ScHARR-Technology Assessment Group - Response to comments

Forest Laboratories

Comment	Assessment Group response
This document addresses the request to provide comments on the Assessment Report developed by the Assessment Group, School of Health and Related Research (ScHARR) Sheffield on behalf of NICE.	No response required
The economic analysis submitted by Forest Laboratories to NICE was not intended to be a full and comprehensive economic analysis, principally because Forest Laboratories were aware of the difficulties associated with the development of health economic evaluations for cystic fibrosis interventions - difficulties highlighted in the Evidence Review Group (ERG) report. We expected that the analysis developed by the ERG during the review process, reflecting their greater resources and expertise, would take advantage of the analysis provided by Forest Laboratories in building a more sophisticated assessment. Our intention was to contribute to the review process where Forest Laboratories could add insight (for example through the utility mapping study), rather than present an exhaustive analysis.	Any party submitting a health economic model to NICE as part of the Technology Appraisal Process should expect that model to be subjected to scrutiny and critical review. This is a key role of the Assessment Group. We identified a number of problems with this analysis and used these issues to inform the design of the independent Assessment Group model. Unfortunately, the mapping analysis did not provide any information regarding the relative benefit of colistimethate sodium DPI over nebulised tobramycin and so we did not use this study.
There was no comprehensive pathway analysis that would illustrate the context in which cystic fibrosis (CF) treatments are used in practice (e.g. Tobi off-months where other antibiotic treatments may be required)	It is not entirely clear is meant by a "comprehensive pathway analysis", however Forest did not present such an analysis in their submission. We elicited a conceptual model from our clinical experts and current guidelines on the use of antibiotic treatments produced by the UK CF Trust Antibiotic Working Group. This information formed the basis of the economic model.
Use of Colobreathe has not been shown to lead to resistance in the COLO/DPI/02/06 trial, whereas TOBI leads to an increase in minimum inhibitory concentration (MIC). The analysis provided by the ERG report does not include the cost implications of increased IV antibiotic use.	It is unclear if and how resistance would impact upon the need for additional antibiotics. We made this point clear on Page 122 of the Assessment Report and we explicitly stated that these potential impacts were not included in the economic analysis. It should be noted that the Forest model did not include this factor either.
The model that was developed appears to provide a simulation of a cohort of patients aged 21 and above, which we believe inaccurately reflects the population to which the reviewed interventions are intended. Therefore we believe that: The model should have included the younger population, reflecting both the clinical trial population and the patient profile in clinical	The model is a cohort model rather than a simulation. We agree that the model does not reflect the distribution of age ranges of patients recruited into COLO/DPI/02/06 as it uses a mean starting age of 21 years. By definition, cohort models reflect the mean characteristics of the cohort rather than the distribution of characteristics of individuals within that cohort. Importantly, as the Assessment Group

practice; the assumptions used by the assessment group exclude over 40% of the patient population enrolled in the Colobreathe trial. Furthermore, the excluded group also represents those in whom Colobreathe similarly shows clinical benefit.	model assumes that survival is unaffected by colistimethate sodium DPI, age only influences treatment duration within the model. We could have included a younger cohort however this would have produced less favourable results for colistimethate sodium DPI and would not change the conclusions of the analysis. If required, we would be willing to undertake such an analysis for the Appraisal Committee.
Despite patient level data being requested by the assessment group, it would appear that no patient level analysis was performed. A patient level simulation rather than a cohort analysis may have been a better approach, given the heterogeneous patient population, in age and other characteristics.	The only patient-level data provided by Forest relates to FEV_1 change between baseline and the end of the (24 weeks). No other patient-level data file was provided by Forest during the appraisal. All of these data were used to inform the transition matrices for colistimethate sodium DPI and nebulised tobramycin. In the absence of information relating to other covariates, the only benefit patient level simulation would afford is the more accurate representation of other-cause mortality (see previous point).
The TOBI population in the Colobreathe trial only included TOBI tolerant patients, resulting in an inaccurate representation of the cohorts compared in the analysis.	It is important to separate out criticisms of the model from criticisms of the evidence base. This is a problem with the design of the trial. The Forest model is based on the same trial population and the same comparator.
The use of absolute FEV_1 values may not provide an accurate estimation of clinical benefit Rather, we suggest that the relative value of FEV,% also be considered to take into account differences in patient characteristics, and the effect of aging - in cystic fibrosis there is much debate about the relevant endpoint. which we do not feel this review has clarified.	It should firstly be noted that the Forest model uses exactly the same absolute FEV_1 data as the Assessment Group, albeit assuming a relationship with mortality rather than HRQoL. We do agree there is considerable uncertainty around the validity of using FEV_1 values as a predictor for any other outcome (e.g. mortality or HRQoL). This is why we presented a review of the validity of FEV_1 as a surrogate for HRQoL and mortality. We did not have any additional information except for FEV_1 at baseline and at the end of the study (i.e. any other covariate) and so we had little option but to extrapolate on this basis. Our sensitivity analysis suggests that the conclusions hold even if no extrapolation is undertaken.
It appears that mortality has not been built into the model, despite the existence of several published studies linking FEV, to mortality: The assessment appears to deny a link between FEV_1 and mortality, which was first demonstrated in the Kerem et al. study.' A more recent study by Goerge et al (2011)3 highlights the correlation between FEV, and mortality. "On the basis of work by Kerem et al in 1992, a forced expiratory volume of one second FEV1 of less than 30% preclicted has been generally accepted as the level of lung function at which median mortality within two years is greater than 50%.' Furthermore, this study compared mortality of	This is inaccurate. The model does include other-cause mortality for CF patients based on Dodge *et al*. We do not deny that a link between FEV_1 and mortality might exist, but we did not include this as the evidence supporting this relationship over the whole range of FEV_1 values is generally weak and should it exist, we do not believe that it can be reliably quantified on the basis of absolute FEV_1 values without consideration of a plethora of potentially relevant covariates. As noted above, we did not have access to any data on these other covariates.

