National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after chemotherapy [ID741]

You are asked to check the ERG report from Kleijnen systematic reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **12pm, Thursday 6 August** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Ramucirumab plus paclitaxel

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p.12 – Ramucirumab plus paclitaxel Statement in ERG report: This represents a 31% (2.27 months) longer median overall survival in the ramucirumab+paclitaxel arm (9.63 months (95% CI **8.6**-10.8) versus 7.36 (95% CI 6.3-8.4) months in the placebo+paclitaxel arm).	Proposed amendment: This represents a 31% (2.27 months) longer median overall survival in the ramucirumab+paclitaxel arm (9.63 months (95% CI **8.5**-10.8) versus 7.36 (95% CI 6.3-8.4) months in the placebo+paclitaxel arm).	Error correction	Correct, the same mistake was made on pages 45 and 66. All three have been corrected.

Issue 2 Population of REGARD trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p..25 – 3.1 Population Statement in ERG report: However, the company replied that "It is not possible to estimate the number of patients in each arm of REGARD for whom treatment in combination with paclitaxel is not appropriate."(Response to Clarification Letter, Question A7).[11] The ERG report did not adequate ely reflect the response given by Lilly to the clarification questions regarding their request for the numbers of patients in each arm and separate data of overall survival and progression-free survival from the REGARD trial for patients for whom treatment in combination with paclitaxel is not appropriate.	Proposed statement: ~~**However,**~~ the company replied that "It is not possible to estimate the number of patients in each arm of REGARD for whom treatment in combination with paclitaxel is not appropriate."(Response to Clarification Letter, Question A7).[11] **Data from the trial were not collected to systematically identify these patients, especially as the REGARD trial was initiated before the RAINBOW trial was designed to evaluated ramucirumab in combination with paclitaxel. More importantly, choice of whether the patient is appropriate for monotherapy or combination therapy is a matter of clinical judgment.** **The licensing restriction of ramucirumab monotherapy to patients for whom treatment in combination with paclitaxel**	The ERG does not present all the information provided by the manufacturer as justification as to why this information cannot be provided. The impact is that the manufacturer's justification appears less valid or robust.	We summarized the company response. Not a factual error.

	is not appropriate was the result of discussion with the Committee for Human Medicines Products and was based on a full consideration of the clinical trial evidence from REGARD and RAINBOW and clinical expert opinion regarding current treatment options available in second-line gastric and gastro-oesophageal junctional cancers (GC/GOJ).		

Issue 3 Table 4.2: Data sources for RCT's of ramucirumab: RAINBOW and REGARD

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 30 – Table 4.2 It is not clear what dates the trial start and finish dates correspond to. For REGARD this is given as **6 Oct 2009 - 26 Jan 2012.**	If the finish date corresponds to the data cut-off point (as seems to be the case for RAINBOW), trial start and finish dates for REGARD should be **6 October 2009 - 25 July 2012.**	Possible incorrect trial date	On page 79 of the CS it is reported: "REGARD took place between 6 October 2009 and 26 January 2012, at 119 centres in 29 countries in North America, Central and South America, Europe, Asia, Australia, and Africa." We took that as the start and finish dates.

Issue 4 Table 4.6 Overview of RAINBOW and REGARD trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p.36 – Table 4.6 Comparator of RAINBOW statement in ERG report: Placebo + paclitaxel 80 mg/m2	For consistency with REGARD comparator description, please reword as: **Equivalent volume of** placebo +	For consistency of ERG reporting between RAINBOW and REGARD	Not a factual error.

administered IV. PBO+PAC	paclitaxel 80 mg/m2 administered IV. PBO+PAC		

Issue 5 Table 4.7: Summary of methodology of RAINBOW and REGARD trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 38 - RAINBOW design Comparator currently stated in ERG report as **PAC**	Proposed statement: **Placebo + PAC**	Point of clarification	Not a factual error. This seems quite clear from earlier descriptions of the RAINBOW trial.

