NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Roxadustat for treating anaemia in people with chronic kidney disease [ID1483]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Roxadustat for treating anaemia in people with chronic kidney disease [ID1483]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from** Astellas Pharma

3. **Evidence Review Group critique of company comments on the ACD**

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

Roxadustat for treating anaemia in people with chronic kidney disease

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td>1</td><td>Company</td><td>Astellas Pharma Ltd</td><td>

Executive summary

Astellas is disappointed to see a preliminary negative recommendation for roxadustat and hopes that additional information and analyses provided in response to this consultation will support a final positive recommendation for roxadustat as a novel oral treatment for adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

In response to the Committee's preferences, the base case has been revised as follows:

Analysis based on DOLOMITES data only
Multiplicative approach to health state utilities implemented
Erythropoiesis stimulating agent (ESA) administration costs applied to peritoneal dialysis patients who require assistance
Roxadustat stopping rule implemented at Hb ≥13g/dL.

Regarding the Committee's preferred approach to modelling additional adverse events and hospitalisations, the Company believes that the additional analyses and more detailed responses provided below will reassure the Committee that the existing approach sufficiently captures the health-related quality of life (HRQoL) and costs associated with these, and the revised base case model is appropriate for decision-making.

Clean and colour-coded versions of the revised model are presented alongside this response, with a log of changes accessible from the title page of each version for ease of reference. As presented within them, the result of making the above changes to the base case results in the following:

Table 1. Cost-effectiveness results

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Previous DOLOMITES only scenario presented in response to ERG clarification question	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

</td><td>Thank you for your comment and changing the base case in line with the committee's preferences. The committee considered the company's approach to using DOLOMITES only trial data, multiplicative health state utilities, ESA administration costs for people on peritoneal dialysis and roxadustat stopping rule. See sections 3.6, 3.9, 3.13 and 3.14 of the FAD for a summary of the committee discussion and conclusions.</td></tr>
</table>

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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>(C7.b)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Revised base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; [redacted]

Scenario analyses are also presented in relation to reflecting harms and costs of higher Hb levels and assuming that the benefits of roxadustat do not last indefinitely over the 25-year time horizon. More detail is provided below but the results demonstrate that these scenarios do not have a significant impact on the cost-effectiveness of roxadustat.

No alternative data sources were identified to enable scenario analysis using different distributions of ESA. However, the most extreme scenarios whereby 100% use of each ESA is assumed were included in the original submission. These have been reproduced using the revised base case for information and further details are provided below.

The company does recognise the potential impact of confidential ESA tenders on decision-making. However, the company has increased the discount level through an updated simple Patient Access Scheme, to further ensure that roxadustat offers a cost-effective treatment option for the NHS.
</td><td></td></tr>
<tr><td>2</td><td>Company</td><td>Astellas Pharma Ltd</td><td>
“Health states which reflect the harms and costs of having Hb levels over 120 g/L”

Table 45 in the clarification questions response has been provided below (as Table 2) for ease of reference and shows the estimated average number of years spent in each health state for the cohort at a per person level while they are alive using the DOLOMITES data only.

The average roxadustat patient spends [redacted]% of their lifetime in the ≥13 Hb level health state whereas the average ESA patient spends [redacted]% of their lifetime in the ≥13 Hb level health state, meaning a relatively small proportion of patient time is spent within this health state, and any impact of stratified harms and costs in this health state on cost-effectiveness is likely to be negligible.

Table 2. Predicted health state occupancy within the cost-effectiveness model over a lifetime horizon (DOLOMITES data only)

<table>
<tr><th>Hb level (g/dL)</th><th>Roxadustat</th><th>ESA</th></tr>
<tr><td><7</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>7 – 7.99</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>8 – 8.99</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>9 – 9.99</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>10 – 10.99</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>11 – 11.99</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>12 – 12.99</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td>Thank you for your comment and changing the model in line with the committee’s preferences. The committee considered the additional harms and costs modelled for higher Hb levels. See section 3.10 of the FAD for a summary of the committee discussion and conclusion.</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td>≥ 13</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Total years alive</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>

The probability of having an adverse event (AE) in the model is calculated using the number of events in each arm and total patient exposure time, giving a constant probability of AEs for each treatment, irrespective of Hb levels.

To capture the harms and costs of patients at higher Hb levels, the model now allows the user to select “Published sources (Stroke relative risk applied to MI and VATs)” (MI, myocardial infarction; VAT, vascular access thrombosis) as an input option for adverse events. This uses the probability of stroke derived from published sources to generate Hb-specific adverse event probabilities rather than use a common value across all Hb categories. In the absence of such stratification in the literature for other adverse events in the model, this option applies the relative risk of stroke events in each Hb level to MI and VAT. This allows the user to explore scenarios where both MI and VAT risk also differ by Hb health state.

Table 3. Cost-effectiveness results including relative risk for stroke applied to MI and VAT
<table>
<tr><th rowspan="2">Scenario</th><th colspan="2">Roxadustat</th><th colspan="2">ESA</th><th>Δ</th><th>Δ</th><th>ICER</th><th>[redacted]</th></tr>
<tr><th>Costs</th><th>QALYs</th><th>Costs</th><th>QALYs</th><th>Costs</th><th>QALYs</th><th></th><th></th></tr>
<tr><td>Revised base case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Relative risk for stroke applied to MI and VAT Harms and costs of AEs at higher Hb</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Key: MI: myocardial infarction; VAT: Vascular access thrombosis; QALYs: quality-adjusted life years; ICER: incremental cost effectiveness ratio; [redacted]

As can be seen from the above, applying harms and costs at higher Hb levels makes a negligible difference both costs and QALYs.
</td><td></td></tr>
<tr><td>3</td><td>Company</td><td>Astellas Pharma Ltd</td><td>Including stopping rule to reflect clinical practice for roxadustat and ESA

The Summary of Product Characteristics (SmPC) for roxadustat specifies withholding treatment at Hb 13 or higher and resuming only when Hb is less than 12g/dL. To reflect this in the model, an optional stopping rule has been added for roxadustat at Hb ≥13 and included in the revised base case. As Hb ≥13 is not associated with a utility benefit in the model (i.e. patients have utility equivalent to population norms), setting the stopping rule to “yes” removes the accrual of treatment costs for roxadustat in this health state. Disutilities from other sources such as AEs</td><td>Thank you for your comment and changing the base case in line with the committee’s preferences. The committee considered the company’s approach to</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
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<tr><td></td><td></td><td></td><td>and dialysis status still apply.

For darbepoetin alfa, its SmPC states that a dose reduction should be considered if Hb exceeds 12g/dL followed by a second dose reduction if Hb continues to increase. If this does not have the desired effect, doses should be temporarily withheld until Hb begins to decrease upon which therapy should be reinitiated at a lower dose. As the dosing of darbepoetin alfa in the DOLOMITES trial was in accordance with the SmPC, the raw data is considered reflective of clinical practice and its stopping rule. Furthermore, as mentioned by the clinical experts at the Committee meeting, ESA treatment is rarely stopped in practice with doses either reduced or the interval between doses increased. Therefore, it is considered that the model appropriately reflects clinical practice for ESA in patients with Hb levels of 13 or higher.</td><td>the roxadustat stopping rule and the justification for excluding a stopping rule for ESAs. See sections 3.13 and 3.14 of the FAD for a summary of the committee discussion and conclusions.</td></tr>
<tr><td>4</td><td>Company</td><td>Astellas Pharma Ltd</td><td>Health-state transition probabilities and extrapolation of benefit based on data from the entire duration of the DOLOMITES trial

The company believes this is a factual inaccuracy as the health state transition probabilities and extrapolation of benefit are based on the entire length of trial data not 12 weeks. The first 12 weeks of data were only used to determine health state distribution at baseline.

It should also be noted that data were available up to a maximum of 104 weeks depending on the length of time individuals had been recruited to the study. To ensure long term extrapolations were as accurate as possible all available data were used.

Furthermore, all statistical analysis and baseline characteristics in the DOLOMITES only scenario previously presented were based on the DOLOMITES study only. Separate statistical analyses were conducted for the pooled roxadustat model and the DOLOMITES only scenario.

Therefore, the company would like to confirm that in the revised DOLOMITES only base case all statistical analysis and baseline characteristics are based on the DOLOMITES study only.</td><td>Thank you for your comment and for the additional confirmation that all analyses were based on the DOLOMITES study only. The factual inaccuracy has been revised in the FAD. See section 3.8.</td></tr>
<tr><td>5</td><td>Company</td><td>Astellas Pharma Ltd</td><td>Approach to modelling hospitalisations

In the DOLOMITES clinical trial, hospitalisations were categorised according to whether they were related to anaemia, adverse events or other reasons as summarised in Table 16 provided in the clarification questions response and replicated below (as Table 4) for ease of reference.

