Novartis Pharmaceuticals UK Ltd
[redacted]

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Switchboard: [redacted]
Direct Line: [redacted]
Email: [redacted]

To Robert Fernley, Technology Appraisals Administrator – Committee D

Date 02 May 2012

Concerning **THE ScHARR TAR ON COLISTIMETHATE SODIUM POWDER AND TOBRAMYCIN POWDER FOR INHALATION FOR THE TREATMENT OF *Pa* LUNG INFECTION IN CF**

Dear Robert,

Novartis welcomes the opportunity to comment on this report and its technical content. Following a thorough review of the ScHARR TAR, this letter sets out our comments – firstly a summary of what we perceive to be the critical issues, and subsequently more detailed information relating to these and other related points.

Novartis considers the TAR to have significant limitations and that several oversights should be addressed prior to this document informing the evidence foundation upon which the Appraisal Committee will base its recommendations.

Key Points

- 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.
- 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.
- 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.
- Given the comparability of the efficacy and safety profiles for TOBI Podhaler to comparator products, [redacted]

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Glossary

BOCF	Baseline Observation Carried Forward
CI	Confidence Interval
CF	Cystic Fibrosis
CFU	Colony Forming Units
EAGER	**E**stablish **A** new **G**old standard **E**fficacy and safety with tobramycin in cystic fib**R**osis
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ITT	Intention to Treat
LOCF	Last Observation Carried Forward
MHRA	Medicines and Healthcare products Regulatory Agency
Pa	Pseudomonas aeruginosa
PP	Per protocol
ScHARR	The University of Sheffield School of Health and Related Research
SD	Standard Deviation
SPC	Summary of Product Characteristics
TAR	Technology Assessment Report

(1) The peer-reviewed EAGER trial conclusively 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.

At odds with the EMA and UK clinical expert opinion, the TAR questions the validity of the non-inferiority conclusion reached within the largest clinical trial conducted for pseudomonas treatment, EAGER (n=553). The EAGER trial provides robust, unambiguous evidence that TOBI Podhaler is non-inferior to TOBI nebuliser solution which has been published in the peer-reviewed *Journal of Cystic Fibrosis* in January 2011 and accepted by the EMA in July 2011. The TAR challenges the EAGER trial based on the following arguments:

- **Retrospective application of the EMA recommendations to assess robustness of a clinical trial which pre-dates these guidelines**

  "The quality of the included studies was generally poor to moderate…with non-adherence to the EMA research guidelines being [a] key problem" (TAR, page 6).

  The conduct of the EMA-approved EAGER study pre-dates the EMA Guideline on the Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis. Therefore assessing the EAGER trial primarily on EMA Guidelines is unreasonable given the guidelines were not in place even when EAGER had fully completed with the last visit for the last patient. The TAR concludes that EAGER failed to adhere to these guidelines on numerous points (TAR, pages 5-7, 17-20, 39, 41, 45-48, 50-53, 59, 63, 73-74, 103, 147, 149,

151). Whilst Novartis generally supports much of the robustness of the recent EMA Guidelines, it is misleading to retrospectively apply these guidelines to an EMA-approved product supported by a clinical development programme which had started several years prior to their issue; EMA Guidelines came into effect on 30 April 2010 and EAGER commenced on 06 February 2006 (first patient, first visit) and concluded on 12 March 2009 (last patient, last visit). Focussing the critical appraisal of EAGER primarily against the EMA guidelines fails to take into account the more relevant assessment of whether study design and patient characteristics are reflective of UK clinical practice; UK clinical expert opinion strongly supports that EAGER unquestionably fulfils this criterion.

- **Unfounded statistical criticism of the EAGER trial**

"Both DPI formulations have been shown to be non-inferior to nebulised tobramycin as measured by FEV1%. However, the results of these trials should be interpreted with caution due to the means by which the results were analysed..." (TAR, page 8).