patients with <30%, of predicted FEV, between two datasets (1990 and 2003). "Median survival for patients who entered the cohort most 'recently (2002-3) was 5.3 years, more than twice that for those who entered the study in the early 1990s, when median survival was less than two years, similar to the value published by Kerem et al in 1992." Although the available data and FEVI-mortality correlation may have changed over time (reflecting improvements in the clinical management of CF), there is still a clear link between FEV r and mortality. A disease model developed by Buzzetti et al." also used the correlation between FEV! and death to accurately predict mortality rates in their validation sample.	It should be noted that the Forest submission initially referred to the FEV_1→mortality relationship as a "suggestion" rather than a "demonstration." Most importantly, the population evaluated in George *et al* is substantially different to the patient population recruited into COLO/DPI/02/06 – In George et al, an initial FEV_1<30% was an entry criteria. This represents less than 10% of COLO/DPI/02/06 trial population. It is noteworthy that the Buzetti model referred to by Forest also included other covariates alongside FEV_1.
The Assessment Report commented on the low number of patients available in the estimation dataset (93 patients used for utility mapping purposes), yet it appears that the utility data used in the *de novo* analysis by the ERG was derived from a pool of 75 patients.	COLO/DPI/02/06 did not include any measurement of HRQoL using a preference-based measure. Consequently, HRQoL estimates had to be derived from external sources and some assumptions between HRQoL and health state had to be made. We believe that the direct elicitation of EQ-5D utility by FEV_1 stratum is more appropriate than an indirect mapping approach which cannot differentiate between either treatments or health state. This decision was therefore based on a judgment that the direct EQ-5D study was more *relevant* than Forest's mapping study.
Furthermore, the mean age of patients used to derive utilities in tile ERG model was 28 years old compared to an average of 21.1 years in the Colobreathe trial population.	We agree that the populations in COLO/DPI/02/06 and the Bradley EQ-5D study are not identical. It is unclear how we could rectify this.
It appears that the costs of antibiotics taken during the off months of TOBI treatment have not been captured in the model. In addition, the costs of replacing nebuliser spare parts and other consumables have not been accounted for in the ERG analysis.	The model includes the costs of antibiotics when consumed. As noted in Table 40 (page 111) we did not include cyclical switching between colistimethate sodium and tobramycin as there was no evidence of either safety or efficacy. The Forest model did not include this either. The results of the model do include a notional cost of consumables (see Page 119). The Forest model did not include this.
Although patients numbers are limited the proposed model should have included transplantation and associated downstream costs (as well as mortality), which contribute significantly to the economic burden of CF treatment. It should be noted that those patients who received lung transplantation required 56 weeks to regain baseline FEV_1 function.	We did include transplantation as an event as this will be an option for a small number of patients. However, as there were no lung transplants in the COLO/DPI/02/06 trial, and therefore no comparative evidence of a difference between treatment groups, the incremental cost is zero and therefore has no impact on the ICER whatsoever. The Forest model did not include this.
An attempt to estimate treatment administration time and the effects on carers would have been useful to better quantify the cost of treatment. Reduction in carer and supervision time could have a significant impact on loss of productivity	The Assessment Group model did not include these factors. We highlighted that treatment administration time may be important on Page 122. However the COLO/DPI/02/06 trial did not measure treatment time or carer effects. We are unaware of any reliable