Table 4. Summary of hospitalisations during efficacy emergent period (Full Analysis Set) in DOLOMITES

<table>
<tr><th>Parameter</th><th>Category/statistic</th><th>Roxadustat (N=323)</th><th>Darbepoetin alfa (N=292)</th></tr>
<tr><td rowspan="2">Hospitalisation</td><td>Yes</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Number of</td><td>Mean (SD)</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>Thank you for your comment and submitting additional evidence. The committee considered the hospitalisation rates due to adverse events and other reasons in its discussions. It concluded that hospitalisations costs should be based on hospitalisations rates measured directly from the DOLOMITES trial. See section 3.11 of the FAD</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

hospitalisations	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Total duration of hospitalisation (days)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Average duration of each hospitalisation (days)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Number of days of hospitalisation per PEY (patient-exposure year)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Reason for hospitalisation	Anaemia	[redacted]	[redacted]
	Adverse event	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Time to first hospitalisation	Number of Patients with Event [4] (Percentage)	[redacted]	[redacted]
	Cumulative Time at Risk (years)	[redacted]	[redacted]
	Incidence Rate (per 100 Patient Years at Risk)	[redacted]	[redacted]
	Hazard Ratio [5]	[redacted]	
	95% CI	[redacted]	
	P value	[redacted]	

Approximately [redacted] of hospitalisations in the roxadustat arm were related to adverse events compared to approximately [redacted] in the ESA arm. The 'other' category accounted for [redacted] of patients in the roxadustat arm vs. [redacted] of patients in the ESA arm. These were not further categorised within the pre-specified trial analysis. Each hospitalisation classified as other was linked with a free text field within the clinical summary report. By identifying each of these occurrences and interpreting the descriptions, these were further categorised. The majority of other hospitalisations were described as [redacted] or [redacted] ([redacted] and [redacted] for roxadustat and darbepoetin alfa respectively). [redacted] They have therefore been excluded from Table 5 below.

Table 5. Summary of 'other' hospitalisations in DOLOMITES

Category	Roxadustat	Darbepoetin alfa
[redacted]	[redacted]	[redacted]

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
[redacted]

Furthermore, combining this information with the exposure time used in the economic model for adverse events to calculate an incident rate ratio, found no significant difference in the rate of hospitalisations between roxadustat and ESA.

Table 6: Adverse Event related hospitalisations

<table>
<tr><th>Treatment</th><th>Number of patients with events</th><th>Total exposure in 3-monthly cycles</th><th>Cycle probability of Hospitalisation</th></tr>
<tr><td>ESA</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Roxadustat</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Incident rate ratio: [redacted]

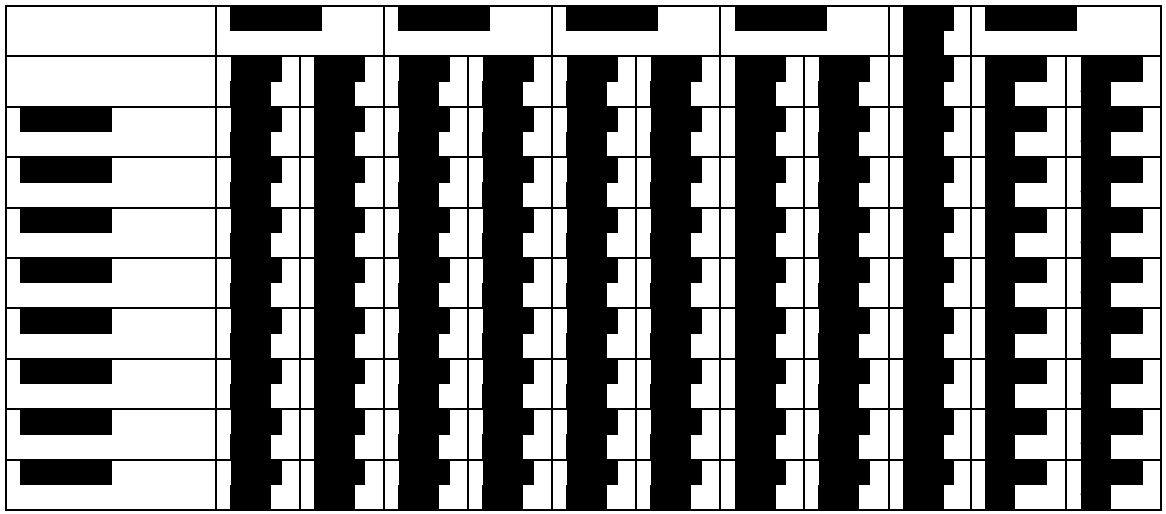
Table 7: ‘Other’ related hospitalisations

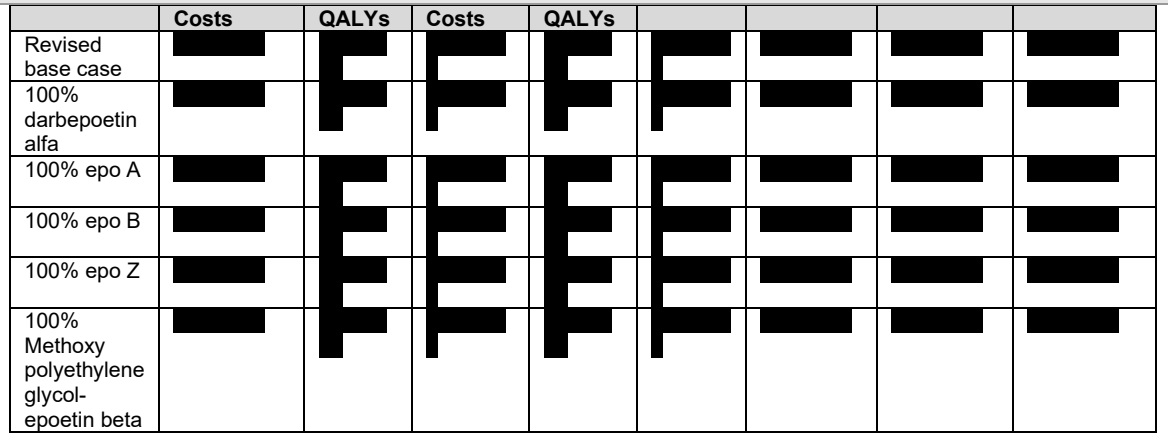
<table>
<tr><th>Treatment</th><th>Number of patients with events</th><th>Total exposure in 3-monthly cycles</th><th>Cycle probability of Hospitalisation</th></tr>
<tr><td>ESA</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Roxadustat</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
Incident rate ratio: [redacted]

Thus, inclusion of hospitalisations due to ‘other’ reasons would be unlikely to significantly alter the cost-effectiveness findings. However, if it were to be included, it would favour roxadustat due to its lower cycle probability.
</td><td></td></tr>
<tr><td>6</td><td>Company</td><td>Astellas Pharma Ltd</td><td>
Inclusion of additional adverse events

In response to the concern about potentially relevant adverse events being excluded from the model, the company technical engagement response included an impact calculation of severe treatment emergent adverse events (grade 3+) that occurred in more than 3% of the trial population in the DOLOMITES study. [redacted] adverse events were identified: [redacted] with negligible differences between treatment arms.

These differences were minimal both in terms of costs and quality of life and the inclusion of these adverse events in the cost-effectiveness model is unlikely to impact the final comparative results. This was acknowledged by the ERG in
</td><td>Thank you for your comment. The committee considered the additional evidence provided. See section 3.12 of the FAD for a summary of the committee discussion and conclusions.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			their comments on the Company's response to technical engagement, where this issue was no longer to be regarded as a key issue. All adverse events that differed in incidence by >2% between roxadustat and darbepoetin alfa were reviewed and further categorised by severity as can be seen in Table 8 below. It was considered that grade 3+ AEs were most likely to affect costs or utilities. The occurrence of such events was minimal in number and comparable between arms. Therefore, the inclusion of further adverse events is unlikely to impact the results of the cost effectiveness analysis. *Table 8: All adverse events differing by >2% between treatment arms by severity*  Grade 1=Mild; Grade 2=Moderate; Grade 3=Severe; Grade 4=Life-threatening; Grade 5=Death.	
7	Company	Astellas Pharma Ltd	**Scenario analysis for different distributions of ESA** As no alternative data sources for ESA distributions were identified, it was not possible to undertake the requested scenario analysis. However, scenario analyses where 100% use of a single ESA was assumed were included in the original submission to demonstrate cost-effectiveness in the most extreme, albeit unlikely, scenarios. The result of the updated scenario analyses using the revised based case in Table 9 below show that roxadustat is [redacted]. It should also be noted that the model includes the functionality for the user to alter the distribution of ESA to explore this further. *Table 9. Results of scenario analyses* **Scenario** | **Roxadustat** | **ESA** | **Δ Costs** | **Δ QALYs** | **ICER** | [redacted]	Thank you for your comment. The committee discussed the ESA distribution assumptions in the model and the company's and ERG's revised base cases and scenario analyses. See sections 3.14 and 3.15 of the FAD for a summary of the discussion and conclusions.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 TUNE was a retrospective chart review Real World Evidence study in the UK and two other European countries exploring treatment patterns, sociodemographic and clinical characteristics of non-dialysis dependent patients with anaemia associated with CKD stages 3-5. Across the UK, TUNE involved [redacted] healthcare professionals and [redacted] patient records spanning [redacted] months. Furthermore, the TUNE study was used to inform the budget impact assessment agreed with NHS England on the basis that it provided the most robust estimate of ESA distribution in the UK. Alternative sources were not indication-specific and would therefore introduce further uncertainty to decision-making. The revised base case continues to use the TUNE study as best estimate of ESA use within this patient population in UK clinical practice. This was validated with clinical experts who confirmed the estimates from the TUNE study were in line with their expectation given there is a tendency to use long-acting ESAs in the non-dialysis space.	
8	Company	Astellas Pharma Ltd	**Estimating average roxadustat dose** The company would like to clarify that the average roxadustat dose for each Hb level was based on data from people in all roxadustat trials for the pooled data analysis only. Only data from the DOLOMITES trial was used for the DOLOMITES analyses. The revised DOLOMITES base case therefore uses data from DOLOMITES only to calculate average roxadustat doses. As treatment doses were calculated on weekly doses reported in the trial (which are adjusted for patient weight), the average roxadustat and ESA doses used in the economic model are reflective of the average weight of patients in the DOLOMITES trial.	Thank you for your comment and the clarification. Section 3.13 of the FAD has been updated to reflect this information.
9	Company	Astellas Pharma Ltd	**Proposed positioning of roxadustat** On page 7 of the appraisal consultation document (ACD) it states that “the proposed positioning for roxadustat does	Thank you for comment and the clarification. Section 3.3 of the FAD

