Ceritinib for the treatment of ALK positive non-small cell lung cancer previously treated with crizotinib

Novartis response to clarification questions

Section A: Literature searching, inclusion criteria, and study selection

A1. Priority Question.

Systematic review for clinical effectiveness studies:

- Please provide the full search strategy for each database that was used in the literature searches and populate the table in Appendix 3 of the company submission with the numbers of studies retrieved for each line.

- ***Novartis response:***

  Please see word document "Hits of Clinical Evidence SLR_for Appendix 3".

- Please provide references of the 126 included randomised controlled trials, the other 147 included non-randomised controlled trials and the articles excluded at level II screening according to the PRISMA diagram (Figure 2, page 37 of the company submission).

- ***Novartis response:***

  Please see excel file "References for clinical evidence SLR".

- The eligibility criteria in Table 6 (page 35 of the company submission) suggests outcomes of adverse events and health-related quality of life were not included. If this is correct please provide references of the 238 articles excluded because of ineligible outcomes at level I screening (see PRISMA diagram, Figure 2, page 37 of the company submission).

- ***Novartis response:***

  Please see excel file "References for clinical evidence SLR".

Section B: Clarification on clinical effectiveness data

B1. Priority Question.

In Table 28, page 76 of the company submission what is the source of the data for the meta-analysis? Please provide further details of the pooling methods, including any caveats/limitations to this approach. Please provide details / methods of the Blinded Independent Review Committee (BIRC).The company submission suggests that the BIRC

was used for both progression-free survival and overall survival, however, BIRC data were not available for overall survival. Please clarify. Also, please clarify the methods used for meta-analysis of median overall survival.

Novartis response:

The meta-analysis used pooling without adjustment, incorporating ASCEND-1 (data cut-point 14th April 2014) and ASCEND-2 (data cut-point 13th August 2014) data as outlined in section 4.11.1 and 4.11.2 of the submission. Data were extracted from the clinical study report in de facto individual patient data (data were reported per patient in the ASCEND-1 study report; data were digitized to pseudo-IPD for patients in the ASCEND-2 study report). For the ASCEND-1 study, only data for patients being treated with 750 mg orally of ceritinib on a once-daily dosing schedule, and who had been treated previously with crizotinib, were included. This is consistent with the patients in the ASCEND-2 study, which facilitated pooling.

Pooling was undertaken by an unadjusted method in which individual trial data were combined for each trial as follows:

- *time in months since randomisation to progression*
- *time in months since randomisation to death*
- *time in months since randomisation to censoring (i.e., lost to follow-up from the study).*

Then, for the pooled data, PFS was considered as time of survival from randomisation to progression or death, and OS was considered as time of survival from randomisation to death.

B2. <u>Priority Question</u>.

Table 18, page 67 of the company submission notes the number of prior treatment regimens for participants in the 2 studies. Please provide details for what these prior treatments included and a breakdown of the number of patients that received each prior treatment.

Novartis response:

[redacted]

[redacted]

[redacted]

[redacted]

B3. Please clarify how many patients in each centre (please provide the country) took part in ASCEND-1 and ASCEND-2. Please provide data for adverse events suspected to be study drug related by "race" (categorised as Asian, Caucasian and "other").

Novartis response:

[redacted]

[redacted]

[redacted] *Unfortunately Novartis was not able to develop tables for adverse events suspected to be study drug related by "race" in the requested time frame.*

[redacted]

[redacted]

[redacted] *Unfortunately Novartis was not able to develop tables for adverse events suspected to be study drug related by "race" in the requested time frame.*

B4. The company submission states that the RECIST criteria have recently been updated. Please outline the differences between RECIST v1 (ASCEND-2) and RECIST v1.1 (ASCEND-1) criteria and the impact that this might have on objective response rate assessment (see page 64, Table 17 of the company submission).

Novartis response:

The RECIST criteria are pre-specified in the ASCEND-1 and ASCEND-2 protocols. ASCEND-1 was based on RECIST 1.0 and ASCEND-2 was based on RECIST 1.1. The publication (Eisenhauer et al, 2009)[1] provides full details.