and therefore on the costs attributed to the interventions. A recent paper by Sansgiry *et al* commented on the importance of including indirect costs associated with the disease when modellinq.	comparative source that could currently be used to estimate these potential factors. With respect to the point about indirect costs and lost productivity, the Sansgiry *et al* paper is based on a US setting – the NICE Reference Case does not include indirect costs (see Section 5.5.11 of the NICE Methods Guide). The Forest model did not include any of these factors.
The impact on carer's health related quality of life and time was not considered in the analysis. This is likely to represent an important cost to carers and potentially in some cases, where paid carers are involved, to Personal Social Services (PSS) - part of the NICE base case.	Carer's HRQoL was not included in either the Assessment Group model or the Forest model. In the absence of any evidence, it is unclear how this could have been incorporated into the analysis with any degree of credibility.
The probabilistic sensitivity analysis conducted by the assessment group model suggests that Colobreathe is not cost effective for the majority of the scenarios investigated. However the COLO/DPI/02/06 trial demonstrated non-inferiority compared to Tobi; the results of the cost- effectiveness analysis should also indicate a similar trend, yet the initial analysis shows differences that we believe do not reflect the outcomes of the Colobreathe trial. Furthermore, the sensitivity analyses performed by the assessment group are unlikely to reflect the uncertainty surrounding the trial since none of the alternative analyses represent non-inferiority (ICER approaching 0).	This suggests a misunderstanding regarding the appropriate use of evidence in health economic models. Non-inferiority does not mean that two treatments are identical – it means that the experimental intervention is not statistically significantly worse than the comparator by more than a specified margin. The patient-level FEV_1 data provided by Forest indicate a slight overall worsening in FEV_1 and this is reflected in the FEV_1 transition matrices and the model results (hence the estimated QALY loss resulting from colistimethate sodium DPI). It should also be noted that if the two treatments were truly identical (and there was some cost difference), the ICER would tend towards plus or minus infinity rather than zero.
Overall, the analysis provided by the assessment group and the presentation of key results such as the ICER does not seem sufficiently robust and clear. It is likely that other reviewers of this report may be led to misinterpret the findings. It is our view that the conclusions drawn from this analysis should be considered as speculative. We hope that the Assessment Committee will take into account the contents of this letter along with the need for better treatments for cystic fibrosis, the clinical evidence in support of Colobreathe, and the wider benefits for both patients and caregivers. We also hope that the Assessment Committee will place less weight on the modelling as the Evidence Review Group has already commented on the difficulties of modelling this condition.	Our report was peer reviewed internally by two clinical peer reviewers, a methodological peer reviewer and three experts working as part of the review team. It was later peer reviewed by a further four external peer reviewers. We have responded to all peer review comments. Like any model-based analysis, the economic results produced by the model should be interpreted in light of the limitations of the evidence base used to inform that model. We have highlighted these problems throughout the report. The Assessment Group is of the view that there are difficulties and challenges in modelling cystic fibrosis however the conclusions that can be drawn from the *de novo* economic analysis are clear.

Novartis Pharmaceuticals

Comment	Assessment Group response
Key comments (Novartis response page 1)	
The TAR questions the non-inferiority conclusion of the EAGER trial (TOBI Podhaler vs TOBI nebuliser solution) due to a number of factors which are addressed below in detail. EAGER is the largest Pa clinical trial available and provides robust, unambiguous evidence that these two formulations, which have the same molecular structure and deliver similar amounts of tobramycin to lung, offer a comparable safety profile and non-inferiority with respect to efficacy. This evidence has been published in the peer-reviewed Journal of Cystic Fibrosis in January 2011 and accepted by the EMA in July 2011.	The Assessment Report clearly highlights the uncertainties and ambiguities within the trial results and this is our role. In particular we note the lack of usable data relating to harder measures of clinical outcomes (e.g. exacerbations) and the use of an ITT analysis without imputation in the primary analysis given the high degree of attrition and amount of missing values which are unaccounted for. Data submitted in Novartis' response to the TAR relating to LOCF analysis were not made available to the Assessment Group, even though these were requested. It is also unclear which time point (20 or 24 weeks) these data relate to. The Assessment Group is not obliged to agree with the EMA, as the regulatory process serves a different role to NICE's appraisal process.
TOBI Podhaler offers convenience and reduced administration time in comparison to TOBI nebuliser solution. These benefits are discounted throughout the TAR and discussion around the off-label use of alternative nebulisers, which are of unproven efficacy and safety, is misleading.	The appropriate interpretation evidence relating to convenience and administration time is unclear. Whilst satisfaction was higher for tobramycin DPI so too was attrition.
A substantial amount of clinical data for the comparators and interventions outlined in the Final Scope has been excluded from the TAR's assessment (eg, the complete exclusion of the most recently launched tobramycin Pa product, Bramitob). The evidence base presented to the Committee is therefore incomplete.	Our reasons for not presenting other comparators in a network meta-analysis are clearly described in Appendix 4.
Given the comparability of the efficacy and safety profiles for TOBI Podhaler to comparator products, [redacted].	We disagree. Achieving non-inferiority is not the same as demonstrating that two compounds are equivalent. Cost-minimisation masks the true uncertainty surrounding comparative clinical benefits and does not form part of NICE's Reference Case. The decision problem is best addressed using an analytical framework which quantifies the uncertainty surrounding the incremental costs and effects of competing interventions i.e. cost-utility analysis, rather than one which inherently assumes that the interventions are exactly equivalent.
Specific bullet point responses (Novartis response page 2 onwards)	
Novartis response, Point 1 The peer-reviewed EAGER trial conclusively	It is our role to critically appraise the available evidence and to highlight uncertainties and