"The EAGER trial data were not transformed, nor was a non-parametric test performed, though no test of normality was apparently planned or performed either. No imputation was performed on the Novartis data, and only limited data were presented at 24 weeks. Some adjusted comparative data were presented, with adjustments for main effects treatment, baseline FEV1% predicted and pooled centre" (TAR, page 54).

Whilst the EAGER trial conclusively found TOBI Podhaler to be non-inferior to TOBI nebuliser solution with respect to efficacy, the TAR challenged these findings as 'both studies can be criticised for statistical analysis techniques' (TAR, pages 52, 54-55, 73-74, 189) and that the EAGER statistical omissions could lead to a high risk of attrition bias. As stated in the EPAR, "sensitivity analyses were conducted to assess the impact of patient discontinuation on the non-inferiority comparison" (EPAR, August 2011, page 31). EMA marketing authorisation for TOBI Podhaler in July 2011 thus factored these additional single imputation methods into the final determination that TOBI Podhaler is non-inferior to TOBI nebuliser solution. In contrast to the several post-hoc analyses presented for Colobreathe, similar imputation methods supported the non-inferiority conclusion reached by EAGER for TOBI Podhaler compared to TOBI nebuliser solution with respect to FEV_1% predicted after three cycles of treatment. The Assessment Group's claim of overestimating efficacy for TOBI Podhaler by not taking into account discontinuation is therefore unfounded. ITT and PP population imputation analyses are presented below for your consideration, with further appropriate imputation analyses available on request.

Sensitivity Analysis for Non-Inferiority Patients: Whole Cohort (ITT population)

	TOBI Podhaler (n=308)	TOBI Nebuliser Solution (n=209)	LS Mean Difference (SD)	[redacted] CI of difference
LOCF	[redacted]	[redacted]	[redacted]	[redacted]
BOCF	[redacted]	[redacted]	[redacted]	[redacted]

Sensitivity Analysis for Non-Inferiority Patients: Whole Cohort (PP population)

	TOBI Podhaler (n=225)	TOBI Nebuliser Solution (n=171)	LS Mean Difference (SD)	[redacted] CI of difference
LOCF	[redacted]	[redacted]	[redacted]	[redacted]
BOCF	[redacted]	[redacted]	[redacted]	[redacted]

Furthermore, the TAR suggests that in comparison to the COLO/DPI/02/06 trial, EAGER did not present a similarly comprehensive statistical assessment of the data. This interpretation is highly misleading and suggests that ScHARR did not consider the data and discussion points within the Colobreathe EPAR to draw appropriate concluding statements. Novartis confirms that the reason for the streamlined analyses is due to the EAGER trial reaching its pre-planned endpoints. Neither additional *a priori* tests nor exclusion of a large sub-group of data (i.e., Ukrainian population, n=66/374 ITT population within COLO/DPI/02/06) were required to conclusively illustrate the non-inferiority of TOBI Podhaler to TOBI nebuliser solution with respect to efficacy. Suggestive comparisons on the statistical analyses conducted by both manufacturers are therefore unwarranted and misleading.

- **Unsubstantiated conclusions regarding trial design and findings: FEV1%, resistance, cough, exacerbations, chronic lung function definition and trial duration**

"Both DPI formulations have been shown to be non-inferior to nebulised tobramycin as measured by FEV1%. However, the results of these trials should be interpreted with caution due to means by which the results were analysed, the length of follow up, and concerns about the ability of FEV1% to accurately represent changes in lung health. The impact of resistance to tobramycin is not known. When considered alongside other outcomes, it would appear possible that patients on DPI formulations experience more exacerbations, but spend less time on antibiotics, experience more cough adverse events and may be more likely to not tolerate the treatment. As such, the advantages and non-inferiority of DPI treatments compared to nebulised tobramycin remain unclear when all relevant outcomes are considered (TAR, page 151).

Novartis is extremely concerned that the above statement reflects the "main conclusion of the assessment" (TAR, page 151). Expert clinical opinion is needed to address many of the unfounded clinical conclusions and appropriately place parameters into the context of treatment for cystic fibrosis patients.