The comparison of the efficacy results observed in ASCEND-2 and ASCEND-1 may have been affected by differences in the method used to evaluate tumour response. The use of different versions of RECIST criteria for tumour response assessments does not facilitate the comparison of ORRs in the two studies as RECIST 1.0 and its successor, RECIST 1.1, differ in several major ways (Therasse et al, 2000[2] , Eisenhauer et al, 2009[1]):

- *RECIST 1.0 allows up to 10 target lesions with up to 5 per each individual organ, whereas, RECIST 1.1 allows a maximum of 5 lesions with up to 2 per individual organ;*
- *RECIST 1.0 does not clearly define what constitutes a new lesion whereas RECIST 1.1 clearly defines a new lesion;*
- *RECIST 1.0 minimum measurable lesion is 20 mm except for spiral computed tomography (CT) where minimum is 10 mm and RECIST 1.1 uses 10 mm for all radiological methods.*

Although it could be possible that the different response rates observed in the ASCEND-1 and ASCEND-2 trials might have been due to the different RECIST criteria used, patients treated in the two studies seemed to have derived similar clinical benefit as evidenced by the similar DCR, median DOR and median PFS. This was also supported by the similar waterfall plot from ASCEND-1 and ASCEND-2.

[redacted]

[redacted]

[redacted]

[redacted]

B6. In the company submission, Figure 5 (page 59) and Figure 7 (page 61), the numbers and reasons for withdrawals after receiving treatment for the ASCEND 2 and ASCEND 1 studies are provided. Please provide further details on when withdrawals occurred from these 2 studies if possible. Please also provide details of how withdrawals from the study are accounted for in the analyses.

Novartis response:

[redacted]

B7. On page 72 of the company submission the results for objective response rate from the 13th August cut-off in ASCEND 2 are stated to be 'consistent with those seen at the 26th February cut off" – please provide the 26th February cut off data.

Novartis response:

The 26th February cut-off data for the objective response rate from ASCEND-2 is available in the "LDK378A2201 – updated results (13th Aug 2014)" clinical study report provided along with the submission. The comparison of the 13th August 2014 and 26th February 2014 data for objective response rate by Investigator assessment can be found on page 17 of this document, Table 4-2. Above this table, the clinical study report makes the statement that "ORR by Investigator assessment with the updated cutoff is similar to that at the time of the primary analysis". For convenience, this data is provided below in Table 1.

Table 1: Summary of best overall response per Investigator assessment in data cut-off 13th August 2014 and data cut-off 26th February 2014

	Data cut-off: 13th August 2014 N=140, n (%)	Data cut-off: 26th February 2014 N=140, n (%)
Best overall response		
Complete response (CR)	4 (2.9)	3 (2.1)
Partial response (PR)	50 (35.7)	49 (35.0)
Stable disease (SD)	54 (38.6)	56 (40.0)
Progressive disease (PD)	19 (13.6)	19 (13.6)
Unknown (UNK)	13 (9.3)	13 (9.3)
Overall response rate (ORR: CR + PR) – n (%) [95% CI][a]	54 (38.6) [30.5, 47.2][b]	52 (37.1) [redacted][b]
Disease Control Rate (DCR: CR+PR+SD) – n (%) [95% CI][a]	108 (77.1)	108 (77.1)

	[69.3, 83.8]	[69.3, 83.8]

N: The total number of patients in the full analysis set. It is the denominator for percentage (%) calculation.
n= Number of patients who are in the corresponding category.
[a] Exact binomial 95% Confidence Interval
[b] p-value<0.001 associated with exact test of H0: ORR<= 25% vs. H1 ORR>25% based on exact binomial distribution indicates statistical significance (one-sided) at the 0.025 level.
Abbreviations: CI, confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown
Source: ASCEND-2 updated results (cut-off August 2014)

The comparison of the 13th August 2014 and 26th February 2014 data for objective response rate by BIRC assessment can be found on page 18 of "LDK378A2201 – updated results (13th Aug 2014)" clinical study report, Table 4-3. Above this table, the clinical study report makes the statement that "As was observed based on Investigator assessment, the ORR by BIRC assessment with the updated cutoff is also similar to that at the time of the primary analysis". For convenience, this data is provided in Table 2.