supports the non-inferiority of TOBI Podhaler to TOBI nebuliser solution with respect to efficacy and also reports a comparable safety profile between the two EMA-approved pseudomonas treatment options.	ambiguities therein. This is what we have done. In addition, the assertions made by Novartis regarding UK clinical experts are not accompanied by details of which experts were consulted or what their views were.
Point 1 bullet#1 Retrospective application of the EMA recommendations to assess robustness of a clinical trial which pre-dates these guidelines	This argument is inappropriate. Whilst the application of the EMA recommendations to this trial is retrospective, non-compliance with these recommendations is still useful for highlighting potential weaknesses and biases in the available data.
Point 1 bullet#2 Unfounded statistical criticism of the EAGER trial	Our statistical criticisms of the EAGER trial are appropriate. We requested ITT analyses with imputation for missing data over the course of the appraisal but these were not provided by Novartis. The data presented by the manufacturer in this response to NICE were not previously made available to the Assessment Group, but in fact supports our concern that the analysis without imputation overestimates the treatment effect, in that the effect point estimate is a negative value (though still non-inferior) as opposed to a positive value in the analysis presented in the manufacturer's original submission to NICE. This could potentially have underestimated the ICER, had this point estimate been used for the purpose of economic modelling. Unfortunately, the Novartis submission did not include an economic model. The comparison to the COLO/DPI/02/06 trial statistical analyses is reasonable. Novartis are incorrect in that the primary and secondary analyses presented by Forest were not *post hoc*, nor were the sensitivity analyses excluding Ukrainian data used to draw any concluding remarks by either Forest of the Assessment Group.
Point 1 bullet#3 Unsubstantiated conclusions regarding trial design and findings: FEV1%, resistance, cough, exacerbations, chronic lung function definition and trial duration	The Assessment Group sought the opinion of numerous clinical advisors throughout the assessment, plus other clinical peer reviewers, all of whom were satisfied with the validity of the conclusions of the assessment. (1) FEV_1% predicted – Regardless of the common usage of FEV_1% as an outcome measure, the Assessment Group's clinical advisors commented on the weaknesses associated with FEV_1%. In addition, the data presented in the EAGER trial does not meet the EMA guidelines in two ways: (a) it is not supported by hard clinical outcomes such as

	exacerbations, and (b) patients were only followed up for 24 weeks and some data were only reported at 20 weeks. As such, the weaknesses of FEV_1% need even closer scrutiny as the conclusions of non-inferiority within the EAGER trial rest solely on this outcome. The Assessment Group's discussion of this issue is entirely appropriate. (2) Resistance – contrary to the manufacturer's interpretation of our report, the Assessment Group make it clear on several occasions that measures of resistance have unknown clinical implications. (3) Cough – [redacted] Novartis have not provided robust evidence to either support or refute this possible relationship. (4) Exacerbations – The Assessment Group requested data relating to exacerbations but these were not provided by Novartis before the Assessment Report was due for submission (data later provided for a PAS analysis). Novartis later clarified that exacerbation data were not specifically collected in EAGER. As such, the best alternative is probably to use lung disorder as a proxy, as indicated by the EAGER trial publication (Konstan *et al*). This is what we have done. We stated that the rate of lung disorders was higher in the DPI group because it was. (5) Chronic lung infection – the Assessment Report based the statement about patient selection on the available evidence. Novartis' statement in the response to the TAR that all patients experienced chronic infection throughout the trial was not made in the submission, but would constitute a confirmation that all patients were chronically infected, and would effectively satisfy EMA definitions of chronic lung infection. The definition of chronic lung infection would appear to be variable; the quote given by Novartis is somewhat paraphrased. The complete quote reads: "Chronic infection with P. aeruginosa is defined in this document as the regular culture of the organism from the sputum or respiratory secretions, on 2 or more occasions extending over 6 months or a shorter period if accompanied by a sustained rise of anti-Pseudomonal antibodies (Hoiby, 1974 [III]; Brett et al, 1992 [III]). Recently a more precise definition into 4 groups "chronic", "intermittent", "free" and "never" has been suggested (Lee et al, 2003 [III]). It is now well established that the