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			not include people on dialysis (including peritoneal dialysis).” The company would like to clarify that the proposed positioning of roxadustat does include people on dialysis, however, roxadustat would be only be initiated in people who were not on dialysis at that time. Patients receiving roxadustat who went on to receive dialysis treatment would be able to remain on treatment with roxadustat. Furthermore, the cardiovascular disease safety concern mentioned relates to the switching of dialysis patients who are stable on ESA treatment to roxadustat. In line with the licence for roxadustat, switching of these patients should only be considered when there is a valid clinical reason and are therefore are not considered as the target patient population for this submission.	has been updated to reflect this information.
10	Company	Astellas Pharma Ltd	**Non-inferiority trials can still demonstrate improvement to standard of care** The company considers it important to recognise that although the active comparator trial was non-inferiority by design, this does not mean that there is no difference between roxadustat and the comparator. In DOLOMITES the primary efficacy analysis was powered to allow a demonstration of statistical non-inferiority should the estimated outcome in the roxadustat arm not differ from the darbepoetin alfa arm by more than a pre-specified and justified amount (the non-inferiority margin of 15%). The powering of the study has no impact on the resulting point estimates of efficacy themselves, and a result in which roxadustat appears superior to darbepoetin alfa could be observed while still allowing a claim of statistical non-inferiority. There is nothing in the design of a non-inferiority study that prevents the estimates of test treatment outcome being favourable compared with those of the comparator.	Thank you for your comment. The committee considered the points raised and acknowledged that the company were not claiming superiority of roxadustat over ESAs.
11	Company	Astellas Pharma Ltd	**Scenario analysis regarding the benefits of roxadustat not lasting indefinitely over 25-year time horizon** The long-term plausibility of the model extrapolations was validated with clinicians. Table 2 (in point 2 above) provides an estimated average number of years spent in each health state for the cohort at a per person level while they are alive using the DOLOMITES only trial. The average roxadustat patient spends [redacted] of their time in the target Hb range (10 to 11.99) whereas the average patient in the ESA arm spends [redacted] of their time in the same target Hb range. These outcomes were validated by clinical experts who agreed that the state occupancy results were in line with their expectations given the Renal Registry guidelines. The 22nd UK Renal Registry report estimated that approximately 60% of patients on in-centre haemodialysis in England have a Hb level between 10.00 and 12.00 g/dL [REF]. Furthermore, the model was built with the functionality to maintain the proportion in state at any given time point, to enable the user to test the sensitivity of the results to changes in state over time. This functionality can be accessed via a switch on the model set-up page (“Maintain Hb level after set time point?”). Previous sensitivity analyses fixing the proportion in state at 5, 10 and 15 years were presented in response to ERG clarification question C7 (c). We have updated these scenario analyses using the revised base case and present the results below:	Thank you for your comment and providing the scenario analyses. The committee discussed the assumptions and results of the scenario analyses. See section 3.8 of the FAD for a summary of the discussion and conclusions.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

1. DOLOMITES data, proportion in state fixed after 5 years
2. DOLOMITES data, proportion in state fixed after 10 years
3. DOLOMITES data, proportion in state fixed after 15 years

Table 10. Results of scenario analyses

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]							
1	[redacted]							
2	[redacted]							
3	[redacted]							

All three scenarios show that fixing the proportion in state over time (i.e. ignoring the impact of time after set points), results in negligible differences to costs and QALYs.

In response to the Committee's specific request for scenario analyses exploring altering the extrapolation of treatment effect over the time horizon of the model, the Company has added functionality in the model to allow the treatment benefit of roxadustat to fall to that of ESA. This can be implemented immediately (at any time point), or gradually (treatment effect begins to decline at timepoint A, matching ESA effect by timepoint B) by selecting this option in the model set up page.

The three scenarios explored are presented below:

1. Roxadustat efficacy matches ESA efficacy immediately after the DOLOMITES trial (month 25 in the model)
2. Roxadustat efficacy gradually declines from the end of DOLOMITES trial, matching ESA by year 3 in the model
3. Roxadustat efficacy gradually declines from the end of DOLOMITES trial, matching ESA by year 5 in the model

Table 11. Results of scenario analyses

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]							
4	[redacted]							

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			5 [redacted] 6 [redacted] All scenario analyses performed resulted in negligible differences to costs and QALYs.	
12	Company	Astellas Pharma Ltd	**Eight health state model structure** The company welcomes the Committee's recognition that the economic model based on Hb-defined health states suitably reflects anaemia associated with CKD. The company also recognises the Committee's concerns regarding the number of health states within the model and the choice to use 1g/dL increments to define these. However, in line with a disease area demarked by 1g/dL measurements of Hb, as well as the available published precedence in this area, the company believes that presented model appropriately reflects this disease area whilst retaining suitable sensitivity to differences between roxadustat and ESA, in order to robustly support decision-making. In addition to the papers supporting this by Yarnoff et al., Lawler et al., and Finkelstein et al., highlighted in the ACD, the positive correlation between Hb levels and HRQoL in patients with CKD has also been recognised elsewhere in the literature, with a published cost-effectiveness analysis by Glenngård et. al. 2008 following a similar stratification of HRQoL by Hb level in patients with anaemia associated with CKD. The association between Hb level and HRQoL was also confirmed in the roxadustat clinical trial programme. The figure presented below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle) for utility values at increasing Hb levels. These data show that utilities increase with increments of 1 g/dL in the patient's Hb level and the statistical model provides a reasonable estimate for the average utility value stratified by Hb level (evidence previously provided in response to clarification question C10). *Figure 1: Utility values by increasing Hb level (showing observed data in red and predicted values in blue)*	Thank you for your comment. The committee considered the evidence presented. See section 3.7 of the FAD for a summary of the discussion and conclusions.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 A similar observation was made for the trends in roxadustat and ESA treatment doses, which are key drivers of incremental costs in the economic analyses. Treatment starting doses are weight dependent, with maintenance doses titrated according to each patient's response to treatment, and evolution of Hb levels in clinical practice. Therefore, there is an intrinsic link between the treatment effect and the treatment dose associated with it. The figures below show the observed data within the clinical trials demonstrating a change in weekly treatment dose for both roxadustat and ESA with increasing Hb levels (shared previously in response to clarification question C14). *Figure 2: Mean roxadustat weekly dose, mg (observed data)*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Figure 3: Mean ESA weekly dose, mcg (observed data)*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 Modelling with fewer health states (e.g. 3) may miss important differences between treatment arms, as moving from Hb 7 to Hb 10, would not involve the same change to HRQoL and costs as a movement from Hb 9 to Hb 10. This would lead to a loss of granularity between treatment arms. Furthermore, as the baseline characteristics of patients in both arms of the DOLOMITES trial was well-balanced, and due to the long-term proportion in state extrapolations not favouring roxadustat (as previously demonstrated through treatment benefit duration scenarios and lifetime average health state occupancy), we do not believe that a more granular model with eight health states unfairly advantages roxadustat. As 1g/dL increments in Hb level have been shown to be associated with differences in costs and utilities by both published literature and the clinical trial evidence, the company believes the use of eight health states is well justified and demonstrates the nuances which could be important in demonstrating the value of roxadustat in decision-making.	

