated in the ACD. It is in this context that we register our concerns and queries about the	Commented noted.

Nominating organisation	Comment [sic]	Response
	outcome of the appraisal and its implications. The appraisal concluded that the level of event-free survival (EFS) and overall survival (O/S) associated with immunotherapy were insufficient compared to the costs of the intervention. Increases of 5.6% and 7.7% respectively may not be considered statistically or methodologically significant, but they are hardly insignificant for the children who benefit. A few more years for a young child can represent a doubling (or more) of their life expectancy, benefiting the child, the parents and the wider family. This is quite different to applying the same criteria to an adult. We also note that extended life provides additional time during which new treatments might become available which may further help the child to live longer and survive long term. The appraisal also concluded that one of the three end-of-life criteria was not met, with the apparent paradox that, despite the EFS and O/S figures, children are considered likely to live too long for the median life expectancy criterion to apply. This leads us to observe that while the unit costs of immunotherapy may be considered high by NICE standards, the numbers of children who will receive the treatment is small. Hence the overall cost to the NHS is not actually that high. (It also prompts us to enquire whether any reduction in the proposed pricing of the antibody by the supplier would affect the analysis and the recommendation of the Committee.) In terms of the methodology, we respect the effort and expertise of the ERG,	Comment noted. Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 2). However, the committee has considered that the NICE Board should clarify whether the short life expectancy criterion should apply to children as it is applied to adults (see section 4.21 of FAD).

Nominating organisation	Comment [sic]	Response
	but we do have some queries about a few aspects of the methodology and subsequent interpretations. In particular: • We assume that the decision to retain the reference discount rate rather than allow the 1.5% rate for those likely to survive long-term will have had an impact. In lay terms, this assessment is based on whether a person who survives long term can be expected to be a burden on the NHS due to additional health problems. While we accept that there are consequences of the disease and its treatment, it is not clear that these are sufficient to assume that a survivor will need a noticeably higher level of NHS care in the future. Hence we ask whether the 3.5% rate could not have reasonably been applied. • The choice of data cut by the ERG was significantly influenced by the decision to close the control arm of the relevant CPG study and the consequent impact on numbers, but we understand very well the clinical and ethical decision to do that, given the data emerging at that time. It seems unfortunate that the consequences of this decision should appear to have had an impact on the view taken of the trial data. The Appraisal Committee described cis-retinoic acid (CRA) as the existing standard treatment, but in practice (as the Committee is aware), immunotherapy together with CRA is currently considered to be included in	Comment noted. The committee concluded that the non-reference case discount rate could apply because the 2014 analysis showed that the dinutuximab regimen could be considered to cure neuroblastoma in a small proportion of patients. It also concluded that this discount rate should be applied to both costs and outcomes in line with the current methods guide. (section 4.17 of the FAD). Comment noted. The committee noted that APN311 is not currently licensed for treating neuroblastoma and because its use in a research setting is viewed as use in new and experimental circumstances, the committee agreed that APN311could not be

Nominating organisation	Comment [sic]	Response
	the standard treatment for children with high risk disease in the UK. This is currently provided within the SIOPEN High Risk Neuroblastoma clinical trial into which more than 95% of UK high risk patients are entered. We know that clinicians believe that patients should continue to have access to the antibody in the context of clinical trials so that medical science can establish the role of the therapy and the best way to administer it. Now is not the time to stop (by stopping patient access to the antibody) continuing and further evaluation of this exciting treatment option which has already been shown to improve EFS in this aggressive disease. Treatment options are currently limited, and we must point out that should such treatment no longer be available in the NHS, for example if no variant of immunotherapy is approved and licensed, it is almost certain that parents will seek it in other jurisdictions, with very significant financial, economic and social costs in addition to the personal impact. We understand that this may not be considered to fall within NICE's remit, but it is our responsibility to point out this potential consequence. It will be clear from the above that many of our questions and concerns relate to whether the standard NICE methodology, including the allowed discretion and exceptions, are suitable for appraising an intervention of this type and for children suffering with this aggressive disease (and indeed other cancers). In other words, regardless of the details of this particular appraisal, we are concerned that it would be extremely difficult for <u>any</u> promising treatment for neuroblastoma to be approved. Any clinical trial will experience a significant challenge in accrual, given the relatively small	considered established practice (see section 4.2 of FAD).

Nominating organisation	Comment [sic]	Response
	numbers of babies, infants and older children affected and the smaller subset that will meet the entry criteria for a given trial, so the data and its analysis will always be affected (and we refer again to the potential impact of an ethically-driven clinical decision to prioritise provision of a treatment over maintaining the strict controls for a clinical trial). Over 30 years' experience has shown us that it is not realistic to expect a 'silver bullet' treatment or cure, but it seems that anything less would struggle to pass a current NICE appraisal. For an organisation dedicated to improving treatment for children with cancer, this is a disturbing thought, and not a message that we would wish affected families and the wider public to receive. This is the more worrying given existing concerns about the relevance to children's cancer of recent NICE publications (e.g. the Referral for Suspected Cancer Guidelines, and the quality standard for sarcoma). We therefore urge that NICE undertake to look at the methodology used to assess whether it is fit for purpose in this very specialised rare disease group. This is work that could be done with Neuroblastoma UK and other interested children's cancer charities as well as professional bodies such as the CCLG, and the National Cancer Research Institute. We will liaise with such parties in anticipation of such an assessment, and to communicate our views of the appraisal and our aspirations for the future in response to public and media interest.	

Comments received from commentators

Commentator	Comment [sic]	Response
Roche	No comments	

Summary of comments received from members of the public

Theme	Response
Emphasising severe impact of neuroblastoma on families, careers, health and finances	Comment noted. The committee is aware of the significant burden that neuroblastoma places on patients and their families and carers (see section 4.1 of FAD).
Treatment adverse effects: sterility, growth issues, hearing issues and higher risk of secondary cancer as a consequence of induction treatment	
Cost of dinutuximab is excessive	Comment noted.
Treatments which extend life in children should be valued differently to treatments extending life in adults	Comment noted. Deciding which treatments to recommend involves balancing the needs and wishes of individuals and the groups representing them against those of the wider population. This sometimes means treatments are not recommended because they do not provide sufficient benefit to justify their cost (Social Value Judgements; 'Principles for the development of NICE guidance', principle 2). However, the committee has considered that the NICE Board should clarify whether the short life expectancy criterion should apply to children as it is applied to adults (see section 4.21 of FAD).
No alternative treatments in the UK although a clinical trial for a different treatment is ongoing in the UK, not all children meet the criteria to join it and some children in trial are taken off if they do not meet milestones	Comment noted. The committee is aware of the significant burden that neuroblastoma places on patients and their families and carers. Based on the evidence presented, the committee concluded that dinutuximab does not represent a cost-effective use of NHS resources and that it should not be recommended for treating high-risk neuroblastoma in patients of 1-17 years, whose disease has at least partially responded to induction chemotherapy, myeloablative therapy and autologous stem cell transplant (see section 4.24 of FAD).

NICE Submission - dinutuximab (Unituxin) [ID799]

Company Comments on Appraisal Consultation Document (ACD)
1 December 2015

In response to the ACD issued in October 2015, United Therapeutics (the Company) wishes to provide comments on aspects of the preliminary NICE Appraisal. Of particular note are: the tendency to make highly unfavourable assumptions unsupported by convincing evidence when addressing issues of uncertainty, applying inconsistent standards with regards to discounting of future quality-of-life benefits, and, most importantly, undervaluing the proven overall survival advantages in a devastating, ultra-orphan, paediatric oncology indication. The Company contends that NICE has routinely taken unsupported and pessimistic views regarding cure, relapse rates, and administration costs. With regards to discounting future health benefits, the Company believes an inconsistent standard is being applied as compared to the precedent of mifamurtide for the treatment of osteosarcoma (TA235). In addition, the Company asserts that NICE is undervaluing the overall survival advantage of dinutuximab despite evidence from 226 patients spanning 8 years.

The Company urges the NICE Appraisal Committee (the Committee) to reconsider the provisional decision to 'not recommend' dinutuximab, based on:

1. The innovative nature of dinutuximab in an ultra-orphan paediatric oncology indication with no European Medicines Agency (EMA)-approved therapeutic alternatives;
2. The unreasonable interpretation of the clinical and cost-effectiveness evidence submitted; and
3. The inconsistency with previous decision-making in the technology appraisal of mifamurtide for the treatment of osteosarcoma (TA235).

This document outlines specific points that the Company would ask the Committee to reconsider.

Dinutuximab as an Innovative Treatment Option with No EMA-Approved Therapeutic Alternatives

NICE concluded in the ACD that "the dinutuximab regimen represents a novel approach as a maintenance therapy for treating high-risk neuroblastoma, but the evidence of the health gains specifically from dinutuximab remains uncertain." While the contribution of each component of the dinutuximab regimen is difficult to appreciate, many clinicians consider the health gains associated with the regimen to be robust. In response to NICE's preliminary decision, several clinicians (who were involved in the Children's Oncology Group [COG] trial for dinutuximab and who have first-hand experience treating patients with high-risk neuroblastoma with dinutuximab) have reached out directly to the Company to emphasize dinutuximab's role as standard of care, the ethical decision to halt the clinical trial, the belief that patients will not relapse if they have not relapsed in the first 5 years after treatment with dinutuximab, and the quality-of-life associated with children receiving dinutuximab and post-dinutuximab treatment. Quotes from many of these clinicians are included below:

- *"For several years now we have considered this agent as standard of care for neuroblastoma patients in first response. This has revolutionized our approach to this deadly disease, and the neuroblastoma parent community has embraced the concept of a novel mechanism designed to prevent relapse, as relapse of high-risk neuroblastoma after standard intensive chemotherapy is not currently curable. Dinutuximab therapy makes sense scientifically, and in this ultra-rare indication we think that there is outstanding clinical support for the routine use of this agent in the care of high-risk neuroblastoma patients."* – John M Maris, MD; Children's Hospital of Philadelphia

- *I am confident that dinutuximab improves the survival for children with [high-risk] neuroblastoma whose disease has been responsive to upfront induction and consolidation chemotherapy. For this reason, I consider dinutuximab to be standard of care for this cohort of children and it would*

be deemed unethical to deny them the opportunity to receive such therapy. Both treating physicians and families understand that the administration of dinutuximab has acute toxicity. However, it is remarkable that patients are able to resume their normal life activities in between treatment courses and following completion of therapy. Based on my interaction with numerous families and patients, I am confident that they believe this therapy has markedly less impact to their lives compared to standard chemotherapy they had previously received as treatment for their high-risk neuroblastoma. Finally, the vast majority of children with high-risk neuroblastoma will not experience recurrence after 5 years from completion of this therapy and now have the opportunity to embark on a developmentally appropriate life." – Julie R. Park, MD; Seattle Children's Hospital

- *"Dinutuximab for many years has been standard of care for the treatment of patients with [high-risk] neuroblastoma. It has indeed revolutionized the therapy of these children and we have first-hand seen patients with disease resistant to known therapy clear resistant disease while undergoing treatment with it. Furthermore, it has significantly affected the overall survival of our patients with this deadly disease. Although the therapy administration is intensive, patients and families have not only embraced the therapy but appreciate the opportunity to be able to use a targeted agent for their tumor. In fact, many of my patients are able to go to school in between cycles of therapy, something impossible for chemotherapy agents. Their lives are nearly normal during the therapy and become very normal very quickly after its completion. It is truly a pleasure to be able to not only have disease response but have more normalcy because of the use of this agent. When I see my patients in clinic who have not relapsed after 5 years from end of therapy, I can be rest assured that their chance of relapse decreases to almost nothing and I can reassure the families that they can concentrate on the future, rather than concern about a relapse at that time. In summary, dinutuximab is a drug that has shown in all arenas to be the agent with significant impact and changed the lives of the children and families in a positive manner. I look forward to using this drug for many years to come and explore ways to improve its efficacy over the years to come."* – Araz Marachelian, MD; Children's Hospital Los Angeles

Furthermore, due to the very limited size of the patient population and dinutuximab's specific indication, the overall budget impact for dinutuximab in England is very small, representing a cost of <£2.5 million annually.

Unreasonable Interpretation of the Clinical and Cost-Effectiveness Evidence Submitted

In the ACD, NICE did not recommend dinutuximab based on a number of factors that contributed to a higher base case ICER than was estimated in the Company's submission and in the Evidence Review Group's (ERG) report. The assumptions with the most significant impact on the ICER for dinutuximab are the Committee's assertions that "for both the event-free and overall survival data, the curves converge between 6.5 and 11 years" and "the dinutuximab regimen delayed but did not prevent cancer-related events." The Company does not believe these to be fair or scientifically-credible interpretations of the data provided to the Committee. The event-free survival (EFS) and overall survival (OS) curves do not converge, as seen in the Kaplan-Meier curves in the Company submission. Also, as stated in the Company submission, the ANBL0032 trial was not powered (and not intended to be powered) to test a difference beyond 3 years. The ANBL0032 trial was powered and the sample size estimated to evaluate differences in EFS at 3 years; any analyses of EFS after this time point are considered statistically under-powered and ad-hoc in nature.

Randomisation in the ANBL0032 trial was stopped early based on the efficacy demonstrated by immunotherapy after the sixth pre-specified interim analysis at the recommendation of the safety monitoring committee that it would be unethical to continue randomising patients to standard therapy at that point. All interim analyses were pre-specified and utilized an efficacy monitoring scheme based on the Lan-DeMets approach with spending function $\alpha^{*}t^{2}$, which controlled the overall Type I error rate

across the planned interim analyses. NICE stated that "the trial should not have been stopped because the stopping criteria had not been reached". Despite the sixth and final interim analysis not reaching the full monitoring boundary (observed p-value = 0.0115 vs. boundary p-value determined *a priori* = 0.0108), the safety monitoring committee, with agreement from the COG Group Chair, felt the lack of significance at the hundredths place of the p-value was still sufficient evidence to conclude efficacy and warrant the ethical halting of randomisation into this trial. The safety monitoring committee regarded the efficacy as "on the boundary" at the 0.01 level. The safety monitoring committee had previously conducted five interim analyses, all of which demonstrated a trend towards the efficacy of immunotherapy, which further provided confidence in this therapy's effect. Upon learning of these NICE assumptions, Julie R. Park, MD of Seattle Children's Hospital, reached out to the Company to reiterate that the trial was halted when it was considered to have reached the appropriate point at which to stop randomisation, so children with neuroblastoma were able to receive an improved, life-saving therapy:

> *"As chair of the [Children's Oncology Group] COG Neuroblastoma Scientific Committee, I have had the opportunity to continually review our progress for treating high-risk neuroblastoma. The ANBL0032 trial has been pivotal in our understanding of therapy for children with high-risk neuroblastoma and represents a seminal clinical development in improving survival for these children that does not include further dose escalation of conventional chemotherapy known to have extreme long term toxicities for developing children. As you are aware, high-risk neuroblastoma is an orphan disease, representing less than 500 children per year in all of North America and thereby a very difficult disease to study. It has been our priority to perform randomized clinical trials for this disease, but unlike malignancies occurring in adults, we do not have the patient numbers to quickly or easily conduct a large randomized trial. Furthermore, our improvement in outcome has been slow and incremental; thus close monitoring and early stopping of a trial are required so that we do not delay the ability to offer improved therapy to children. The ANBL0032 was conducted through COG with oversight by the [National Cancer Institute Cancer Therapy Evaluation Program] NCI CTEP. Based on close monitoring of an independent DSMB, the study was stopped and while this allowed more children to have the benefit of this life saving therapy, we are left with limited numbers of patients to provide more extensive statistical analyses."*

The Company therefore asserts that the clinical and cost-effectiveness assumptions by NICE are not reasonable interpretations of the evidence, as they place a greater weight on statistically underpowered, ad-hoc analyses of inadequate sample size rather than the adequately powered analyses which provided the basis for EMA marketing authorisation of dinutuximab throughout the European Union. The Company acknowledges that there are long term data available for NICE to consider; however, the Company strongly feels that these long term data have been over-interpreted by NICE when considering the benefit of dinutuximab to patients with high-risk neuroblastoma.

Additionally it is important to note that the Kaplan-Meier curves for EFS and OS never converge or overlap, with dinutuximab always favoured over isotretinoin alone. This lack of convergence supports the conclusion that dinutuximab does cure many patients and provides a long-term health benefit for patients with high-risk neuroblastoma. Furthermore, NICE's clinical and patient experts, as well as the Company's clinical experts, all indicated that relapses after 5 years are extremely rare, supporting the base case economic model assumptions in the Company's submission. NICE acknowledged in the ACD that the clinical experts who participated in the First Appraisal meeting "stated that relapse after 5 years appears to be increasing", but this statement is not universally agreed upon and is based on anecdotal observation from only two clinicians who have limited to no experience using dinutuximab, and who are applying clinical opinion of a different therapy to this appraisal.

The Company also believes the Committee did not provide adequate weight to the substantial OS benefit associated with dinutuximab. The logrank p-value = 0.0301 for OS in the ANBL0032 trial (March 2014 data), represents a significant difference in OS for immunotherapy vs. isotretinoin alone. Despite this, the

Committee states “the dinutuximab regimen does not cure neuroblastoma, but rather prevents relapse of the disease”. The Company and clinical experts disagree with this assertion, and consider the results beyond 5 years to reinforce that many patients experience cure with dinutuximab treatment, providing an impactful long-term health benefit in an ultra-orphan disease that affects children and that has no other EMA-approved alternatives for treatment. For this reason, the Company provided a scenario utilising a 1.5% discount rate, the precedent for which was set in the NICE appraisal of mifamurtide in osteosarcoma in a paediatric population (TA235). As was highlighted in the Company’s submission and by members of NICE at the NICE First Appraisal meeting on October 6th 2015, the Company believes the mifamurtide technology appraisal to be very relevant to the dinutuximab technology appraisal in light of the long-term health benefits associated with immunotherapy treatment. TA235 and the 'Guide to the methods of technology appraisal' issued by the Board of NICE states:

> *“Where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs"*

In the mifamurtide technology appraisal, it was noted that treatment improved OS from 71% to 78% at 8 years compared with chemotherapy alone and that patients treated with mifamurtide who are cured are expected to have a long and sustained benefit and regain normal life expectancy. As such, for the mifamurtide technology appraisal, the Committee concluded that both criteria were met and a discount rate of 1.5% should be used for health effects. For mifamurtide, the analysis of disease-free survival was not statistically significant at interim analysis or at 8 years. Despite this, no concern was cited by NICE that mifamurtide did not provide a cure, but rather prevented relapse. Dinutuximab treatment statistically significantly improved OS (p=0.02), demonstrating OS rates of 75% and 86% in the isotretinoin and dinutuximab arms, respectively, at 2 years in the data analysis from January 2009 (Yu 2010). Likewise, in the March 2014 data analysis, dinutuximab statistically significantly improved OS (p=0.03), demonstrating OS rates of 59% and 74% in the isotretinoin and dinutuximab arms, respectively, at 4 years (Yu 2014). Relapses after 5 years are considered to be extremely rare, and patients who survive neuroblastoma are expected to have normal or near-normal life expectancy. The OS benefit associated with dinutuximab is larger than that of mifamurtide; therefore, it would be clearly inconsistent with the precedent set in TA235 if a 1.5% discount rate is not applied for dinutuximab. The Company strongly believes that a 1.5% discount rate for outcomes must be applied in the case of dinutuximab, to be consistent with the assumptions made in the mifamurtide NICE appraisal.