	clinical state can worsen when chronic P. aeruginosa infection becomes established." The Assessment Group does not feel that this constitutes strong evidence that UK clinical practice differs from the EMA definition. Rather, it implies that there is no established consensus. The Assessment Group feel that it would be useful for the Appraisal Committee to seek further clinical opinion on this matter, as Novartis' point may be valid. The important issue is what is generally used in the UK now, not what has been used historically. It is possible that the EMA guidelines, which are more recent than the source quoted by Novartis, may influence UK practice. (6) Treatment duration – this is useful observational evidence and should be considered by the Committee. Note that this study was only published in abstract form in October 2011. Ultimately however it does not change the uncertainty in the results of the EAGER trial.
Point 1 bullet#4 Statements challenging comparable safety profiles of TOBI Podhaler and TOBI nebuliser solution: Clinical significance of differing discontinuation rates	We have included the relevant safety data from the EAGER trial (Table 40 in the TAR). No statistical analyses were provided and so our description of the evidence is necessarily based on numerical values with appropriate caveats. The data presented in Novartis' response were not presented in their original submission, and are not reported in full here. It is unclear what tests have been performed on the data, and no significance values have been presented. The discussion is speculative, though the Assessment Group feels that Novartis' suggestion that the open-label nature of the trial may account for some of the differences between drop-outs appears reasonable. Whether it accounts for all of the difference remains unclear and it is therefore reasonable to question this.
Point 2 (page 7 Novartis response) References to newer, faster nebulisers are unacceptable for tobramycin since this reflects an unproven off-label use with limited data indicating substantially reduced delivery.	The Assessment Group agree that there is little data relating to the efficacy of the PARI LC Plus, but as faster nebulisers are being used more often in practice, it was necessary to make this point.
Point 3 Omission of data which biases the interpretation of the COLO/DPI/02/06 trial	Novartis' argument that the run-in period for tobramycin represents a source of bias has several counter-arguments: (i) The crux of this argument is whether tobramcyin run-in period may still be having an effect (has not washed out) once treatment with Colobreathe commences. No evidence has been presented by Novartis to show exactly what the wash-out period for tobramycin is once treatment has ceased. (ii) Novartis have not demonstrated that a peak

	occurs for Colobreathe. (iii) Most patients in the EAGER trial were not tobramycin naive (around 75%-80% had received tobramycin in the previous 3 months, 25% had received it one month previously), and if the argument is that tobramycin does not wash out after a month, then the comparison of TobiPodhaler to nebulised tobramycin is also subject to the same criticism levelled at COLO/DPI/02/06 trial, although perhaps to a lesser extent. (iv) Novartis state that a switch from tobramycin to aztreonam induced a peak in response (though this statement is not supported with a reference), and imply that a similar peak could have been seen for the switch from tobramycin to Colobreathe. This peak is not seen in McCoy 2008, where patients switch from 28 days on TIS run-in to aztreonam. A peak is seen, however, in Retch Bogart 2008, where patients are switched to aztreonam when they have received no tobramycin for 56 days. It seems that the peak may only occur for aztreonam when patients have been antibiotic-free for more than a month. (v) An FEV_1% peak when aztreonam treatment commences does not imply the same for colistimethate treatment.
Point 4 Microbial response data unavailable for main comparator intervention	Our clinical advisors informed us of problems with this measure, and whilst it does appear in the EMA guidance, lower emphasis has been placed on this outcome in the assessment report accordingly.
Point 5 Lack of consideration of the available evidence	The Assessment Group investigated the network of evidence in detail, as described in Appendix 4 of our report. It was not possible to include Bramitob in the network for two reasons: (1) The comparator in the Bramitob trial was placebo. Trials that also used placebo that could have allowed construction of a viable network were excluded from the network because they were performed in children (Konstan *et al*, EVOLVE), were in patients with less severe disease (Nasr 2006) or did not clearly have a chronic infection (Ramsey 1999). The data available for Ramsey 1999 does not mention any selection criteria for chronic infection, and does not even state that patients are chronically infected. Patients only had to have one positive culture, which could easily lead to patients with intermittent infection being included. (2) The Bramitob trial was only conducted for 4 weeks. Due to the FEV_1% peak seen in the first 4 weeks of tobramycin administration, this trial is not sufficiently long to estimate long-term efficacy. The Assessment Group chose to consider both outcome time points, as patients on tobramycin will