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

Roxadustat for treating anaemia in people with chronic kidney disease [ID1483]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 16 February 2022. Please submit via NICE Docs.

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

Comment number	**Comments** Insert each comment in a new row.

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Roxadustat for treating anaemia in people with chronic kidney disease [ID1483]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 16 February 2022. Please submit via NICE Docs.

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1.	**Executive summary** Astellas is disappointed to see a preliminary negative recommendation for roxadustat and hopes that additional information and analyses provided in response to this consultation will support a final positive recommendation for roxadustat as a novel oral treatment for adult patients with symptomatic anaemia associated with chronic kidney disease (CKD). In response to the Committee's preferences, the base case has been revised as follows**:** • Analysis based on DOLOMITES data only • Multiplicative approach to health state utilities implemented • Erythropoiesis stimulating agent (ESA) administration costs applied to peritoneal dialysis patients who require assistance • Roxadustat stopping rule implemented at Hb ≥13g/dL. Regarding the Committee's preferred approach to modelling additional adverse events and hospitalisations, the Company believes that the additional analyses and more detailed responses provided below will reassure the Committee that the existing approach sufficiently captures the health-related quality of life (HRQoL) and costs associated with these, and the revised base case model is appropriate for decision-making. Clean and colour-coded versions of the revised model are presented alongside this response, with a log of changes accessible from the title page of each version for ease of reference. As presented within them, the result of making the above changes to the base case results in the following: *Table 1. Cost-effectiveness results* **Scenario** / **Roxadustat** (Costs, QALYs) / **ESA** (Costs, QALYs) / **Δ Costs** / **Δ QALYs** / **ICER** / [redacted] Previous DOLOMITES only scenario presented in response to ERG clarification question (C7.b) — [redacted] Revised base case — [redacted] Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; [redacted] Scenario analyses are also presented in relation to reflecting harms and costs of higher Hb levels and assuming that the benefits of roxadustat do not last indefinitely over the 25-year time horizon. More detail is provided below but the results demonstrate that these scenarios do not have a significant impact on the cost-effectiveness of roxadustat. No alternative data sources were identified to enable scenario analysis using different distributions of ESA. However, the most extreme scenarios whereby 100% use of each ESA is assumed were included in the original submission. These have been reproduced using the revised base case for information and further details are provided below. The company does recognise the potential impact of confidential ESA tenders on decision-making. However, the company has increased the discount level through an updated simple Patient Access Scheme, to further ensure that roxadustat offers a cost-effective treatment option for the NHS.

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2. **"Health states which reflect the harms and costs of having Hb levels over 120 g/L"**

Table 45 in the clarification questions response has been provided below (as Table 2) for ease of reference and shows the estimated average number of years spent in each health state for the cohort at a per person level while they are alive using the DOLOMITES data only.

The average roxadustat patient spends [redacted]% of their lifetime in the ≥13 Hb level health state whereas the average ESA patient spends [redacted]% of their lifetime in the ≥13 Hb level health state, meaning a relatively small proportion of patient time is spent within this health state, and any impact of stratified harms and costs in this health state on cost-effectiveness is likely to be negligible.

Table 2. Predicted health state occupancy within the cost-effectiveness model over a lifetime horizon (DOLOMITES data only)

Hb level (g/dL)	Roxadustat	ESA
<7	[redacted]	[redacted]
7 – 7.99	[redacted]	[redacted]
8 – 8.99	[redacted]	[redacted]
9 – 9.99	[redacted]	[redacted]
10 – 10.99	[redacted]	[redacted]
11 – 11.99	[redacted]	[redacted]
12 – 12.99	[redacted]	[redacted]
≥ 13	[redacted]	[redacted]
Total years alive	[redacted]	[redacted]

The probability of having an adverse event (AE) in the model is calculated using the number of events in each arm and total patient exposure time, giving a constant probability of AEs for each treatment, irrespective of Hb levels.

To capture the harms and costs of patients at higher Hb levels, the model now allows the user to select "Published sources (Stroke relative risk applied to MI and VATs)" (MI, myocardial infarction; VAT, vascular access thrombosis) as an input option for adverse events. This uses the probability of stroke derived from published sources to generate Hb-specific adverse event probabilities rather than use a common value across all Hb categories. In the absence of such stratification in the literature for other adverse events in the model, this option applies the relative risk of stroke events in each Hb level to MI and VAT. This allows the user to explore scenarios where both MI and VAT risk also differ by Hb health state.

Table 3. Cost-effectiveness results including relative risk for stroke applied to MI and VAT

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relative risk for stroke applied to MI and VAT Harms and costs of AEs at higher Hb	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: MI: myocardial infarction; VAT: Vascular access thrombosis; QALYs: quality-adjusted life years; ICER: incremental cost effectiveness ratio; [redacted]

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	As can be seen from the above, applying harms and costs at higher Hb levels makes a negligible difference both costs and QALYs.
3.	**Including stopping rule to reflect clinical practice for roxadustat and ESA** The Summary of Product Characteristics (SmPC) for roxadustat specifies withholding treatment at Hb 13 or higher and resuming only when Hb is less than 12g/dL. To reflect this in the model, an optional stopping rule has been added for roxadustat at Hb ≥13 and included in the revised base case. As Hb ≥13 is not associated with a utility benefit in the model (i.e. patients have utility equivalent to population norms), setting the stopping rule to "yes" removes the accrual of treatment costs for roxadustat in this health state. Disutilities from other sources such as AEs and dialysis status still apply. For darbepoetin alfa, its SmPC states that a dose reduction should be considered if Hb exceeds 12g/dL followed by a second dose reduction if Hb continues to increase. If this does not have the desired effect, doses should be temporarily withheld until Hb begins to decrease upon which therapy should be reinitiated at a lower dose. As the dosing of darbepoetin alfa in the DOLOMITES trial was in accordance with the SmPC, the raw data is considered reflective of clinical practice and its stopping rule. Furthermore, as mentioned by the clinical experts at the Committee meeting, ESA treatment is rarely stopped in practice with doses either reduced or the interval between doses increased. Therefore, it is considered that the model appropriately reflects clinical practice for ESA in patients with Hb levels of 13 or higher.
4.	**Health-state transition probabilities and extrapolation of benefit based on data from the entire duration of the DOLOMITES trial** The company believes this is a factual inaccuracy as the health state transition probabilities and extrapolation of benefit are based on the entire length of trial data not 12 weeks. The first 12 weeks of data were only used to determine health state distribution at baseline. It should also be noted that data were available up to a maximum of 104 weeks depending on the length of time individuals had been recruited to the study. To ensure long term extrapolations were as accurate as possible all available data were used. Furthermore, all statistical analysis and baseline characteristics in the DOLOMITES only scenario previously presented were based on the DOLOMITES study only. Separate statistical analyses were conducted for the pooled roxadustat model and the DOLOMITES only scenario. Therefore, the company would like to confirm that in the revised DOLOMITES only base case all statistical analysis and baseline characteristics are based on the DOLOMITES study only.
5.	**Approach to modelling hospitalisations** In the DOLOMITES clinical trial, hospitalisations were categorised according to whether they were related to anaemia, adverse events or other reasons as summarised in Table 16 provided in the clarification questions response and replicated below (as Table 4) for ease of reference. *Table 4. Summary of hospitalisations during efficacy emergent period (Full Analysis Set) in DOLOMITES*

Parameter	Category/statistic	Roxadustat (N=323)	Darbepoetin alfa (N=292)
Hospitalisation	Yes	[redacted]	[redacted]
	No	[redacted]	[redacted]
Number of hospitalisations	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]

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	Min, Max	[redacted]	[redacted]
Total duration of hospitalisation (days)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Average duration of each hospitalisation (days)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Number of days of hospitalisation per PEY (patient-exposure year)	Mean (SD)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Reason for hospitalisation	Anaemia	[redacted]	[redacted]
	Adverse event	[redacted]	[redacted]
	Other	[redacted]	[redacted]
Time to first hospitalisation	Number of Patients with Event [4] (Percentage)	[redacted]	[redacted]
	Cumulative Time at Risk (years)	[redacted]	[redacted]
	Incidence Rate (per 100 Patient Years at Risk)	[redacted]	[redacted]
	Hazard Ratio [5]	[redacted]	
	95% CI	[redacted]	
	P value	[redacted]	

Approximately [redacted] of hospitalisations in the roxadustat arm were related to adverse events compared to approximately [redacted] in the ESA arm. The 'other' category accounted for [redacted] of patients in the roxadustat arm vs. [redacted] of patients in the ESA arm. These were not further categorised within the pre-specified trial analysis. Each hospitalisation classified as other was linked with a free text field within the clinical summary report. By identifying each of these occurrences and interpreting the descriptions, these were further categorised. The majority of other hospitalisations were described as [redacted] or [redacted] ([redacted] and [redacted] for roxadustat and darbepoetin alfa respectively). [redacted] They have therefore been excluded from Table 5 below.