Administration costs: The ERG calculated administration costs in their base case using the average number of hospital days from the ANBL0032 trial and the cost of an elective inpatient stay for treating brain tumours or cerebral cysts with the highest complication and comorbidity level and NHS reference costs for the delivery of complex chemotherapy (ERG base case analysis). The ERG also calculated alternative administration costs using the average number of hospital days from the ANBL0032 trial and the costs for the delivery of complex chemotherapy and the mean costs of hospitalisation for an elective inpatient stay for the treatment of paediatric brain tumours (ERG scenario analysis). The ERG scenario analysis, using the alternative administrations costs, resulted in much higher administration costs for dinutuximab compared to the ERG base case analysis. Clinicians at the dinutuximab NICE First Appraisal meeting, who have **not** used dinutuximab for the treatment of high-risk neuroblastoma, provided feedback that “using the average number of hospital days from the ANBL0032 study (69 days) may have underestimated the number of days a patient with neuroblastoma would be hospitalised when having treatment with the dinutuximab regimen”. The Company believes this clinician sentiment is a subjective observation based on experience with a different, non-interchangeable immunotherapy (Aperion Biologic’s CHO.14.18 per the SIOPEN clinical trial program) rather than on data for dinutuximab and that the clinician’s opinion swayed the Committee to decide to inappropriately increase the administration costs associated with dinutuximab in their model:

> “However, considering the clinical experts’ concern that average number of hospital days from the ANBL0032 study seemed to underestimate the number of days a patient with

high-risk neuroblastoma would be hospitalised, the Committee concluded that the costs used in the ERG's scenario analysis may still underestimate the administration costs of the dinutuximab regimen".

Additionally, although the Committee noted there was no specific code available for the maintenance treatment of high-risk neuroblastoma - ("The Committee accepted that without a specific code, the cost of an elective inpatient stay for treating paediatric brain tumours could be considered the most applicable for patients having dinutuximab.") - they elected to use the higher administration costs presented in the ERG scenario analysis. The Company feels this is another example of the Committee electing to choose a highly unfavourable assumption based on anecdotal data against dinutuximab.

To better inform the Committee of the number of hospital days, the Company is providing data from study ANBL0931, a phase 3 open-label safety study of dinutuximab, and is requesting approval from NICE for the additional evidence to be considered. These additional data are included in an appendix to this document (APPENDIX A). These data provide evidence that, contrary to the conclusion made by the Committee, the ERG scenario analysis, using the alternative administration costs, likely overestimates, rather than underestimates the administration costs of the dinutuximab regimen. As such, the Company believes that the base case administration costs adopted by the Committee represent an inappropriately high estimate for the cost of administration of dinutuximab, and not the most likely clinical scenario.

The cost of administration is an important factor in the economic analysis of dinutuximab. Based on NICE's base case assumptions, if dinutuximab were priced at £0, the product would still have an ICER greater than £50,000 per QALY, which is above the NICE cost-effectiveness threshold. Under the base case assumptions proposed by NICE, an innovative and beneficial treatment for neuroblastoma, an ultra-orphan disease, in a paediatric population administered in an inpatient setting would be unable to demonstrate cost-effectiveness at any price, due to the health system and associated administration costs.

Use of a weighted average dose: NICE's base case assumptions used a weighted average dose to determine the total cost of drug when determining the ICER for dinutuximab. The Company agrees that a weighted average approach is reasonable to determine the total cost of drug. In patients with a body surface area (BSA) greater than 1 m^2, more than 4 vials may be required to achieve the recommended dose for dinutuximab. While a higher BSA does result in a greater drug cost for dinutuximab, very few patients are likely to have a BSA requiring more than 4 vials. In the dinutuximab clinical trial ANBL0032, only 4.8% of patients had a BSA greater than 1 m^2. Based on this assumption, the weighted average dose per cycle for patients receiving dinutuximab would be 4.2 vials. The Company would like to confirm that NICE's base case model uses this same weighted average dose per cycle.

Health-related Benefits which are not captured in the Economic Analysis

In addition to the issues with the economic analysis assumptions described above, there exist substantial health-related benefits which are not captured in the economic analysis. While NICE recognized in the ACD there were benefits not captured in the economic analysis (eg, neuroblastoma is a devastating disease affecting children), it could not form an opinion of the extent of benefit.

Health-related quality-of-life benefits extend beyond those which are captured in the economic analysis for dinutuximab. Benefits extend not only to patients (whom in this case, are often young children), but to parents, siblings, and other caregivers as well. These quality-of-life benefits are difficult, if not impossible to comprehensively quantify in the context of an economic model, and include parental anxiety and mental health, strain on family relationships, and the time required of parents or other family members providing care for a child with high-risk neuroblastoma.

There are health-related quality-of-life reductions due to toxicity related to immunotherapy. However, physicians with experience using dinutuximab in the US express confidence that immunotherapy has markedly less negative impact on health-related quality-of-life compared to standard chemotherapy that

patients had previously received as induction and consolidation therapy for their high-risk neuroblastoma. Physicians have indicated that the lives of patients undergoing treatment with dinutuximab are nearly normal during the therapy and that patients resume normal quality-of-life quickly after completing therapy.

As noted above, several physicians in the US with experience using dinutuximab, reached out to the Company upon learning of the preliminary decision by NICE to not recommend dinutuximab. Many of the statements from these physicians related to the quality-of-life of patients with high-risk neuroblastoma who have been treated with dinutuximab are noted above. As noted above, John M Maris, MD, Giulio D'Angio endowed professor of paediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania has indicated that based on the preclinical and clinical data as well as first-hand experience, dinutuximab is considered the standard of care in patients with high-risk neuroblastoma and has revolutionized the approach to treating high-risk neuroblastoma.

Additionally, the Committee acknowledged the severity of the disease and the importance of generating health benefits for this patient population, but could not form an opinion about the extent of the impact of health-related benefits not captured in the model. While there is no published evidence detailing the burden of neuroblastoma affecting children, young adults, and their families, Gavin and Wendy Lindberg (Co-Founders of The EVAN Foundation and parents of Evan Lindberg, who was diagnosed with neuroblastoma) provided insight to their journey throughout Evan's treatment:

> *"High-risk neuroblastoma is one of the most devastating diagnoses a family can receive. To learn that your young child has less than a 30% chance of long-term survival is beyond heartbreaking. Our son Evan was diagnosed with Stage IV, n-myc amplified neuroblastoma in 2006 at the age of three. He fought with incredible courage and grace for four years before succumbing to this insidious disease in 2010. Evan was just seven years-old when he passed. He was our only child.*
>
> *Throughout Evan's treatment, we leaned on two things; the promise of treatment advances in neuroblastoma, and the hope that somehow our son would beat the odds. Both were essential in caring for a child with neuroblastoma. A snapshot of what Evan was forced to endure is below:*
>
> - *1,430 days as a patient – not one without treatment or recovery.*
> - *6 weeks of high dose chemotherapy and neutropenic recovery.*
> - *100+ nights in the hospital [for induction, consolidation, and maintenance treatments].*
> - *75+ nights in Ronald McDonald Houses away from home*
> - *4 relapses and 4 Phase I clinical trials*
> - *7 surgeries, 4 of which were brain surgeries (1 emergency surgery)*
> - *35+ week-long rounds of "low-dose" intravenous chemotherapy.*
> - *25 excruciatingly painful days of immunotherapy (3F8) and recovery.*
> - *Weeks of radiation to brain, spine, abdomen and hip.*
> - *A constant stream of CTs, MRIs, MIBG's, bone marrow pulls, blood draws, shots, physical therapy and other procedures.*
> - *Pain, nausea and discomfort as constant companions.*
>
> *The same week in 2010 that we took Evan home from the hospital for the last time to begin hospice care, the results of the Phase III, ch14.18 trial were published. Although this was ground-breaking news in the world of neuroblastoma, it left us with a hollow feeling. We did not enroll Evan in the ch14.18 trial. We opted for another immunotherapy option at Memorial Sloan Kettering Cancer Center in New York. To learn that the trial was stopped early after two years because of the difference in survival between ch14.18 and isotretinoin was remarkable. While there would have been value from a statistical standpoint in seeing data beyond two-years, we agree with the Children's Oncology Group [COG] that it would have been unethical to continue the trial given the difference in survival rates.*

We will never know if Unituxin would have made a difference for our son. However, we take some comfort in knowing that the option was available to us. Options equal hope and Unituxin is an important therapeutic option. It is the first therapy approved to treat children with high-risk neuroblastoma. It has more clinical data associated with it than any other neuroblastoma treatment. It answered the longstanding question whether immunotherapy contributes to the long-term survival of high-risk patients. It is the standard of care for children in the United States.

We understand that there is a SIOPEN clinical trial open to eligible neuroblastoma patients in the UK that provides an immunotherapy treatment option. What happens to those children who do not meet the eligibility criteria for the trial? Are they relegated to treatment with isotretinoin with no opportunity to benefit from immunotherapy unless they travel to the U.S.? Throughout Evan's treatment, we met families from England who uprooted their lives to come to the U.S. to enroll in the COG ch14.18 trial. What an incredible hardship to endure on top of the devastation of dealing with a neuroblastoma diagnosis.

We appreciate the cost considerations that NICE takes into account when making determinations about coverage. We don't envy the challenging position you are in or the difficult decisions you have to make. In our view, however, the one segment of the population that deserves every consideration when it comes to the expenditure of healthcare resources aimed at prolonging life is children. Even if Unituxin is not curative for some patients and might only prolong life for one or two years, that is priceless time for a child and their family.

Given that Unituxin is the only EMA-approved therapy for high-risk neuroblastoma, we encourage you to find a way to make the treatment available to patients in England and Wales. Families seeking every opportunity to give their child the best chance at the longest possible life will be forever grateful. Thank you in advance for your consideration of our views."

Revised Economic Analysis

As outlined above, the Company recommends the following changes to the Committee's base case analysis:

- Utilizing a 1.5% discount rate for outcomes, due to the long term health benefits associated with dinutuximab treatment and precedent set by the mifamurtide for the treatment of osteosarcoma (TA235) decision
- Utilizing a 5 year cure point, given the significant uncertainty associated with the survival analysis data
- Utilizing the ERG base case analysis cost per hospital day as opposed to the Committee's higher estimates (utilizing the ERG scenario analysis)
- Utilizing a weighted average of 4.2 dinutuximab vials per treatment course, to ensure that the product utilization is not over-estimated

With these modifications to the model, the base case ICER is reduced to £50,329 per QALY.

The Company believes that dinutuximab represents a significant and innovative therapeutic advance for a rare paediatric disease with severe health consequences. As such, dinutuximab is now considered the standard of care for patients with high-risk neuroblastoma in the US. The treatment delays disease progression, improves overall survival, and offers a potential cure to neuroblastoma patients. The Company believes that these and other health-related quality-of-life benefits may not have been adequately and fully captured in the preliminary ACD economic analysis presented by the NICE Appraisal Committee. The Company believes the revisions contained herein represent a fair assessment of the evidence and result in dinutuximab representing a good therapeutic value for money for patients with a devastating ultra-orphan paediatric condition. The Company would like to work with the NICE Committee to ensure access to dinutuximab for this patient population.

NEUROBLASTOMA UK
FIGHTING CHILDHOOD CANCER

[redacted]

24 November 2015
By email

To whom it may concern

Response of Neuroblastoma UK to the Appraisal Consultation Document (ACD) on dinutuximab (maintenance, after therapy) [ID799]

Neuroblastoma UK (formerly the Neuroblastoma Society) was established as a registered charity in 1982 by parents of children who had died of neuroblastoma. Since then we have raised and invested millions of pounds to support scientific and clinical research studies, some of which have latterly been in collaboration with other charities. Research grants are made following a robust appraisal process, incorporating peer appraisal by UK and international specialists, and supervised by a Scientific Advisory Board including European experts. Among other outcomes, our research projects typically generate a number of papers in ranking scientific journals. We also work in collaboration with the International Society of Paediatric Oncology European Neuroblastoma (SIOPEN) and the Children's Cancer & Leukaemia Group (CCLG) to support the establishment and conduct of international clinical trials, and organise a biannual UK research symposium attended by up to 200 researchers and clinicians.

This preamble demonstrates our commitment to rigorous scientific investigation and an evidence-based approach to evaluating the effectiveness of candidate treatments. We have been associated with immunotherapy treatment for neuroblastoma patients since its first introduction into the treatment strategy in the European (SIOPEN) High Risk Neuroblastoma trial. Hence we have followed closely the spectrum of emerging data and results on immunotherapy in the context of high risk disease. We acknowledge the importance of thorough and rigorous appraisal of available evidence using consistent methodology, as demonstrated in the ACD.

It is in this context that we register our concerns and queries about the outcome of the appraisal and its implications.

The appraisal concluded that the level of event-free survival (EFS) and overall survival (O/S) associated with immunotherapy were insufficient compared to the costs of the intervention. Increases of 5.6% and 7.7% respectively may not be considered statistically or methodologically significant, but they are hardly insignificant for the children who benefit. A few more years for a young child can represent a doubling (or more) of their life expectancy, benefiting the child, the parents and the wider family. This is quite different to applying the same criteria to an adult. We also note that extended life provides additional time during which new treatments might become available which may further help the child to live longer and survive long term.

The appraisal also concluded that one of the three end-of-life criteria was not met, with the apparent paradox that, despite the EFS and O/S figures, children are considered likely to live too long for the median life expectancy criterion to apply. This leads us to observe that while the unit costs of immunotherapy may be considered high by NICE standards, the numbers of children who will receive the treatment is small. Hence the overall cost to the NHS is not actually that high. (It also prompts us to enquire whether any reduction in the proposed pricing of the antibody by the supplier would affect the analysis and the recommendation of the Committee.)

In terms of the methodology, we respect the effort and expertise of the ERG, but we do have some queries about a few aspects of the methodology and subsequent interpretations. In particular:

- We assume that the decision to retain the reference discount rate rather than allow the 1.5% rate for those likely to survive long-term will have had an impact. In lay terms, this assessment is based on whether a person who survives long term can be expected to be a burden on the NHS due to additional health problems. While we accept that there are consequences of the disease and its treatment, it is not clear that these are sufficient to assume that a survivor will need a noticeably higher level of NHS care in the future. Hence we ask whether the 3.5% rate could not have reasonably been applied.

- The choice of data cut by the ERG was significantly influenced by the decision to close the control arm of the relevant CPG study and the consequent impact on numbers, but we understand very well the clinical and ethical decision to do that, given the data emerging at that time. It seems unfortunate that the consequences of this decision should appear to have had an impact on the view taken of the trial data.

The Appraisal Committee described cis-retinoic acid (CRA) as the existing standard treatment, but in practice (as the Committee is aware), immunotherapy together with CRA is currently considered to be included in the standard treatment for children with high risk disease in the UK. This is currently provided within the SIOPEN High Risk Neuroblastoma clinical trial into which more than 95% of UK high risk patients are entered. We know that clinicians believe that patients should continue to have access to the antibody in the context of clinical trials so that medical science can establish the role of the therapy and the best way to administer it. Now is not the time to stop (by stopping patient access to the antibody) continuing and further evaluation of this exciting treatment option which has already been shown to improve EFS in this aggressive disease. Treatment options are currently limited, and we must point out that should such treatment no longer be available in the NHS, for example if no variant of immunotherapy is approved and licensed, it is almost certain that parents will seek it in other jurisdictions, with very significant financial, economic and social costs in addition to the personal impact. We understand that this may not be considered to fall within NICE's remit, but it is our responsibility to point out this potential consequence.

It will be clear from the above that many of our questions and concerns relate to whether the standard NICE methodology, including the allowed discretion and exceptions, are suitable for appraising an intervention of this type and for children suffering with this aggressive disease (and indeed other cancers). In other words, regardless of the details of this particular appraisal, we are concerned that it would be extremely difficult for any promising treatment for neuroblastoma to be approved. Any clinical trial will experience a significant challenge in accrual, given the relatively small numbers of babies, infants and older children affected and the smaller subset that will meet the entry criteria for a given trial, so the data and its analysis will always be affected (and we refer again to the potential impact of an ethically-driven clinical decision to prioritise provision of a treatment over maintaining the strict controls for a clinical trial). Over 30 years' experience has shown us that it is not realistic to expect a 'silver bullet' treatment or cure, but it seems that anything less would struggle to pass a current NICE appraisal.

For an organisation dedicated to improving treatment for children with cancer, this is a disturbing thought, and not a message that we would wish affected families and the wider public to receive. This is the more worrying given existing concerns about the relevance to children's cancer of recent NICE publications (e.g. the Referral for Suspected Cancer Guidelines, and the quality standard for sarcoma). We therefore urge that NICE undertake to look at the methodology used to assess whether it is fit for purpose in this very specialised rare disease group. This is work that could be done with Neuroblastoma UK and other interested children's cancer charities as well as professional bodies such as the CCLG, and the National Cancer Research Institute. We will liaise with such parties in anticipation of such an assessment, and to communicate our views of the appraisal and our aspirations for the future in response to public and media interest.

Yours faithfully

[redacted]

[redacted] Neuroblastoma UK

Comments on behalf of Solving Kids Cancer

In our assessment, the committees report into the evaluation of dinutuximab has several shortcomings.