	not always benefit from the full effect of "on-treatment" efficacy. Novartis appear to have misunderstood the Assessment Group's point on page 55, where we state that [redacted] This is a within-arm comparison, not a between-arm comparison as Novartis appear to have interpreted it. Our point here is that data is on a downward trend from 20 to 24 weeks in all arms, thus showing the need for consideration of both timepoints, and supporting the need for longer-term data to investigate whether this overall downward trend continues.
Point 6 Benefits of TOBI Podhaler are not adequately presented within the TAR	Any issues with contamination will have affected the efficacy and adverse event results within the trial and did not require separate consideration. Other considerations listed by Novartis such as no requirement for cold storage or electricity were not delineated in the manufacturer's submission. Had preference-based quality of life measures been used to assess the benefits of the competing treatments, this would have provided some evidence to either support or refute Novartis' claims. Otherwise, these benefits are not evidenced and can only be considered in a non-quantitative fashion by the committee. The Assessment Report already gives a balanced view: *"Nebulisers with quicker delivery time (around 5 minutes), such as the PARI eFlow jet nebuliser are now on the market and are in widespread use (personal communication: Dr Diana Bilton, Consultant Physician / Honorary Senior Lecturer, Department of Respiratory Medicine, Royal Brompton Hospital). However, these quicker nebulisers may still require time to maintain (cleaning) and assemble. With respect to the relative advantages and disadvantages, it remains unclear whether the reduced treatment burden and improved treatment satisfaction scores would remain significant when compared to the newer, quicker nebulisers."*
Factual inaccuracies (Novartis reponse page 10-11)	
Throughout the document TOBI Podhaler is referred to as TOBI + Podhaler which implies that the therapy is TOBI (tobramycin nebuliser solution) plus an inhaler, when in fact it is a different formulation i.e. tobramycin dry powder. The TAR should reflect the trade name, TOBI Podhaler, when discussing the drug and the term Podhaler inhaler when discussing the inhaler device. For example on pages 39 and 42, the following statement is incorrect: "tobramycin DPI used..... with the TOBI	The incorrect naming of the device and drug occurs only a few times in comparison to the total number of times the intervention is referred to. This is a small error and does not affect the assessment.

Podhaler device". On page 37: "TOBI used in conjunction with the Podhaler...". These both should state TOBI® Podhaler® used with the Podhaler® device as TOBI used in conjunction with the Podhaler is an altogether different formulation.	
As stated within the Novartis Manufacturer Submission, [redacted].	Not a factual inaccuracy. The Assessment Group were unable to find the information referred to relating to study 2303 and the submission states that this study is ongoing.
Page 5 presents the FEV_1 transition strata (99-70%, 69-40%, <40%) which is of questionable relevance given the labelling for 25-75% predicted	Not a factual inaccuracy. The definition of states was driven by the EQ-5D study funded by Novartis.
Page 13 discussions regarding renal transplant should also note that colistin is also nephrotoxic.	Not a factual inaccuracy. Whilst Colistin is nephrotoxic at high concentrations, the correlation of decreasing renal function is associated with aminoglycocide use, rather than colistin use alone. See Al-Aloul et al (2005) and Masoli et al (2005)
Page 14, figure 2 lacks the legend for gender.	Not a factual inaccuracy, just an omission. The omission of the legend has been rectified for the monograph.
Page 17 states, "The presence of a microbial infection is ascertained using sputum colony density". Presence of microbial infection can be ascertained qualitatively without assessing sputum colony density	We agree – to be more accurate we could have stated "can be" rather than "is". This does not influence the validity of our conclusions.
Page 17 states, "Sputum samples can be obtained either spontaneously (through expectoration) or can be induced by the use of throat swabs...". Throats swabs do not collect sputum. They assess bacteria but are done when sputum is not obtained.	We agree – this is a minor inaccuracy that does not affect the conclusions of the report.
Page 22, figure 6 incorrectly refers to salmeterol as an inhaled steroid. This figure and text could perhaps also note that some patients do not nebulise due to the burden despite having chronic Pa and instead use IVs, with the attendant risks, as per the text in the paragraph below the figure.	We agree – this has already been rectified for the monograph. It does not affect the conclusions of the report.
Page 24 incorrectly states that "Since 1st April 2011,... has adopted a 'payment by results tariff'." The national currency is not due for full implementation until April 2013.	Not a factual inaccuracy. This was taken directly from a press release from the CF Trust. "Adopted" is not necessarily the same as "fully implemented". We purposefully used their wording.
Page 26 does not clearly state that the post marketing events listed are for TOBI nebuliser solution and not TOBI Podhaler.	Novartis' statement is incorrect. The possible adverse events are listed for TobiPodhaler on the EMC as indicated by the Assessment Report text.
Page 35 presents the study characteristics which suggests that the COLO/DPI/02/06 trial (n=380) is "slightly smaller" than the EAGER trial (n=533). The Colobreathe EPAR reports that 66 of the 374 ITT patients (Ukrainian population) were excluded to reach the primary non-	Novartis' statement is incorrect. Non-inferiority was met for Colobreathe when all patients were included in the ITT analysis (LOCF), using a non-parametric analysis as normality was not met under logarithmic transform. The Ukrainian data were not excluded.