p.38 - REGARD design Stated in ERG report as: Phase III, randomised, double-blind, placebo-controlled study of **RAM +PAC versus PAC**	Should be stated as Phase III, randomised, double-blind, placebo-controlled study of **RAM + BSC versus PBO + BSC**	Error correction	Correct. This has been corrected.
p.38 - REGARD duration of study Statement in ERG report: **2.3 years**	Proposed statement: **2 years and 3 months**	Error correction	Not a factual error. 2 years and 3 months is 2.25 years, rounded this is equal to 2.3 years.
p. 39 - REGARD Secondary outcomes Duration of Response abbreviated in ERG report as **DCR**. The abbreviation DCR refers to disease control rate.	Use different abbreviation for Duration of Response or remove abbreviation.	Error correction	Abbreviation has been removed
p.39 - RAINBOW Secondary outcomes Statement in ERG report: Progression-Free Survival, Time to Progression, Objective response rate (ORR) defined as the number of randomised patients who achieved complete response (CR) or partial response (PR) divided by the ITT population. Quality of Life (QoL): Assessed using EORTC QLQ-C30 (version 3.0), and the European Quality of Life-5 Dimensions (EQ-5D). Time to deterioration (TTD) in EORTC QLQ-C30. **Time to deterioration (TTD) in ECOG PS** and Safety (NCI CTCAE, version 4.02)	Proposed statement: Progression-Free Survival, Time to Progression, Objective response rate (ORR) defined as the number of randomised patients who achieved complete response (CR) or partial response (PR) divided by the ITT population. Quality of Life (QoL): Assessed using EORTC QLQ-C30 (version 3.0), and the European Quality of Life-5 Dimensions (EQ-5D). Time to deterioration (TTD) in EORTC QLQ-C30. ~~**Time to deterioration (TTD) in ECOG PS and**~~ Safety (NCI CTCAE, version 4.02)	Error correction Please remove time to deterioration of ECOG PS as a secondary outcome for RAINBOW, as it was a post hoc analysis (not a secondary outcome)	TTD was mentioned in the CS (Table 32, page 88) as a secondary outcome. Not a factual error.
p.39 - REGARD Secondary outcomes Statement in ERG report: Progression-Free Survival, Investigator-assessed Objective response rate (ORR),	Proposed statement: Progression-Free Survival, Investigator-assessed Objective response rate (ORR),	Error correction Please remove time to deterioration of ECOG PS as a secondary	Same as above

Duration of Response (DCR), QoL (EORTC QLQ-C30 (version 3.0)), **Time to deterioration of ECOG PS** and Safety (NCI CTCAE, version 4.02)	Duration of Response (DCR), QoL (EORTC QLQ-C30 (version 3.0)), ~~**Time to deterioration of ECOG PS and**~~ Safety (NCI CTCAE, version 4.02)	outcome for REGARD, as it was a post hoc analysis (not a secondary outcome)	

Issue 6 Table 4.8: Major eligibility criteria of the RAINBOW and REGARD trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 40 – RAINBOW exclusion criteria Statement in ERG report: Current chronic **platelet** therapy, NSAIDs.	Proposed statement: Current chronic **anti-platelet** therapy, NSAIDs.	Correction	We copied this from Table 13 (CS, page 52): "Current chronic platelet therapy, NSAIDs."

Issue 7 Treatment exposure and discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 41 – Treatment exposure and discontinuation Statement in ERG report: Discontinuation following an adverse event: In the ramucirumab arm, **11.3%** (25) of patients discontinued treatment due to AEs...	Proposed statement: Discontinuation following an adverse event: In the ramucirumab arm, **10.5%** (25) of patients discontinued treatment due to AEs…	Error correction	This was taken from page 90 in the CS: "In the RAM arm, 11.3% (25) of patients discontinued treatment due to AEs,.."