Firstly, the difficulties of conducting a clinical trial in this population did not seem to be fully understood. The high relapse and mortality rate of children with high risk neuroblastoma does mean that families will go to extreme ends to make sure their children receive the best possible treatment. If the ANBL0032 trial had not been stopped early because of the clear difference in efficacy, it is not certain that the trial would have continued to accrue patients at the rate suggested. At the time this was an unproven treatment that entailed significant hospital stays and therefore there was the real possibility that families would choose to enrol their children on other clinical trials. In this context, it is an achievement that the trial accrued in the way it did. It should be understood that there are special challenges to conducting a randomised control trial in high risk neuroblastoma patients. The numbers of children who are diagnosed is very small and the numbers available for the trials are even smaller. These are challenges that do not exist in many adult cancers and many other childhood cancers. These extra difficulties do not seem to have been taken into account in the committee's assessment, and if they had been, they would have been more favourable to the ANBL0032 trial. The subsequent analysis of the early results led to the landmark New England Journal of Medicine paper in September 2010, which has contributed to this treatment becoming the standard of care in the US, Canada, Australia and New Zealand.

Because NICE is such a respected organisation, the decision to reject the treatment will be a devastating blow for the feasibility of conducting trials into new treatments for this disease. Without the ability to have these trials progress to a reimbursable treatment, the decision is likely to have a negative impact on pharmaceutical interest in the disease.

Eurocare studies that have assessed the survival rates of cancer diagnosis across Europe, have in the past identified neuroblastoma as one of the few paediatric cancers that showed a significantly poorer survival rate in Europe compared to North America. Much effort has been expended to close this gap and this decision could reverse the gains made. If this does happen, families may be left with the impression that their children's chance of survival has been directly set by a chiefly financial decision. In this context value for money will only truly make sense when there is an alternative treatment path. In this case there is none, except a place on a trial of an untested drug.

Lastly, a key part of the analysis of dinutuximab used an extrapolated and fitted curve to the survival data. We believe that this use was unwarranted because; in the context of neuroblastoma patients there was no presented evidence that the population group would respond in this way and more specifically in this case, the statistical evidence at 4 or more years from the commencement of treatment was too weak. It also does not appear that the committee took into account that the key trial was not run by United Therapeutics and was chiefly designed to test for 2 year event free survival – not 10. While we can be disappointed with the price set by United Therapeutics for dinutuximab, the attempt to use extrapolated ten year data in this population of extremely vulnerable children does not appear appropriate.

We urge the committee to reassess the decision and take into account the special circumstances surrounding both the trial that generated the data in question and the patient group the treatment will serve.

[redacted] | [redacted]
The Neuroblastoma Children's Cancer Alliance UK

Response to Appraisal consultation document "Dinutuximab for treating high risk neuroblastoma" – Released October 2015

Many thanks for the opportunity to comment on the consultation documentation released in October 2015.

We would like to make the following comments:

i) On page 20 of the consultation document, it is stated that *"The Committee considered current clinical practice within the UK for treating high-risk neuroblastoma It is understood that Isotretinoin is the standard of the care for patients in the UK for patients with high risk neuroblastoma who have received induction chemotherapy followed by surgery…"*

As stated in the meeting on 6th October 2015, virtually all children in the UK with high risk neuroblastoma have received anti-GD2/CHO based immunotherapy since 2010, as part of the SIOPEN HR-NBL-1 or SIOPEN LTI trials. In view of the results of ANBL0032 study (released in 2009) it was felt unethical and unacceptable to consider Isotretinoin alone as the 'standard' arm in the HR-NBL-1 study and all patients within the study have received ch14.18/CHO. For the very small number of patients that have not been eligible for ch14.18/CHO within one of these SIOPEN trials, we have sought to obtain anti-GD2 antibody for the child through another source, e.g. the Idis Managed Accessed Programme. Therefore some form of anti-GD2 antibody therapy, in addition to Isotretinoin, has effectively been considered a standard of care in the UK for these children since 2010.

ii) We acknowledge that the differences in overall survival and event free survival between the standard and immunotherapy arm have been lost by 10 years, in part due to the small numbers of patients at the later time points. Whilst in an ideal word a further, larger, randomised study would be conducted (with Isotretinoin as standard arm and Dinutuximab immunotherapy as the experimental arm), it is very unlikely that it will ever be possible to conduct such as study as Isotretinoin alone would be unacceptable to most parents and clinicians.

iii) Within the UK our priority will be to continue to try and ensure that we have clinical trials open to improve the delivery and efficacy of anti-GD2 therapy, and to ensure children have access to this form of immunotherapy, this may not always be possible. We are therefore likely to be faced with children and families seeking to travel abroad for therapy if the treatment is not available through NHS funding.

iv) We feel some consideration to the young age of the patients involved, and the 'value' that parents and society place on extension of an incurable child's life. Extending a 5 year old child's life for e.g. 5 years, even if he or she subsequently dies from their disease, is likely to be viewed as hugely valuable, providing the quality of extended life is good. In addition, extension of survival, even if only for a few years, offers the hope to parents that an innovative and effective treatment may become available within that time, and change an otherwise poor prognosis to a better one.

v) In the consultation meeting, comparison was made with the previous appraisal of Mifamurtide. We would be grateful if clarification could be provided as to the

special circumstances that were applied in this appraisal, which may potentially be applicable to Dinutuximab.

This statement represents the personal views of:

Dr Juliet Gray, Associate Professor and Consultant in Paediatric Oncology, University of Southampton

Dr Martin Elliott, Consultant Paediatric Oncologist, Leeds Teaching Hospital NHS Trust

Appraisal Consultation Responses

Nicholas Bird, Patient Expert, 25 Nov 2015

1. Specific Comments

1.1 [Section 2.3, Page 4]

Considering the development path for dinutuximab, that UTC only came on to the scene at a relatively late stage to commercialize its manufacture, that it has received a Creating Hope Act voucher which it sold for $350M, that it is already able to sell into the U.S. healthcare system, that the administration costs associated with the treatment are high, the amount that the company is seeking to charge per child is too high. That said the potential payback for pharmaceutical companies developing drugs to treat children with cancer, most of which are ultra-rare diseases with very small patient populations, is very limited. It should be recognised that dis-incentivising drugs companies from investing in this area will only result in more difficult climate, and it will ultimately be children with cancer, and by extension their families, who will suffer even more.

1.2 [Section 3.16, Page 11]

ANBL0032. The specific and very technical point about the criteria for early stopping having not been met, was highlighted for its significance and used to cast doubts about the validity and integrity of the research that was conducted, and results that were collected. This should be viewed in the context of the trial, and the implications that an ultra-rare disease such as neuroblastoma has for conducting clinical research.

Meaningful Phase III clinical trials can only be run through wide-scale collaborative efforts. ANBL0032 was a trial operated by the Children's Oncology Group and was open at institutions across North America and beyond. To put this in context, ANBL0032 is still open at 191 locations across United States, Canada, Australia, and New Zealand; a significant number of which would have been involved in the randomization study.

The trial opened for enrolment in October 2001 and had been running for 8 years when it was stopped early for efficacy and ethical reasons. Had it continued then it was not expected to complete enrolment until mid-2012. It was conducted using best practise, with a data review committee, and independent data safety monitoring committee (Page 300, Committee Papers Oct 2015). It underwent several revisions to the study design, in consort with the FDA, including amending the alpha in spending function from 0.05 to 0.025. The results from January 2009 were not reproduced in June 2009, this was a different data cut and any such retrospective analysis should be set against the background of how the trial was being conducted in real-time.

It's also worth noting that it took more than 7 years to accrue a sufficient number of patients to determine the significant 2-year EFS difference. The trial may have been stopped early, but the process of getting there was slow and arduous.

The trial was closed early for efficacy *and* for ethical reasons as the difference between the two arms was large; it was deemed not ethical to enrol more children on a randomized trial and thereby deny them access to anti-GD2 immunotherapy. Indeed, such was the moral and ethical dilemma, that it was decided earlier children who had been enrolled on the control arm would be subsequently offered anti-GD2 immunotherapy on a compassionate basis.

When viewed in the appropriate context it should be seen why ANBL0032 was closed early, and why it would be completely impossible to repeat this research. The simple fact is that researchers internationally agree that anti-GD2 immunotherapy is now an important part of high-risk neuroblastoma treatment, and it would be impossible to conduct a randomized trial in which some children did not receive this intervention. Not least because the parent community would be completely up in arms were any such trial to be conducted, even if researchers believed there was merit in doing it.

1.3 [Section 3.17, Page 12]

When clinicians discuss outcomes with parents, a time point 5-years of continuous remission is often used as the time at which an individual family can feel more hopeful about long-term survival i.e. it is most appropriate for thinking about an individual child's risk of relapse.

Five-year survival is also the benchmark for comparing survival outcomes in high-risk neuroblastoma. This is a major bone of contention with parents because we recognise that 5-year overall survival does not necessarily mean a child is cured and will live to grow up.

However, it is a benchmark that is used for assessing incremental improvements in outcomes due to changes in treatment and care.

In assessing improvements in outcomes from clinical trial research in high-risk neuroblastoma is it usual for 2yr or 3yr EFS to be reported, and long-term results (not always published) would tend to look at 5yr OS.

The following from Children's Oncology Group regarding another high-profile randomized Phase III trial of Bone Marrow Transplant indicates this point.
http://jco.ascopubs.org/content/32/36/4174.full

It is my view that 5-year OS from March 2014 should be used. There are still 74 and 53 patients at risk, compared to 10-years out when these numbers have dwindled to 9 and 7 (Figure 13: Kaplan-Meier plot of OS, March 2014, Page 307, Committee Papers Oct 2015). This seems a woefully inadequate number of patients on which to base any kind of worthwhile quantitative comparison. The trial was open from Oct 2001 through January 2009, and using analysis of 10-year survival data from March 2014 surely means that, by definition, only those children who were enrolled before March 2004 would be contributing to the longest time periods in that analysis?

In many respects the ANBL0032 is being twice penalized because it accrued so slowly - caused by the limited number of eligible patients available. Not only is this a bad thing itself in terms of being able to answer research questions as quickly as possible, it now becomes a further hindrance because the data is being analysed in this manner.

When considering EFS or OS, the paradigm of neuroblastoma relapse being uniformly fatal is now being challenged. The use of salvage chemotherapy, targeted drugs, novel agents, and

anti-GD2 immunotherapy in a relapse setting means that long-term survivors of relapsed neuroblastoma are a growing population, and this can reasonably be expected to continue.

1.4 [Section 3.18, Pages 12 - 13]

Notwithstanding the above comment, using a modelled cure rate of 47% in both arms is not appropriate. At 10-years the difference is 5.6% in EFS and 7.7% in OS. If 10-year survival data is to be used these are the appropriate numbers. Whilst the data is the data, the horizontal survival curve in the standard therapy arm beyond four years, and occurrence of late relapses in the dinutuximab arm, does not mean that it is appropriate to fit a parametric model and therefore close the difference down to zero. The relapse rate is discrete, and should not be modelled in this way. It is unknown what the data will show beyond 10-years, or how the results will look when a larger number of patients have reached 10 years of follow-up.

1.5 [Section 4.16 - 4.17, Pages 30 - 32]

It would appear that the decision about whether or not it is appropriate to use a 1.5% outcome discount rate, is highly dependent on the decision regarding which data cut, and follow-up duration, is the most appropriate to use. The decision to use the weakest set of results; 10-years from March 2014 with a model-fitted overlay provides the poorest justification for using a 1.5% outcome rate. Again the committee should reconsider this decision. In particular, it should consider contributions of the international paediatric oncology research community as to what is considered best practise when conducting research in this particular field in order to guide its use of the available data.

1.6 [Section 4.23, Page 34]

The median life expectancy for patients with high-risk neuroblastoma was 4 years.

“Population-based survival curves created using the most recent data available for patients aged 1 to 14 with neuroblastoma in Great Britain (December 2002 to December 2005) show a median survival of approximately 4 years (Stiller 2012). “ (Pages 84-85, Committee Papers)

I believe this may be incorrect. The Population-based survival curve from this paper is for children diagnosed with neuroblastoma at age 1-14. This would include the 50% of children diagnosed with low and intermediate risk neuroblastoma, for whom the prognosis is generally excellent.

A common cause of misinterpretation (and misuse) or statistics is referring to neuroblastoma as a single disease when the dichotomy of outcomes between high-risk neuroblastoma and other risk groups is extreme.

2. General Comments

2.1 The amount of time that the participants were given to prepare for the meeting was insufficient. Receiving a mountain of paperwork on 2nd October (I think?) for a meeting on the 6th did not leave enough time for any careful consideration prior to the meeting itself. Moreover, there was no real guidance as to the most pressing considerations that would ultimately affect the Committee's decision. None of the experts, clinical or patient, had any first-hand experience of how a NICE appraisal meeting works.

2.2 The three drivers to the ICER are; cost of treatment, perceived benefit, and discount rate. The discount rate is strongly linked to perceived benefit which rests entirely upon the interpretation of ANBL0032. During the appraisal meeting the view of the Evidence Review Group regarding this trial was largely accepted without challenge. UTC had no involvement with this clinical trial, neither did the clinical experts. Moreover, there appeared to be no expertise on the Committee regarding paediatric oncology, or of running clinical trials in this kind of patient population. The appraisal ought to be able to accept the views of experts in the field of high-risk neuroblastoma regarding the particular challenges of conducting clinical research in this ultra-rare disease. It ought also to specifically refer directly to the investigators involved in ANBL0032 as to how the trial was designed, conducted, and the results are being interpreted within the international research community. It should use this information to decide which data cut, and outcome duration is the most appropriate to use. UTC were not involved in the research and development of this drug, only coming in at a much later stage during its commercialisation.

2.3 Why are the committee requiring event-free survival data at 10 years after randomization? Why are they assessing effectiveness using cure as the primary determinant? Are these approval criteria the same as those routinely applied in the assessment of adult cancer drugs, and if not why not? It cannot be the case that more stringent criteria are applied when deciding whether or not to approve drugs for children with cancer? Otherwise, how is that fair? And how will drugs for such diseases ever get approved?

2.4 High-risk neuroblastoma is a disease that kills small children. The incidence in the UK is around 50, and fewer than half of those will currently survive with the best available treatments. There was an average of 37 deaths per year due to neuroblastoma (SNS cancers) in Great Britain from 1996-2005 (http://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/mortality#heading-One). The disease accounts for around 5% of incidence and 10% of deaths due to cancer in children; around half of the incidence, but the vast majority of deaths, are due to high-risk neuroblastoma. The point being that outcomes are poor, and too many children are being lost to this disease.

There is enormous unmet need for better, safer, and less toxic treatments for these children – and indeed for children with cancer in general. Improvements are almost always slow and incremental. And the debate about their true effectiveness often continues even after they've become part of standard therapy; Rapid COJEC induction therapy, Autologous Stem Cell

Transplant, Isotretinoin. Some would question the strength of the scientific evidence that resulted in these becoming part of standard treatment over the years. And certainly there has never been any published 10-year EFS follow-up on any of these clinical trials. However, with their introduction long-term survival for children diagnosed with high-risk neuroblastoma has gradually improved. Gradually and incrementally, not dramatically.

Ch14.18 was 30-years in the making. It is the first new drug to be approved, anywhere in the world, for use in children with neuroblastoma in decades. There is very poor engagement from pharmaceutical companies as development costs can be high, and the potential payback very limited by the size of the patient population. This provides a hugely challenging environment for researchers to work in, and is an enormous source of frustration for the parents of these children. Poor funding and poor access to new drugs, means limited research, which in turn means stifled progress.

These are all important aspects of the treatment of childhood cancer which cannot be captured in a very dry and technical cost-benefit analysis, such as has been undertaken. The appraisal process also does not take into account any of the wider implications that this decision might have on the drug development landscape, and therefore on the ability of researchers to make that next incremental, yet vital, improvement in outcomes.

2.5 How often, comparatively, does NICE appraise a drug for paediatric cancer? Or an ultra-rare disease that affects children? Are the NICE guidelines even adequate when it comes to assessing these kinds of diseases? That are chronically under-funded, in desperate need of better and less toxic therapies, and where even the smallest of children are given drugs developed to treat adults. Although the £/QALY may be significantly higher than the threshold at which approval is usually given, the total numbers of patients is very small, and comprised of a very special sub-set of the population. There needs to be a wider consideration of how the process deals with diseases and patient populations that are 'special' by their rarity, their vulnerability, and their inability to advocate for themselves. The costs of drugs solely for these patients, without having any other adult indication, are bound to be significantly higher.

Is it appropriate that the approval process for a drug for a disease that affects a small number of children under five is conducted in exactly the same way as would be a drug for, say, prostate or breast cancer?

Or that a disease for which there has never before been an approval request, and for which the number of approval requests will by definition be very small, be subject to the same scrutiny as a disease where there are lots of potential treatments available and perhaps the decision comes down to the fact that not all of them can be funded.

Should there not be a mechanism whereby approval requests for diseases like high-risk neuroblastoma are taken offline; where clinical experts are engaged to assess the effectiveness, and approval can be given in principle subject to some kind of agreement on price? This is not to suggest dismissing the scientific evidence, but to question whether the balance is right in this instance.

In my experience when childhood cancer and adult cancers are thought of in the same way, childhood cancer always comes off worst. How can that be justified?

NICE can approve many drugs for the same adult cancer, for which the cost-benefit number is within range. The drug company can sell it more inexpensively and make money due to the number of units sold. And because of the incidence of the disease, the cost of this drug to the NHS will be large. However, based on a supposed large cost-benefit number NICE cannot approve one single drug for a paediatric cancer for which the absolute cost will still be (comparatively) miniscule.

So not only does the whole drug development situation work against children with these ultra-rare diseases, so too does the approval system when assessing those tiny number of drugs that do actually get developed and seen through to approval.

Children with this disease deserve to be given every possible chance to grow up. If 37 children die of neuroblastoma per year, and this drug can save only 1 of them, how can that not in itself be sufficient to find a way for it to be approved?

2.6 A negative decision will adversely affect UK families with children suffering from neuroblastoma regarding how they view NHS provision. A treatment that is approved by the FDA and EMA, yet denied to children in the United Kingdom will be seen as an indictment of a second-rate healthcare system that does not care about its country's children.

2.7 A negative decision will be in direct contradiction of the international consensus amongst researchers that anti-GD2 immunotherapy improves outcomes for children with neuroblastoma, and is significant in saving the lives of children who prior to current day therapy had a dismal prognosis.

2.8 A negative decision will leave UK children at the absolute mercy of supply of ch14.18/CHO by APEIRON Biologics (APN), a direct competitor of United Therapeutics (UTC), in order for them to have continued access to anti-GD2 immunotherapy in this country. APEIRON have filed their own approval request in the UK, and clearly, there are commercial considerations already in play here. Should UTC's Unituxin not be approved, it is difficult to see how APN's APN311 could ever gain approval considering the only Phase III randomized study data remains unpublished, and comes from the SIOPEN clinical trial which has no standard therapy arm. The reason for this being the consensus that anti-GD2 is an established and accepted part of standard therapy, and to deny any child access to it would be unethical.