FEV_1% predicted

The TAR questions at length whether FEV_1% has the ability to accurately represent changes in lung health followed by a brief conclusion which states "whilst there may be a role for $FEF_{25-75\%}$ and CT and MRI may be useful in certain circumstances, FEV_1% is currently the recommended primary endpoint for clinical trials, and, owing to the number of studies linking FEV_1% to prognosis, a key indicator of disease progression used to monitor patients' health" (TAR, pages 17, 19). The conclusion that FEV_1% is the core primary marker in Cystic Fibrosis is further confirmed by the EMA's regulatory

assessment of TOBI Podhaler (TOBI Podhaler EPAR, page 29). Endorsement of FEV_1% as a valid endpoint is confusingly omitted when discussing FEV_1% throughout the remainder of the document; instead numerous statements questioning the validity of FEV_1% to accurately represent changes in lung health are contradictorily presented (TAR, pages 8, 51, 151). [redacted]

Resistance

The TAR presents a significant amount of information stressing resistance as one of the factors challenging whether TOBI Podhaler is non-inferior to TOBI nebuliser solution (TAR, page 6, 8, 18, 59, 60, 73, 74, 150, 151). Statements within the TAR which suggest clinical or statistically significant changes in MICs are invalid as there is no threshold defining a cut-off for susceptibility for inhaled antibiotics (TAR, pages 6, 18, 59, 73, 147). For the avoidance of confusion, it is reiterated that there is no agreed definition of resistance for inhaled antibiotics for chronic pulmonary infection in CF. Application of such data is therefore non-scientific and misleading. Moreover, the impact of any changes in insusceptibility would be identical for both TOBI nebuliser solution and TOBI Podhaler given the closely comparable pharmacokinetic exposures.

Cough

The non-inferiority of TOBI Podhaler compared to TOBI nebuliser solution was further challenged due to an increase of cough in the TOBI Podhaler arm (TAR, pages 6, 8, 73-74, 142, 146-147, 151). Whilst the TAR repeatedly speculates that an increased incidence of cough is likely to lead to non-adherence and patients not tolerating the therapy (TAR, pages 8, 146, 151), the clinical background of cough is only placed into context at one occasion: "*Cough is a known side effect of dry powder formulations and is thought to generally reduce over time, with improved technique, and may be controlled with use of bronchodilators to some extent, in some patients*" (TAR, page 70). Furthermore, the TAR fails to capture that most of the cough events in the EAGER trial were mild or moderate in intensity. The frequency of severe coughs was low and balanced between the TOBI Podhaler and TOBI nebuliser solution treatment groups. The compliance in both groups was well matched, contrary to the concern regarding non-adherence. [redacted]

Exacerbations

The TAR suggests that the TOBI Podhaler treatment group within EAGER has an increased incidence of lung disorder (classified by ScHARR as 'acute exacerbations') which further questions the non-inferiority conclusion (TAR, page 73, 151). As stated by Novartis within the clarification questions to the ScHARR on 22 August 2011, [redacted] Furthermore, the TAR inappropriately uses the parameter 'lung disorder' as a proxy for 'acute exacerbation'. These two endpoints are not equivalent and therefore it is clinically misleading to assume comparability. Novartis'

clarification response thoroughly defined the term 'lung disorder' which provides evidence to support that these two parameters are not equivalent. As 'acute exacerbation' was not a specified end-point of the EAGER trial, data was not collected on this parameter and a detailed definition is not warranted, as was the case within the COLO/DPI/02/06 trial.

