Obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukaemia [ID650]

PenTAG (ERG) replies to factual inaccuracies identified by Roche in PenTAG report to NICE

22nd August 2014

Issue 1 The assumptions underlying the ERG's alternative indirect comparison are not clearly stated and evaluated

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	Page number per corrected version of ERG report 22 Aug
The ERG have compared the ratio of the median PFS observed for patients aged above and below age 65 in Knauf 2009 in order to support the claim that the relative efficacy of bendamustine and chlorambucil is not impacted by age. This is subsequently utilised to justify the application of the ITT PFS HR from Knauf (which featured patients eligible for fludarabine) to patients ineligible for fludarabine based therapy in the UK (who have more comorbidities and are significantly older – median age 73 in CLL11). The report does not fully reflect the assumptions underlying this application. Section 1.2.2 page 17	The assumptions underlying the ERG's alternative indirect comparison should be clearly stated and evaluated for their validity. The key assumptions not stated in the report are as follows: (1) The extent to which a patient is ineligible for fludarabine has no bearing on the patient's tolerability to, and subsequent efficacy of, bendamustine or chlorambucil (2) The comparison of the efficacy of bendamustine and chlorambucil in patients above and below age 65 is sufficient to conclude that the relative efficacy of these agents would be equivalent in patients of median age 73	The inclusion and description of the key assumptions underlying the ERG's alternative scenarios are essential if the report is to be utilised by the Committee to reach a 'fair' decision on obinutuzumab with chlorambucil. As it stands the report is factually inaccurate as it does not include this information.	Added to p17-18 of our report: "For the indirect comparison to be appropriate, we assume that the PFS hazard ratio of bendamustine versus chlorambucil for patients unsuited to fludarabine can be approximated by the PFS hazard ratio of bendamustine versus chlorambucil in the bendamustine trial for patients aged ≥65. Specifically, the median age in CLL11 was 73 years. Assuming that patients in CLL11 were all unsuited to fludarabine, we therefore assume that the PFS hazard ratio of bendamustine versus chlorambucil for patients aged ≥65 equals that for patients aged 73. We believe these assumptions are reasonable."	p20

Issue 2 The alternative indirect comparison approaches are not clearly stated and their impact evaluated

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
The executive summary doesn't report that a PFS HR between Ob Clb and R benda was derived from the MTC and that the ERG have opted not to use this in favour of use of an estimate derived from an unproven and assumed relationship between response rates and PFS (with response rates derived from a sample of 28 patients). This information, including the resulting ICER if using the MTC-derived HR, should be reflected in the executive summary (and elsewhere in the document where this is mentioned). Section 1.2.3 page 18	Text should be added to explain the assumptions underlying the ERG's analysis, and the results of the economic evaluation including use of the MTC-derived PFS HR for Ob Clb and R benda should be presented. It should be noted in the text that in the age-adjusted large network this HR is 0.37, rather than the 0.76 estimated using the ERG's approach (i.e. use of the available data on PFS results in the relative efficacy of obinutuzumab chlorambucil increasing compared to use of an unproven relationship between response rates and PFS). Please note that we do not believe benda and R benda are appropriate comparators to Ob Clb as the patients eligible for these regimens are fundamentally different.	The inclusion and description of the key assumptions underlying the ERG's alternative scenarios are essential if the report is to be utilised by the Committee to reach a 'fair' decision on obinutuzumab with chlorambucil. As it stands the report is factually inaccurate as it does not include this information.	Added to p18 of our report: "Therefore, in their base case, Roche used an indirect method to estimate the PFS hazard ratio between obinutuzumab + chlorambucil and bendamustine + rituximab." And added to p19 "The PFS HR between bendamustine + rituximab and obinutuzumab + chlorambucil estimated by Roche's mixed treatment comparison is: 0.52 estimated by the fixed effects model, 0.59 estimated by the random effects model and 0.37 from the fixed effects model with age as a covariate (see p288, Appendix 3.3 Roche's report). However, we believe that little importance should be attached to these estimates, because the two treatments are connected via many other (3) treatments, two of which include fludarabine." For the reasons given in the last sentence, we do not believe it worthwhile to use the PFS HRs from the MTC in the economic evaluation. We explain our assumptions behind our base case ICER between obinutuzumab + chlorambucil and bendamustine + rituximab in detail in our report.	Added to p21 of our report: "Therefore, in their base case, Roche used an indirect method to estimate the PFS hazard ratio between obinutuzumab + chlorambucil and bendamustine + rituximab." And added to p21 "The PFS HR between bendamustine + rituximab and obinutuzumab + chlorambucil estimated by Roche's mixed treatment comparison is: 0.52 estimated by the fixed effects model, 0.59 estimated by the random effects model and 0.37 from the fixed effects model with age as a covariate (see p288, Appendix 3.3 Roche's report). However, we believe that little importance should be attached to these estimates, because the two treatments are connected via many other (3) treatments, two of which include fludarabine." For the reasons given in the last sentence, we do not believe it worthwhile to use the PFS HRs from the MTC in the economic evaluation. We explain our assumptions behind our base case ICER between obinutuzumab + chlorambucil and bendamustine + rituximab in detail in our report.