inferiority endpoint. Data therefore presented to support the non-inferiority conclusion for Colobreathe are based upon a reduction of 17% of their ITT patient population and in total contains 42% less patients than the EAGER trial.	
Page 38, table 4 is incomplete as it does not state that all patients in COLO/DPI/02/06 were required to have 2 cycles of TOBI nebuliser solution prior to randomisation: Trial duration was not 24 weeks but instead should reflect 16 weeks intervention with TOBI cycles, then 24 weeks.	Not a factual inaccuracy. This is a matter of interpretation. The Assessment Group have chosen to represent the data in the way they see most appropriate.
Page 45, table 8 quotes incorrect percentages for the reasons for withdrawal in EAGER. Whilst the EAGER trial intervention column n numbers are correct the following percentages are incorrect: (1) Other figures have not been rounded up, therefore for consistency, the "consent withdrawn "should state 7.8% instead of 8.0%. (2) The administrative reason" is quoted as 1.2% instead of 0.3%. (3) The "protocol violation" is quoted as 0.3% instead of 1.9%.	Minor errors agreed
Page 47 states that MIC50 is reported for EAGER. This should read mean peak MIC. Page 47 states that the revised BSAC breakpoints were published in 2011, following completion of the EAGER trial. The text below omits that it is therefore not feasible for EAGER to retrospectively adhere to these breakpoints. "Both trials provided these data at the old British Society for Antimicrobial Chemotherapy (BSAC) breakpoint of 8mg/L for resistance, but only COLO/DPI/02/06 reported this outcome at the new breakpoint issued by BSAC of 4 mg/L."	The COLO/DPI/02/06 trial was also conducted before the BASC breakpoint was updated.
Page 48, Table 10 should include that Knudson 1976 was used to calculate FEV_1% predicted.	This information was not contained within either the manufacturer's submission or the relevant journal publication and was therefore not included in the table.
Page 51, Table 11 contains multiple incorrect entries for the EAGER study. "Was primary endpoint appropriately chosen" Should read YES as per guidance received from EMA (EPAR, 2011). "If a study endpoint is the efficacy of respiratory function, was the endpoint appropriate" Should read YES as per guidance received from EMA (EPAR 2011). "Is the study classified as a confirmatory study" Should read YES as phase III taken together with EVOLVE study are confirmatory studies (EPAR 2011).	We do not agree with some of the conclusions the EPAR has reached. The EPAR for Colobreathe was also not available.

Page 52 suggests that selection bias could not be fully assessed for the COLO/DPI trials as no baseline data is available separately for intervention and control groups. These data are available within the Colobreathe EPAR.	
The TAR in its current form does not assess all of the available evidence to inform this appraisal. Overall, additional clinical input from UK experts is required to correct for misleading statements and comparisons which seriously undermine the credibility of the assessment. Based on the concerns raised above, Novartis questions the validity of the TAR and believes that significantly more work is needed before the TAR is presented to the committee.	The Assessment Group believe that the TAR has performed its function of assessing the available evidence and presenting points for discussion, such that the committee can consider all aspects of this appraisal to reach a fully informed decision. Had Novartis provided complete and referenced information in their initial submission, and undertaken a closer reading of the TAR and the Colobreathe trial, many of the criticisms levelled at the TAR would have been avoided. As it stands, the Assessment Group feels the TAR represents a fair assessment, given the limitations of the evidence available to us at the time. In addition, we do not believe that any of our major conclusions would be altered by any of the criticisms or new information provided by Novartis at this late stage.

British Thoracic Society (BTS)

Comment	Assessment Group response
For the economic appraisal, the team have used the European list price for the Podhaler. However, Novartis have agreed to reduce its cost in the UK (so long as the product is delivered by a stipulated home care company) to less than that of TOBI. This means that the QUALY price will be reduced and this may well alter the conclusions regarding its cost effectiveness.	We have used the list price provided by Novartis during the appraisal. We have also presented an addendum for a proposed PAS submitted by Novartis.