Issue 8 Table 4.9: Reasons for treatment discontinuation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 42 – Table 4.9			
REGARD “patients treated” currently stated in ERG report as: Ramucirumab - 14 (5.9) Placebo - 1 (0.9)	REGARD “patients treated” should be stated as: Ramucirumab - 236 Placebo - 115	Error correction	Correct. This has been corrected.
No data currently provided in ERG report for RAINBOW “treatment ongoing”.	RAINBOW “treatment ongoing” should include the following data: **Ramucirumab + Paclitaxel - 13** **Placebo + Paclitaxel - 7** For clarity, “Treatment ongoing” could be reworded to "Treatment ongoing at trial data cut-off date"	Incomplete table	This was not reported in Figure 7 (CS, page 58), but we have added it to the corrected page in the ERG report.
REGARD “treatment ongoing” currently stated in ERG report as: **Ramucirumab - 16** **Placebo - 3**	REGARD treatment ongoing should be stated as: **Ramucirumab - 14** **Placebo - 1**	Error correction	Correct. This has been corrected.
RAINBOW AE currently stated in ERG report as: **Placebo + Paclitaxel – 39 (11.8)**	RAINBOW AE should be stated as: **Placebo + Paclitaxel – 38 (11.3)**	Error correction	Correct. This has been corrected.

Issue 9 Use of the term "investigators" in the ERG report

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The term "investigators" has been used in various contexts in the ERG report, some of which are not appropriate or correct.			We have used the term investigators loosely. Generally meaning the people conducting the trials and producing the CS.
p.42 – Treatment exposure and discontinuation Statement in ERG report: **According to the investigators**, the majority of the patients who withdrew consent experienced a Grade ≥ 3 adverse event or serious adverse event within 2 weeks before or after discontinuation of therapy.	Proposed statement: ~~**According to**~~ **As assessed by the investigators**, the majority of the patients who withdrew consent experienced a Grade ≥ 3 adverse event or serious adverse event within 2 weeks before or after discontinuation of therapy.	Use of the term "according to the investigators" is not appropriate in this context.	Not a factual error.

p.44 – Patient characteristics in two trials Statement in ERG report: The **investigators** state that region 1 was most similar to the UK, (although the criterion by which this was determined was not stated). We assume this refers to the submission.	Proposed statement: The ~~**investigators**~~ **company submission** states that region 1 was most similar to the UK, (although the criterion by which this was determined was not stated).	Incorrect use of term "investigators".	Not a factual error.
p.45 – Overall survival Statement in ERG report: According to the **investigators** ramucirumab+paclitaxel reduced the relative risk of death from any cause in this population by 19% (HR = 0.807; 95% CI: 0.678, 0.962; p=0.0169) compared with placebo+paclitaxel.	Proposed statement: ~~**According to the investigators**~~ **R**amucirumab+paclitaxel reduced the relative risk of death from any cause in this population by 19% (HR = 0.807; 95% CI: 0.678, 0.962; p=0.0169) compared with placebo+paclitaxel.	Use of the term "according to the investigators" is not appropriate in this context.	Not a factual error.
p.59 - Heterogeneity Statement from ERG report: The **company** **investigators** noted several sources of heterogeneity which were identified across the studies included in the analyses. We assume this refers to the submission.	Proposed statement: The ~~**company investigators**~~ **manufacturer** noted several sources of heterogeneity which were identified across the studies included in the analyses.	Use of the word "investigators" is not appropriate in this context.	Not a factual error.

Issue 10 Patient characteristics in two trials

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 44 – Patient characteristics in two trials Statement in ERG report: As most patients in both trials had gastric cancer (75 to 80%), the evidence from this study is more limited with respect to gastroesophageal cancer and as a greater	Proposed statement: As most patients in both trials had gastric cancer (75 to 80%), the evidence from this study is more limited with respect to gastroesophageal **junction** cancer and as	More accurate	Not a factual error.

proportion of the recruited patients were male (70%), the evidence is more limited for female participants.	a greater proportion of the recruited patients were male (70%), the evidence is more limited for female participants.		

Issue 11 Results of the RAINBOW trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p.44 – Results of the RAINBOW trial			
Data cut-off point stated in ERG report as 22 May 2012	Data cut-off point should be stated as 12 July 2013	Error correction	Correct. This has been corrected.
Statement in ERG report: Efficacy analyses were performed using the ITT population, which included all randomised patients who received at least 1 dose of the allocated intervention.	Proposes amendment: Efficacy analyses were performed using the ITT population~~, which included all randomised patients who received at least 1 dose of the allocated intervention.~~	Incorrect statement. The definition given corresponds to the safety population, not the ITT population.	Correct. This has been corrected.