Chronic lung function
The patient population within the EAGER trial are challenged within the TAR as not truly selecting chronically infected patients (TAR, page 39, 41). As the EAGER population all had an [redacted] at baseline, were diagnosed with CF and also found Pa throughout the trial, this strongly suggests the patients to be chronically infected with Pa. Moreover, the majority of the trial population were adults and the epidemiological data indicate that [redacted] are chronically infected with Pa. As discussed above, the TAR inappropriately applies the EMA guidelines retrospectively which recommend three positive cultures in the last six months, rather than the two positive cultures which were applied as inclusion criteria within EAGER. The TAR speculates that this may indicate an inclusion of patients with intermittent infections within the EAGER trial. However, UK clinical practice strongly refutes this as seen within the CF Trust Guidelines which define chronic infection with pseudomonas aeruginosa as "the regular culture of the organism from the sputum or respiratory secretions, on 2 or more occasions extending over 6 months" (CF Trust, 2006, page 7). UK expert clinical opinion further supports that there is no clinically meaningful difference between 2 or 3 cultures and thus the chronically infected status of the patients within EAGER should not be questioned. Novartis argues that UK-specific guidelines which were available prior to the start of EAGER and UK clinical practice are a more appropriate source for the definition of chronic lung infection.

Treatment duration
The TAR states the short treatment duration of the available clinical trials as a key point of uncertainty within the evidence base (TAR, pages 6, 8, 53, 74, 90, 93, 103, 147, 150, 151). Novartis presents the attached abstract which assessed the effects of long-term tobramycin on lung function decline for your consideration. The study found for patients prescribed tobramycin for 3 years or longer (n=6,026), the association between use and FEV_1% predicted rate of decline was statistically significant (0.054% pred/year for every 10% of increased use, 95% CI: 0.004 to 0.035, P=0.0364). The study concluded that increased tobramycin use is a predictor of slower rate of decline in FEV_1 with patients on tobramycin ≥ 3 years showed more improvement than patients on tobramycin <3 years.

- **Statements challenging comparable safety profiles of TOBI Podhaler and TOBI nebuliser solution: Clinical significance of differing discontinuation rates**

"The EAGER trial suggests a less favourable profile for tobramycin DPI across almost all of the common adverse events (especially cough and dysphonia) as compared against nebulised tobramycin" (TAR, page 42).

"More patients in the DPI intervention arms withdrew due to adverse events in both trials. The statistical and clinical significance of differences in…adverse event data is unknown" (TAR, page 147-148).

(2) 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 TAR questions the incremental benefits of TOBI Podhaler with respect to reduced treatment administration time (TAR, pages 8, 10, 18, 20, 68, 78). TOBI nebuliser solution is approved for use specifically with the PARI LC Plus nebuliser (TOBI Podhaler SPC). Whilst alternative nebulisers are available on the market, there is no robust data to suggest that these nebulisers are clinically effective, nor safe for tobramycin administration. The CF Trust patient forum provides additional evidence that patients are often confused about the correct dose of TOBI nebuliser solution with the off-label use of these alternative nebulisers which can lead to under dosing. The approved labelling for TOBI nebuliser solution specifically states the use of TOBI nebuliser solution with the PARI LC Plus nebuliser which follows from robust evidence presented in Ramsey 1999.

(3) Omission of data which biases the interpretation of the COLO/DPI/02/06 trial

Patients within the COLO/DPI/02/06 trial were required to have 2 cycles of TOBI nebuliser solution prior to randomisation which questions its comparability with EAGER and

specifically makes the conclusion of non-inferiority to TOBI more difficult. This run-in phase introduces a significant and highly clinically relevant bias. The trial duration was therefore not 24 weeks but instead 16 weeks intervention with TOBI nebuliser solution cycles followed by 24 weeks treatment with either of the two active treatments. Within the tobramycin-naive population of EVOLVE (TOBI Podhaler versus placebo), a deliberate and notable peak occurred in the first 4 weeks, followed by sustained efficacy (Konstan 2010a) which is commonly seen after an acute switch of antibiotic. This sustained efficacy was also documented for Bramitob as seen in the below figure reproduced from Chuchalin 2007.