2.9 Without approval of Unituxin children in the UK would be solely reliant upon continued access to anti-GD2 immunotherapy through clinical trails, even though it is considered part of standard therapy. Continuous access to APN311 cannot be relied upon, and whilst this is not a case of UTC vs APEIRON, putting APEIRON in a position of such strength regarding access to ch14.18 in the UK would be potentially dangerous.

International researchers agree that anti-GD2 immunotherapy is an established part of neuroblastoma treatment. As such, UK children should have the *right* to ch14.18, and their parents the *choice* of whether or not to enrol them on a clinical trial seeking to make further improvements. They should not be forced to enrol on clinical trials to receive what is now considered to be a standard treatment.

2.10 A negative decision raises the prospect that children in the UK could, at some point in the future, be unable to receive anti-GD2 immunotherapy in this country. The prospect of parents having to raise hundreds of thousands of pounds and travel abroad to access a treatment that clinicians agree is part of recognised standard therapy would be completely indefensible. The potential fallout would be enormous, and political.

2.11 The idea that anti-GD2 is not part of standard therapy, and it remains a possibility for children in the UK to go back to receiving isotretinoin alone as a maintenance therapy, as they did before 2009, is incomprehensible.

Parents do not care whether UTC or APEIRON, whether ch14.18/SP2/0 or ch14.18/CHO. They don't care whether one, or other, or both, drugs are approved. They want their healthcare system to provide the best available treatment for their children.

2.12 Neuroblastoma does not simply affect the lives of children. The effects are felt throughout families, and communities. It is not uncommon for parents to have to give up their careers to care for their children, or simply through being unable to work due to stress. They must live off welfare, disability and carers allowances. The strain on relationships leads to marriage breakdown and divorce, people lose their houses. It really is no exaggeration to say that neuroblastoma ruins lives. How these effects can ever be captured and understood in an economic cost model is hard to envisage.

Name	[redacted]
Organisation	
Role	
Job title	
Location	
Conflict	
Disclosure	
Comments	Our first and only child has been diagnosed with High risk Neuroblastoma in March 2014 a week before his first anniversary. We enrolled him into the SIOPEN clinical trial and has been treated at Great Ormond Street Hospital in London. Treatment lasted until June 2015 (15 months) The 15 (long) months of the treatment have severally impacted our lives, careers, health, revenues of the family and particularly us as parents. The mother (university professor) had to stop working for 15 months, the father (financial Engineer) stopped working for 10 months and then was working half time for 5 months. Now we have to try to restart our life where we left it 15 months ago with the knowledge that our son has a 50% chance to relapse in the next two years. (relapse is almost equivalent to death in 90% of the cases). If he makes it he will be sterile, with growth issues, 4 reduced vertebra (irradiated ones), have hearing issues and have a much higher risk to get a secondary cancer as a consequence of the first phase of the only treatment available. Still we are lucky he is still alive, others didn't have that chance. The current treatment for High Risk Neuroblastoma, is a desperate attempt to use all the tools available to medicine to eradicate this deadly cancer. The treatment is designed to create several near death experiences in the hope that the cancer cells won't recover and the good cells will. Even with all of that, the Event Free survival rate after 3Y is between 30 and 50% Chemotherapy and radiation have very high level of toxicity and have a lot of very worrying long term effects, the only ray of hope in all this is the immunotherapy approach. Long term effect are close to none (as far as we currently know) and it increases by 10% the survival rate. An additional 10% may seems small but increasing the survival rate from 30% to 40% mean saving 33% more patients who could enjoy a few decades of life. We sincerely hope that some additional funding will be provided to research and develop new treatments to increase the survival rate and in the future to obsolete the current

	devastating chimio/radio mix. We understand the antibodies drugs are expensive. It could make sense not to make the American version available to UK patients as long as the European Siopen is accepting new patients. However in 2017 when the trial will stop, I sincerely hope that one of the antibody drug will be available to UK patients. Unfortunately the COG Dinutuximab (Unituxin) will probably never be compared in a trial against the European Siopen ch14.18 anti-GD2 antibody, but I hope NICE will approve one of the drugs. What we would have done if no antibodies treatment was available in the UK?: Well, we already decided to travel to France for the radiation therapy part of the treatment. (Proton therapy could spare some toxicity compared to photons, but won't be available in the UK before 2018). Therefore if antibodies were not available in the UK when our son needed it, there is no doubt we would have travelled to get them. This would have had a much higher impact on us physically and financially. When doing the cost/return ratios and analysis, we would kindly suggest to take into account the following: Few patients will be eligible for the drug anyway, even if the cost is around GBP 120k, it should be kept in mind that, immunotherapy increase by 33% the number of patient saved. And for each surviving patient about 60 years of life (or more) is at stake. It is very different than for adult type of cancers. This disease is rare, has a low occurrence but devastating consequences on the patients and families when the disease strikes. Parents are often in their 30's and have to stop working at a time of their career when they are supposed to receive a good income and pay a lot of taxes. The UK is a leading country in the field of Neuroblastoma research (NewCastle running the trial, Great Ormond Street treating a lot of patients, eminent professors and European specialists are based in the UK). We hope the UK will remain a leading player in the search for a decent cure for High Risk Neuroblastoma and will keep on providing access to an antibody treatment to its patients. Thank you for your consideration
Submission date	25/11/15

Name	[redacted]
Organisation	

Role	
Job title	
Location	
Conflict	
Disclosure	
Comments	In 2011 my 3 year old son was diagnosed with high-risk neuroblastoma, and our world came crashing down around us the instant those words were delivered. His disease was so extensive that we asked our oncologist if it would be completely futile to put him through treatment. The oncologist assured us that he had a chance, a small chance, of beating this disease and at that point we focussed our minds on doing absolutely everything it would take to help him do that. Our son endured the frontline treatment protocol for high-risk neuroblastoma for 6 months, at which point we realised he had stubborn disease in his liver which was not responding to the treatment. His consultant offered specialist radiotherapy as a potential solution. This felt like the right thing to do but came at a huge cost – he would have to go off the protocol which was offering anti-GD2 antibody. This drug was showing promising results, perhaps an extra 20% chance of beating this disease. When the estimated survival rate for your child is ~40%, and you have the opportunity to raise it to potentially ~60%, you will grab that chance with both hands. We explored the option of receiving anti-GD2 antibody off protocol through compassionate use, but this could not be guaranteed. On Father's Day 2012 we made the decision to launch a public appeal to raise the £250,000 it would take for us to access the therapy in the US. We didn't care that it meant uprooting our family, moving halfway around the world, travelling with a very sick child and his baby sister. We didn't care that we'd leave behind our friends and family for 8 months, leave our jobs, home, travel to a new hospital where no one was familiar and we'd have no support. We didn't care that the price tag was quarter of a million pounds. With an opportunity on the table to potentially extend the life of our precious 3 year old son we were not going to let that slip by. We considered selling our home, our cars, everything, but it wouldn't bring us close to the £250,000 needed. Instead we launched a phenomenal fundraising drive. I blogged, shared our "story" on social media, completed numerous television and radio interviews. I shared our "story" and family album with the world and begged the public to help us access a treatment which could potentially buy us more time with our son. My husband organised events, gathered supporters, and shook buckets on the streets of our town and far beyond. This all happened while I nursed my son through high dose chemotherapy and stem cell transplant, one of the most agonising treatments children with this disease have to endure, and while my husband worked full time to support our family. The stress this put upon us as parents, and as a family

	unit, cannot be overstated. After 102 days of intense fundraising we hit our target of £250,000. During this time we hadn't eaten properly, hadn't slept properly, and were separated from each other and under extreme pressure. As parents with a desperately sick child, nothing mattered other than putting his immediate medical needs first, and after much research and getting endorsement from our sons oncologist - accessing anti-GD2 antibody became the focus of this. We were under no illusion that this therapy was a "miracle cure", but we knew that it had the potential to give him that extra chance. To give us just a little more time with him. We couldn't ignore that fact, and very strongly felt that as his parents it was our duty to do everything within our power to get him what he needed. We were not the only ones who felt this way, and we know of several other families throughout the UK who have undertaken the same agonising decisions and followed the same difficult path to get this same treatment. High-risk neuroblastoma is a notoriously difficult disease to treat and parents are playing a very active role in pushing the boundaries of research in this area. The precedent for accessing United Therapeutics anti-GD2 antibody abroad has already been set, many families worked hard to raise hundreds of thousands of pounds to do that in the last number of years before the Apeiron antibody became more readily available, and many were supported by the Neuroblastoma Alliance charity (as we were). This charity became known as the Neuroblastoma Children's Cancer Alliance (NCCA) UK, and is now Solving Kids' Cancer. If the United Therapeutics antibody is rejected by NICE, and if for any reason the Apeiron antibody is no longer available within the UK on trial, or if there is any gap in availability of this antibody, then parents will feel compelled to do exactly what my family had to do. Solving Kids' Cancer has worked hard to turn the focus away from families needing to access therapy abroad, but this decision could take things right back to the situation as it was in the UK years ago. The pressure this would add to families going through the devastation of a serious childhood cancer diagnosis is just not acceptable. It is morally wrong to have a therapy considered as proven and "standard" for children in the US turned down for children in the UK. The message this sends to parents, to the wider public, and to drugs companies working in the area of paediatric cancers is so damaging, that the ramifications must be seriously considered by the panel from all angles. I've strived, as have many other parents, to show the pharmaceutical companies that this is an avenue that they must explore as the needs of children with cancer are completely unmet at present, and the decisions made by NICE will have significant impact on this. The cost per QALY, and the cost per child, may be high in an absolute sense but with such small

	numbers of children affected by high-risk neuroblastoma in the UK then this must also be given serious consideration. My understanding of this decision making process highlights even more that the more specific needs of children dealing with cancer in the UK are being completely overlooked. How can anyone consider the extension of a 3 year olds life by 5 years equal to the extension of a 63 year olds life by 5 years? It is simply not the same and never will be, and that cannot be justified by anyone on the panel. As a parent I will not stop raising awareness of these issues, and advocating for all children being dealt this cruel hand and not just my own precious son. Please take time to gain a greater understanding of this complex situation beyond the figures presented in this document.
Submission date	25/11/15

Name	[redacted]
Organisation	
Role	
Job title	
Location	
Conflict	
Disclosure	
Comments	Dear NICE, My child was diagnosed in May 2009 with high risk Neuroblastoma, she was just seven years old. I realised after a short time that her prognosis was very poor and that the chances of her disease reoccurring were stacked against her. Our happy, carefree lives were over that day, replaced by an existence of fear, statistics, opiates, scans, chemotherapy and a constant unimaginable sadness. My work was immediately effected and during the four and a half years my little girl was ill, I was forced to leave my job in order to care for her. Consequently my career has suffered and I doubt I will ever achieve was I aspired to do before my daughters diagnosis. My other child was ten when his sister became unwell, he remembers very little about his life pre-cancer. He is now seventeen and although physically healthy, his childhood too was a victim of cancer. When my daughter was being treated I was in utter disbelief at the protocol for high risk Neuroblastoma. It is rapid and vicious. The initial eight cycles of various combinations of chemotherapy given every ten days left little time for recovery. She spent much of those 80 days inpatient with infection. This was followed by stem cell harvest, surgery to hopefully remove the primary tumour, stem cell transplant and radiotherapy given every day, for fifteen days. The final phase of the protocol was ninety days of Accutane (if my memory

	serves me correctly). It didn't take me long to realise that for children in North America, the treatment protocol for high risk Neuroblastoma didn't end with Accutane but instead combined Accutane with Antibody Therapy. This is standard treatment at the end of therapy. When your child's prognosis is so poor, you tend to be of the view that your she needs to have every chance possible to overcome this disease We made the easy decision that she deserved to receive this therapy and our friends, family and community raised the £230,000 to pay for the treatment that we hoped would make the difference. We travelled to The US and lived there for six months so she could receive Dinutuximab with GMCSF and IL2 (along with Accutane) as part of her consolidation treatment. I feel the cost of nearly £130,000 for Dinutuximab per child is clearly excessive but could you consider approving it on principle and for negotiations to then take place with United Therapeutics with a view to cost reduction? It simply cannot be right that the same process for approving drugs used for adult cancers with far higher cases per year is also used for this small number of the most vulnerable children on the planet. My child relapsed and subsequently died but I do not regret the choice we made in seeking Dinutuximab as part of her treatment. It is inconceivable that this therapy may not be available to our children here in the UK, forcing families to fundraise and travel long distances to ensure their child has every chance they deserve. My child is dead and the plea to reconsider the current decision and approve Dinutuximab will not bring her back but it may help those children in the UK who have just been diagnosed and those not yet diagnosed with high risk Neuroblastoma to receive the treatment that will give them the best chance of survival. Yours Faithfully, [redacted] [redacted]
Submission date	25/11/15

Name	[redacted] [redacted]
Organisation	
Role	
Job title	
Location	
Conflict	

Disclosure	
Comments	I'm writing to ask that you reconsider your decision not to recommend dinutuximab for children with Neuroblastoma. I want to be a voice of the future children to be diagnosed with Neuroblastoma as they so desperately need one. My son was diagnosed with stage 4 high risk Neuroblastoma at the tender age of 2. A previously happy and healthy child we were catapulted into the devastating world of childhood cancer and it was a thousand times worse than we could ever have imagined. Faced with a grim prognosis and endless horror stories we started to research the treatments that we felt would give him the best chance of survival. We read up on the immunotherapy that America offered in their protocol and felt it far superior to what he was being offered. Still reeling from such devastating news, we were faced with having to raise over 200,000 to access dinutuximab and increase his chance of survival. Thanks to a huge effort from our community we raised the money and in December 2011 we boarded a plane to Children's hospital of Philadelphia where our son was given dinutuximab with GMCSF and Il2. He is now a happy and healthy 6 year old. What about the children who aren't fortunate enough to raise that amount of money? What about the children who can't travel? How can you put a figure on what their life is worth? How can you put such a high figure on a drug and then say our children are not worth it? Most children diagnosed with Neuroblastoma are under 5. Innocent victims of a cruel twist of fate, they deserve EVERY opportunity to fight this beast. Yes Neuroblastoma is rare, but that is of no comfort to the families that are taken into a side room and hear that word for the first time. Surely the fact it is rare means that the overall cost may actually not be that high? Childhood cancer is so desperately underfunded. Whilst large companies are happy to use our children in huge advertising campaigns, the actual amount being spent on research is unacceptable. I hope that you hear our pleas and reconsider. Yours faithfully

	[redacted] [redacted] Mum to a beautiful boy now finally getting to live his life.
Submission date	25/11/15

Name	[redacted] [redacted]
Organisation	n/a
Role	Carer
Job title	School Administrator
Location	
Conflict	None
Disclosure	None
Comments	My son was diagnosed with stage 4 high risk neuroblastoma in July 2009 - at the time of diagnosis he was given just a 20% chance of survival. He was 22 months old. He underwent 3 months of a combination of aggressive chemotherapy, an 11 hour surgery, high dose chemotherapy followed by a stem cell transplant, 2 weeks of radiotherapy, 6 month of cis-retonolic acid. He finished treatment the day before his 3rd birthday. Immunotherapy was not available to him, at that time it was only available in the USA as a stage 1 clinical trial, with no published results. Against the odds he achieved remission. At the age of 4 the cancer returned in his bones and bone marrow, we were told that this is unfortunately typical of neuroblastoma despite initial positive response to front line treatment. We were told there was no set treatment plan for relapse and very little chance of his survival. We were given the option of doing nothing and making the most of our time with our precious son. However he was not symptomatic, he looked and felt well and there was no way we could give up on him. Again he underwent months of aggressive chemotherapy, internal radiation treatment at UCLH London, and although the disease burden was reducing it had not gone. The only option in the UK was more chemotherapy with no evidence that this would help. His bone marrow was very weak and we were at risk of causing him to become aplastic. At this point results of the immunotherapy trial from the USA had been published showing a significant improvement in survival rates . A similar clinical trial was available in Germany offering ch14.18 with IL-2. The treatment in Germany was about half the price of that offered in the US. A funding application was put forward to our local health authority and it was approved. For 7 months we travelling to Greifswald, Germany, driving so as to avoid exposing our son to infection from the plane journey. The journey was 16 hours each way. We spent 2 weeks in Greifswald and 2 weeks in the UK. The treatment was very aggressive, the side effects were severe but we were trying to save our sons life. After 4 months of treatment we received the news that we had hoped and prayed for, he was again in complete remission. He completed the 7 months of treatment.

	We have no doubt that he would not be alive today if we had not taken him to Germany for this treatment. Surely no parent should be told there are no options when in fact there are valid proven options only they are deemed to be too costly. The impact on our family life has been huge, I lost my job of 24 years as a claims underwriter, my husbands business suffered, my son could not go to school - the impact on our family would have been very different if the treatment would have been available in this country. My understanding is that ch14.18 immunotherapy treatment has had the biggest impact on survival rates for Neuroblastoma for many years. This has been proven with the US clinical trial. I realise that SIOPEN are also conducting a clinical trial but to enrol on a trial you have to meet certain criteria, not all children meet this criteria. If your child does not meet milestones and timescales they can be taken off trial. At the time of my son receiving immunotherapy in Germany it **was** available in the UK but ONLY if you were enrolled on the SIOPEN trial for front line treatment and not for relapse. He therefore failed to meet the criteria to receive it in this country. There needs to be an alternative in place for these children, that does not involve them travelling hundreds of miles from home away from friends and family, at a time when the whole family need support. If the SIOPEN clinical trial closes, as it is scheduled to do so in 2017, and there is no follow-up to immediately replace it then the only way that UK children can access this treatment is to travel abroad. Please don't let this happen. Sadly in 2012 at the age of 5 my son's cancer returned for a second time and again there were no options available to him in the UK. Again we choose to take him outside of the UK where we believe options are more accessible. We had to fund raise to pay for this treatment. He again achieved a complete remission. My son was in treatment for cancer for approx 4 years, he is now a happy, healthy 9 year old, in full time main stream education. He loves football, badminton and his x-box and talks about becoming a doctor when he grows up. I very much look forward to that day. Thank you for giving me the opportunity to submit comments for your consideration.
Submission date	1st December

APPENDIX A. Mean Days of Hospitalisation in the Immunotherapy + Isotretinoin Arm of ANBL0931

A.1. Summary of Additional Evidence to be Considered by NICE

The Committee/ERG inappropriately applied hospitalisation days for a subgroup of patients experiencing infection to the entire study population from study ANBL0032. Using the 69 hospital days from study ANBL0032 (see Table A1) is clearly inappropriate to apply to the entire study population, as it represents a small subgroup of patients with high hospital utilisation. This subgroup of patients with infection represents between 6% and 28% of the entire study population, depending on the course of therapy (see Table A1). Extrapolating this utilisation rate to the entire study population greatly overestimates the cost of administration of dinutuximab and is an irrational assumption. This is one of the main factors contributing to the ICER of dinutuximab remaining unfavourable even if provided at zero cost.