Issue 3 The impact of using a lower dose of chlorambucil in CLL11 than in clinical practice is stated to result in the efficacy of obinutuzumab being over-estimated.

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
The statement that "If, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab + chlorambucil versus chlorambucil is over-estimated in CLL11" is incorrect. Section 1.2.1 page 14	The word 'over-estimated' should be replaced with 'uncertain'. The report should be amended to reflect the fact that any link between the dose of chlorambucil and extended PFS would similarly impact the outcomes observed in each arm of the CLL11 study.	The dose of chlorambucil was the same in all 3 arms of the CLL11 study (ObClb, Clb, RClb; 0.5mg/kg d1 + d15 q28days). Any Clb-dose-related effect on efficacy would therefore be present in ALL arms of the study. Whilst it may be claimed that the difference in dosing of chlorambucil introduces uncertainty into the evaluation it is factually inaccurate to claim this will over-estimate the efficacy of obinutuzumab + chlorambucil as each arm will be similarly biased.	We thank Roche for raising this good point. Amended on p14: "If, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab + chlorambucil versus chlorambucil is uncertain in CLL11." Added to p32: "If chlorambucil is more effective at higher doses, but obinutuzumab + chlorambucil is insensitive to the dose of chlorambucil, the estimated effectiveness of obinutuzumab + chlorambucil versus chlorambucil is uncertain in CLL11, and the ICER of obinutuzumab + chlorambucil versus chlorambucil of >£28,000 may therefore be an underestimate. However, our clinical expert believes it is plausible that if chlorambucil is more effective at higher doses, then so too is obinutuzumab + chlorambucil. In this case, any bias in the effectiveness of obinutuzumab + chlorambucil versus chlorambucil in CLL11 is reduced, and the ICER of >£28,000 per QALY is more accurate. However, we are not aware of any randomised trials comparing chlorambucil or obinutuzumab +	We thank Roche for raising this good point. Amended on p16: "If, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab + chlorambucil versus chlorambucil is uncertain in CLL11." Added to p32: "If chlorambucil is more effective at higher doses, but obinutuzumab + chlorambucil is insensitive to the dose of chlorambucil, the estimated effectiveness of obinutuzumab + chlorambucil versus chlorambucil is uncertain in CLL11, and the ICER of obinutuzumab + chlorambucil versus chlorambucil of >£28,000 may therefore be an underestimate. However, our clinical expert believes it is plausible that if chlorambucil is more effective at higher doses, then so too is obinutuzumab + chlorambucil. In this case, any bias in the effectiveness of obinutuzumab + chlorambucil versus chlorambucil in CLL11 is reduced, and the ICER of >£28,000 per QALY is more accurate. However, we are not aware of any randomised trials comparing chlorambucil or obinutuzumab + chlorambucil at differing doses of chlorambucil, so we cannot be certain of