Table 5. Summary of 'other' hospitalisations in DOLOMITES

Category	Roxadustat	Darbepoetin alfa
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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	[redacted]

Furthermore, combining this information with the exposure time used in the economic model for adverse events to calculate an incident rate ratio, found no significant difference in the rate of hospitalisations between roxadustat and ESA.

Table 6: Adverse Event related hospitalisations

Treatment	Number of patients with events	Total exposure in 3-monthly cycles	Cycle probability of Hospitalisation
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]

Incident rate ratio: [redacted]

Table 7: 'Other' related hospitalisations

Treatment	Number of patients with events	Total exposure in 3-monthly cycles	Cycle probability of Hospitalisation
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]

Incident rate ratio: [redacted]

Thus, inclusion of hospitalisations due to 'other' reasons would be unlikely to significantly alter the cost-effectiveness findings. However, if it were to be included, it would favour roxadustat due to its lower cycle probability.

6.	**Inclusion of additional adverse events** In response to the concern about potentially relevant adverse events being excluded from the model, the company technical engagement response included an impact calculation of severe treatment emergent adverse events (grade 3+) that occurred in more than 3% of the trial population in the DOLOMITES study. [redacted] adverse events were identified: [redacted] with negligible differences between treatment arms. These differences were minimal both in terms of costs and quality of life and the inclusion of these adverse events in the cost-effectiveness model is unlikely to impact the final comparative results. This was acknowledged by the ERG in their comments on the Company's response to technical engagement, where this issue was no longer to be regarded as a key issue. All adverse events that differed in incidence by >2% between roxadustat and darbepoetin alfa were reviewed and further categorised by severity as can be seen in Table 8 below. It was considered that grade 3+ AEs were most likely to affect costs or utilities. The occurrence of such events was minimal in number and comparable between arms. Therefore, the inclusion of further adverse events is unlikely to impact the results of the cost effectiveness analysis.

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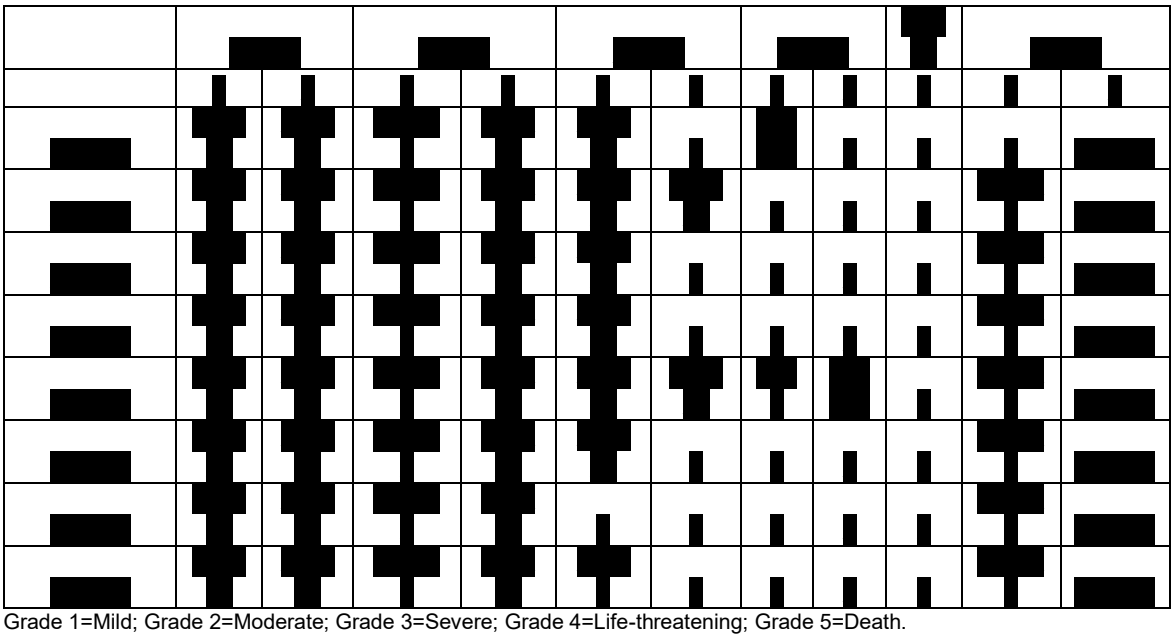
Table 8: All adverse events differing by >2% between treatment arms by severity



Grade 1=Mild; Grade 2=Moderate; Grade 3=Severe; Grade 4=Life-threatening; Grade 5=Death.

7. **Scenario analysis for different distributions of ESA**

As no alternative data sources for ESA distributions were identified, it was not possible to undertake the requested scenario analysis. However, scenario analyses where 100% use of a single ESA was assumed were included in the original submission to demonstrate cost-effectiveness in the most extreme, albeit unlikely, scenarios. The result of the updated scenario analyses using the revised based case in Table 9 below show that roxadustat is [redacted]. It should also be noted that the model includes the functionality for the user to alter the distribution of ESA to explore this further.

Table 9. Results of scenario analyses

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]							
100% darbepoetin alfa	[redacted]							
100% epo A	[redacted]							
100% epo B	[redacted]							
100% epo Z	[redacted]							
100% Methoxy polyethylene glycol-epoetin beta	[redacted]							

TUNE was a retrospective chart review Real World Evidence study in the UK and two other European countries exploring treatment patterns, sociodemographic and clinical characteristics of non-dialysis dependent patients with anaemia associated with CKD stages 3-5. Across the UK, TUNE involved [redacted] healthcare professionals and [redacted] patient records spanning [redacted] months.

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	Furthermore, the TUNE study was used to inform the budget impact assessment agreed with NHS England on the basis that it provided the most robust estimate of ESA distribution in the UK. Alternative sources were not indication-specific and would therefore introduce further uncertainty to decision-making. The revised base case continues to use the TUNE study as best estimate of ESA use within this patient population in UK clinical practice. This was validated with clinical experts who confirmed the estimates from the TUNE study were in line with their expectation given there is a tendency to use long-acting ESAs in the non-dialysis space.
8.	**Estimating average roxadustat dose** The company would like to clarify that the average roxadustat dose for each Hb level was based on data from people in all roxadustat trials for the pooled data analysis only. Only data from the DOLOMITES trial was used for the DOLOMITES analyses. The revised DOLOMITES base case therefore uses data from DOLOMITES only to calculate average roxadustat doses. As treatment doses were calculated on weekly doses reported in the trial (which are adjusted for patient weight), the average roxadustat and ESA doses used in the economic model are reflective of the average weight of patients in the DOLOMITES trial.
9.	**Proposed positioning of roxadustat** On page 7 of the appraisal consultation document (ACD) it states that “the proposed positioning for roxadustat does not include people on dialysis (including peritoneal dialysis).” The company would like to clarify that the proposed positioning of roxadustat does include people on dialysis, however, roxadustat would be only be initiated in people who were not on dialysis at that time. Patients receiving roxadustat who went on to receive dialysis treatment would be able to remain on treatment with roxadustat. Furthermore, the cardiovascular disease safety concern mentioned relates to the switching of dialysis patients who are stable on ESA treatment to roxadustat. In line with the licence for roxadustat, switching of these patients should only be considered when there is a valid clinical reason and are therefore are not considered as the target patient population for this submission.
10.	**Non-inferiority trials can still demonstrate improvement to standard of care** The company considers it important to recognise that although the active comparator trial was non-inferiority by design, this does not mean that there is no difference between roxadustat and the comparator. In DOLOMITES the primary efficacy analysis was powered to allow a demonstration of statistical non-inferiority should the estimated outcome in the roxadustat arm not differ from the darbepoetin alfa arm by more than a pre-specified and justified amount (the non-inferiority margin of 15%). The powering of the study has no impact on the resulting point estimates of efficacy themselves, and a result in which roxadustat appears superior to darbepoetin alfa could be observed while still allowing a claim of statistical non-inferiority. There is nothing in the design of a non-inferiority study that prevents the estimates of test treatment outcome being favourable compared with those of the comparator.
11.	**Scenario analysis regarding the benefits of roxadustat not lasting indefinitely over 25-year time horizon** The long-term plausibility of the model extrapolations was validated with clinicians. Table 2 (in point 2 above) provides an estimated average number of years spent in each health state for the cohort at a per person level while they are alive using the DOLOMITES only trial. The average roxadustat

patient spends [redacted] of their time in the target Hb range (10 to 11.99) whereas the average patient in the ESA arm spends [redacted] of their time in the same target Hb range. These outcomes were validated by clinical experts who agreed that the state occupancy results were in line with their expectations given the Renal Registry guidelines. The 22nd UK Renal Registry report estimated that approximately 60% of patients on in-centre haemodialysis in England have a Hb level between 10.00 and 12.00 g/dL [REF].