Table A1: Number and Percentage Hospitalised, and Mean Days of Hospitalisation in the Immunotherapy + Isotretinoin Arm of Study ANBL0032

Course	Number Hospitalised (%)	Mean ± SD Days of Hospitalisation
1 (n=138)	24 (17%)	10 ± 5.0
2 (n=127)	29 (23%)	14 ± 6.8
3 (n=120)	13 (11%)	10 ± 3.3
4 (n=113)	32 (28%)	14 ± 6.2
5 (n=105)	11 (10%)	11 ± 6.9
6 (n=99)	6 (6%)	10 ± 5.7

To better inform the Committee of the number of hospital days, the Company is providing data from study ANBL0931, an open-label, Phase 3 safety study consisting of 104 patients with high-risk neuroblastoma who received the same treatment regimen as administered in study ANBL0032. Study ANBL0931 was completed after study ANBL0032, and represents more recent treatment patterns, greater physician experience with dinutuximab, and a larger sample size of patients receiving dinutuximab at each course of therapy. Table A2 presents the mean number of days of hospitalization across all patients in study ANBL00931, the sum of which over the 6 courses is 39 hospitalised days for the entire study population, not a subgroup experiencing infection.

Table A2: Mean Days of Hospitalisation in the Immunotherapy + Isotretinoin Arm of Study ANBL0931 (Clinical Study Report DIV-NB-303 [COG Protocol ANBL0931])

Course	Mean ± SD Days of Hospitalisation
1 (n=104)	7 ± 5.4
2 (n=100)	10 ± 4.0
3 (n=98)	6 ± 2.3
4 (n=90)	9 ± 3.6
5 (n=88)	6 ± 3.3
6 (n=82)	1 ± 2.7

Revised Economic Analysis Using Revised Mean Days of Hospitalisation

As outlined in the Company comments on the ACD, as well as in this APPENDIX, the Company recommends the following changes to the Committee's base case analysis:

- Utilizing a 1.5% discount rate for outcomes, due to the long term health benefits associated with dinutuximab treatment and precedent set by the mifamurtide for the treatment of osteosarcoma (TA235) decision
- Utilizing a 5 year cure point, given the significant uncertainty associated with the survival analysis data
- Utilizing the updated number of hospital days and the ERG base case analysis cost per hospital day as opposed to the Committee's higher estimates (utilizing the ERG scenario analysis hospital days and costs)
- Utilizing a weighted average of 4.2 dinutuximab vials per treatment course, to ensure that the product utilization is not over-estimated

With these modifications to the model, the base case ICER is reduced to £48,061 per QALY.

Dinutuximab for treating high-risk neuroblastoma

ERG review of company's response to NICE following ACD

20th January 2016

1. Overview

Following the first appraisal meeting of dinutuximab for the maintenance treatment of high-risk neuroblastoma in children and young people aged 12 months to 17 years (6th October 2015), United Therapeutics (the Company) made a request to submit revised economic analysis and additional evidence to support the clinical and cost-effectiveness of dinutuximab in combination with GM-CSF, IL-2 and isotretinoin. The company's response is based on four concerns:

1. Further consideration should be given to the innovative nature of dinutuximab in an ultra-orphan paediatric oncology indication with no European Medicines Agency (EMA)-approved alternatives;
2. The unreasonable interpretation of the clinical and cost-effectiveness evidence submitted;
3. The inconsistency with the previous NICE technology appraisal of mifamurtide for the treatment of osteosarcoma (TA235) in relation to the discount rate used for health outcomes; and
4. Further consideration should be given to the health-related benefits which are not captured in the economic analysis.

The ERG was requested by NICE to provide additional commentary and validity checks on the revised analyses submitted by the company in response to the ACD. In the sections below, the ERG has commented on concerns 2 and 3. For concerns 1 and 4, the company has provided additional testimonies by clinicians and patients and the Appraisal Committee are invited to read these.

Due to the limited resource available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. The ERG review should be read alongside the company's response to the ACD.

2. Unreasonable interpretation of the clinical and cost-effectiveness evidence

The company expressed concern about the interpretation of the clinical and cost-effectiveness evidence relating to the following areas of uncertainty:

Use of 2014 data instead of statistically powered 2009 data from the ANBL0032 study population and convergence of survival estimates

The company states that the assumptions with the most significant impact on the incremental cost-effectiveness ratio (ICER) for dinutuximab are the Appraisal Committee's assertion that "for both the event-free and overall survival data, the curves converge between 6.5 and 11 years" and "the dinutuximab regimen delayed but did not prevent cancer-related events." The company argues that these are not fair or scientifically-credible interpretations of the data provided to the Committee given that the event-free survival (EFS) and overall survival (OS) curves never converge or overlap. Furthermore, the company states that the pivotal ANBL0032 trial was not powered to test a difference between immunotherapy and standard therapy beyond 3 years. The company believes that greater weight has been placed on statistically underpowered, ad-hoc analyses of inadequate sample size (March 2014 data) rather than the adequately powered analyses (January 2009 data) which they say provided the basis for the EMA marketing authorisation of dinutuximab.

Figures 1 and 2 show the Kaplan-Meier curves for EFS and OS, respectively, based on the pivotal ANBL0032 study population (March 2014 data). This data represents the most up to date findings from this study population. The EFS and OS data from the earlier data cut (January 2009) are encompassed within these survival curves; therefore sufficient weight has been given to this data. However, the longer follow-up data gives us additional information about the long-term survival of these same patients. The sample size at 5 years is sufficiently large with 50% and 65% of patients still at risk of EFS and OS, respectively, at 5 years. Therefore, although the trial was not powered to detect a statistical difference between treatments beyond 3 years, it is difficult to argue that the sample size is not large enough to be confident that the difference between treatments is any less real in the longer follow-up dataset. It is also worth noting that the EMA did consider the March 2014 data on overall survival. In fact the efficacy analysis for this data cut was performed at the request of the EMA. Finally, in the company's response to the ERG's points for clarification, it was stated that the OS data in the primary analysis (January 2009) was not considered mature enough and therefore the Children's Oncology Group (COG) and National Cancer Institute (NCI) amended the protocol to include the later analysis for OS post the close of randomisation.

The survival curves for immunotherapy and standard therapy never actually converge but the Appraisal Committee is referring to the fact that the immunotherapy curve moves closer towards the standard therapy curve in the direction of convergence between 6.5 and 11 years for both EFS and OS, i.e. dinutuximab is always favoured over isotretinoin alone but the incremental survival benefit becomes smaller and smaller over the long term. The ERG

analysis of this data (see Section 4.4 of ERG report) indicates that the proportion of children 'cured' of events (EFS) in the standard therapy and immunotherapy arms are 47.0% and 47.7%, respectively, i.e. an additional 0.7% for immunotherapy. This suggests that similar proportions of children are cured of cancer-related events regardless of treatment received, and that immunotherapy is delaying the time to relapse rather than preventing events. For overall survival, the proportion of children cured in the standard therapy and immunotherapy arms are 48.8% and 65.7%, respectively, i.e. an additional 16.9% for immunotherapy. This suggests that immunotherapy delays and possibly prevents premature mortality. The Appraisal Committee considered the evidence on both EFS and OS, as indicated in Section 4.4 of the ACD.

Figures 1 and 2 also indicate that relapse events after 5 years did occur in the immunotherapy arm of the pivotal ANBL0032 study population, while relapse events after 5 years in the standard therapy arm were rare.

Figure 1: Event-free survival in ANBL0032 trial (March 2014 data)

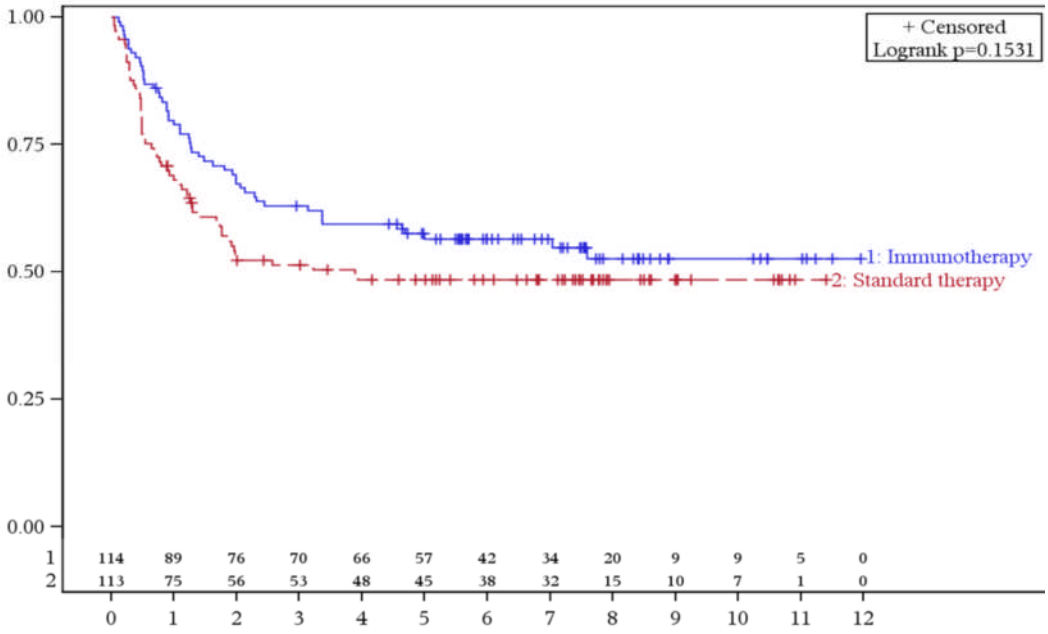
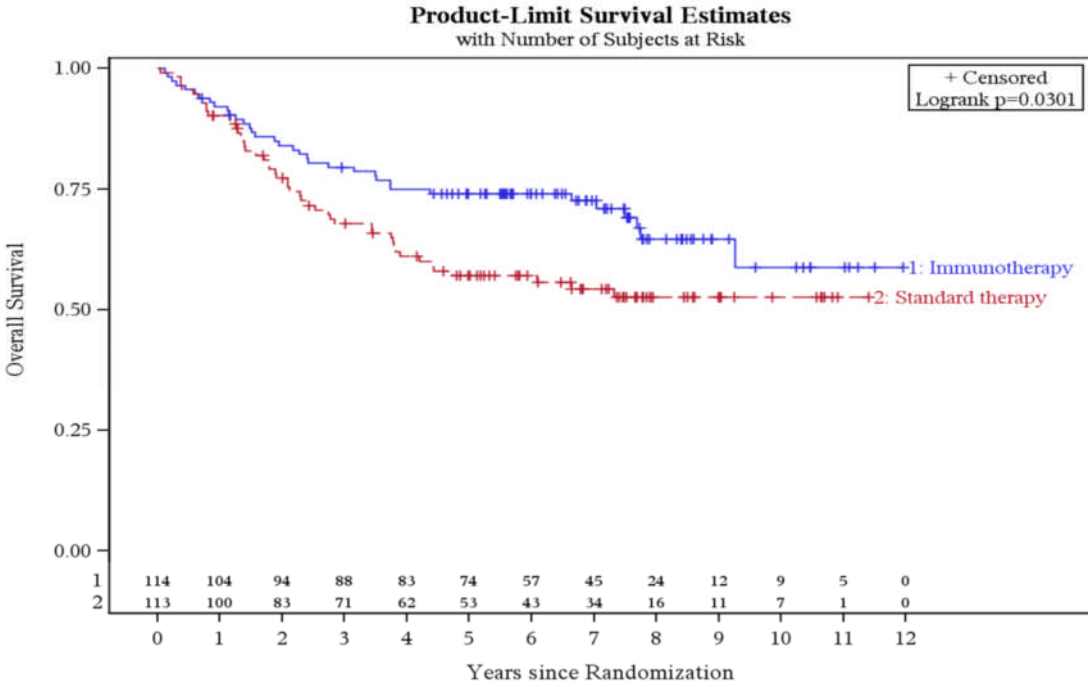


Figure 2: Overall survival in ANBL0032 trial (March 2014 data)



Early stopping of the ANBL0032 trial

The company states that randomisation in the ANBL0032 trial was stopped early based on the efficacy demonstrated by immunotherapy. The ERG, however, has concerns over the validity of this early stopping. The purpose of sequential monitoring of a clinical trial is to ensure that, if a trial is stopped early, the evidence of benefit is clear. To achieve this, the stopping rules must be properly adhered to. Stopping the trial because results are "close enough" to the boundary based on an a-priori belief that the treatment is effective is not statistically appropriate as it may bias the results (and is ethically questionable). The ERG notes that there were also concerns as to whether there were errors in the data used to perform the sequential monitoring (see Table 7 of the ERG report), raising further uncertainty as to whether stopping the trial was appropriate.

Administration costs of dinutuximab

The company expressed concern that the Appraisal Committee used a highly unfavourable estimate of the administration costs for dinutuximab. This was based on two concerns: i) use of a large number of hospital days from the ANBL0032 trial for the administration of the dinutuximab regimen; and ii) use of a less favourable delivery code for the costing of inpatient stay from NHS Reference costs.

For the first of these concerns, the company originally provided the average number of hospital days per treatment course in the immunotherapy arm of the pivotal ANBL0032 study population. This corresponded to a total of 69 hospital days (see Table 28 of the ERG report). However, the company have now indicated in their revised analyses following the ACD that these hospital days were only for a subgroup of patients experiencing an infection and do not apply to the whole study population receiving the dinutuximab regimen. In order to inform the number of hospital days for the population who receive dinutuximab, the company have submitted additional evidence from study ANBL0931, a phase 3 open-label safety study of dinutuximab (which was briefly discussed in Section 4.2.2.2 of the ERG report). Table A2 of the company's response to the ACD indicates that this study had an average of 39 hospital days in the immunotherapy arm.

Although the ERG is now satisfied that the original data may have been for a subgroup of patients experiencing an infection and therefore could have potentially overestimated the number of hospital days for patients receiving immunotherapy, it remains unclear to the ERG why the company have not been able to provide the number of hospital days for the population of patients who received immunotherapy in the pivotal trial (ANBL0032). The reduction in the average number of hospital days from 69 to 39 is expected to have a significant impact on the ICER (see Section 4 below).

The company's second concern relates to the use of a less favourable delivery code for calculating the cost of hospital inpatient stay. In the absence of a delivery code for inpatient stay in NHS Reference costs, or a specific code for neuroblastoma, the cost of each of the hospital days above was based on the average cost per hospital stay and mean length of stay for the treatment of paediatric brain tumours with the highest complication and comorbidity level (code PM42A). Under this code, the cost per hospital day was estimated to be £991.92. This contrasts with the estimate of £449.87 per hospital day based on the code for the treatment of brain tumours or cerebral cysts with the highest complication and comorbidity level (code AA24C), which was originally used by the company in a scenario analysis in response to the ERG's points for clarification. In the company's revised analyses, they advocate the use of the latter cost per hospital day (£449.87) with the average number of hospital days from study ANBL0931 (39 days). Table 1 provides a summary of the alternative approaches used to estimate the administration costs of the dinutuximab regimen. The impact of the company's revised scenario on the cost-effectiveness results is shown in Section 4 below.

Table 1: Summary of the administration costs for immunotherapy

Scenario	Administration costs	Source of costs	Concern expressed
Company's original base-case analysis	Dinutuximab = £1,908 for courses 1, 2, 3, 4 and 5 each. IL-2 = £1,908 for courses 2 and 4 each, first dose of IL-2 on days 1-4 (administration costs of second dose of IL-2 on days 8-11 = £0 because administration alongside dinutuximab) GM-CSF = £142.50 for courses 1, 3 and 5 each **Total administration costs over 6 cycles = £13,784**	NHS Reference costs for procurement inpatient chemotherapy drugs for regimens in Band 10	ERG expressed concern that procurement costs are not costs of delivery of treatment. Furthermore, they do not consider the number of days that the patient is hospitalised for the administration of treatment.
ERG's original scenario 1 analysis	Dinutuximab = £28,399 for all 5 courses (Table 29 of ERG report). IL-2 = £0 since calculated as part of the dinutuximab cost based on number of hospitalised days included in the immunotherapy arm of the pivotal ANBL0032 study. GM-CSF = £142.50 for courses 1, 3 and 5 each **Total administration costs over 6 cycles = £28,827**	Use costs associated with hospital length of stay rather than procurement. The company provided the average number of days of hospitalisation per treatment course in the immunotherapy arm of the pivotal ANBL0032 study population (corresponding to a total of 69 hospitalised days, see Table 28 of ERG report). Cost per hospital day = £449.87 based on the mean cost (£7,743.11) and mean length of stay (17.21 days) for an elective inpatient stay for the treatment of brain tumours or cerebral cysts with the highest complication and comorbidity level (code AA24C) NHS reference cost for delivery of complex chemotherapy = £370.84 (code SB14Z)	No delivery code for inpatient stay. ERG used the data provided by the company in response to the ERG's points for clarification The company have indicated in their revised analyses following the ACD that the number of days of hospitalisation per treatment course in the immunotherapy arm of the pivotal ANBL0032 study population is only for a subgroup of patients experiencing an infection

ERG's original scenario 2 analysis	Dinutuximab = £60,377 for all 5 courses (Table 29 of ERG report). IL-2 = £0 since calculated as part of the dinutuximab cost based on number of hospitalised days included in the immunotherapy arm of the pivotal ANBL0032 study. GM-CSF = £142.50 for courses 1, 3 and 5 each **Total administration costs over 6 cycles = £60,805**	Same as ERG scenario 1 but using an alternative inpatient code for the treatment of paediatrics: Cost per hospital day = £991.92 based on the mean cost (£3,169.17) and mean length of stay (3.20 days) for an elective inpatient stay for the treatment of paediatric brain tumours with the highest complication and comorbidity level (code PM42A)	No delivery code for inpatient stay. ERG used the data provided by the company in response to the ERG's points for clarification but specifically for a paediatric patient population. This is the Committee's preferred assumption in the ACD. The company have indicated in their revised analyses following the ACD that the number of days of hospitalisation per treatment course in the immunotherapy arm of the pivotal ANBL0032 study population is only for a subgroup of patients experiencing an infection
Company's revised analysis following ACD	Dinutuximab = £16,520 for all 5 courses. IL-2 = £370.84 for courses 2 and 4 each. GM-CSF = £142.50 for courses 1, 3 and 5 each **Total administration costs over 6 cycles = £17,689**	Alternative source for number of days of hospitalisation per treatment course. Using data from study ANBL0931, an open label, Phase 3 safety study in the immunotherapy arm for the entire study population, i.e. not a subgroup experiencing infection. This results in 39 hospitalised days over 6 treatment courses compared with 69 days from ANBL0032 study population for infection. Cost per hospital day = £449.87 based on the mean cost (£7,743.11) and mean length of stay (17.21 days) for an elective inpatient stay for the treatment of brain tumours or cerebral cysts with the highest complication and comorbidity level (code AA24C) NHS reference cost for delivery of complex chemotherapy = £370.84 (code SB14Z)	