Table 2: Summary of best overall response per BIRC assessment in data cut-off 13th August 2014 and data cut-off 26th February 2014

	Data cut-off: 13th August 2014 N=140, n (%)	Data cut-off: 26th February 2014 N=140, n (%)
Best overall response		
Partial response (PR)	50 (35.7)	[redacted]
Stable disease (SD)	38 (27.1)	[redacted]
Progressive disease (PD)	15 (10.7)	[redacted]
Non-CR/Non-PD	22 (15.7)	[redacted]
Unknown (UNK)	15 (10.7)	[redacted]
Overall response rate (ORR: CR + PR) – n (%) [95% CI][a]	50 (35.7) [27.8, 44.2]	48 (34.3) [26.5, 42.8] [b]
Disease Control Rate (DCR: CR+PR+SD) – n (%) [95% CI][a]	88 (62.9) [54.3, 70.9]	[redacted] [redacted]

N: The total number of patients in the full analysis set. It is the denominator for percentage (%) calculation.
n= Number of patients who are in the corresponding category.
[a] Exact binomial 95% Confidence Interval
Non-CR/Non-PD refers to best overall responses that are neither CR nor PD per RECIST 1.1 criteria for patients with non-measurable disease only at baseline.
Abbreviations: BIRC, Blinded independent central review committee; CI, confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown
Source: ASCEND-2 updated results (cut-off August 2014)

B8. On page 86 of the company submission it is stated that the adverse event results were 'suspected to be study drug related'. Please clarify how this was defined.

Novartis response:

In both the ASCEND-1 and ASCEND-2 trials the judgement as to whether the AE was study drug related was decided by the study investigator.

Details of the definitions and reporting of adverse events are available in Section 8.1.1 of the "ASCEND-2 clinical study report" (page 6599) and Section 7.1.1 of the "ASCEND-1 protocol", both of which are provided along with the submission [reference numbers 8 and 75, respectively, in our evidence submission].

Once an AE was detected, the AE was followed until its resolution or until it was judged to be permanent. Assessment of AEs was made at each visit (or more frequently, if necessary),

and this included an assessment of the suspected relationship to the study treatment. ("ASCEND-2 clinical study report" Section 8.1.1 (page 6600) and "ASCEND-1 protocol" Section 7.1.1). Specifically, adverse events were categorised as "Yes" or "No" in terms of whether there was a 'reasonable possibility that AE is related' [to the study treatment], as described in the "ASCEND-2 clinical study report", Section 8.1.1 (page 6599), and the "ASCEND-1 protocol", Section 7.1.1.

B9. Please provide numbers of patients in ASCEND1 and 2 who received other treatments post progression and details of these treatments, if possible.

Novartis response:

[redacted]

B10. The company submission states that some patients don't tolerate crizotinib. Please provide the definition used for not tolerating crizotinib and the numbers of participants in the ASCEND studies who did not tolerate crizotinib.

Novartis response:

The Food and Drug Administration in the US granted accelerated approval to ceritinib on 29th April 2014 for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

The approval of ceritinib was based on the results of the ASCEND-1 open-label clinical trial enrolling a total of 163 patients with metastatic, ALK-positive, NSCLC who had progressed

on or were intolerant to crizotinib.

[redacted]

Please note that ceritinib (Zykadia®) holds a marketing authorisation in the European Union "for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib" and that intolerance to crizotinib is not mentioned in the EU label.

B11. The adverse events for ASCEND 3 and the treatment naive subgroup of ASCEND 1 are presented in the company submission in Appendices 5 and 6, respectively. Please provide a pooled analysis of the treatment emergent adverse events for ceritinib from all studies (including from other ongoing trials such as ASCEND 4 & 5 if available).

Novartis response:

The ceritinib (Zykadia®) summary of product characteristics[3] reports safety data from a total of 525 patients with tumours confirmed to have genetic abnormalities in ALK (515 ALK-positive NSCLC patients and 10 non-NSCLC patients) and treated at the dose of 750 mg in four open-label, single-arm clinical studies (studies X2101, A2201, A2203 and X1101). The median duration of exposure to ceritinib was 33.0 weeks (range: 0.3 to 106.1 weeks). Adverse events (AEs) with an incidence of ≥10% were diarrhoea, nausea, vomiting, fatigue, liver laboratory test abnormalities, abdominal pain, decreased appetite, constipation, rash, blood creatinine increased, oesophageal disorder and anaemia. Grade 3-4 AEs with an incidence of ≥5% were liver laboratory test abnormalities, fatigue, diarrhoea, nausea and hyperglycaemia.