Furthermore, the model was built with the functionality to maintain the proportion in state at any given time point, to enable the user to test the sensitivity of the results to changes in state over time. This functionality can be accessed via a switch on the model set-up page ("Maintain Hb level after set time point?"). Previous sensitivity analyses fixing the proportion in state at 5, 10 and 15 years were presented in response to ERG clarification question C7 (c). We have updated these scenario analyses using the revised base case and present the results below:

1. DOLOMITES data, proportion in state fixed after 5 years
2. DOLOMITES data, proportion in state fixed after 10 years
3. DOLOMITES data, proportion in state fixed after 15 years

Table 10. Results of scenario analyses

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

All three scenarios show that fixing the proportion in state over time (i.e. ignoring the impact of time after set points), results in negligible differences to costs and QALYs.

In response to the Committee's specific request for scenario analyses exploring altering the extrapolation of treatment effect over the time horizon of the model, the Company has added functionality in the model to allow the treatment benefit of roxadustat to fall to that of ESA. This can be implemented immediately (at any time point), or gradually (treatment effect begins to decline at timepoint A, matching ESA effect by timepoint B) by selecting this option in the model set up page.

The three scenarios explored are presented below:

4. Roxadustat efficacy matches ESA efficacy immediately after the DOLOMITES trial (month 25 in the model)
5. Roxadustat efficacy gradually declines from the end of DOLOMITES trial, matching ESA by year 3 in the model
6. Roxadustat efficacy gradually declines from the end of DOLOMITES trial, matching ESA by year 5 in the model

Table 11. Results of scenario analyses

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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	5 [redacted] 6 [redacted] All scenario analyses performed resulted in negligible differences to costs and QALYs.
12.	**Eight health state model structure** The company welcomes the Committee's recognition that the economic model based on Hb-defined health states suitably reflects anaemia associated with CKD. The company also recognises the Committee's concerns regarding the number of health states within the model and the choice to use 1g/dL increments to define these. However, in line with a disease area demarked by 1g/dL measurements of Hb, as well as the available published precedence in this area, the company believes that presented model appropriately reflects this disease area whilst retaining suitable sensitivity to differences between roxadustat and ESA, in order to robustly support decision-making. In addition to the papers supporting this by Yarnoff et al., Lawler et al., and Finkelstein et al., highlighted in the ACD, the positive correlation between Hb levels and HRQoL in patients with CKD has also been recognised elsewhere in the literature, with a published cost-effectiveness analysis by Glenngård et. al. 2008 following a similar stratification of HRQoL by Hb level in patients with anaemia associated with CKD. The association between Hb level and HRQoL was also confirmed in the roxadustat clinical trial programme. The figure presented below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle) for utility values at increasing Hb levels. These data show that utilities increase with increments of 1 g/dL in the patient's Hb level and the statistical model provides a reasonable estimate for the average utility value stratified by Hb level (evidence previously provided in response to clarification question C10). *Figure 1: Utility values by increasing Hb level (showing observed data in red and predicted values in blue)* [redacted]

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	A similar observation was made for the trends in roxadustat and ESA treatment doses, which are key drivers of incremental costs in the economic analyses. Treatment starting doses are weight dependent, with maintenance doses titrated according to each patient's response to treatment, and evolution of Hb levels in clinical practice. Therefore, there is an intrinsic link between the treatment effect and the treatment dose associated with it. The figures below show the observed data within the clinical trials demonstrating a change in weekly treatment dose for both roxadustat and ESA with increasing Hb levels (shared previously in response to clarification question C14). *Figure 2: Mean roxadustat weekly dose, mg (observed data)*  *Figure 3: Mean ESA weekly dose, mcg (observed data)*  Modelling with fewer health states (e.g. 3) may miss important differences between treatment arms, as moving from Hb 7 to Hb 10, would not involve the same change to HRQoL and costs as a movement from Hb 9 to Hb 10. This would lead to a loss of granularity between treatment arms. Furthermore, as the baseline characteristics of patients in both arms of the DOLOMITES trial was well-balanced, and due to the long-term proportion in state extrapolations not favouring roxadustat

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	(as previously demonstrated through treatment benefit duration scenarios and lifetime average health state occupancy), we do not believe that a more granular model with eight health states unfairly advantages roxadustat. As 1g/dL increments in Hb level have been shown to be associated with differences in costs and utilities by both published literature and the clinical trial evidence, the company believes the use of eight health states is well justified and demonstrates the nuances which could be important in demonstrating the value of roxadustat in decision-making.

Insert extra rows as needed

Checklist for submitting comments

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

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

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

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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<table>
<tr><th>Comment number</th><th>Comments

Insert each comment in a new row.
Do not paste other tables into this table, because your comments could get lost – type directly into this table.</th><th>ERG response</th></tr>
<tr><td>1.</td><td>

Executive summary

Astellas is disappointed to see a preliminary negative recommendation for roxadustat and hopes that additional information and analyses provided in response to this consultation will support a final positive recommendation for roxadustat as a novel oral treatment for adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

In response to the Committee's preferences, the base case has been revised as follows**:**

- Analysis based on DOLOMITES data only
- Multiplicative approach to health state utilities implemented
- Erythropoiesis stimulating agent (ESA) administration costs applied to peritoneal dialysis patients who require assistance
- Roxadustat stopping rule implemented at Hb ≥13g/dL.

Regarding the Committee's preferred approach to modelling additional adverse events and hospitalisations, the Company believes that the additional analyses and more detailed responses provided below will reassure the Committee that the existing approach sufficiently captures the health-related quality of life (HRQoL) and costs associated with these, and the revised base case model is appropriate for decision-making.

Clean and colour-coded versions of the revised model are presented alongside this response, with a log of changes accessible from the title page of each version for ease of reference. As presented within them, the result of making the above changes to the base case results in the following:

Table 1. Cost-effectiveness results

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				

</td><td>Please see responses to each Key point below.</td></tr>
</table>

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	Previous DOLOMITES only scenario presented in response to ERG clarification question (C7.b) [redacted] Revised base case [redacted] Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; [redacted] Scenario analyses are also presented in relation to reflecting harms and costs of higher Hb levels and assuming that the benefits of roxadustat do not last indefinitely over the 25-year time horizon. More detail is provided below but the results demonstrate that these scenarios do not have a significant impact on the cost-effectiveness of roxadustat. No alternative data sources were identified to enable scenario analysis using different distributions of ESA. However, the most extreme scenarios whereby 100% use of each ESA is assumed were included in the original submission. These have been reproduced using the revised base case for information and further details are provided below. The company does recognise the potential impact of confidential ESA tenders on decision-making. However, the company has increased the discount level through an updated simple Patient Access Scheme, to further ensure that roxadustat offers a cost-effective treatment option for the NHS.	
2.	**"Health states which reflect the harms and costs of having Hb levels over 120 g/L"** Table 45 in the clarification questions response has been provided below (as Table 2) for ease of reference and shows the estimated average number of years spent in each health state for the cohort at a per person level while they are alive using the DOLOMITES data only. The average roxadustat patient spends [redacted]% of their lifetime in the ≥13 Hb level health state whereas the average ESA patient spends [redacted]% of their lifetime in the ≥13 Hb level health state, meaning a relatively small proportion of patient time is spent within this health state, and any impact of stratified harms and costs in this health state on cost-effectiveness is likely to be negligible. *Table 2. Predicted health state occupancy within the cost-effectiveness model over a lifetime horizon (DOLOMITES data only)* **Hb level (g/dL)** / **Roxadustat** / **ESA** <7 / [redacted] / [redacted] 7 – 7.99 / [redacted] / [redacted]	Thank you for providing this (further) clarification/information.

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8 – 8.99	[redacted]	[redacted]
9 – 9.99	[redacted]	[redacted]
10 – 10.99	[redacted]	[redacted]
11 – 11.99	[redacted]	[redacted]
12 – 12.99	[redacted]	[redacted]
≥ 13	[redacted]	[redacted]
Total years alive	[redacted]	[redacted]

The probability of having an adverse event (AE) in the model is calculated using the number of events in each arm and total patient exposure time, giving a constant probability of AEs for each treatment, irrespective of Hb levels.

To capture the harms and costs of patients at higher Hb levels, the model now allows the user to select "Published sources (Stroke relative risk applied to MI and VATs)" (MI, myocardial infarction; VAT, vascular access thrombosis) as an input option for adverse events. This uses the probability of stroke derived from published sources to generate Hb-specific adverse event probabilities rather than use a common value across all Hb categories. In the absence of such stratification in the literature for other adverse events in the model, this option applies the relative risk of stroke events in each Hb level to MI and VAT. This allows the user to explore scenarios where both MI and VAT risk also differ by Hb health state.