Use of weighted average dose to determine the total drug costs of dinutuximab

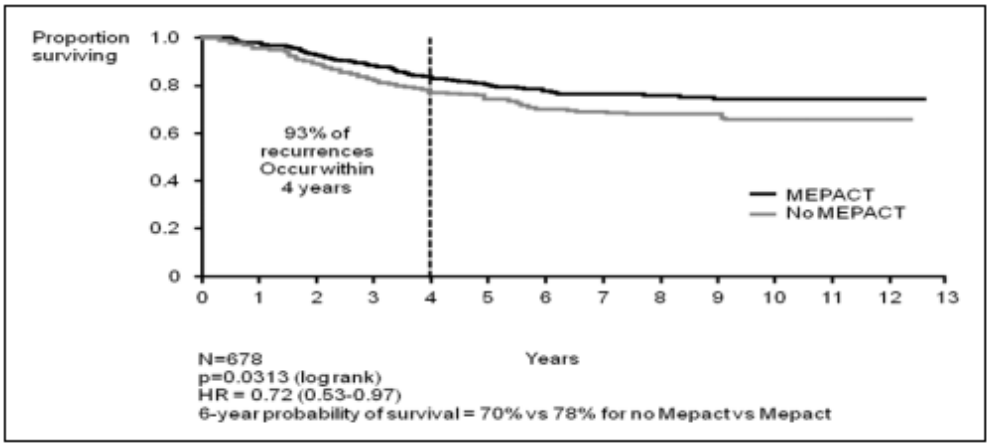
The company agrees with the ERG's approach to use a weighted average dose to determine the total drug costs of dinutuximab. In patients with an average body surface area (BSA) of 0.65 m^2, 4 vials of dinutuximab are required, while in patients with a BSA greater than 1 m^2, 8 vials may be required to achieve the recommended dose for dinutuximab. In the ANBL0032 study population, 4.8% of patients had a BSA greater than 1 m^2. In response to the ACD, the company asked for confirmation that the Committee's preferred assumptions uses a weighted average dose of 4.2 vials per cycle (=95% using 4 vials and 5% using 8 vials) for dinutuximab. The ERG can confirm that an average dose of 4.19 vials per cycle (=95.2% using 4 vials and 4.8% using 8 vials) was used in the model (i.e. using the same approach as indicated by the company). The resulting average cost of dinutuximab is £26,792 per course, which is compared to £25,560 per course used in the company's original submission (i.e. without taking account of extra vials needed for patients with greater BSA). This drives the difference in the ICER seen in Table 45 of the ERG report.

3. Inconsistency with TA235 in relation to the discount rate used for outcomes

The company strongly argues that a 1.5% discount rate per annum should be applied to health outcomes (and 3.5% to costs) due to the precedent that was set in the NICE Technology Appraisal of mifamurtide in osteosarcoma in a paediatric population (TA235). The company states that the overall survival benefit associated with dinutuximab is larger than that observed for mifamurtide and, therefore, the company considers it inconsistent if a 1.5% discount rate is not applied for dinutuximab given the precedent set in TA235.

The ERG has reviewed the Final Appraisal Determination (FAD) and associated documents for mifamurtide for the treatment of osteosarcoma. Figure 3 shows the overall survival data informing the efficacy of mifamurtide compared with chemotherapy alone. The OS data, which was the primary endpoint of the pivotal trial (INT-0133), showed that after a median follow-up of 7.9 years, adding mifamurtide to chemotherapy statistically significantly improved overall survival compared with chemotherapy alone with an OS of 71% in the control arm and 78% in the mifamurtide arm (hazard ratio for death 0.72 [95% confidence interval 0.53 to 0.97]). However, adding mifamurtide to chemotherapy did not statistically significantly increase disease-free survival (intermediate endpoint) compared with chemotherapy alone (hazard ratio for disease-free survival 0.78 [95% confidence interval 0.61 to 1.01]).

Figure 3: Overall survival in osteosarcoma patients treated with and without mifamurtide. Source: Takeda UK new submission of evidence to NICE: Mifamurtide for the treatment of Osteosarcoma: 10th December 2009



In the appraisal of mifamurtide the Committee considered it reasonable that patients in the disease-free health state at 12.25 years, which marks the end of the trial follow-up duration, could be assumed to have a mortality rate equivalent to that of the general population. It also considered it reasonable that those patients in the post-recurrence disease-free state (a Markov model state made up of 23 temporary states to accommodate cycle dependent monitoring costs after recurrence) who did not have an event within 5 years (disease-free) could be assumed to have the same mortality rate as that of the general population.

With respect to the discount rate used to assess cost-effectiveness in this appraisal, the Committee reached the conclusion in the first FAD (issued in October 2010) that the reference case discount rates of 3.5% for costs and outcomes were the most appropriate based on the 2008 NICE Guide to the Methods of Technology Appraisal.

However, in July 2011, the NICE Board issued clarification of the Guide to the Methods of Technology Appraisal on the discounting of health benefits in special circumstances. The updated clarification is highlighted in bold below:

"The annual rate of 3.5%, based on recommendations of the UK Treasury for the discounting of costs, should be applied to both costs and National Institute for Health and Clinical Excellence 2 July 2011 health effects. ***Where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for***

health effects and 3.5% for costs.*"* Source: National Institute for Health and Clinical Excellence. Discounting of health benefits in special circumstances. July 2011.

In August 2011, a second FAD was released for the appraisal of mifamurtide for the treatment of osteosarcoma. Among a number of other considerations (including a revised patient access scheme) the Committee reconsidered the sensitivity of the cost-effectiveness results to the discount rate used for health outcomes. On this occasion, the Committee noted the clarification to the Guide to the Methods of Technology Appraisal issued by the board of NICE and noted that the two criteria were met:

i) Mifamurtide is a treatment with curative intent that increased the overall survival from 71% to 78% compared with chemotherapy alone in the whole trial;
ii) Patients who are cured are expected to have a long and sustained benefit and regain normal life expectancy.

The Committee concluded that a discount rate of 1.5% should be used for health outcomes. This reduced the company's best-case probabilistic ICER from £56,700 to £36,000 per QALY gained. The committee further concluded that there were additional important issues affecting the health-related quality of life which had not been adequately captured in the economic analysis.

The ERG does not consider the Technology Appraisal of mifamurtide as a precedent for dinutuximab. The NICE Guide to the Methods of Technology Appraisal was updated in 2013 since the appraisal of mifamurtide. The ERG believes that the criteria specified in the updated 2013 guide should be used for dinutuximab (in the same way as the Committee considered the criteria that were available in the Methods Guide at the time of the appraisal for mifamurtide). The 2013 Guide to the Methods of Technology Appraisal states the following in relation to the use of a non-reference case discount rate:

"In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs." Source: National Institute for Health and Care Excellence. Guide to the Methods of Technology Appraisal 2013. April 2013.

The ERG notes that it is difficult to justify the first criteria on the following basis:

- The evidence from the pivotal trial ANBL0032 suggests that around half of all patients will not relapse regardless of treatment received. This suggests that the dinutuximab regimen does not restore patients to near or full health who would otherwise die or have very severely impaired quality of life.

The Appraisal Committee for dinutuximab have considered all the criteria for non-reference case discounting in Section 4.17 of the ACD and concluded that it does not apply.

4. Revised economic analysis

The company recommends the following changes to the Committee's preferred assumptions:

- Utilizing a 1.5% discount rate for health outcomes, due to the long term health benefits associated with dinutuximab treatment and the precedent set by the appraisal of mifamurtide for the treatment of osteosarcoma (TA235);
- Utilizing a 5 year cure point, given the significant uncertainty associated with the survival analysis data;
- Utilizing the ERG's original scenario 1 analysis for cost per hospital day (£449.87) as opposed to the Committee's higher estimate for cost per hospital day (£991.92);
- Utilizing a weighted average of 4.2 dinutuximab vials per treatment course, to ensure that the product utilization is not over-estimated.

Based on these recommendations, the company has presented two revised ICERs in response to the ACD:

All of the above + using the revised number of hospital days from study ANBL0931 (39 days)	£48,061 per QALY gained
All of the above + using the number of hospital days from study ANBL0032 (69 days)	£50,329 per QALY gained

Table 2 presents a comparison between the company's revised analysis and the Committee's preferred assumptions, with the key differences highlighted in bold. The main differences relate to the discount rate, the cure point and the administration costs of the dinutuximab regimen. There is one additional difference relating to the mortality rate in the

failure state after the cure point, but this difference is likely to have occurred due to a misunderstanding in the ACD. In Section 4.12 of the ACD, it implies that the general population mortality with an adjustment of 5.6 from the Childhood Cancer Survivor study was applied to patients in the stable and failure health states of the model after the cure point by the ERG. However, this mortality ratio was only applied to the stable state (not the failure state). The company's base case of a monthly probability of death of 5.1% for the failure state was used in the ERG's analyses. Although the ERG had concerns about the 5.1% rate, it was not considered appropriate to apply the general population mortality (with or without an adjustment factor of 5.6) to the failure state due to i) the company's assumption that people who survive in the failure state receive the costs of topotecan combination of therapies for the rest of their life; and ii) the assumption that patients in the failure state have the same mortality rate as patients who are cured in the stable state seems unrealistic. The implications of this assumption are discussed further in Appendix A. With this latter difference removed, the ERG re-calculates the company's revised ICER to be:

Company's revised ICER using the number of hospital days from study ANBL0931 (39 days)	£48,984 per QALY gained
Company's revised ICER using the number of hospital days from study ANBL0032 (69 days)	£52,308 per QALY gained

Table 3 shows the impact of each of the company's revised assumptions on the Committee's preferred ICER. The individual assumptions which have the most impact are the cure point of 5 years and the discount rate of 1.5% per annum on health outcomes. The combined impact of the company's revised assumptions reduces the ICER from £139,612 to £48,984 per QALY gained.

Table 2: Comparison of company's revised analysis and Committee's preferred assumptions

Parameter	Committee's preferred assumptions	Company's revised analysis
Data from study ANBL0032	March 2014 data	March 2014 data
EFS and OS data	Observed Kaplan-Meier data up to cure threshold	Observed Kaplan-Meier data up to cure threshold
Cure point	**10 years**	**5 years**
Mortality	Standardised mortality rate of 5.6 applied to the general population mortality for stable state after the cure point **Mortality rate of 5.1% per month applied to the failure state after the cure point**	Standardised mortality rate of 5.6 applied to the general population mortality for stable state after the cure point **General population mortality adjustment of 5.6 also applied to the failure state after the cure point (Note that this difference is likely to be due to a misunderstanding in the ACD – see Appendix A)**
Reduction in health-related quality of life (HRQoL)	13% relative to general population	13% relative to general population
Administration cost of dinutuximab	**1) Number of days in hospital based on data from ANBL0032 (69 days).** **2) Cost per day in hospital £991.92**	**1) Number of days in hospital based on data from ANBL0931 (39 days).** **2) Cost per day in hospital £449.87**
Body surface area (BSA)	Weighted average of BSA above and below $1m^2$ from pivotal trial	Weighted average of BSA above and below $1m^2$ from pivotal trial
Discount rate	**3.5% per annum on costs and health outcomes**	**1.5% on health outcomes and 3.5% on costs**

Table 3: Cost-effectiveness results for company's revised assumptions

	Total costs	Total LYs	Total QALYs	Incre. costs	Incre. LYs	Incre. QALYs	ICER (£/QALY)
Committee's preferred assumptions							
Standard therapy	£53,983	13.06	10.21	-	-	-	-
Immunotherapy	£258,015	15.02	11.68	£204,032	1.97	1.46	£139,612
Scenario 1: Committee's preferred assumptions with change in the cure point from 10 years to 5 years							
Standard therapy	£47,130	12.92	10.18	-	-	-	-
Immunotherapy	£244,131	15.54	12.23	£197,001	2.62	2.05	£96,096
Scenario 2a: Committee's preferred assumptions with change in the number of days in hospital from 69 to 39 days and cost per day of £991.92							
Standard therapy	£53,983	13.06	10.21	-	-	-	-
Immunotherapy	£236,863	15.02	11.68	£183,000	1.97	1.46	£125,742
Scenario 2b: Committee's preferred assumptions with change in the number of days in hospital from 69 to 39 days and cost per day of £449.97							
Standard therapy	£53,983	13.06	10.21	-	-	-	-
Immunotherapy	£219,913	15.02	11.68	£166,050	1.97	1.46	£114,096
Scenario 3: Committee's preferred assumptions with change in the discount rate from 3.5% to 1.5% on health outcomes							
Standard therapy	£53,983	19.65	15.30	-	-	-	-
Immunotherapy	£258,015	22.46	17.40	£204,032	2.81	2.10	£98,753
Scenarios 1 and 2b combined							
Standard therapy	£47,130	12.92	10.18	-	-	-	-
Immunotherapy	£202,850	15.54	12.23	£155,720	2.62	2.05	£75,959
Scenarios 1, 2b and 3 combined (company's revised results)							
Standard therapy	£47,130	19.44	15.22	-	-	-	-
Immunotherapy	£202,850	23.52	18.40	£155,720	4.08	3.18	£48,984[†]

[†] The company's revised results with a 1.5% discount rate on costs as well as health outcomes results in an ICER of £49,748.

Appendix A: Mortality rate applied to the failure state after the cure point

In Section 4.12 of the ACD, it implies that the general population mortality with an adjustment of 5.6 from the Childhood Cancer Survivor study was applied to patients in the stable and failure health states of the model after the cure point. However, this mortality rate was only applied to the stable state (not the failure state). The company's original base case analysis used a monthly probability of death of 5.1% for the failure state after the cure point. In the ERG report, the ERG expressed concern that this 5.1% rate gives rise to an important structural assumption in the model (See Section 5.2.5.2 of the ERG report), whereby a differential treatment effect persists beyond the cure point due to a different proportion of patients in the failure state on immunotherapy compared with standard therapy at the point at which the curves are extrapolated over a lifetime horizon (see Figure 13 of the ERG report). Furthermore, it means that the mortality risk applied to the failure state differs within the trial period (which is captured in the OS estimates) from the mortality risk that is applied after the trial period. The ERG noted that the implications on the cost-effectiveness results would be minimal when there is a smaller difference between treatments in the proportion of patients in the failure state at the cure point. However, it could have a more marked effect when there is a greater difference between treatments at the cure point.

In a scenario analysis, the ERG attempted to remove this structural concern created by the 5.1% monthly mortality rate by applying the same fixed mortality assumption at the cure point to both the stable and failure states, i.e. by assuming that any difference between treatments in terms of mortality after relapse/progressive disease is captured within the trial follow-up period and only the difference observed at the cure point is maintained over the long-term (see Section 6.4.1 of the ERG report). However, the impact of this assumption on total costs and total QALYs was quite significant. This is because the company assumes that upon treatment failure patients in the model receive topotecan combination of therapies on a monthly basis until death (at £3,683 per month). Under this fixed mortality assumption, patients in the failure state are assumed to live considerably longer (since they now have the same mortality rate as the general population compared to the very high rate of death of 5.1% per month). As a consequence, these patients incur considerably more costs associated with topotecan therapies. The implications on total costs and QALYs are substantial (see Table A1 below). Although the ERG explored the implications of this assumption, the ERG does not favour this scenario.

In summary, although the ERG had concerns about the 5.1% monthly mortality rate applied to the failure state after the cure point, the ERG did not consider it appropriate to apply the general population mortality (with or without an adjustment factor of 5.6) to the failure state

due to i) the company's assumption that people who survive in the failure state receive the costs of topotecan combination of therapies for the rest of their life; and ii) the assumption that patients in the failure state have the same mortality rate as patients who are cured in the stable state seems unrealistic.

In the Committee's preferred assumptions, the mortality rate of 5.1% per month is applied to the failure state at a cure point of 10 years. In the company's revised analysis, the general population mortality rates (with the adjustment factor of 5.6) are applied to both the stable and failure states. This is likely to be due to a misunderstanding in Section 4.12 of the ACD. The results of the company's revised analysis are presented in Table A1 below. Figure A1 shows the overall survival curves for immunotherapy and standard therapy used in the company's revised analysis with this assumption, together with a cure point of 5 years. The figure shows that the modelled estimates of OS (company model) are a poor fit to the observed OS data beyond 5 years.