Table 3 shows the frequency category of AEs reported for ceritinib in patients treated at the starting dose of 750 mg in four clinical studies.

AEs are listed according to MedDRA system organ class. Within each system organ class, the AEs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each AE: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 3: AEs in patients treated with ceritinib at a dose of 750 mg

System organ class Preferred term	Ceritinib N=525 %	Frequency category
Blood and lymphatic system disorders		
Anaemia	11.4	Very common
Metabolism and nutrition disorders		
Decreased appetite	41.1	Very common
Hyperglycaemia	7.8	Common
Hypophosphataemia	5.3	Common
Eye disorders		
Vision disorder[a]	7.4	Common
Cardiac disorders		
Pericarditis[b]	5.9	Common
Bradycardia[c]	1.9	Common
Respiratory, thoracic and mediastinal disorders		
Pneumonitis[d]	3.2	Common

Gastrointestinal disorders		
Diarrhoea	83.8	Very common
Nausea	79.8	Very common
Vomiting	62.9	Very common
Abdominal pain[e]	48.2	Very common
Constipation	25.1	Very common
Oesophageal disorder[f]	15.0	Very common
Hepatobiliary disorders		
Abnormal liver function tests[g]	2.1	Common
Hepatotoxicity[h]	0.6	Uncommon
Skin and subcutaneous tissue disorders		
Rash[i]	19.0	Very common
Renal and urinary disorders		
Renal failure[j]	2.1	Common
Renal impairment[k]	1.3	Common
General disorders and administration site conditions		
Fatigue[l]	50.5	Very common
Investigations		
Liver laboratory test abnormalities[m]	50.5	Very common
Blood creatinine increased	17.7	Very common
Electrocardiogram QT prolonged	6.5	Common
Lipase increased	4.6	Common

Includes cases reported within the clustered terms:

[a] Vision disorder (vision impairment, vision blurred, photopsia, vitreous floaters, visual acuity reduced, accommodation disorder, presbyopia)
[b] Pericarditis (pericardial effusion, pericarditis)
[c] Bradycardia (bradycardia, sinus bradycardia)
[d] Pneumonitis (interstitial lung disease, pneumonitis)
[e] Abdominal pain (abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort)
[f] Oesophageal disorder (dyspepsia, gastro-oesophageal reflux disease, dysphagia)
[g] Abnormal liver function test (hepatic function abnormal, hyperbilirubinaemia)
[h] Hepatotoxicity (drug-induced liver injury, hepatitis cholestatic, hepatocellular injury, hepatotoxicity)
[i] Rash (rash, dermatitis acneiform, rash maculopapular)
[j] Renal failure (renal failure acute, renal failure)
[k] Renal impairment (azotaemia, renal impairment)
[l] Fatigue (fatigue, asthenia)
[m] Liver laboratory test abnormalities (alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood bilirubin increased, transaminases increased, hepatic enzyme increased, liver function test abnormal)

Section C: Clarification on cost-effectiveness data

Literature searches, inclusion criteria, and study selection:

C1. Priority Questions.

Systematic review for economic evaluations:

- Please provide the full search strategy for each database that was used in the literature searches and also provide the numbers of studies retrieved for each line (Appendix 9 of the company submission).

- ***Novartis response:***

  Please see excel file "SLR for Economic Evaluations_Search Strategy".

- Please provide the references for the 16 studies excluded at full text review and the other 82 studies selected for extraction (Figure 15, page 87).

- **Novartis response:**

  Please see excel file "SLR for Economic Evaluations_Search Strategy".

Systematic review for health-related quality of life studies:

- Please provide a search strategy for each database with the numbers of studies retrieved for each line (Appendix 10 of the company submission).

- ***Novartis response:***

  Please see word document "Hits of Health Utility SLR_for Appendix 10".