Issue 12 RAINBOW Overall Survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 45 – Overall survival Statement in ERG report: This represents a 31% (2. 27 months) longer median overall survival in the ramucirumab+paclitaxel arm (9.63 months (95% CI **8.6**-10.8) versus 7.36 (95% CI 6.3-8.4) months in the placebo+paclitaxel arm).	Proposes amendment: This represents a 31% (2. 27 months) longer median overall survival in the ramucirumab+paclitaxel arm (9.63 months (95% CI **8.5**-10.8) versus 7.36 (95% CI 6.3-8.4) months in the placebo+paclitaxel arm).	Error correction	See Issue 1.

Issue 13 RAINBOW and REGARD Overall Survival

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 46 – Overall survival (RAINBOW) and p.54 (REGARD) We do not agree with the interpretations of the subgroup analyses performed showing forest plots for univariate analyses of overall survival in both the RAINBOW and REGARD trials.			Not a factual error.
p. 46 – Overall survival (RAINBOW) Statement in ERG report: The subgroup analyses show that ramucirumab+paclitaxel when compared with paclitaxel+placebo is less effective in non-measurable disease, region 3 (Asia), males, elderly, gastric cancer, diffuse and mixed, missing or unknown histological subtypes and in patients who had a previous gastrectomy.	Proposed statement The subgroup analyses show that the ~~ramucirumab+paclitaxel when compared with paclitaxel+placebo is less effective~~ **hazard ratio was numerically higher in non-measurable disease, region 3 (Asia), males, elderly, gastric cancer, diffuse and mixed, missing or unknown histological subtypes and in patients who had a previous gastrectomy compared to the hazard ratio observed in the ITT**.	It is not appropriate to say that the intervention was "less effective" when compared to the control arm in the subgroup analysis as it was not powered to demonstrate significant improvements (or lack of improvement). Additionally, the way the sentence is currently formulated creates the perception that the control arm is favoured in all the subgroups mentioned. However, this is only accurate for non-measurable disease (not statistically significant). All hazard ratios numerically favoured the RAM+PAC arm with the exception of non-measurable disease.	Not a factual error.

p. 54 – Overall survival (REGARD) Statement in ERG report: The subgroup analyses show that ramucirumab when compared with placebo is less effective in females, patients who are not white or Asian, and ECOG score 0.	Proposed statement: The subgroup analyses show that ~~**ramucirumab when compared with placebo is less effective**~~ **the hazard ratio was numerically higher in females, patients who are not white or Asian, and ECOG score 0 compared to the hazard ratio observed in the ITT.**	It is not appropriate to say that the intervention was "less effective" when compared to the control arm in the subgroup analysis as it was not powered to demonstrate significant improvements (or lack of improvement).	Not a factual error.

Issue 14 Table 4.12 and Table 4.20: RAINBOW and REGARD: Progression-free survival results (ITT population)

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 48 and p.56 – Tables 4.12 and 4.20 Statements in ERG report: Number of deaths % Median PFS survival-months (95 % CI)	Proposed statements: Number of deaths **or progression** % Median PFS ~~survival~~ months (95 % CI)	Error correction	Correct. This has been corrected.

Issue 15 Response rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p.48 – Response rate Statement in ERG report: Response rates are reported below. Significant differences in favour of the ramucirumab+ paclitaxel group were observed for objective response rate (complete or partial response according to RECIST criteria), and duration of response. The duration of response is not reported in Table 4.13. Duration for response was not a secondary endpoint for RAINBOW.	Proposed statement: Response rates are reported below. Significant differences in favour of the ramucirumab+ paclitaxel group were observed for objective response rate (complete or partial response according to RECIST criteria)**~~, and duration of response~~**	Error correction. Please see Issue 5 regarding duration of response.	Correct. This has been corrected.