Figure A1: Modelled overall survival data in the company's revised analysis

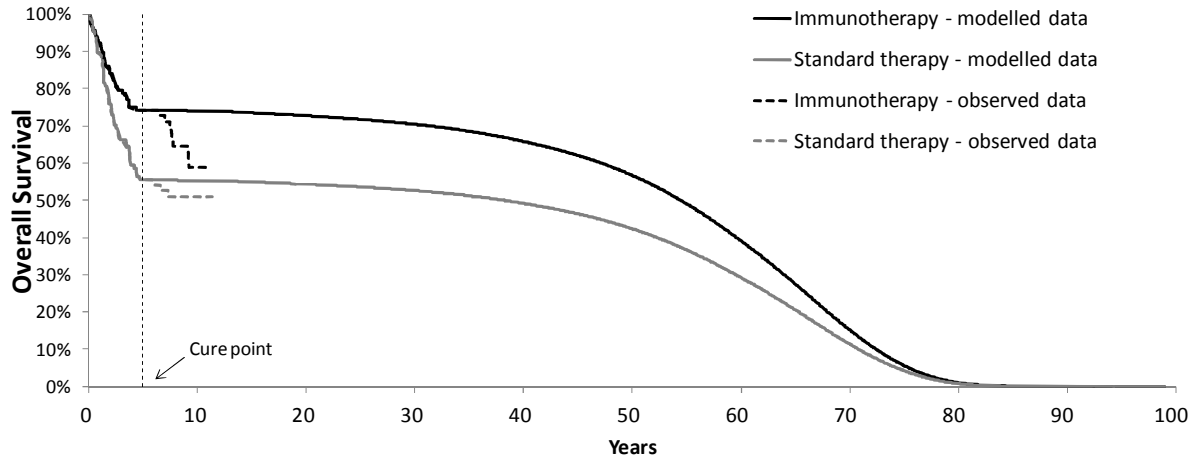


Table A1: Cost-effectiveness results for company's revised analysis with the assumption that the mortality rate for the failure state matches the general population (with an adjustment factor of 5.6) after the cure point

	Total costs	Total LYs	Total QALYs	Incre. costs	Incre. LYs	Incre. QALYs	ICER (£/QALY)
Committee's preferred assumptions							
Standard therapy	£79,978	13.68	10.58	-	-	-	-
Immunotherapy	£301,536	15.97	12.21	£221,558	2.28	1.64	£135,460
Scenario 1: Committee's preferred assumptions with change in the cure point from 10 years to 5 years							
Standard therapy	£115,789	14.47	11.05	-	-	-	-
Immunotherapy	£381,035	18.64	13.97	£265,246	4.16	2.91	£91,004
Scenario 2a: Committee's preferred assumptions with change in the number of days in hospital from 69 to 39 days and cost per day of £991.92							
Standard therapy	£79,978	13.68	10.58	-	-	-	-
Immunotherapy	£277,205	15.97	12.21	£197,227	2.28	1.64	£120,584
Scenario 2b: Committee's preferred assumptions with change in the number of days in hospital from 69 to 39 days and cost per day of £449.97							
Standard therapy	£79,978	13.68	10.58	-	-	-	-
Immunotherapy	£260,255	15.97	12.21	£180,277	2.28	1.64	£110,221
Scenario 3: Committee's preferred assumptions with change in the discount rate from 3.5% to 1.5% on health outcomes							
Standard therapy	£79,978	20.74	15.91	-	-	-	-
Immunotherapy	£301,536	24.14	18.34	£221,558	3.40	2.43	£91,155
Scenarios 1 and 2b combined							
Standard therapy	£115,789	14.47	11.05	-	-	-	-
Immunotherapy	£339,754	18.64	13.97	£223,965	4.16	2.91	£76,841
Scenarios 1, 2b and 3 combined (company's revised results)							
Standard therapy	£115,789	22.09	16.71	-	-	-	-
Immunotherapy	£339,754	28.82	21.37	£223,965	6.72	4.66	£48,083[†]

[†] The company's revised results with a 1.5% discount rate on costs as well as health outcomes results in an ICER of £59,014 (note that this difference occurs due to the lifetime costs associated with topotecan combination of therapies in the failure state)

NICE Submission - dinutuximab (Unituxin) [ID799]

Company Response to Final Appraisal Document (FAD)
6 May 2016

Introduction

Following the second appraisal meeting that took place on 27 January 2016, the National Institute for Health and Care Excellence (NICE) provided United Therapeutics (the Company) with the Committee's preferred assumptions related to the cost-effectiveness of dinutuximab. In March 2016, the Company requested that publication of the Final Appraisal Determination (FAD) be suspended so the Appraisal Committee could consider a recently approved patient access scheme (PAS). Furthermore, within the FAD, the Appraisal Committee identified a few areas of uncertainty and subsequently NICE has requested additional information and analyses to address these issues. In this response, the Company would like to provide this information as the Company is committed to working with NICE to make dinutuximab available in England and Wales for the benefit of patients with neuroblastoma and their families.

The Company herein provides additional analyses for the Committee's consideration to address the areas of uncertainty identified in the FAD, including:

- Applying revised hospitalisation days based on the evidence submitted
- Applying revised hospitalisation cost code based on clinician expert opinion that the base case code likely overestimates costs
- Consideration of end-of-life criteria given that a paediatric population is not a normal end-of-life population and that the short life-expectancy criterion is biased against paediatric cancer
- Applying a PAS, a simple scheme which provides a percentage discount from the dinutuximab UK list price
- Consideration of health-related benefits that are not captured in the economic analysis

In addition to the above, the Company would also request that the Committee consider the following issues as they relate to the appraisal.

- The fact that, under the Committee's preferred (unreasonably pessimistic) assumptions, that dinutuximab would not be cost-effective even at a cost of £0 (ie, a 100% discount), despite its significant improvement in overall survival, effectively eliminating the possibility for the Company to even offer a PAS to reach a cost-effective threshold.
- The fact that a considerable portion of the cost of treatment with dinutuximab is associated with hospitalization and administration costs, that these costs are not something that the Company can control and, furthermore, that the Committee has chosen the most pessimistic estimates of these costs in the face of some uncertainty. To better address the uncertainty, the Company would be willing to collect additional data on these costs assuming that dinutuximab is made available through the Cancer Drugs Fund.
- The fact that the improvement in overall survival associated with dinutuximab compared to isotretinoin results in a cost disadvantage for dinutuximab as patients survive longer, resulting in increased healthcare costs associated with more patients surviving in the failure state and the stable state.
- The fact that only an estimated 14 patients annually will be treated with dinutuximab in England and Wales. This will result in a relatively small budget impact for this technology. Furthermore, the extremely small patient population imposes a significant constraint on the Company when it comes to its ability to offer a more substantial discount.
- The fact that the ultra-orphan status of dinutuximab could not be considered by the Committee because dinutuximab was appraised through the Single Technology Appraisal process. The Company believes that dinutuximab would be more appropriate for appraisal through the Highly Specialised Technology (HST) process. The technology meets all of the HST criteria, with the

potential exception of the condition being chronic and that the technology has the potential for life-long use, and clearly reflects the overarching principle behind the HST process:

- "Given the very small numbers of patients living with these very rare conditions, a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their research and development investment because of the very small populations treated."[1]

That dinutuximab was not appraised using the HST process is a reflection of the continued limitations of the NICE process for patients with ultra-orphan conditions compared to other jurisdictions (e.g., Scotland's PACE process).

Hospitalisation Days

In the FAD, the Appraisal Committee used 69 day of hospitalisation to cover treatment and administration of the dinutuximab regimen. Initially, the Company submitted data from the ANBL0032 trial (an international, multicentre, partly randomised, event-driven trial) with 69 days of hospitalisation (Table 1).

Table 1. Mean Days of Hospitalisation in the Immunotherapy + Isotretinoin Arm of ANBL0032

Course	Mean ± SD days of hospitalisation
1	10 ± 5.0
2	14 ± 6.8
3	10 ± 3.3
4	14 ± 6.2
5	11 ± 6.9
6	10 ± 5.7

However, the original data on hospitalisation from ANBL0032 included only patients with infection and therefore overestimated the average period of hospitalisation and the Company subsequently submitted additional data regarding the duration of hospitalisation from ANBL0931 (an open-label safety study) (Table 2). These data are considered to be more accurate as they are not limited to patients with infection.

Table 2. Mean Days of Hospitalisation in the Immunotherapy + Isotretinoin Arm of ANBL0931

Course	Mean ± SD days of hospitalisation
1	7 ± 5.4
2	10 ± 4.0
3	6 ± 2.3
4	9 ± 3.6
5	6 ± 3.3
6	1 ± 2.7

Additionally, the FAD notes that "The clinical experts stated that the figure of 39 hospital days from ANBL00931 may be a more reasonable estimate than 69 days for a patient with neuroblastoma having treatment with the dinutuximab regimen". The Committee has requested ANBL0032 trial data describing mean days of hospitalisation for patients without infection. Subsequent analysis of the ANBL0032 trial data for patients without infection indicates that there were **a mean of 35 hospitalization days per patient in the immunotherapy plus isotretinoin arm of the trial**, a figure similar to the 39 days from ANBL0931.These data appear in the Appendix below.

Accordingly, below the Company provides updated results from the cost-effectiveness analysis using the lower number of hospitalisation days.

[1] NICE, Highly Specialised Technologies programme: Interim process and methods. May 2013.

Hospitalisation Code

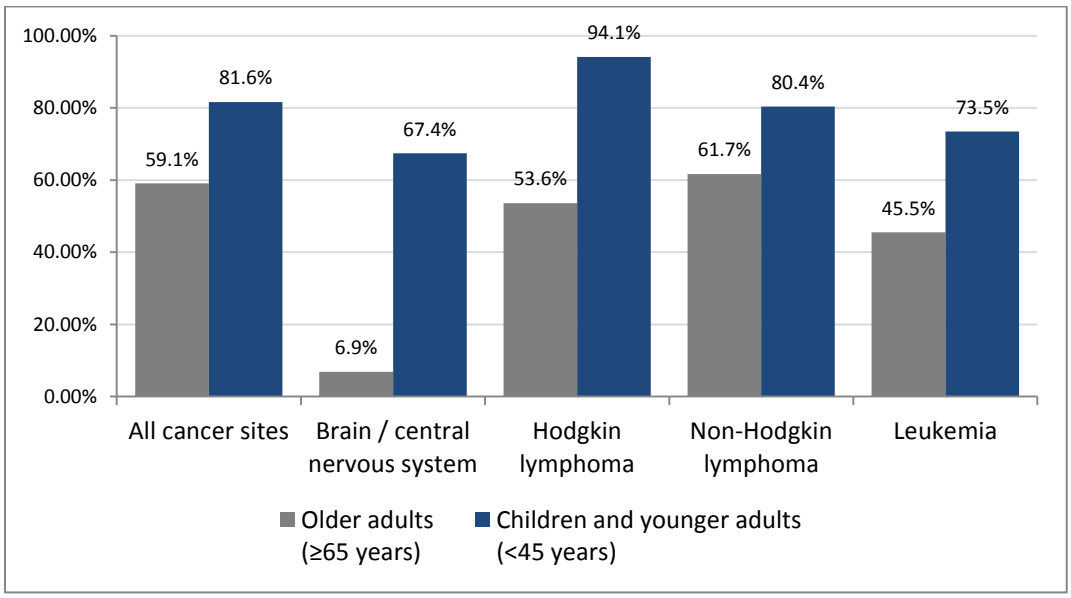
The Company has sought input from clinical experts regarding the most appropriate code to use for hospitalisation to administer dinutuximab in the UK. Unfortunately, it has been difficult to identify a specific code due to the novel nature of the treatment, which has not been studied or used in the UK. Thus, there is no official administration code nor are there clinicians who have used the product in the UK to provide actual coding experience. Accordingly, identifying an appropriate code involves some judgment to select a suitable proxy until the treatment is available and real-world evidence can be obtained regarding coding in the UK. The Company used AA24C (treatment of brain tumours or cerebral cysts with the highest complication and comorbidity level), while the Committee used PM42A (treatment of paediatric brain tumours with the highest complication and comorbidity level). The average daily cost for AA24C is £449.92 compared to £991.92 for PM42A. The Committee preferred the latter code on the grounds that it is specific to paediatric patients; however, during the January NICE Appraisal Committee meeting, the FAD notes that "the clinical experts stated that the NHS reference cost of an elective inpatient stay for treating paediatric brain tumours was too high because it involved high-intensity chemotherapy in an intensive care unit." During the January meeting, a clinical expert noted that she would look into the matter of an appropriate code and NICE staff have since reached out to her to follow up on this matter. The Company has also reached out to another clinical expert to try to obtain additional insight into hospitalisation coding for patients receiving dinutuximab. The Company believes that the AA24C code is the more appropriate code and provides updated results from the cost-effectiveness analysis below using this code. However, the Company appreciates that there is still uncertainty on this matter and believes that additional real-world data collected after a few years of immunotherapy use would help to resolve the issue.

End of Life Criteria

The Appraisal Committee considered the application of end-of-life criteria to the neuroblastoma patient population in the FAD and rejected it. According to the Committee, dinutuximab met the life extension criterion (with a 2.81 life year gain, 4.86 with the non-reference 1.5% discount rate) and met the small patient population criterion (with only 54 estimated patients, compared to a threshold of 7,000). According to the Committee, the treatment did not meet the short life-expectancy criterion as the median life expectancy of patients with high-risk neuroblastoma was 4 years, which is greater than the 2 year threshold in the guidelines. During the January NICE Appraisal Committee meeting, the Company pointed out that the criterion says that life expectancy must be "*normally* less than 24 months" which allows the Committee to exercise discretion in how the criterion is applied to a paediatric population as this is not a typical end-of-life population. In the FAD, the Committee asks that "the NICE Board should clarify whether the short life-expectancy criterion should apply to children as it is applied to adults."

In considering this question, the Company would like to point out that end-of-life criteria have never been applied to a paediatric population in any NICE technology appraisal. Furthermore, children with cancer typically live longer than adults with cancer and, as such, the 2-year life-expectancy threshold is biased against children with cancer, who also stand to lose many more life years than elderly adults with the disease. Figure 1 shows the 5-year relative survival of children and younger adults versus older adults for various cancers commonly affecting children and younger adults.

Figure 1. 5-Year Relative Survival Based on Age at Diagnosis*



* Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2012. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER website, April 2015.

Accordingly, while a 2-year life expectancy may be reasonable to apply to elderly adults, it is arbitrary and unfair to apply the same standard to children and younger adults with cancer. Moreover, the end-of-life issue is critical in the dinutuximab health technology appraisal as there is simply no possible way this highly-effective and innovative treatment, which is considered the standard of care in paediatric oncology, could be cost-effective without the end-of-life criteria, since under the Committee's base case assumptions even a 100% discount by the manufacturer would not meet NICE's £30,000/QALY threshold.

PAS

As noted above, the Company is committed to working with NICE to ensure that dinutuximab is available to patients with neuroblastoma in England and Wales. However, due to the very limited size of the ultra-orphan patient population, the Company is unable to offer a more substantial discount as there are insufficient economies of scale given the extremely small market. However, in the interest of providing a much needed treatment to patients with neuroblastoma, the Company will provide a PAS discount of [redacted] for dinutuximab. This would reduce the price per vial from £6,390 to [redacted] in an effort to improve the technology's cost-effectiveness. The Company would also be willing to entertain a complex PAS if it would help to address the Committee's concerns.

Revised Cost-Effectiveness Results

Table 3 below shows the revised cost-effectiveness under the following scenario:

- Revised hospitalisation days (35 versus 69 days)
- Revised hospital cost code (AA24C versus PM42A code)
- Application of the PAS ([redacted] dinutuximab discount)

Table 3. Cost-Effectiveness Results

	Total costs	Total LYs	Total QALYs	ICER (£/LY)	ICER (£/QALY)
Standard therapy	£61,955	19.61	15.27	-	-
Immunotherapy	[redacted]	22.43	17.38	-	-
Incremental	[redacted]	2.81	2.11	[redacted]	[redacted]

LYs, life years; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

Health-related Benefits which are not captured in the Economic Analysis

Admittedly, according to the revised analyses above, immunotherapy does not meet the £30,000 per QALY threshold (in fact, this would require a discount of more than 80%, which is simply not feasible), nor does it meet a threshold of £50,000 per QALY assuming the end-of-life criteria are applied. However, the ICER of [redacted] per QALY may be sufficiently close to the £50,000 per QALY threshold considering that there are additional health-related benefits which are not captured in the economic analysis. The Committee recognized this in the FAD, stating: "The committee considered that there may be a case for accepting a higher ICER for a patient population of children and young adults to account for the uncaptured health-related benefits of treatment." Accordingly, given the updated assumptions and the PAS, the Company requests that the Committee consider these uncaptured health-related benefits. These benefits extend to parents, siblings, and other caregivers of patients with neuroblastoma. Admittedly, these quality-of-life benefits are difficult, if not impossible, to comprehensively quantify in the context of an economic analysis, but they include parental anxiety and mental health, strain on family relationships, and the time required of parents or other family members providing care for a child with high-risk neuroblastoma. Additionally, if dinutuximab is not available in England and Wales then many families who want their child to receive the best possible treatment will be required to travel out of the country or even overseas. Many of these parents may be forced to quit their jobs in order to travel great distances for treatment of their child, resulting in significant short-term productivity loss, economic stress, and substantial reduction in quality of life. The uncaptured health-related benefits are uncertain, but potentially substantial in a paediatric cancer like neuroblastoma.

Cancer Drugs Fund

Finally, in the event that the Committee is still uncertain that dinutuximab represents a good value for money due to the considerations discussed above, the Company would be willing to commit to collect real-world evidence on the number of days patients are hospitalised and the coding of hospitalisation over a 2-year period assuming dinutuximab is made available to patients through the Cancer Drugs Fund. However, given the small patient population it may be difficult to collect meaningful data during this defined time period. Uncertainty on long-term treatment efficacy (eg, 5-year versus 10-year cure point) might also potentially be evaluated this way, but would be significantly more challenging as it would require a substantially longer period than 2-years to obtain adequate data. If either of these options is chosen, the Company would request that NICE and/or the Committee provide guidance as to the best way to design the data capture in order to satisfy the need for additional information. In the meantime, this option would provide patients with neuroblastoma access to an important therapeutic advance until the uncertainty around these issues can be resolved.

Conclusion

The Company believes that dinutuximab represents a significant and innovative therapeutic advance for an ultra-orphan paediatric disease with severe health consequences. As such, dinutuximab is now considered the standard of care for patients with high-risk neuroblastoma in the US and other countries. The treatment delays disease progression, improves overall survival, and offers a potential cure to

patients with neuroblastoma and their families. The Company believes that these and other health-related quality-of-life benefits should be fully considered by the NICE Appraisal Committee. The Company is pleased to offer a PAS with a [redacted] discount for dinutuximab and hopes that the Committee will help to ensure access to this vital treatment for patients with neuroblastoma in England and Wales.

Appendix

Number of Days Hospitalised ANBL0032

United Therapeutics Corporation
Protocol: ANBL0032 (Data as of 31-Mar-2014)

Adhoc Table 5
Summary of Hospitalizations
Randomized + Stratum 07 Safety Population

		Treatment		
		Immunotherapy + RA	RA Alone	Overall
Overall		(N=141)	(N=109)	(N=246)
Incidence of Hospitalizations		134 (95.0%)	51 (46.8%)	185 (75.2%)
Number of Days Hospitalized	n	134	51	185
	Mean (SD)	34.8 (17.4)	9.8 (11.81)	27.9 (19.55)
	Median	32	6	28
	Min, Max	2, 117	1, 60	1, 117

Hospitalizations reported as missing or zero were removed from calculations.

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Note that the analysis reflects the mean number of days hospitalized with all "0" responses removed (as it is not likely zero responses are accurate).