			chlorambucil at differing doses of chlorambucil, so we cannot be certain of any bias." Last paragraph of p28 corrected and updated: "The mean total dose of chlorambucil was far lower in CLL11 compared to the bendamustine RCT: 329 vs. 549mg (Section 1.2.2, p12). If chlorambucil is more effective at higher doses, the relative dosing in the two RCTs would bias the effectiveness of obinutuzumab + chlorambucil versus bendamustine in favour of obinutuzumab + chlorambucil. The ICER of obinutuzumab + chlorambucil versus bendamustine of >£44,000 may therefore be an underestimate." In p50, deleted: "However, if, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab + chlorambucil vs. chlorambucil is over-estimated in CLL11". p81, deleted "as our clinical expert believes,". p156 edits as above (i.e. per those documented for p28).	any bias." Last paragraph of p32 corrected and updated: "The mean total dose of chlorambucil was far lower in CLL11 compared to the bendamustine RCT: 329 vs. 549mg (Section 1.2.2, p12). If chlorambucil is more effective at higher doses, the relative dosing in the two RCTs would bias the effectiveness of obinutuzumab + chlorambucil versus bendamustine in favour of obinutuzumab + chlorambucil. The ICER of obinutuzumab + chlorambucil versus bendamustine of >£44,000 may therefore be an underestimate." In pp54 and 55, deleted: "However, if, as our clinical expert believes, chlorambucil is more effective at higher doses, the estimated effectiveness of obinutuzumab + chlorambucil vs. chlorambucil is over-estimated in CLL11". p87, deleted "as our clinical expert believes,". p155 edits as above (i.e. per those documented for p32).

Issue 4 Miscellaneous issues – Cost of adverse events

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
We note the discrepancies between our AE costs and the ERG's estimates from seemingly different versions of NHS reference costs 2012/13 and on the whole given that the cost differences are small are happy to use the ERG's version. However the ERG has used costs for all types of stay in hospital (i.e. elective and non-elective). Given that when AEs occur these are unscheduled, the relevant cost for each AE should relate to "non-elective stay" only. Section 5.4.10.5 page 153-155	For the majority of AEs this has little impact but for neutropenia and febrile neutropenia we suggest the cost should be changed from £5993 to either £4519 (non-elective long stay) or £1064 (non-elective short stay).	This correction will allow for a more accurate incorporation of cost of AEs within the economic model.	On advice from Roche we have used non-elective costs from the NHS Reference Costs (2011/2012 and 2012/2013). We used a weighted average of non-elective inpatient long stay and non-elective inpatient short stay costs. While this increases the ICER for the obinutuzumab+chlorambucil vs bendamustine comparison from £26,000/QALY to £27,000/QALY, this does not alter the base case ICER presented by Roche for three of the comparisons (obinutuzumab+chlorambucil vs rituximab+bendamustine or obinutuzumab+chlorambucil vs rituximab+chrloambucil or obinutuzumab+chlorambucil vs chlorambucil). As such we do not pursue this any further. Amended p23 Added: "Although we disagree with several of Roche's unit costs, the ICERs are only incrementally affected by this change." Amended p154-155 Deleted '…, as follows: … the PenTAG base case (Section 6.1, p154)." Added: "For anaemia, pneumonia, and thrombocytopenia (SA03F, haemolytic anaemia without CC; DZ11C, lobar, atypical or viral pneumonia without CC; and, SA12F, thrombocytopenia without CC respectively), we note that the HRG code stated in Roche's submission is no longer used following	On advice from Roche we have used non-elective costs from the NHS Reference Costs (2011/2012 and 2012/2013). We used a weighted average of non-elective inpatient long stay and non-elective inpatient short stay costs. While this increases the ICER for the obinutuzumab+chlorambucil vs bendamustine comparison from £26,000/QALY to £27,000/QALY, this does not alter the base case ICER presented by Roche for three of the comparisons (obinutuzumab+chlorambucil vs rituximab+bendamustine or obinutuzumab+chlorambucil vs rituximab+chrloambucil or obinutuzumab+chlorambucil vs chlorambucil). As such we do not pursue this any further. Amended p25 and 26 Added: "Although we disagree with several of Roche's unit costs, the ICERs are only incrementally affected by this change." Amended p154-156 Deleted '…, as follows: … the PenTAG base case (Section 6.1, p154)."	