Table 3. Cost-effectiveness results including relative risk for stroke applied to MI and VAT

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]							
Relative risk for stroke applied to MI and VAT Harms and costs of AEs at higher Hb	[redacted]							

Key: MI: myocardial infarction; VAT: Vascular access thrombosis; QALYs: quality-adjusted life years; ICER: incremental cost effectiveness ratio; [redacted]

As can be seen from the above, applying harms and costs at higher Hb levels makes a negligible difference both costs and QALYs.

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3.	**Including stopping rule to reflect clinical practice for roxadustat and ESA** The Summary of Product Characteristics (SmPC) for roxadustat specifies withholding treatment at Hb 13 or higher and resuming only when Hb is less than 12g/dL. To reflect this in the model, an optional stopping rule has been added for roxadustat at Hb ≥13 and included in the revised base case. As Hb ≥13 is not associated with a utility benefit in the model (i.e. patients have utility equivalent to population norms), setting the stopping rule to "yes" removes the accrual of treatment costs for roxadustat in this health state. Disutilities from other sources such as AEs and dialysis status still apply. For darbepoetin alfa, its SmPC states that a dose reduction should be considered if Hb exceeds 12g/dL followed by a second dose reduction if Hb continues to increase. If this does not have the desired effect, doses should be temporarily withheld until Hb begins to decrease upon which therapy should be reinitiated at a lower dose. As the dosing of darbepoetin alfa in the DOLOMITES trial was in accordance with the SmPC, the raw data is considered reflective of clinical practice and its stopping rule. Furthermore, as mentioned by the clinical experts at the Committee meeting, ESA treatment is rarely stopped in practice with doses either reduced or the interval between doses increased. Therefore, it is considered that the model appropriately reflects clinical practice for ESA in patients with Hb levels of 13 or higher.	Thank you for providing this (further) clarification/information.
4.	**Health-state transition probabilities and extrapolation of benefit based on data from the entire duration of the DOLOMITES trial** The company believes this is a factual inaccuracy as the health state transition probabilities and extrapolation of benefit are based on the entire length of trial data not 12 weeks. The first 12 weeks of data were only used to determine health state distribution at baseline. It should also be noted that data were available up to a maximum of 104 weeks depending on the length of time individuals had been recruited to the study. To ensure long term extrapolations were as accurate as possible all available data were used. Furthermore, all statistical analysis and baseline characteristics in the DOLOMITES only scenario previously presented were based on the DOLOMITES study only. Separate statistical analyses were conducted for the pooled roxadustat model and the DOLOMITES only scenario.	Thank you for providing this (further) clarification/information.

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<table>
<tr><td></td><td>Therefore, the company would like to confirm that in the revised DOLOMITES only base case all statistical analysis and baseline characteristics are based on the DOLOMITES study only.</td><td></td></tr>
<tr><td>5.</td><td>Approach to modelling hospitalisations

In the DOLOMITES clinical trial, hospitalisations were categorised according to whether they were related to anaemia, adverse events or other reasons as summarised in Table 16 provided in the clarification questions response and replicated below (as Table 4) for ease of reference.

Table 4. Summary of hospitalisations during efficacy emergent period (Full Analysis Set) in DOLOMITES
<table>
<tr><th>Parameter</th><th>Category/statistic</th><th>Roxadustat (N=323)</th><th>Darbepoetin alfa (N=292)</th></tr>
<tr><td rowspan="2">Hospitalisation</td><td>Yes</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>No</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="3">Number of hospitalisations</td><td>Mean (SD)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Median</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Min, Max</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="3">Total duration of hospitalisation (days)</td><td>Mean (SD)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Median</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Min, Max</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="3">Average duration of each hospitalisation (days)</td><td>Mean (SD)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Median</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Min, Max</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="3">Number of days of hospitalisation per PEY (patient-exposure year)</td><td>Mean (SD)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Median</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Min, Max</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td rowspan="3">Reason for hospitalisation</td><td>Anaemia</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Adverse event</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Other</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>See the ERG report for the ERG perspective on this issue (sections 2.3, 3.3 and 3.4).</td></tr>
</table>

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Time to first hospitalisation	Number of Patients with Event [4] (Percentage)	[redacted]	[redacted]
	Cumulative Time at Risk (years)	[redacted]	[redacted]
	Incidence Rate (per 100 Patient Years at Risk)	[redacted]	[redacted]
	Hazard Ratio [5]	[redacted]	
	95% CI	[redacted]	
	P value	[redacted]	

Approximately [redacted] of hospitalisations in the roxadustat arm were related to adverse events compared to approximately [redacted] in the ESA arm. The 'other' category accounted for [redacted] of patients in the roxadustat arm vs. [redacted] of patients in the ESA arm. These were not further categorised within the pre-specified trial analysis. Each hospitalisation classified as other was linked with a free text field within the clinical summary report. By identifying each of these occurrences and interpreting the descriptions, these were further categorised. The majority of other hospitalisations were described as [redacted] or [redacted] ([redacted] and [redacted] for roxadustat and darbepoetin alfa respectively). Upon further enquiry, it was found that these instances [redacted]. They have therefore been excluded from Table 5 below.

Table 5. Summary of 'other' hospitalisations in DOLOMITES

Category	Roxadustat	Darbepoetin alfa
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

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[redacted]			

Furthermore, combining this information with the exposure time used in the economic model for adverse events to calculate an incident rate ratio, found no significant difference in the rate of hospitalisations between roxadustat and ESA.

Table 6: Adverse Event related hospitalisations

Treatment	Number of patients with events	Total exposure in 3-monthly cycles	Cycle probability of Hospitalisation
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]

Incident rate ratio: [redacted]

Table 7: 'Other' related hospitalisations

Treatment	Number of patients with events	Total exposure in 3-monthly cycles	Cycle probability of Hospitalisation
ESA	[redacted]	[redacted]	[redacted]
Roxadustat	[redacted]	[redacted]	[redacted]

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	Incident rate ratio: [redacted] Thus, inclusion of hospitalisations due to 'other' reasons would be unlikely to significantly alter the cost-effectiveness findings. However, if it were to be included, it would favour roxadustat due to its lower cycle probability.	
6.	**Inclusion of additional adverse events** In response to the concern about potentially relevant adverse events being excluded from the model, the company technical engagement response included an impact calculation of severe treatment emergent adverse events (grade 3+) that occurred in more than 3% of the trial population in the DOLOMITES study. [redacted] adverse events were identified: [redacted] with negligible differences between treatment arms. These differences were minimal both in terms of costs and quality of life and the inclusion of these adverse events in the cost-effectiveness model is unlikely to impact the final comparative results. This was acknowledged by the ERG in their comments on the Company's response to technical engagement, where this issue was no longer to be regarded as a key issue. All adverse events that differed in incidence by >2% between roxadustat and darbepoetin alfa were reviewed and further categorised by severity as can be seen in Table 8 below. It was considered that grade 3+ AEs were most likely to affect costs or utilities. The occurrence of such events was minimal in number and comparable between arms. Therefore, the inclusion of further adverse events is unlikely to impact the results of the cost effectiveness analysis. *Table 8: All adverse events differing by >2% between treatment arms by severity* [redacted]	Thank you for providing this (further) clarification/information.

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	[redacted] Grade 1=Mild; Grade 2=Moderate; Grade 3=Severe; Grade 4=Life-threatening; Grade 5=Death.	
7.	**Scenario analysis for different distributions of ESA** As no alternative data sources for ESA distributions were identified, it was not possible to undertake the requested scenario analysis. However, scenario analyses where 100% use of a single ESA was assumed were included in the original submission to demonstrate cost-effectiveness in the most extreme, albeit unlikely, scenarios. The result of the updated scenario analyses using the revised based case in Table 9 below show that roxadustat is [redacted]. It should also be noted that the model includes the functionality for the user to alter the distribution of ESA to explore this further.	Thank you for providing this (further) clarification/information.

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	Table 9. Results of scenario analyses **Scenario** / **Roxadustat** Costs / **Roxadustat** QALYs / **ESA** Costs / **ESA** QALYs / **Δ Costs** / **Δ QALYs** / **ICER** / [redacted] Revised base case 100% darbepoetin alfa 100% epo A 100% epo B 100% epo Z 100% Methoxy polyethylene glycol-epoetin beta TUNE was a retrospective chart review Real World Evidence study in the UK and two other European countries exploring treatment patterns, sociodemographic and clinical characteristics of non-dialysis dependent patients with anaemia associated with CKD stages 3-5. Across the UK, TUNE involved [redacted] healthcare professionals and [redacted] patient records spanning [redacted] months. Furthermore, the TUNE study was used to inform the budget impact assessment agreed with NHS England on the basis that it provided the most robust estimate of ESA distribution in the UK. Alternative sources were not indication-specific and would therefore introduce further uncertainty to decision-making. The revised base case continues to use the TUNE study as best estimate of ESA use within this patient population in UK clinical practice. This was validated with clinical experts who confirmed the estimates from the TUNE study were in line with their expectation given there is a tendency to use long-acting ESAs in the non-dialysis space.	
8.	**Estimating average roxadustat dose** The company would like to clarify that the average roxadustat dose for each Hb level was based on data from people in all roxadustat trials for the pooled data analysis only. Only data from the DOLOMITES trial was used for the DOLOMITES analyses.	Thank you for providing this (further) clarification/information.