Issue 16 Table 4.14: RAINBOW: EORTC QLQ-C30 – global health status results, ITT population

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
P. 49 – Table 4.14 Statement in ERG report: Numbers of patients reporting changes from baseline currently given as RAM+PAC 209 and PBO+PAC **2042**.	Should be stated as: Numbers of patients reporting changes from baseline should be RAM+PAC 209 and PBO+PAC **202.**	Error correction	Correct. This has been corrected.

Issue 17 REGARD Response Rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p.56 – Response rate Statement in ERG report: A significant difference in favour of the ramucirumab group was observed for duration of response.	Proposed amendment: ~~**A significant difference in favour of the ramucirumab group was observed for duration of response.**~~	Error correction Please see Issue 5 regarding duration of response. The duration of response was not analysed (as per statistical analysis plan) due to low patient numbers with complete or partial responses. Therefore this information could not have been provided.	Correct. This has been corrected.

Issue 18 REGARD Health Related Quality of Life

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 57 – Heath related quality of life Statement in ERG report: Also at six weeks, there were higher proportions of patients in the RAM arm for the physical functioning, fatigue and pain subscales.	Proposed amendment: Also at six weeks, there were higher proportions of **stable or improved** patients in the RAM arm for the physical functioning, fatigue and pain subscales.	Clarification statement	Correct. This has been corrected.

Issue 19 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p. 57 – Adverse events Statement in ERG report: Similar **numbers** of patients had at least one serious adverse event (106 [45%] of 236 in the ramucirumab group vs 51 [44%] of 115 in the placebo group), or adverse event leading to death (22 [9%] versus 15 [13%], respectively).	Proposed amendment: Similar **percentages** of patients had at least one serious adverse event (106 [45%] of 236 in the ramucirumab group vs 51 [44%] of 115 in the placebo group), or adverse event leading to death (22 [9%] versus 15 [13%], respectively).	Error correction	Not a factual error.

Issue 20 Table 4.1: Heterogeneity in network of studies for combination therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
p.62 - Schedule used for tumour assessment			
Statement in ERG report for Thuss-Patience 2011: Every three weeks. Radiological assessments were conducted every 6 weeks, but only in the experimental arm	Proposed statement: ~~**Every three weeks.**~~ Radiological assessments were conducted every 6 weeks, but only in the experimental arm	Error correction	Not a factual error: Thuss-Patience et al. report: "Investigations scheduled for both treatment arms: Weekly full blood count and evaluation of side effects, three-weekly history and examination, evaluation of tumour related symptoms, blood chemistry."
Statement in ERG report for Cougar-02: Every 3 weeks (before each treatment cycle). Radiological assessments were conducted at 9 and 18 weeks, but only in the experimental arm	Proposed statement: ~~**Every 3 weeks (before each treatment cycle).**~~ Radiological assessments were conducted at 9 and 18 weeks, but only in the experimental arm	Error correction	Not a factual error: Ford et al. report: "We reviewed patients on active symptom control alone every 3 weeks for the 18-week treatment period."

Issue 21 Unsubstantiated claims regarding current comparator usage in the UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 78 - ERG comment combination therapy The ERG report makes the following claims regarding current clinical practice based speculation about future clinical practice. "But also, since the company claims that RAM+PAC is a suitable treatment option for patients who currently receive BSC, the ERG considers it plausible that also the proportion of patients receiving PAC or other comparator treatments may increase once RAM+PAC receives positive guidance. Finally, the chart review was based on data provided from June to July 2013. Favourable results for DOC from the COUGAR II study were published in December 2013. Although PAC is still not a licenced treatment for the current indication, increasing utilisation may be expected since results were available from December 2013 onwards. In the wake of this, it may also be anticipated that off-label use of IRI and FOLFIRI could increase, and hence the inclusion of these treatments in the comparison could also be considered relevant."	Removal of these statements entirely.	The following statements are speculative and therefore not factually accurate and should therefore not be used in determining what is <u>current</u> clinical practice • The approval of RAM+PAC will lead to an increase in patients receiving PAC or other comparator treatments • Evidence from a trial of docetaxel versus BSC (COUGAR III) is expected to lead to an increase in the usage of paclitaxel • Both of the above points may lead to an increase in irinotecan and FOLFIRI	Not a factual error. These are possible consequences.