PDF of file:

Adhoc_Hospital3_no zero.pdf

Dinutuximab for treating high-risk neuroblastoma

ERG review of company's PAS and additional data

19th May 2016

1. Overview

Following the second appraisal meeting of dinutuximab for the maintenance treatment of high-risk neuroblastoma in children and young people aged 12 months to 17 years (27th January 2016), United Therapeutics (the Company) made a request to NICE that publication of the Final Appraisal Determination (FAD) be suspended so that the Appraisal Committee could consider a recently approved patient access scheme (PAS). In addition, the company submitted revised economic analysis and additional evidence to address some areas of uncertainty identified by the Appraisal Committee. These include:

1. Revised hospitalisation days and relevant code for administration costs of dinutuximab;
2. Application of a PAS which includes a percentage discount from the dinutuximab UK list price;
3. Further consideration of NICE End-of-Life criteria to a paediatric population;
4. Further consideration of health-related benefits that are not captured in the economic analysis.

The ERG was requested by NICE to provide additional commentary and validity checks on the revised analyses submitted by the company. Due to the limited resource available, the additional work undertaken by the ERG does not constitute the same level of formal critique that was applied to the original submission. The ERG review should be read alongside the company's revised analyses.

2. Hospitalisation days and relevant code for administration costs of dinutuximab

Hospitalisation days

At the second appraisal meeting, the committee heard from the company that the original data on number of hospitalisation days for the administration of the dinutuximab regimen from the pivotal ANBL0032 trial (average of 69 days) were only for a subgroup of patients experiencing an infection. The company had submitted additional evidence following the ACD, which showed that the mean number of hospital days for patients without an infection from study ANBL0931 was 39 days. The company have now submitted additional evidence to indicate

that an average of 35 hospital days is recorded in the ANBL0032 trial for patients without infection.

The ERG is satisfied that the new data submitted by the company provides the most appropriate estimate of the number of hospital days for patients who received immunotherapy in the pivotal trial (ANBL0032). The costs associated with infection are considered separately in the model as an adverse event cost. The company's revised cost-effectiveness results and the additional ERG analyses presented below use 35 hospital days for the administration of the dinutuximab regimen, i.e. an average of 7 hospital days for each of the five courses of dinutuximab.[1]

Hospitalisation code

At the second appraisal meeting, the committee noted that there was no specific delivery code for inpatient stay in NHS Reference costs for high-risk neuroblastoma. The company's original analysis based the cost per hospital day on the average cost per inpatient stay and mean length of stay for the treatment of brain tumours or celebral cysts with the highest complication and comorbidity level (code AA24C in NHS Reference costs). Under this code, the cost per hospital day was estimated to be £449.92. In the absence of an alternative code, the ERG used the corresponding code for paediatrics, i.e. the ERG used code PM42A for the treatment of paediatric brain tumours with the highest complication and comorbidity level. Under this code, the cost per hospital day was estimated to be £991.92. At the second appraisal meeting, the committee did not consider code AA24C to be appropriate because it was not specific to a paediatric population. The clinical experts also considered the costs associated with code PM42A for treating paediatric brain tumours to be too high because it involved high-intensity chemotherapy in an intensive care unit. Following the second appraisal meeting, both NICE and the company sought to identify an appropriate paediatric NHS Reference cost code from clinical experts.

In the company's response document, the company states that code AA24C remains the most appropriate code. Consequently, the company's revised analysis uses code AA24C with a cost per hospital day estimated to be £449.92.

NICE received a response from two clinical experts who have provided alternative codes (see document 'Clinical expert responses regarding hospitalisation coding'). Dr Juliet Gray recommends the use of code PA43B for paediatrics with other neoplasms assuming no co-morbidities other than neuroblastoma from the 2016-17 National Tariff Workbook. The equivalent code in NHS Reference costs in 2013-14 and 2014-15 was PM43C. Dr Gray also

[1] Note that the sixth course of the dinutuximab regime is isotrentinoin alone.

provided the average cost of an elective admission to her Trust under this coding in 2014-15, the cost of a bed day on the Piam Brown Ward in 2015-16, and the average spell income for an elective patient for 2016-17. Dr Martin Elliott recommends the use of code SB14Z for the first day of each admission and code SB15Z for each subsequent day from NHS Reference costs.

The ERG notes that the costs reported by the clinical experts refer to different years and also differ from the year of 2013-14, which was used for costing in the company's economic analysis. Therefore, Table 1 summarises the costs for each code for 2013-14 Reference costs, 2014-15 Reference costs, and 2016-17 National Tariff costs, as well as the separate costs reported for one particular Trust.

Table 1: Summary of the cost of an elective inpatient stay for different HRG codes and years

2013-14 NHS Reference costs			
HRG code	HRG code name	Reference cost	Suggested by
PM43C (equivalent to PA43B for 2016/17)	Paediatric Other Neoplasms with length of stay 1 day or more, with CC Score 0	National average cost of £2,953.25 for an average length of stay of 2.97 days, i.e. £994.36 per day	Dr Juliet Gray
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£401 per day Daycase and Regular Day/Night	Dr Martin Elliott
SB15Z	Deliver subsequent elements of a Chemotherapy cycle	£328 per day Daycase and Regular Day/Night	Dr Martin Elliott
AA24C	Brain Tumours or Cerebral Cysts, with CC Score 11+	National average cost of £7,743.11 for an average length of stay of 17.21 days, i.e. £449.92 per day	Company's original and revised analysis
PM42A	Paediatric Brain Tumours with length of stay 1 day or more, with CC score 1+	National average cost of £3,169.17 for an average length of stay of 3.20 days, i.e. £991.92 per day	ERG original analysis
2014-15 NHS Reference costs			
HRG code	HRG code name	Reference cost	Suggested by
PM43C (equivalent to PA43B for 2016/17)	Paediatric Other Neoplasms with length of stay 1 day or more, with CC Score 0	National average cost of £3,191.94 for an average length of stay of 3.03 days, i.e. £1,053.45 per day	Dr Juliet Gray

SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£414 per day Daycase and Regular Day/Night	Dr Martin Elliott
SB15Z	Deliver subsequent elements of a Chemotherapy cycle	£362 per day Daycase and Regular Day/Night	Dr Martin Elliott
AA24C	Brain Tumours or Cerebral Cysts, with CC Score 11+	National average cost of £7,559.80 for an average length of stay of 17.33 days, i.e. £436.23 per day	Code used in company's revised analysis
PM42A	Paediatric Brain Tumours with length of stay 1 day or more, with CC score 1+	National average cost of £3,717.27 for an average length of stay of 3.11 days, i.e. £1,195 per day	Code used in ERG original analysis
2016-17 National Tariff Workbook			
HRG code	HRG code name	Reference cost	Suggested by
PA43B (replacing PM43C)	Other Neoplasms with length of stay 1 day or more, without CC	£2,600 per admission £288 per additional day after 7 days	Dr Juliet Gray
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£453 per day	Dr Martin Elliott
SB15Z	Deliver subsequent elements of a Chemotherapy cycle	£301 per day	Dr Martin Elliott
AA24A (replacing AA24C)	Brain Tumours or Cerebral Cysts, with CC	£944 per admission £200 per additional day after 5 days	Code used in company's revised analysis
PA42Z (replacing PM42A)	Brain Tumours with length of stay 1 day or more	£3,052 per admission £288 per additional day after 9 days	Code used in ERG original analysis
Cost estimates for one Trust (Dr Juliet Gray)			
HRG code	Name	Cost	Suggested by
PA43B	Other Neoplasms with length of stay 1 day or more, without CC	£3,444 per admission in 2014-15 Not broken down by cost per day	Dr Juliet Gray
	Piam Brown Ward	£263 per bed day in 2015-16	Dr Juliet Gray
	Average Spell income for 2016-17	£2,827 per admission £313 per additional day after 7 days	Dr Juliet Gray

2. Revised cost-effectiveness results with PAS

At the second appraisal meeting, the committee considered the following to be the committee's preferred assumptions:

- 1.5% discount rate per annum on costs and health benefits;
- 5.6 mortality ratio for stable health after the cure threshold;
- March 2014 data cut from ANBL0032;
- Kaplan-Meier observed values from ANBL0032 for event-free and overall survival;
- Cure threshold of 10 years;
- Weighted average of 4.2 dinutuximab vials per treatment course;
- 69 hospital days based on hospitalisation data from ANBL0032 originally presented by the company, although it was noted that the company had not provided a corrected analysis of the hospital days from ANBL0032;
- Using the hospital code rate for the delivery of complex chemotherapy for an elective inpatient stay for the treatment of paediatric brain tumours (PM42A), although the committee considered that there may be a more appropriate paediatric hospital code.

The company recommends the following changes to the Committee's preferred assumptions:

- Revised mean number of hospitalisation days from 69 to 35 as discussed above. The ERG is satisfied with this change.

- Revised hospital cost code to AA24C (corresponding to a cost per day of £449.97, NHS Reference costs 2013-14) from PM42A (corresponding to a cost per day of £991.92, NHS Reference costs 2013-14).
  The ERG has undertaken additional analyses using the alternative codes suggested by the clinical experts (Table 1).

- Application of a PAS discount of [redacted] for dinutuximab. This reduces the price per vial from [redacted] to [redacted].
  The ERG notes that the total drug cost of the dinutuximab regime over 6 cycles is reduced from [redacted] to [redacted]. In comparison, the total drug cost of standard therapy is £346.

Table 2 shows the impact of each of the company's revised assumptions on the Committee's preferred ICER. The combined impact of the company's revised assumptions reduces the ICER from £98,798 to [redacted] per QALY gained.

Table 2: Cost-effectiveness results for company's revised assumptions

	Total costs	Total LYs	Total QALYs	Incre. costs	Incre. LYs	Incre. QALYs	ICER (£/QALY)
Committee's preferred assumptions							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	£269,935	22.43	17.38	£207,980	2.81	2.11	£98,798
1: Committee's preferred assumptions with change in the number of days in hospital from 69 to 35 days							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	£247,269	22.43	17.38	£185,313	2.81	2.11	£88,031
2: Committee's preferred assumptions with change in hospital code from PM42A (£991.92 per day) to AA24C (£449.92 per day)							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	£239,705	22.43	17.38	£177,750	2.81	2.11	£84,438
3: Committee's preferred assumptions with PAS							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]
Company's revised results (1, 2, and 3 combined)							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]

LYs, life years; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

The ERG is satisfied with the changes made to the number of hospitalisation days and PAS. However, the revised code for inpatient stay does not represent a relevant code for a paediatric population. Table 3 shows the ERG's revised cost-effectiveness results using the codes suggested by the clinical experts. For consistency with the other costs used in the economic analysis, the ERG has used 2013-14 NHS Reference costs for the alternative codes. The corresponding results using 2014-15 Reference costs and 2016-17 National Tariff Workbook are presented in Appendix A.

The ICER varies between [redacted] and [redacted] per additional QALY for different assumptions about hospital length of stay for the administration costs of dinutuximab.

Table 3: ERG's revised cost-effectiveness results

	Total costs	Total LYs	Total QALYs	Incre. costs	Incre. LYs	Incre. QALYs	ICER (£/QALY)
Scenario 1: Code PM43C (equivalent to PA43B) for paediatric other neoplasms without co-morbidities (corresponds to a cost of £994.36 per day in 2013-14 NHS Reference costs)							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]
Scenario 2: Code SB14Z (corresponds to a cost of £401 per first day in 2013-14 NHS Reference costs) and SB15Z (corresponds to a cost of £328 per subsequent day in 2013-14 NHS Reference costs) for delivery of complex chemotherapy as Daycase and Regular Day/Night							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]
Scenario 3: Cost of £3,444 per admission for each course of dinutuximab (Dr Juliet Gray Trust)							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]
Scenario 4: Cost of £263 per day (Piam Brown Ward)							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]
Scenario 5: Cost of £2,827 per admission for each course of dinutuximab (Average Spell Income for 2016-17, Dr Juliet Gray)							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]

LYs, life years; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

3. End of Life Criteria

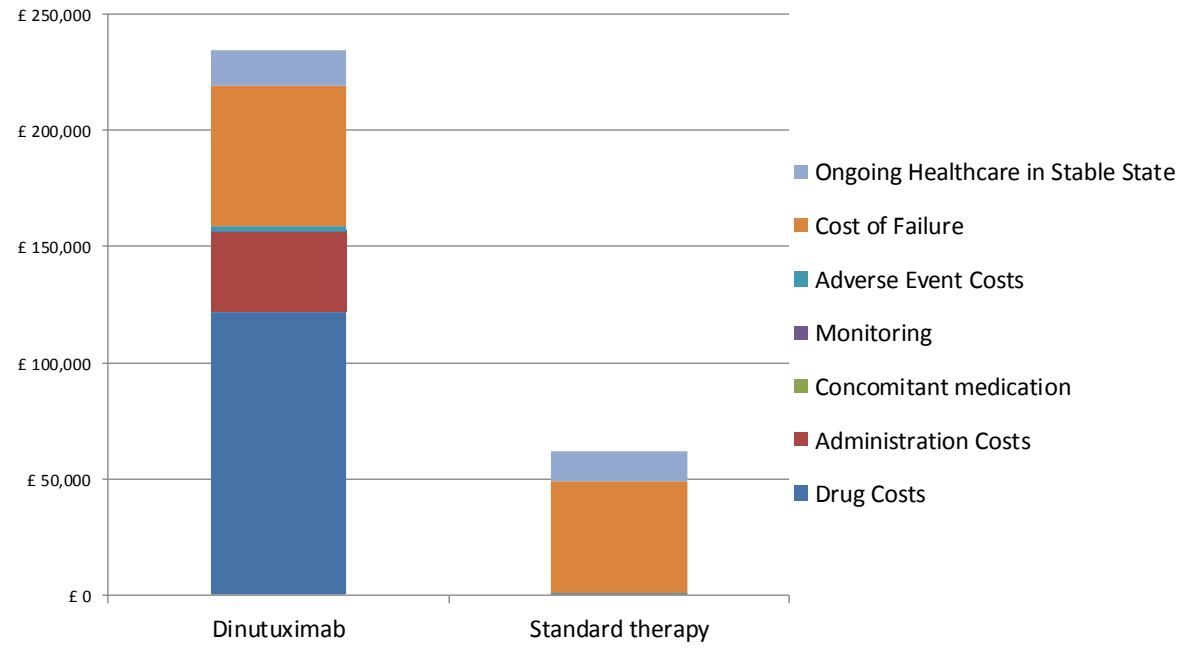
At the second appraisal meeting, the committee considered the NICE End of Life Criteria and concluded that dinutuximab does not fulfil the criterion for short life expectancy. The company have expressed concern that: i) the end-of-life criterion for short life expectancy of "normally less than 24 months" may not be applicable to a paediatric population; and ii) that the end-of-life criteria are critical for the appraisal of dinutuximab since even with a 100% discount on the price of dinutuximab (i.e. cost of £0), the ICER would not meet a £30,000 per QALY threshold.

For the first of these concerns, the ERG notes that the results of the ANBL0032 trial suggest that around half of all children with high-risk neuroblastoma who are eligible for dinutuximab treatment will survive long-term (at least 10 years) regardless of whether they receive dinutuximab or standard therapy treatment. The trial results also suggest that around 75% of patients on standard therapy will survive for 24 months or more. The company's submission also indicates that the median life expectancy for patients with high-risk neuroblastoma is 4 years (Table 14 of the company's original submission). Therefore, the end-of-life criterion for

short life expectancy as set out in the NICE Guide to Methods of Technology Appraisal is not satisfied. Whether this criterion is reasonable for children is a separate issue, which NICE is best placed to address.

For the second concern, the ERG notes that under the committee's preferred assumptions dinutuximab would have an ICER of [redacted] when zero priced (or [redacted] using an average of 35 hospital days instead of 69). This means that the additional benefits of dinutuximab compared with standard therapy in terms of event-free and overall survival are not sufficient to outweigh the difference in total costs even at zero price. Figure 1 shows the breakdown of total costs for dinutuximab compared with standard therapy based on the committee's preferred assumptions, but with application of the PAS and an average of 35 hospitalisation days instead of 69. After the drug cost of dinutuximab itself, a substantial proportion of the difference in total cost between dinutuximab and standard therapy is the administration costs associated with the dinutuximab regimen. A cost disadvantage also occurs for dinutuximab in the failure health state; however, this latter cost difference occurs as an artefact of how the company modelled the failure health state (see section 6.4.1 of the ERG report). If the difference in administration costs between dinutuximab and standard therapy were removed completely (i.e. the cost of administration of dinutuximab was £0), the ICER with the PAS would be [redacted]. This suggests that the long-term benefits associated with dinutuximab are not significantly greater than standard therapy to justify its additional costs.

[redacted]



4. Health-related benefits not captured in the economic analysis

At the second appraisal meeting, the committee acknowledged that there may be health-related benefits not captured in the economic analysis, but raised the issue that the company had not presented any data to demonstrate these uncaptured health-related benefits. The company's response provides further qualitative evidence of the impact of neuroblastoma on parents, siblings and caregivers, which include parental anxiety and mental health, strain on family relationships, short-term productivity loss, economic stress and reduction in quality of life. However, the company have not attempted to quantify these.

The ERG believes that even if these uncaptured health-related benefits were quantified, it is highly unlikely that they would be sufficient to bring the ICER below £50,000 per QALY.

5. Conclusion

None of the revised economic analysis and additional evidence submitted by the company results in an ICER below £30,000 per QALY (or even £50,000 per QALY if a higher threshold was considered).

Appendix A: Cost-effectiveness results by costing year

Table A1: ERG's revised cost-effectiveness results for different year of Reference cost

	Total costs	Total LYs	Total QALYs	Incre. costs	Incre. LYs	Incre. QALYs	ICER (£/QALY)
A: 2014-15 NHS Reference costs							
Scenario A1: Code PM43C (equivalent to PA43B) for paediatric other neoplasms without co-morbidities (corresponds to a cost of £1,053 per day)							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]
Scenario A2: Code SB14Z (corresponds to a cost of £414 per first day) and SB15Z (corresponds to a cost of £362 per subsequent day) for delivery of complex chemotherapy as Daycase and Regular Day/Night							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]
B: 2016-17 National Tariff Workbook							
Scenario B1: Code PA43B for paediatric other neoplasms without co-morbidities (corresponds to a cost of £2,600 per admission for each course of dinutuximab)							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]
Scenario B2: Code SB14Z (corresponds to a cost of £453 per first day) and SB15Z (corresponds to a cost of £301 per subsequent day) for delivery of complex chemotherapy							
Standard therapy	£61,955	19.61	15.27	-	-	-	-
Immunotherapy	[redacted]	22.43	17.38	[redacted]	2.81	2.11	[redacted]

LYs, life years; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio