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Title

Dinutuximab beta for treating neuroblastoma: an evidence review group and decision support unit perspective of a NICE single technology appraisal

Running heading

Dinutuximab beta for treating neuroblastoma: an ERG and DSU perspective

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Abstract

As part of its Single Technology Appraisal (STA) process, the UK National Institute for Health and Care Excellence (NICE) invited the manufacturer (EUSA Pharma) of dinutuximab beta (Qarziba®) to submit evidence of its clinical- and cost-effectiveness for treating neuroblastoma. The BMJ Technology Assessment Group (BMJ-TAG) was commissioned to act as the Evidence Review Group (ERG), reviewing the submission from the company. The Decision Support Unit (DSU) was commissioned to review additional evidence submitted by the company and to undertake further analyses. This article presents the critical review of the company's submissions by the ERG and DSU, further analyses undertaken by the DSU, and the outcome of the NICE guidance. The clinical effectiveness for dinutuximab beta was derived from a phase III randomised controlled trial (RCT) which assessed the safety and efficacy of the addition of interleukin-2 (IL-2) to dinutuximab beta plus isotretinoin. This trial did not inform the relative effectiveness of dinutuximab beta versus isotretinoin alone, which was established practice in the UK for maintenance treatment. In the absence of direct evidence, the company initially conducted a naïve indirect treatment comparison against a historical control, and later performed a matching-adjusted indirect comparison (MAIC) against the isotretinoin arm of an RCT comparing dinutuximab alpha and isotretinoin. The company submitted a partitioned survival analysis model that calculated the incremental cost-effectiveness of dinutuximab beta versus isotretinoin. The company's original incremental cost-effectiveness ratio (ICER) was £22,338 per quality-adjusted life year (QALY) gained. However, the ERG were concerned that the company's ICER was not suitable for decision-making, thus carried initial exploratory analysis as a first step to overcome the naïve estimation of treatment effectiveness in the model. The ERG's analysis estimated an ICER of £111,858 per QALY gained. In their revised analysis incorporating the MAIC and other changes as requested by the appraisal committee, the company's ICER was £24,661 per QALY gained. When the DSU incorporated longer-term isotretinoin data and made corrections to the model, the ICER increased to between £62,886 and £87,164 per QALY gained depending on the choice of survival model. A confidential Patient Access Scheme (PAS) decreased the ICERs. The ICERs with the PAS were over £40,000 per QALY gained, but the NICE committee additionally considered the patient population and its size, the disease severity, the potential for significant survival benefit and

uncaptured health benefits, and recommended dinutuximab beta as a treatment option, subject to the company providing the agreed discount in the PAS.

Key Points for Decision Makers

- There is uncertainty in the clinical- and cost-effectiveness of dinutuximab beta compared to isotretinoin for high-risk neuroblastoma because the clinical evidence relied on a matching-adjusted indirect comparison, in the absence of direct evidence.

- There are several plausible survival models for extrapolating overall survival and event-free survival for dinutuximab beta, leading to uncertainty in the cost-effectiveness analysis.

- The most plausible incremental cost-effectiveness ratio for dinutuximab beta compared to isotretinoin is above £40,000 per quality-adjusted life year gained, but the committee considered additional factors when recommending dinutuximab beta as a cost-effective treatment option.

1 Introduction

The National Institute for Health and Care Excellence (NICE) provides guidance on the use of health technologies within the National Health Service (NHS) in England. NICE considers the clinical- and cost-effectiveness of a technology within its Single Technology Appraisal (STA) programme[1]. In the STA process, the company provides a written submission and executable economic model. These are reviewed by an external independent organisation, known as the Evidence Review Group (ERG). The NICE appraisal committee consider the evidence from the company, the ERG report, expert testimony and input from other consultees in developing its preliminary recommendations in the Appraisal Consultation Document (ACD). After publication of the ACD, the company may provide further analyses for review by the ERG and consideration in developing NICE's final guidance in the Final Appraisal Document (FAD). On occasions, the NICE committee may require further evidence in addition to that presented to the Committee, or beyond the remit of the ERG's reviewing role. In these instances, NICE may commission its Decision Support Unit (DSU) to review and critique additional evidence from the company, or to undertake new analyses.

This paper presents a summary of the ERG[2] and DSU[3, 4] reports for the STA of dinutuximab beta (Qarziba®, EUSA Pharma) for neuroblastoma, the NICE guidance development and the key methodological issues.

2 Decision Problem

Neuroblastoma is a type of paediatric cancer that arises from the embryonic nervous system. Neuroblastoma is a rare disease, with annual incidence in the UK of between 80 and 100 cases[5]. Neuroblastoma is a heterogeneous disease, and children with neuroblastoma are categorised into risk groups (very low, low, intermediate and high) according to their disease stage[6].

Treatment for high-risk neuroblastoma consists of three phases: induction of remission with intensive chemotherapy, consolidation of remission using myeloablative therapy (MAT) and haematopoietic stem cell transplant (SCT), and maintenance therapy with isotretinoin and anti-GD2

immunotherapy[6, 7]. Dinutuximab beta, an anti-GD2 immunotherapy, received its marketing authorisation for the treatment of high-risk neuroblastoma in children and adults, for the European Union in May 2017[8].

This STA focussed on the comparison between dinutuximab beta and isotretinoin in patients with high-risk neuroblastoma who achieved at least a partial response to induction therapy and who had MAT and SCT. The NICE final scope defined the population as patients with high-risk neuroblastoma who have had MAT and SCT[9]. The ERG noted that the company considered a slightly narrower population, as patients had to have achieved at least a partial response to induction therapy. The intervention, dinutuximab beta, was as per the scope. The scope listed isotretinoin and dinutuximab alpha as comparators, the company included isotretinoin but not dinutuximab alpha as its marketing authorisation was withdrawn. The ERG agreed with the choice of comparator. Outcomes included overall survival (OS), event-free survival (EFS), adverse events (AEs), tumour response and health-related quality of life (HRQL). The scope listed subgroups of patients with relapsed or refractory disease, but the company suggested focussing only on high-risk patients who had not previously had dinutuximab beta, the ERG questioned the relevance of the relapsed or refractory populations and clinical experts confirmed that all UK relapsed or refractory patients would have already received dinutuximab beta.

3. Clinical and cost-effectiveness evidence

In this STA, the process was as follows:

1. The company submitted its written submission and economic model[10]
2. The ERG asked clarification questions of the company[10]
3. The company responded to clarification questions and provided revised analyses[10]
4. The ERG produced a report reviewing the company's evidence[10]
5. The NICE appraisal committee discussed the company's evidence and ERG report[10]

6. The NICE appraisal committee requested further analyses from the company[10]
7. The company provided further analyses[10]
8. The DSU asked clarification questions of the company[10]
9. The company responded to clarification questions[10]
10. The DSU produced a report reviewing the company's further analyses, and conducted additional analyses[10]
11. The NICE appraisal committee discussed the company's further analyses and DSU report, and developed the ACD[11]
12. The company responded to the ACD[12]
13. The DSU reviewed the company's response to the ACD and conducted further analyses[12]
14. The NICE appraisal committee discussed the company's response, DSU report and further analyses and developed the FAD[13].

3.1 Clinical evidence submitted by the company

The company provided clinical evidence for the effectiveness of dinutuximab beta in their submission[14]. There was one randomised controlled trial (RCT) in the high-risk population that included dinutuximab beta; APN311-302; but it did not compare dinutuximab beta in combination with isotretinoin against isotretinoin alone[15]. APN311-302 was designed to assess the efficacy and safety of adding interleukin-2 (IL-2) to a regimen of dinutuximab beta plus isotretinoin. APN311-302 was an open-label, randomised, phase III multicentre study (including UK), in patients under 21 years of age with high risk neuroblastoma, established diagnosis according to the International Neuroblastoma Staging System (INSS), at least partial response to induction therapy and no prior chemotherapy except 1 cycle of etoposide and carboplatin. In APN311-302, 406 patients were randomised and 180 patients who received dinutuximab beta plus isotretinoin and 190 patients who received dinutuximab beta plus isotretinoin plus IL-2 were included in the analysis. Dinutuximab beta was administered as five 28-day cycles intravenously at a dose of 20g/m^2/day over five days, and

isotretinoin was administered as six 28-day cycles orally at a dose of 160mg/m^2/day over 14 days. There was no statistically significant difference in EFS or OS between the two arms at any time point. Three-year EFS was 55.4% for the group not receiving IL-2 and 61.2% for the group receiving IL-2. Three-year OS was 64.1% for the group not receiving IL-2 and 69.1% for the group receiving IL-2. Serious AEs were reported in 46% of patients receiving IL-2 and 27% of those not receiving IL-2, most commonly these were infections, pyrexia, respiratory disorders, gastrointestinal disorders and hypotension. Of the common AEs, 238 patients experienced infections: 106 in the group not receiving IL-2 (including 48 grade 3 and 2 grade 4), and 132 in the group receiving IL-2 (including 60 grade 3 and 6 grade 4).

In the absence of direct evidence comparing dinutuximab beta to isotretinoin alone, the company initially performed a naïve indirect treatment comparison to a historical control of an earlier phase of APN311-302 which compared busulfan and melphalan hydrochloride (BuMel) to carboplatin, etoposide and melphalan (CEM) as consolidation MAT, after which 450 patients received isotretinoin alone as maintenance treatment. This was supplemented by a narrative comparison against the isotretinoin arm of an RCT comparing dinutuximab alpha plus IL-2 to isotretinoin in patients with high-risk neuroblastoma who had a response to induction therapy and SCT in a study by Yu et al (2010) ([16]). In response to a request from the NICE committee, the company provided an unanchored matching-adjusted indirect comparison (MAIC) comparing the combined dinutuximab beta arms of APN311-302 against isotretinoin arm in Yu et al (2010). The MAIC adjusted for age, INSS stage, tumour N-myc proto-oncogene protein (MYCN) status and response before SCT.

3.2 ERG and DSU critique of clinical evidence and additional analyses

The ERG noted that the open-label design of APN311-302 introduced bias, the lack of pre-specified time-point for disease assessment meant that it is unclear whether EFS captured the exact point of disease progression, and that the data presented were not the Intention to Treat (ITT) population. They further noted that the short-term study dosing schedule was unlikely to be in line with clinical practice

where dinutuximab beta would be given over 10 days and not 5, and that there was a paucity of evidence regarding the effect of the infusion rate on outcomes. Finally, they noted the immaturity of the data for EFS and OS and that, therefore, there is uncertainty in determining the clinical effectiveness particularly regarding whether benefit would be maintained in the long term.

In their clarification questions, the ERG proposed that a MAIC of the combined APN311-302 data compared to the isotretinoin arm in Yu et al (2010) was viable and would provide a more robust evidence base than the historical control. This was because the historical control was a retrospective collection of data from an essentially non-randomised study, and that the naïve indirect treatment comparison was subject to the same potential biases as a MAIC, and from additional confounding due to imbalance in the prognostic factors and effect-modifying factors.

The DSU reviewed the company's MAIC comparing dinutuximab beta and isotretinoin, and highlighted errors in the company's approach. The DSU reported that the number of patients used in calculating the proportions of patients in APN311-302 was incorrect, and ignored that 5 patients' INSS status were unknown in Yu et al (2010), and categorical variables did not all have a reference case. The company had included the individual patient data (IPD) from APN311-302 in the economic model, and so the DSU corrected the errors and re-ran the MAIC. The EFS and OS for isotretinoin and for dinutuximab beta from the observed data and the company and DSU's MAICs are shown in Figure 1.

3.3 Cost-effectiveness evidence submitted by the company

The company developed a partitioned survival analysis model with health states defined as Event-Free, Failure and Death. The model had a short-term element, in which the proportion of patients in each health state was calculated from survival analysis of EFS and OS data, and a long-term element. Patients in the long-term element could not move from Event-Free to Failure, as it was assumed that patients who were Event-Free at this point were cured. The time point at which the model changed

from short-term to long-term was termed the "cure threshold" and was assumed to be 10 years in the base case. In the long-term model, the mortality of patients in the Event-Free state was 5.6 times the mortality for the general population, based on a report from the Childhood Cancer Survival Study[17] and the mortality of patients in the Failure state was 90% higher than patients in the Event-Free state.

Through the STA, the company used a number of different approaches to estimate the transitions between states in the short-term model for dinutuximab beta and isotretinoin. Initially, the company used unadjusted Kaplan–Meier (KM) data for isotretinoin OS from the historical control and estimated EFS KM data, and took a similar approach for dinutuximab beta data. In response to the ERG's clarification questions, the company used Gompertz survival distributions for years where KM data were not available. As an alternative, the company also provided a hazard ratio for the indirect comparison of dinutuximab beta versus isotretinoin for OS, adjusted for prior treatment, MYCN, age and INSS stage at diagnosis. Following the request from the committee to conduct the MAIC, the company fitted parametric models to isotretinoin OS and EFS from Yu et al (2010) and matching-adjusted dinutuximab beta OS and EFS from APN311-302. The company used KM data for years 1–6 and the Gompertz extrapolation beyond this.

The company included common treatment-emergent AEs listed in the Summary of Product Characteristics (SmPC)[18] for dinutuximab beta (pain, hypersensitivity, severe capillary leak syndrome, eye problems, peripheral neuropathy, pyrexia/infection, and vomiting/diarrhoea). Data on the proportion of patients having AEs were based on a safety database which included high-risk and relapsed or refractory neuroblastoma patients[14]. In the additional analysis, the company made a distinction between pyrexia and infection and added grade3-4 infection rates based on APN311-302 for the group with and without IL-2.

The company did not initially specifically model treatment discontinuation, implicitly assuming that EFS was representative of time on treatment. In later analyses, the company subtracted the proportion of patients discontinuing due to toxicity from the EFS to estimate time on treatment.

To model HRQL, the company used UK general population norms for EuroQol-5 Dimension (EQ-5D)[19] and applied a percentage decrement for having neuroblastoma (the Event-Free state) and recurrent disease (the Failure state). The company initially used a logistic regression to estimate general population norms, but later replaced this with a published algorithm[20]. The decrement for Event-Free was 12.5%, calculated from the relationship between high-risk neuroblastoma utilities and general population utilities measures using Health Utilities Index (HUI) 3. The decrement for the Failure state was 41.7%, calculated from the relationship between utility for recurrent disease[21] and the general population[22]. The company did not include utility decrements for AEs, due to a lack of available data.

The company included costs for drug acquisition, administration and hospitalisation, concomitant medication, disease management and AEs, valued at 2016 prices. Drug acquisition costs were based on unit prices and the number of units consumed based on body surface area (BSA). The company initially used the median BSA from APN311-302, but later revised this to use a weighted average cost based on the distribution of patients across BSA categories. The company initially included the costs of concomitant IL-2 for all patients with isotretinoin and dinutuximab beta, which was later removed as there was no anticipated clinical benefit and clinicians advised that IL-2 would not be co-prescribed as standard. Administration costs for dinutuximab beta were initially assumed to involve 7.5 inpatient hospital days for cycle 1 and 2.5 for cycle 2, with the remainder of cycles in an outpatient setting. This was later revised to 10 inpatient hospital days in cycle 1 and 5 in cycle 2. The company included the costs for concomitant medication to manage pain and allergic reactions associated with dinutuximab beta treatment. Resource use for the Event-Free state was based on a study of healthcare resource use in the British Childhood Cancer Survivor Study[23] and costed using NHS reference costs. Costs for the Failure state included treatment with topotecan and cyclophosphamide and filgrastim – these were initially applied until death, but later revised to be applied for one year, beyond which the resource use for the Event-Free state was applied. Costs for AEs were included, costed using NHS reference costs.

3.4 ERG and DSU critique of cost-effectiveness evidence and additional analyses

The ERG and DSU agreed with the model structure but had concerns about a number of model inputs. The ERG were severely concerned with the estimation of treatment effect, specifically regarding the assumptions used in the initial approach, the survival analysis method used to fit Gompertz distributions and the use of the naïve indirect treatment comparison.

The ERG disagreed with carrying out a naive analysis of treatment effectiveness and felt that the company's model was not suitable for decision making. The ERG undertook an exploratory analysis for illustrative purpose only, estimating a hazard ratio for isotretinoin EFS and OS relative to dinutuximab beta (based on the relationship between dinutuximab alpha and isotretinoin) and using the extrapolated Gompertz distribution instead of KM data for dinutuximab beta.

The DSU had similar concerns regarding the methods for survival analysis following the MAIC, which used least squares optimisation to fit parametric models. The DSU noted that the ERG had identified KM data from a later cut-off of the study comparing isotretinoin with dinutuximab alpha[16] which reported 12 years of EFS and OS data for isotretinoin[24]. The DSU performed survival analysis of the MAIC-adjusted dinutuximab beta data – this was not necessary for isotretinoin as the KM data could be used directly in the model with no requirement for extrapolation. In their survival analysis, the DSU considered standard parametric models and flexible spline-based models to allow for more complex hazard functions. According to statistical measures of goodness of fit (Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)) and visual inspection, the Generalised Gamma, Gompertz, log normal and spline models had the best internal validity for OS, and the Generalised gamma and spline models for EFS. Clinical experts advised that events after five years would be rare, suggesting that models which flattened somewhat after five years may be most appropriate. The DSU noted that if events after five years were impossible, models which were completely flat after five years would equate to using a five-year cure threshold. Longer-term data for dinutuximab beta were not available, but 12-year data for dinutuximab alpha were[25].

Given the expected similarities between dinutuximab alpha and beta, the DSU used the shape of the best-fitting dinutuximab alpha models and the relationship between dinutuximab alpha and isotretinoin to inform model selection[25]. The DSU therefore felt that the Gompertz and spline with 2 knots for OS and the Gompertz and spline with 1 knot for EFS should be considered potentially plausible. A comparison of the DSU and company's OS models are presented in Figure 2, and EFS models in Figure 3.

The ERG had concerns about the source of AE data and whether it was applicable to patients receiving dinutuximab beta as a continuous infusion, but found the impact of scenario analysis was negligible. The ERG noted that most patients in the SmPC safety dataset received IL-2, and that IL-2 increased the risk of AEs. The DSU considered that the company's adjustment to model infection rates separately for dinutuximab beta with and without IL-2 was appropriate.

The DSU considered that the company's approach to discontinuation was inaccurate, and preferred to use the proportion of patients treated per cycle reported in APN311-302.

The ERG critiqued the cost data, considering a scenario analysis including wastage for gabapentin (a concomitant medication which excluded wastage) and using the cost of a hospital day for chemotherapy administration rather than chemotherapy procurement costs. The ERG further noted that treatment in the failure state was likely overestimated as it should only be given until further disease progression or one year[26]. The DSU considered that the company's revised analysis, which incorporated these changes, was appropriate.

The ERG were concerned about the logistic regression for UK general population utility norms, requesting that the published algorithm[20] be used instead, so the DSU considered that the company's revised analysis using this algorithm was appropriate. The ERG had concerns regarding the utility decrements, specifically that one study[22] used HUI3 which was not developed for use in children, and that this was combined with the HUI2 values in another study[21] when the measures may not be comparable. Furthermore, the company's approach assumed that the populations in the two studies were comparable, despite differences in age, and that patients in the second study did not

have neuroblastoma[21]. Overall, the ERG were unable to draw final conclusions as to which utility values should be used, and considered it a source of uncertainty. The ERG noted that excluding the impact of AEs on HRQL may overestimate the QALY gain for dinutuximab beta, but considered that this impact would be minimal.

The ERG corrected the dinutuximab beta administration costs in the model and stated that they would have preferred the drug acquisition costs to use an average number of vials according to the distribution of BSA, which the company addressed in their revised analysis. Similarly, the company's revised analysis addressed the ERG's concerns about the costs of chemotherapy administration and wastage of concomitant medication.

The company's base case incremental cost-effectiveness ratio (ICER) was £22,338 per QALY gained in their original submission, and the ERG's corrections increased this to £31,366 per QALY gained. In the ERG's exploratory analysis, the ICER was £111,858 per QALY gained. After addressing the changes requested by the appraisal committee, the company's ICER was £24,661 per QALY gained. Taking into consideration the corrections and revisions made by the company, ERG and DSU, the DSU's final analysis estimated that the mean deterministic ICER ranged from £62,886 to £87,164 (probabilistic: £69,000 to £80,000) per QALY gained depending on the choice of survival model for OS and EFS (Table 1). A confidential Patient Access Scheme (PAS) discount decreased the ICERs.

4. Key methodological issues

The key methodological issues in the evidence base were the indirect treatment comparison and extrapolation of EFS and OS. Naïve indirect treatment comparisons are inherently biased, and while a MAIC can address the bias arising from imbalance in the prognostic factors and measured treatment-effect modifiers it is not without limitations[27].

Extrapolation beyond observed data is uncertain and therefore methods to analyse survival data should be as robust as possible and alternative extrapolations should be considered. The approach taken by the company was not transparent, and it transpired, not correct. Extrapolations are less

uncertain where longer-term data are used. The approach taken by the DSU, using the most recent data for isotretinoin increased the ICERs substantially. The DSU's scenario analyses demonstrated that using alternative plausible survival functions could increase the ICER by over £20,000 per QALY gained.

5. NICE guidance

On 22 August 2018, NICE recommended dinutuximab beta as an option for treating high-risk neuroblastoma in patients aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by MAT and stem cell transplant only if they have not already had anti-GD2 immunotherapy and the company provides dinutuximab beta according to the commercial arrangement.

5.1 Consideration of Clinical and Cost-Effectiveness Issues in the Final Appraisal Determination

This section presents a summary of the key issues considered by the committee. A full discussion of all issues is presented in the FAD[13]. The committee felt that the evidence for relapsed or refractory neuroblastoma was not relevant and focussed only on high risk neuroblastoma.

Consideration of clinical effectiveness

The committee concluded that despite the limitations of immature data, lack of fixed cut-off data and potential biases of the open-label design, APN311-302 represented the best source of evidence for dinutuximab beta, but it did not inform the relative effectiveness of dinutuximab beta compared to isotretinoin. The committee noted that the MAIC showed dinutuximab beta improved EFS and OS compared with isotretinoin, and that the later cut-off of isotretinoin data was most appropriate for the comparator data.

The committee noted the non-significant difference for EFS and OS between the groups with and without IL-2 in APN311-302, and clinical experts advised that IL-2 would not be used in clinical practice. The committee noted that dinutuximab beta was associated with AEs, but that these were more common when given in combination with IL-2.

Consideration of cost effectiveness

The committee accepted the structure of the economic model. The committee noted that the long-term benefit of dinutuximab beta was uncertain and so considered a range of extrapolations for EFS and OS, noting that Gompertz and Spline models are the most plausible for both. The committee preferred a 10-year cure threshold, but considered a range of thresholds in its decision making. The committee felt that the cost, utility, discount rate and discontinuation data in the final DSU model were appropriate.

End of Life criteria

The committee considered that dinutuximab beta did not meet end-of-life criteria[1]. The modelled life expectancy of isotretinoin alone was approximately 31 to 34 years so did not meet the criterion for short life-expectancy, although the survival gain was in the range of 3–5 years which did meet the criterion for survival gain. The committee recognised that the survival gain was substantial, but due to the uncertainty, could not be confident of the extent of proportional gain in relation to life expectancy.

6. Conclusion

The committee considered a range of ICERs, given the uncertainty in the long-term benefit of dinutuximab beta. The committee considered the ICERs for the committee's preferred assumptions were above £40,000 per QALY gained and above the range normally considered cost-effective by NICE. However, in addition to considering the ICERs, the committee considered the patient

population and its size, the disease severity, the potential for significant survival benefit, and effect of end of life costs (decreasing ICERs by £1,000 per QALY gained) and uncaptured benefits not included in the ICERs. The uncaptured health-related benefits were noted to include the effect of neuroblastoma on reducing quality of life for young patients and their families and the impact of bereavement on families. The committee was prepared to be flexible in its decision making given the rarity and severity of the disease, and noted the importance of potentially generating life-long health benefits in the patient population. Considering all of these factors, the committee was able to recommend dinutuximab beta as a cost-effective treatment option.

Data Availability Statement

The model used in the current study are not publically available as were part of the NICE appraisal process.

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This summary of the DSU and ERG report was compiled after NICE issued the FAD. All authors have commented on the submitted manuscript and have given their approval for the final version to be published. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of NICE or the Department of Health. Any errors are the responsibility of the authors. The authors would like to thank Nwamaka Umeweni and Anna Brett for their support throughout the appraisal and for reviewing this manuscript.

Author contributions

Becky Pennington and Shije Ren were members of the DSU who reviewed the company's additional analyses and wrote the DSU reports. Becky Pennington critiqued the economic modelling and undertook new economic analyses. Shije Ren critiqued the statistical analyses and performed the

MAIC and survival analyses. Samantha Barton, Mariana Bacelar and Steve Edwards were members of the ERG who reviewed the company's submission and wrote the ERG report. Samantha Barton critically appraised the company's submission, critically appraised the clinical evidence and cross-checked the company's search strategies. Mariana Bacelar critically appraised the company's submission and economic model, cross-checked the company's search strategies, critically appraised the economic evidence and carried out economic analyses. Steve Edwards critically appraised the company's submission and validated the statistical analyses. All authors were involved in drafting and commenting on this document. This summary has not been externally reviewed by PharmacoEconomics.

Compliance with Ethical Standards

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Conflicts of Interest

Becky Pennington, Shije Ren, Samantha Barton, Mariana Bacelar and Steven J. Edwards report no conflicts of interest.

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Figure captions and legends

Figure 1: Matching-adjusted indirect comparison results

DSU: Decision Support Unit, ESS: effective sample size, MAIC: matching-adjusted indirect comparison

Figure 2: Comparison of company and DSU overall survival data

DSU: Decision Support Unit, OS: overall survival

Figure 3: Comparison of company and DSU event-free survival data

DSU: Decision Support Unit, EFS: event-free survival

Table 1: Results of final analysis

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

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