			amendments to complication and comorbidity (CC) lists. We therefore refer to NHS Reference Costs 2011/2012 for the most recent available value and inflate to 2012/2013 using the inflation indices from the Unit Costs of Health and Social Care.(83) On advice from Roche we use a weighted average of non-elective inpatient long and short stay costs. While this increases the ICER for the obinutuzumab+chlorambucil vs bendamustine comparison from Roche's base case of £26,000/QALY to £27,000/QALY, it does not alter the base case ICER presented by Roche for the other three comparisons (obinutuzumab+chlorambucil vs rituximab+bendamustine or obinutuzumab+chlorambucil vs rituximab+chlorambucil or obinutuzumab+chlorambucil vs chlorambucil). As such we do not pursue this any further." Amended p28-32, p157-164 Deleted adverse events from PenTAG base case. Amended p20 (to reflect removal of AEs from the PenTAG base case): This constitutes Item 5 in the PenTAG base case (Section 1.5, p28).	Added: "For anaemia, pneumonia, and thrombocytopenia (SA03F, haemolytic anaemia without CC; DZ11C, lobar, atypical or viral pneumonia without CC; and, SA12F, thrombocytopenia without CC respectively), we note that the HRG code stated in Roche's submission is no longer used following amendments to complication and comorbidity (CC) lists. We therefore refer to NHS Reference Costs 2011/2012 for the most recent available value and inflate to 2012/2013 using the inflation indices from the Unit Costs of Health and Social Care.(83) On advice from Roche we use a weighted average of non-elective inpatient long and short stay costs. While this increases the ICER for the obinutuzumab+chlorambucil vs bendamustine comparison from Roche's base case of £26,000/QALY to £27,000/QALY, it does not alter the base case ICER presented by Roche for the other three comparisons (obinutuzumab+chlorambucil vs rituximab+bendamustine or obinutuzumab+chlorambucil vs rituximab+chlorambucil or obinutuzumab+chlorambucil vs chlorambucil). As such we do not pursue this any further." Amended p33-36, p156-159 Deleted adverse events from PenTAG base case.

				Amended p23 (to reflect removal of AEs from the PenTAG base case): This constitutes Item 5 in the PenTAG base case (Section 1.5, p28).

Issue 5 Availability of PFS HR between R benda and R Clb

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
The report states that data from the MaBLe study will become publicly available in October 2014 (Section 1.5 page 28). This is factually inaccurate. Section 1.5 page 28	This statement should be updated to reflect the fact that data from MaBLe are unlikely to be publicly available before EHA in June 2015.	The MaBLe data was due to be presented at the American Society of Hematology conference in Q4 2014. Following a delay in the closing of the study database and subsequent validation of the response data observed this is no longer the case. It is expected this data will be presented at EHA in June 2015.	p19 edited: "Veronique Leblond, lead author of the MaBLe study tells us that results will be available in October 2014. However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015." From p21, and p28 deleted: "However, we understand that PFS data should be available from October 2014." p77 added: "However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015" p91, deleted: "in October 2014".	p21 edited: "Veronique Leblond, lead author of the MaBLe study tells us that results will be available in October 2014. However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015." From p23, and p31 deleted: "However, we understand that PFS data should be available from October 2014." p84 added: "However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015"

			p145, deleted: "However, we understand that PFS data should be available from October 2014" p156 changed to: "Veronique Leblond, lead author of the MaBLe study tells us that results will be available in October 2014. However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015."	p96, deleted: "in October 2014". p143, deleted: "However, we understand that PFS data should be available from October 2014" p155 changed to: "Veronique Leblond, lead author of the MaBLe study tells us that results will be available in October 2014. However, Roche tell us in their factual accuracy comments that they believe they will be first available at the European Hematology Association (EHA) meeting in June 2015."