Royal College of Physicians (RCP)

Comment	Assessment Group response
Please take this email as confirmation that the RCP wishes to endorse the submission of the BTS.	No response required

Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF)

Comment	Assessment Group response
Nebuliser set-up and cleaning times: (p.8) As nebulisers also require set up time and then thorough cleaning and drying, DPIs will save time. (p.8) Newer nebulisers such as the Ineb and eflow devices are now available and allow for faster treatment times compared to conventional nebulisers. However, Tobramycin nebuliser solution still takes >7-8 minutes just to nebulise in either the eflow or the Ineb and this does not include any set up or cleaning time. Colistin nebulisers also have to be reconstituted from a dry powder which therefore increases the total time required. (p.68) With regards to the use of quicker nebulisers, they still require time to maintain (cleaning) and assemble. It should therefore be acknowledged that this adds approximately 10-15 mins in addition to the nebulise time as well. (p.124) In the economic analysis although the newer nebuliser devices are quicker than conventional systems, the actual treatment time would still require nebuliser set up and cleaning times, whereas a DPI would not require this.	We agree that potentially DPIs may save time however neither Novartis nor Forest submitted comparative evidence to support this claim. We would argue that within the economic analysis the benefits of reduced treatment time should be considered in terms of their impact on health outcomes. Without evidence this is cannot be quantified.
Airway clearance for CF	Point noted.

p.23 The ACPCF feel that the sentence 'many cystic fibrosis centres would advocate some form of airway clearance using either traditional percussion/drainage via chest physiotherapy or using positive expiratory pressure (PEP) devices' is an outdated description of appropriate airway clearance in CF. it would be more appropriate to state 'would advocate recognised airway clearance techniques' and reference the ACPCF 'Standards of care and good clinical practice for the physiotherapy management of CF' (CF Trust, June 2011)	
Nebulisers required post lung transplant (p.23) Nebulised antibiotics are commonly used for the first 6 months post transplant to assist in treatment of *pseudomonas* in sinus cavities.	Point noted.
Service costs: (p.28) table 3 re Promixin : It should be made clear that the cost includes the provision of an Ineb device and all consumables and follow on service costs. (p.28) table 3 re other drugs: It should be made clear that additional equipment costs are applicable to these nebulised drugs. Nebuliser device, consumables, filter cases and service costs are all in addition to the drug costs for Colomycin, Tobramycin and Aztreonam.	The points regarding Promixin and nebuliser costs are made later on in the report (both on page 120).
EAGER trial: (p.41) Although it is stated that many allowed medications could affect FEV_1 measurements, it should be acknowledged that these would be considered as standard medical treatments for comprehensive CF care.	The table simply reports the inclusion/exclusion criteria from the trial (as reported) rather than statements requiring justification or comment from the Assessment Group.
Cough as a known side effect of DPIs/Treatment adherence: (p.70) Although 'cough' is quoted as a known side effect of using a DPI, it should be acknowledged that cough may also be reduced if appropriate education regarding inhalation technique and cough control are taught during the initiation dose. Therefore any adverse effects of cough from taking a DPI are minimised and short-lived. (p.146) Although with the use of DPIs it is unclear whether side effects such as cough will negatively impact on adherence, it should be acknowledged that appropriate education regarding cough control may reduce this. Therefore the convenience of a DPI may result in improved adherence once the patient is used to taking the medication, and is aware of appropriate cough control techniques.	This may well be true but our principal goal was to assess the available evidence and this did not reflect the suggestions made here by the ACPCF.

Also, more drugs are being developed as dry powders e.g. Mannitol. Therefore the use of DPIs will become more common and patients will be used to this mode of delivery.	
Costs: (p.77) As the Wolter et al study was carried out in Australia and all costs are quoted in Australian dollars it is difficult to apply this study's relevance and outcomes to clinical practice in the UK. (p.102) If the DPI price of Colobreathe is so much higher than the nebuliser version, it will be very difficult to justify a change to a DPI. (p.114) It is very difficult to apply economic models to individual drugs in CF care, because the disease is multi-factorial and requires combinations of drug therapies for optimal management.	We agree that Wolter et al has at best a weak relevance to this appraisal. We included the three published economic studies to demonstrate some of the problems of evaluating CF therapies. We also agree that there are certain problems associated with the economic evaluation of CF therapies, most of which are related to limited evidence collection and questionable relationships between surrogate and final endpoints, but we would argue that the economic decision-making framework is as appropriate for CF as any other disease or condition. It is not our role to comment on whether colistimethate sodium DPI should be used in place of nebulised antibiotics.

Health Improvement Scotland

Comment	**Assessment Group response**
Comments not replicated here	We agree that there are many limitations in the evidence. The reviewer makes a number of interesting points that may be useful for the Committee. These are presented more in the form of a commentary than a critique and therefore we do not feel we need to respond.