- Please provide the references for the 148 studies excluded along with reasons for exclusion of each study at level II (Figure 22, page 103 of the company submission).

- ***Novartis response:***

  Please see excel file "References for health utility SLR".

Systematic review for costs and resource use – update of systematic review for crizotinib NICE submission:

- Please provide a search strategy for each database with numbers of studies retrieved for each line (Appendix 12 of the company submission).

- **Novartis response:**

  Please see word document "Hits for costs and resource use SLR".

- The company present a list and details of 18 studies meeting eligibility criteria. Please provide the references for the 14 articles excluded at full text screening (Figure 23, page 109 of the company submission).

- **Novartis response:**

- *Please see word document "Hits for costs and resource use SLR".*

C2. <u>Priority Question</u>.

Given that no progression-free survival data were available for ALK positive patients, please clarify why a decision was made to use data from EGFR positive patients, rather than any other NSCLC subgroup?

Novartis response:

The clinical expert consulted [redacted] *for this submission by Novartis confirmed that the clinical-pathological characteristics of ALK +ve*

NSCLC patients are very similar to those of NSCLC patients with EGFR mutations. In fact, EGFR mutations tend to occur predominately in patients with adenocarcinoma, who are light smokers or who have never smoked; and in patients who are relatively young (mean age ~ 50-years-old).

In a study by Shaw et al, 2009[4] looking at the clinical features of ALK +ve patients the authors concluded that in patients with NSCLC who have clinical characteristics associated with EGFR mutation but who have negative EGFR testing, as many as one in three patients may harbor EML4-ALK. This would imply that the prevalence of ALK +ve is around 33% when we select patients who have the EGFR mutation characteristics.

Because of these baseline characteristics similarities, data from the EGFR TKIs trial by Shepherd et al, 2005 [5] was deemed suitable to inform the comparator arm of the model, with respect to PFS data.

C3. <u>Priority Question</u>.

Please explain why an adjustment has not been made to account for the higher utility values one would expect for best supportive care, given its lower adverse event profile.

It is stated that adverse event disutilities were not applied to the pre-progressive health state in the ceritinib arm of the model, as these should already have been captured in the utility data collected in the trial. However, the same utility values are used for the best supportive care arm, indicating that adverse event disutilities have also been applied here. We consider that this may be inappropriate since elsewhere no adverse events resulting from best supportive care are assumed. Please clarify whether the best supportive care arm includes disutility from treatment and, if so, justify why this approach was taken.

Novartis response:

In the base case analysis Novartis assumed that patients in the progression free health state and on BSC would have the same utility value as those on treatment with ceritinib. The utility value from the ceritinib trial captures both the disutility due to adverse events with ceritinib but also the benefit of being on active treatment (with ceritinib). Novartis believes that the benefit of being on active treatment counterbalances the disutilites from any AEs experienced by being on ceritinib for patients in the progression-free health state. Patients on BSC have a worse prognosis compared to those on active treatment and as such would also be expected to experience a much lower quality of life (see alternative published utility values by Nafees et al, 2008[6] and Chouaid et al, 2013[7] for patients with NSCLC and yet to progress). Novartis made this conservative assumption in order to ensure that all patients in the economic analysis would have the same QOL when in the progression free health state. Novartis believes that it is unlikely that patients on BSC would experience a better QOL compared to those on active treatment due to the worse prognosis for these patients.

Furthermore this assumption is only relevant for the progression-free health state, as literature-derived values are used for those with progressive disease, where no disutilites from AE are considered as patients are not on any active treatment.

C4. <u>Priority Question</u>.

It is recognised that an indirect comparison could not be made between ceritinib and best

supportive care (after crizotinib). However, please clarify why the comparison presented was not adjusted for baseline characteristics that may affect overall survival or progression free survival?

Novartis response:

The Ou et al, 2014[8] publication reports the baseline characteristics of patients who either continued crizotinib (n=120) or did not continue crizotinib (n=74). In the base case analysis, in order to estimate the overall survival of patients in the BSC arm, Novartis used the overall survival data (extrapolated from the Kaplan-Meier curves reported in the publication) of patients who did not continue crizotinib and that did not receive any systemic therapy (n=37) (see Figure 1B in Ou et al, 2014[8]). Unfortunately Novartis did not have access to the baseline characteristics data for this subgroup in order to attempt to perform an adjustment for baseline characteristics.

C5. Priority Question.

The company state that, in the data informing the Ou study, assignment to the various treatment options was not randomised, but rather based on prognostic factors. Patients assigned to the best supportive care group are likely therefore to be those anticipated not to benefit from further treatment. This particular best supportive care group is therefore also likely to be a group with worse prognosis, potentially leading to underestimation of the overall survival with best supportive care. Please explain how this potential bias was taken into account and methods used to adjust for it.

Novartis response:

In the submission Novartis decided not to perform any adjustment as it believes that patients in the BSC arm in the Ou et al, 2014[8] study would be representative of those who would be receiving BSC in UK clinical practice. [redacted] *Furthermore in the management of ALK +ve patients, only those patients who are unable to receive another line of treatment would go on to receive BSC, which means that they would be expected to have a worse prognosis, otherwise clinicians would most likely be prescribing an alternative active treatment for these patients.*

C6. Priority Question.

The Weibull extrapolation was chosen for best supportive care overall survival, although it was statistically the worst fitting model. On page 96 of the company submission it is briefly stated that the other extrapolations were not considered as “reliable”. Please provide reasons for why the other extrapolations were considered unreliable.

Novartis response:

The log-logistic and log-normal extrapolations for best supportive OS produced implausibly

high long-term rates of survival (patients were still alive at 240 months see table 48 in submission); although the log-cumulative hazards provided a weak suggesting of non-monotonic hazards, these curves were believed to over-estimate survival benefits of BSC. The Gompertz also seemed to over-estimate survival benefits of BSC. The Weibull extrapolation was chosen for best supportive care overall survival based on external validity (feedback received from the clinical expert consulted [redacted]) but also to ensure that the same parametric function for OS would be used in both arms of the model (for ceritinib and BSC).

C7. <u>Priority Question</u>.

Please provide tables similar to Table 48 on page 96 of the company submission for overall survival projections with ceritinib, and progression-free survival projections for ceritinib and best supportive care, using each of the different possible survival functions.

Novartis response:

Please see below tables 4,5 and 6.

Table 4: Proportions of patients alive (%) with ceritinb using different parametric models

Year	exponential	Weibull	Gompertz	log-logistic	log-normal
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Proportions of patients progression free (%) with ceritinb using different parametric models

Year	exponential	Weibull	Gompertz	log-logistic	log-normal
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Proportions of patients progression free (%) with BSC using different parametric models

Year	exponential	Weibull	Gompertz	log-logistic	log-normal

1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

C8. Only adverse events which occurred in more than 5% of trial participants were included in the model. This potentially excluded rare but serious adverse events which could have very high costs or disutilities associated with them. Are there any rare but serious events that were not captured in the model? If so, please provide an estimate of the likely impact of including them.

Novartis response:

Table 7 presents all the pooled grade 3-4 adverse events from the ASCEND-1 and ASCEND-2 trials.

Table 7: Pooled grade 3-4 adverse events from the ASCEND-1 and ASCEND-2 trials

	Pooled Analysis Ceritinib 750 mg (n=303) Grade 3/4 n (%)	Unit Cost (£)	Source
Abdominal Pain	[redacted]	£0.00	Assume no cost
Abdominal Pain Upper	[redacted]	£0.00	Assume no cost
Alanine Aminotransferase Increased	[redacted]	£0.00	Assume no cost
Amylase Increased	[redacted]	£0.00	Assume no cost
Anaemia	[redacted]	£2,065.62	NHS Reference Costs 2012-13 NHS Trust HRG data Average Iron Deficiency Anaemia (SA04G- SA04L)
Aspartate Aminotransferase Increased	[redacted]	£0.00	Assume no cost
Asthenia	[redacted]	£2,065.62	Assume same as Anaemia
Blood Alkaline Phosphatase Increased	[redacted]	£0.00	Assume no cost
Decreased appetite	[redacted]	£0.00	Assume no cost
Diarrhoea	[redacted]	£617.81	As per submission
Dyspepsia	[redacted]	£0.00	Assume no cost
Electrocardiogram QT prolonged	[redacted]	£0.00	Assume no cost
Fatigue	[redacted]	£0.00	Assume no cost
Gamma-glutamyltransferase increased	[redacted]	£0.00	Assume no cost
Hepatic function abnormal	[redacted]	£0.00	Assume no cost
Hyperglycaemia	[redacted]	£0.00	Assume no cost
Hypophosphataemia	[redacted]	£0.00	Assume no cost
Lipase Increased	[redacted]	£0.00	Assume no cost
Nausea	[redacted]	£693.23	As per submission