Issue 6 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
The statement 'It also does not model second line treatment with fludarabine' as a criticism of the Roche model. Section 1.3.2 page 20	The statement should be removed.	The criticism is inappropriate as the HTA patient population is patients for whom fludarabine is unsuitable.	We disagree. Our clinical advisor suggests that after good response on 1st-line treatment, patients may become sufficiently fit to tolerate fludarabine. Indeed, this was also assumed in the bendamustine model for the NICE STA. Amended p20 Sentence changed to: "It also does not model second line treatments such as FCR, and bendamustine."	We disagree. Our clinical advisor suggests that after good response on 1st-line treatment, patients may become sufficiently fit to tolerate fludarabine. Indeed, this was also assumed in the bendamustine model for the NICE STA. Amended p23 Sentence changed to: "It also does not model second line treatments such as FCR, and bendamustine."

Issue 7 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
The statement does not make sense: 'At a willingness to pay of £30,000 per QALY, obinutuzumab + chlorambucil and chlorambucil provide the best value for money, and offer very similar value. Obinutuzumab + chlorambucil is poor value. Rituximab + chlorambucil offers slightly worse value.' Section 1.5.3 page 32	The statement should be clarified.	In this statement obinutuzumab + chlorambucil is described as providing the best value and as poor value at the same time. This appears to be an error, or if not is a very confusing way of summarising the results of the economic evaluation. It would be preferable to clarify or revise this statement.	Thank you for spotting this error. "Obinutuzumab + chlorambucil is poor value." deleted from p32 and p161.	Thank you for spotting this error. "Obinutuzumab + chlorambucil is poor value." deleted from p36 and p160.

Issue 8 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
On page 15 the following statement needs alteration 'In addition, the obinutuzumab + chlorambucil arm had a	The word obinutuzumab (bolded) should be changed to rituximab.	The correction is necessary for the accurate meaning of the sentence as the obinutuzumab + chlorambucil arm is compared to the	Amended p15, p102: Corrected as advised.	Amended p17, p99

statistically significant greater event-free survival (p<0.0001 both), end of treatment response (p<0.0001 versus both chlorambucil and rituximab + chlorambucil), MRD-negative rate (26.79 [19.5 - 34.1] versus chlorambucil and 23.06 [17.0 - 29.1] versus **obinutuzumab** + chlorambucil), best overall response (p<0.0001 versus chlorambucil and p=0.0001 versus **obinutuzumab** + chlorambucil), disease free survival (p<0.0001 versus chlorambucil and p=0.0475 versus **obinutuzumab** + chlorambucil), and time to new treatment (p<0.0001 versus chlorambucil and p=0.0018 versus **obinutuzumab** + chlorambucil) compared to chlorambucil and rituximab + chlorambucil.' Section 1.2.1.1 page 15		rituximab + chlorambucil arm, not to itself. .		

Issue 9 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
'The incidence of IRRs (infusion related reactions), neutropenia, thrombocytopenia, leukopenia, **anaemia, pyrexia, and nasopharyngitis** was higher (> 5% difference) in the obinutuzumab based arm than in the rituximab + chlorambucil or chlorambucil arms of the study.' Section 1.2.1.1 page 15	The words anaemia, pyrexia and nasopharyngitis (bolded), should be removed from this statement as there is not a >5% difference in the incidence of these adverse events between any of the treatment arms as per the table below (sourced from Table B30 and Table B31 of the Roche submission).	The difference in the incidence of anaemia, pyrexia and nasopharyngitis is not >5% between any of the treatment arms as per the table below (sourced from Table B30 and Table B31 of the Roche submission. This correction is necessary for the accurate reporting of data.	Thank you for spotting this error. Amended p15, p74, p93 We agree that the sentence should be amended as proposed: "The incidence of IRRs (infusion related reactions), neutropenia, thrombocytopenia, leukopenia, was higher (>5% difference) in the obinutuzumab based arm than in the rituximab + chlorambucil or chlorambucil arms of the study."	Thank you for spotting this error. Amended p18, p81, p99 We agree that the sentence should be amended as proposed: "The incidence of IRRs (infusion related reactions), neutropenia, thrombocytopenia, leukopenia, was higher (>5% difference) in the obinutuzumab based arm than in the rituximab + chlorambucil or chlorambucil arms of the study."