Issue 22 Use of data from Roy in the network meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 86. When discussing the trial Roy et al (2013) the ERG report fails to highlight that the hazard ratios for the comparison of docetaxel and irinotecan are not actually reported in the publication and that the estimated hazard ratios for OS and PFS are based on the digitisation of the curves.	Suggest the following statement is amended to: For the indirect treatment comparison for OS, in the base case, results from the evidence network excluding Roy et al[28] is used. Roy et al 2013 is a randomised phase II study including three treatment arms (i.e. DOC (N=44), IRI (N=44) and a highly stable liposomal nanocarrier formulation of irinotecan (N-44)). **The hazard ratios for Roy are not however explicitly reported and were estimated by digitisation.** ~~Therefore, the ERG thinks that NMA results including Roy et al 2013 may be more reliable.~~ Therefore, in one of the additional scenario analyses, results from the NMA including Roy et al 2013[28] will be used. Also in another additional scenario analysis, PFS HR from Roy et al[28] is used (1.26) instead of 1 between IRI and DOC.	By not providing this piece of contextual information, it is difficult for the reader to fully judge the robustness of the evidence provided by Roy et al, and whether it is appropriate to include or exclude it.	Not a factual error. Limitations of Roy et al were already listed in the clinical effectiveness part.

Issue 23 Utility values used in REGARD

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 91. The ERG report states that the EQ-5D data from RAINBOW was used in the monotherapy economic model because EQ-5D values were considered better than a mapping of the EORTC and because there were insufficient post-baseline data available to rapid disease progression in both arms. The ERG report fails to highlight that the CS provided evidence that the baseline EORTC-QLQ-C30 values were similar across the two trials implying that patients had a similar health-related quality of life at the beginning of the trial, which was the utility value which was used in both economic models.	Suggest the following statement is amended to: In the REGARD trial, HRQL was only measured with the QLQ C-30, the EQ-5D was not included. Mapping was not performed by the company. First, this was considered second best to direct use of EQ-5D. Second, this would require data imputation since there were insufficient post-baseline data available due to the rapid disease progression in both arms. **Thirdly, evidence was presented which indicated that there was no difference in the baseline HRQL for patients in either trial.**	The ERG does not present all the information provided by the manufacturer as justification for using the EQ-5D value from the RAINBOW trial in the monotherapy model. The impact is that the manufacturer's justification appears less valid or robust.	Not a factual error. The ERG team will not follow the proposed amendment, because, in the evidence presented in the company submission (Table 24, Appendix 10), it can be seen that statistically significant differences ($p<0.05$) exist between some of the baseline mean scores of RAINBOW and REGARD trials (e.g. in physical functioning scale and in nausea and vomiting symptom scale).

Issue 24 REGARD Weight/BSA

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 95 – Patient weight/BAA Statement in ERG report: "For monotherapy, patient characteristics from the REGARD study were used. The base case analysis used the average of all patients (weight=63.33 kg, BSA=1.71m^2) in the trial (i.e. 65.19), and as a scenario analysis weight/BSA from the patient population in region 1 (weight=68.15kg, BSA=1.78m^2, given in CS Table 91)." There are two figures for weight quoted for all patients in the REGARD study – 63.33kg and 65.19kg. The correct figure should be weight=65.19kg. The BSA is also incorrectly quoted for the REGARD trial (all patients). The correct figures is BSA=1.73m^2.	Proposed statement: For monotherapy, patient characteristics from the REGARD study were used. The base case analysis used the average of all patients **~~(weight=63.33 kg, BSA=1.71m^2)~~** in the trial **(weight=65.19 kg, BSA=1.73m^2)**, and as a scenario analysis weight/BSA from the patient population in region 1 (weight=68.15kg, BSA=1.78m^2, given in CS Table 91).	Error correction	Correct. This has been corrected.

Issue 25 Incremental costs in base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 103 - Combination therapy Statement in ERG report: "Incremental costs were **£81,809** corresponding to an ICER of £118,209." The first figure is incorrect and should be £39,595.	Proposed statement: Incremental costs were **£39,595** corresponding to an ICER of £118,209.	Error correction	Correct. This has been corrected.