Neutropenia	[redacted]	£38.16	As per submission
Pneumonia	[redacted]	£1,064.69	NHS Reference Costs 2012-13 NHS Trusts HRG Data Average Upper Respiratory Tract Disorders (PA65A - PA65C)
Pneumonitis	[redacted]	£1,064.69	Assume same as Pneumonia
Pruritus	[redacted]	£0.00	Assume no cost
Pyrexia	[redacted]	£3,633.60	NHS Reference Costs 2012-13 NHS Trusts HRG data Pyrexia of Unknown Origin with length of stay 5 days or more (WA05Z)
Transaminases Increased	[redacted]	£0.00	Assume no cost
Vomiting	[redacted]	£0.00	Included in the cost of managing nausea
Weight decreased	[redacted]	£0.00	Assume no cost
TOTAL Cost		**£145.46**	

[redacted] *In the economic analysis we have captured the costs of managing nausea, fatigue, diarrhoea (based on the day case costs for PA28A - Feeding Difficulties and Vomiting, with CC Score 1 370 Oncology and PA21A - Infectious or Non-Infectious Gastroenteritis, with CC Score 1+ 370 Oncology from the NHS reference costs 2012/2013). The AEs costs for the lab abnormalities (ALT elevation, AST elevation, Gamma-glutamyltransferase and blood alkaline phosphatase increase) were assumed to be zero as they would be managed by dose reductions or interruptions as per SmPC[3] of ceritinib. The cost of managing fatigue was also assumed to be zero.*

Below are the results of a scenario analysis where we have assigned costs to all grade 3-4 AEs from the ASCEND-1 and ASCEND-2 trials (see Table 7). The impact on the ICER is minimal (£62,543 in this scenario versus £62,456 in the submitted base case).

Table 8: Scenario analysis using all grade 3- 4 AEs from the ASCEND-1 and ASCEND-2 trials

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
BSC	7,203	0.42	0.25				
Ceritinib	59,228	1.77	1.08	52,025	1.35	0.83	62,543

C9. An assumption was made that all adverse events would occur within the first month of treatment. Please provide the trial data to support this assumption.

Novartis response:

In the ASCEND-2 study, the median time to first dose interruption was 1.4 months (range: 0.1 to 7.5 months); therefore, it was felt a reasonable assumption to include all AEs in the first cycle of the economic model. Also this ensured that all the AE's would be captured in the

analysis as a one-off (rather than trying to estimate how many AEs would occur each month in the progression-free health state).

C10. It is stated that lab abnormalities were assumed to have a cost of 0, as they would be managed by dose adjustments. Presumably, however, there would be a cost associated with the physician's time in managing such adjustments, and potentially additional tests to monitor the adjusted doses. Please estimate the effect of including these costs in the analyses.

Novartis response:

Below are the results of a scenario analysis where we have assumed two additional blood tests (Schedule of Reference Costs, directly accessed pathology Services, DAPS05-Haematology) and two additional outpatient visits (Schedule of Reference Costs, all NHS trusts and NHS foundation trusts - WF01A, Non-Admitted Face to Face Attendance, Follow-up, 370 - Medical Oncology) to manage dose adjustments due to lab abnormalities. The total cost of managing dose adjustments for patients with lab abnormalities was estimated at £292.10. The impact on the ICER is minimal (£62,567 in this scenario versus £62,456 in the submitted base case).

Table 9: Scenario analysis assuming additional resource use to manage lab abnormalities

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	
BSC	7,203	0.42	0.25				
Ceritinib	59,248	1.77	1.08	52,045	1.35	0.83	62,567

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