Issue 10 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
'We believe the best estimate is 0.76, compared to Roche's estimate of **68**. Section 1.3.3 page 21	The number 68 should be corrected to 0.68.	The correction is necessary for the accurate reporting of data.	Amended p21 Corrected as advised.	Amended p23 Corrected as advised.

Issue 11 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
On pages 102 and 146 Figure 21 and Figure 27 have a different line thickness compared with the original figures provided in the submission Section 5.2.5.1 page 102 and Section 5.4.8.2 page 146	The original figures presented in the Roche submission should be used.	This change will facilitate the reading of the figures.	Amended p102 and 146 We recreated these figures from Roche's model to make the axes titles more legible and provide the committee with a PFS graph for all arms included in the model (Figure 21). As we do not believe the line thickness to be a point of factural accuracy and believe the figures are clear as they are, we have not altered them. However, we thank you for raising to our attention that we were not explicit in stating that these figures were recreated by the ERG and therefore have included them in our Errata to make this explicit (pages 102 and 146).	Amended p107 and 144 We recreated these figures from Roche's model to make the axes titles more legible and provide the committee with a PFS graph for all arms included in the model (Figure 21). As we do not believe the line thickness to be a point of factural accuracy and believe the figures are clear as they are, we have not altered them. However, we thank you for raising to our attention that we were not explicit in stating that these figures were recreated by the ERG and therefore have included them in our Errata to make this explicit (pages 107 and 144).

Issue 12 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
Cost of Rbenda is incorrect at £7,000. Section 1.3.5.1 page 21	The cost of Rbenda should be corrected.	The cost of RClb is reported as £10,000, as £300 for Clb and as £7,000 for benda. Therefore, the price	Amended p21 Changed to £16,000 (from Table 33).	Amended p24 Changed to £16,000 (from Table 33).

		of £12,000 for Rbenda is not accurate.		

Issue 13 Miscellaneous issues

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response	
'We note that some discrepancy between Goede et al's paper and the submission exists in relation to the description of the number of countries and number of centres involved in the trial. Goede et al describe the trial as "conducted in 26 countries; 189 centres enrolled patients" (Goede et al, pp 2), while in the Manufacturer's Submission Roche state that study CLL11 was "conducted in 250 centres in 25 countries" (Source: Roche Submission, Section 6.7.2, Table B23, pp80; Section 6.10.2, pp123). There is a further inconsistency in reporting, with Goede et al reporting "this global study was conducted in 269 centres of 26 countries" in their supplementary appendix (4)' Section 4.1.4 page 53	The following values should be used: 269 centres and 26 countries (as per Goede et al. 2014).	This discrepancy is due to differences in the number of countries and centres who enrolled patients versus those countries/centres who opened the study and differences with the number of centres enrolling into stage1a of the study versus stage 2 which continued enrolment once stage 1a was closed.	We thank you for this clarification and have added a paragraph explaining this clarification. Amended p53 "Roche have clarified that this discrepancy is due to differences between centres that enrolled patients and those which opened the study, as well as the number of centres enrolling into different stages of the study. It therefore appears that the figures cited in Goede at al. (2014) were correct and that the study was conducted in 26 countries, with 269 centres (4)."	We thank you for this clarification and have added a paragraph explaining this clarification. Amended p58 "Roche have clarified that this discrepancy is due to differences between centres that enrolled patients and those which opened the study, as well as the number of centres enrolling into different stages of the study. It therefore appears that the figures cited in Goede at al. (2014) were correct and that the study was conducted in 26 countries, with 269 centres (4)."