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	The revised DOLOMITES base case therefore uses data from DOLOMITES only to calculate average roxadustat doses. As treatment doses were calculated on weekly doses reported in the trial (which are adjusted for patient weight), the average roxadustat and ESA doses used in the economic model are reflective of the average weight of patients in the DOLOMITES trial.	
9.	**Proposed positioning of roxadustat** On page 7 of the appraisal consultation document (ACD) it states that "the proposed positioning for roxadustat does not include people on dialysis (including peritoneal dialysis)." The company would like to clarify that the proposed positioning of roxadustat does include people on dialysis, however, roxadustat would be only be initiated in people who were not on dialysis at that time. Patients receiving roxadustat who went on to receive dialysis treatment would be able to remain on treatment with roxadustat. Furthermore, the cardiovascular disease safety concern mentioned relates to the switching of dialysis patients who are stable on ESA treatment to roxadustat. In line with the licence for roxadustat, switching of these patients should only be considered when there is a valid clinical reason and are therefore are not considered as the target patient population for this submission.	See the ERG report for the ERG perspective on this issue.
10.	**Non-inferiority trials can still demonstrate improvement to standard of care** The company considers it important to recognise that although the active comparator trial was non-inferiority by design, this does not mean that there is no difference between roxadustat and the comparator. In DOLOMITES the primary efficacy analysis was powered to allow a demonstration of statistical non-inferiority should the estimated outcome in the roxadustat arm not differ from the darbepoetin alfa arm by more than a pre-specified and justified amount (the non-inferiority margin of 15%). The powering of the study has no impact on the resulting point estimates of efficacy themselves, and a result in which roxadustat appears superior to darbepoetin alfa could be observed while still allowing a claim of statistical non-inferiority. There is nothing in the design of a non-inferiority study that prevents the estimates of test treatment outcome being favourable compared with those of the comparator.	This comment does not address the main points raised by the ERG which is that the non-inferiority margin was inadequately justified. The ERG refers the company to relevant NICE guidance https://www.nice.org.uk/process/pmg32/chapter/clinical-effectiveness, which, in turn, refers to more purely methodological papers that explain non-inferiority margins in more detail (see eAppendix of this document: https://jamanetwork.com/journals/jama/fullarticle/1487502)

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		Moreover, the ERG does not understand the company's apparent claim that a non-inferiority trial can demonstrate a difference. The ERG believes that this is based on a misunderstanding of non-inferiority tests. In a non-inferiority test, the null hypothesis is that there is a difference (of at least a certain size, delta, or the non-inferiority margin). If the null hypothesis is rejected, then subject to the inherent uncertainty of statistical tests, we can only infer that the test intervention (roxadustat in this case) was not inferior to the control. *Provided that the non-inferiority margin* is adequately justified (see above), rejection of the null hypothesis in a non-inferiority test will also suggest (again, subject to inherent statistical uncertainty) that the test intervention is superior to no treatment, which brings us to the point about the adequacy of the non-inferiority margin.
11.	**Scenario analysis regarding the benefits of roxadustat not lasting indefinitely over 25-year time horizon** The long-term plausibility of the model extrapolations was validated with clinicians. Table 2 (in point 2 above) provides an estimated average number of years spent in each health state for the cohort at a per person level while they are alive using the DOLOMITES only trial. The average roxadustat patient spends [redacted] of their time in the target Hb range (10 to 11.99) whereas the average patient in the ESA arm spends [redacted] of their time in the same target Hb range. These outcomes were validated by clinical experts who agreed that the state occupancy results were in line with their expectations given the Renal Registry guidelines. The 22nd UK Renal Registry report estimated that approximately 60% of patients on in-centre haemodialysis in England have a Hb level between 10.00 and 12.00 g/dL [REF].	Thanks for providing this (further) clarification/information.

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Furthermore, the model was built with the functionality to maintain the proportion in state at any given time point, to enable the user to test the sensitivity of the results to changes in state over time. This functionality can be accessed via a switch on the model set-up page ("Maintain Hb level after set time point?"). Previous sensitivity analyses fixing the proportion in state at 5, 10 and 15 years were presented in response to ERG clarification question C7 (c). We have updated these scenario analyses using the revised base case and present the results below:

1. DOLOMITES data, proportion in state fixed after 5 years
2. DOLOMITES data, proportion in state fixed after 10 years
3. DOLOMITES data, proportion in state fixed after 15 years

Table 10. Results of scenario analyses

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]							
1	[redacted]							
2	[redacted]							
3	[redacted]							

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

All three scenarios show that fixing the proportion in state over time (i.e. ignoring the impact of time after set points), results in negligible differences to costs and QALYs.

In response to the Committee's specific request for scenario analyses exploring altering the extrapolation of treatment effect over the time horizon of the model, the Company has added functionality in the model to allow the treatment benefit of roxadustat to fall to that of ESA. This can be implemented immediately (at any time point), or gradually (treatment effect begins to decline at timepoint A, matching ESA effect by timepoint B) by selecting this option in the model set up page.

The three scenarios explored are presented below:

4. Roxadustat efficacy matches ESA efficacy immediately after the DOLOMITES trial (month 25 in the model)

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5. Roxadustat efficacy gradually declines from the end of DOLOMITES trial, matching ESA by year 3 in the model
6. Roxadustat efficacy gradually declines from the end of DOLOMITES trial, matching ESA by year 5 in the model

Table 11. Results of scenario analyses

Scenario	Roxadustat		ESA		Δ Costs	Δ QALYs	ICER	[redacted]
	Costs	QALYs	Costs	QALYs				
Revised base case	[redacted]							
4	[redacted]							
5	[redacted]							
6	[redacted]							

All scenario analyses performed resulted in negligible differences to costs and QALYs.

12. **Eight health state model structure**

The company welcomes the Committee's recognition that the economic model based on Hb-defined health states suitably reflects anaemia associated with CKD.

The company also recognises the Committee's concerns regarding the number of health states within the model and the choice to use 1g/dL increments to define these. However, in line with a disease area demarked by 1g/dL measurements of Hb, as well as the available published precedence in this area, the company believes that presented model appropriately reflects this disease area whilst retaining suitable sensitivity to differences between roxadustat and ESA, in order to robustly support decision-making.

In addition to the papers supporting this by Yarnoff et al., Lawler et al., and Finkelstein et al., highlighted in the ACD, the positive correlation between Hb levels and HRQoL in patients with CKD has also been recognised elsewhere in the literature, with a published cost-effectiveness analysis by Glenngård et. al. 2008 following a similar stratification of HRQoL by Hb level in patients with anaemia associated with CKD.

See the ERG report (section 4.2.2 and related ERG key issue) for the ERG perspective on this issue.

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	The association between Hb level and HRQoL was also confirmed in the roxadustat clinical trial programme. The figure presented below shows the statistical model predictions (blue triangle) versus the raw observed data (red circle) for utility values at increasing Hb levels. These data show that utilities increase with increments of 1 g/dL in the patient's Hb level and the statistical model provides a reasonable estimate for the average utility value stratified by Hb level (evidence previously provided in response to clarification question C10). *Figure 1: Utility values by increasing Hb level (showing observed data in red and predicted values in blue)*  A similar observation was made for the trends in roxadustat and ESA treatment doses, which are key drivers of incremental costs in the economic analyses. Treatment starting doses are weight dependent, with maintenance doses titrated according to each patient's response to treatment, and evolution of Hb levels in clinical practice. Therefore, there is an intrinsic link between the treatment effect and the treatment dose associated with it.	

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	The figures below show the observed data within the clinical trials demonstrating a change in weekly treatment dose for both roxadustat and ESA with increasing Hb levels (shared previously in response to clarification question C14). *Figure 2: Mean roxadustat weekly dose, mg (observed data)*  *Figure 3: Mean ESA weekly dose, mcg (observed data)*	

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	[redacted] Modelling with fewer health states (e.g. 3) may miss important differences between treatment arms, as moving from Hb 7 to Hb 10, would not involve the same change to HRQoL and costs as a movement from Hb 9 to Hb 10. This would lead to a loss of granularity between treatment arms. Furthermore, as the baseline characteristics of patients in both arms of the DOLOMITES trial was well-balanced, and due to the long-term proportion in state extrapolations not favouring roxadustat (as previously demonstrated through treatment benefit duration scenarios and lifetime average health state occupancy), we do not believe that a more granular model with eight health states unfairly advantages roxadustat. As 1g/dL increments in Hb level have been shown to be associated with differences in costs and utilities by both published literature and the clinical trial evidence, the company believes the use of eight health states is well justified and demonstrates the nuances which could be important in demonstrating the value of roxadustat in decision-making.	

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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References

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