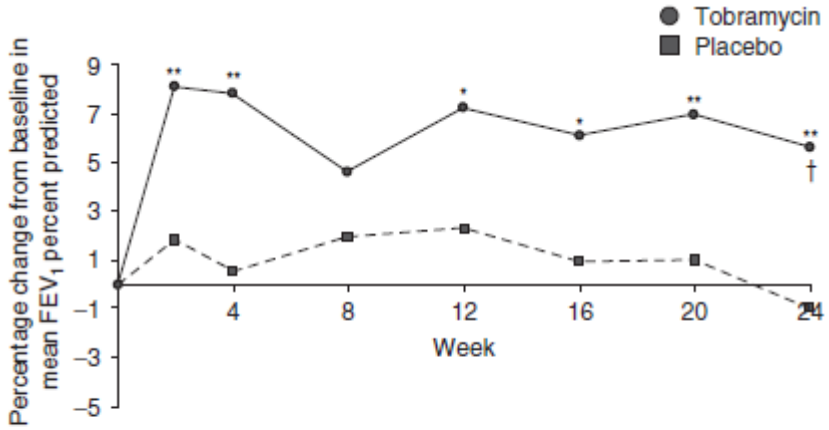

Fig. 2. Change from baseline in mean forced expiratory volume in 1 second (FEV_1) percent predicted. * $p < 0.01$, ** $p < 0.001$ vs placebo; † $p < 0.001$ vs baseline.

Whilst TOBI nebuliser solution was seen to peak rapidly in Ramsey 1999 (TOBI nebuliser solution vs placebo), this effect was seen only mildly seen for TOBI Podhaler and TOBI nebuliser solution in EAGER with patients who were not tobramycin-naive.

Furthermore, the significance of a switch in antibiotic treatment should not be ignored. In patients switching from TOBI nebuliser solution to aztreonam, there is a notable peak in FEV_1% which is associated with the acute switch in treatment. These data and their impact do not seem to have been taken into account in assessing whether Colobreathe is appropriately considered to be non-inferior to TOBI nebuliser solution. The complete absence of response to a switch to Colobreathe after 2 cycles of TOBI nebuliser solution is not addressed. .

Taken as a whole, these data refute the claim that the effect of two cycles of TOBI nebuliser solution leading into COLO/DPI/02/06 washes out as the published evidence demonstrate that inhaled tobramycin has a sustained efficacy and this run-in phase therefore creates a substantial bias which refutes the comparability of EAGER and COLO/DPI/02/06.

(4) Microbial response data unavailable for main comparator intervention

A microbiological outcome for all trials of broncho-pulmonary infection should be assessed to determine the clinical efficacy of antipseudomonal antibiotics (TAR, pages 17, 47, 59). Whilst EAGER collected change in Pa density (log10[CFU]/g sputum) from baseline which found

TOBI Podhaler and TOBI nebuliser solution to have similar antibacterial effects, the COLO/DPI/02/06 trial did not include any sputum density tests which further calls into question the comparability between these two trials (TAR pages 47, 59) in relation to TOBI nebuliser solution.

(5) Lack of consideration of the available evidence

Whilst the Final Scope suggests comparators should include all colistimethate sodium and tobramycin for nebulised inhalation treatment options, overly restrictive exclusion criteria in the Assessment Group's review of the evidence have reduced the available evidence base down from 13 to 3 clinical trials (which limits the evidence network to 3 of the 7 products available in the UK for Pa treatment). Several tobramycin trials were excluded without robust justification at the 20/24 week time point. Most notable is the entire exclusion of the most recently available Pa tobramycin treatment, Bramitob (tobramycin 300mg/4mL tobramycin nebuliser solution) which therefore leaves TOBI nebuliser solution as the sole comparator product. Ramsey 1999 (TOBI nebuliser solution versus placebo) is also cited for exclusion as ScHARR could not confirm whether patients had chronic Pa infections. As discussed above in Point 1 (chronic lung infections), the exclusion of Ramsey 1999 based on retrospectively applied criteria which is not supported by UK clinical practice and guidelines is flawed.

The TAR suggests that the most appropriate time point to compare between trials is at 24 weeks. However, the majority of available evidence (Ramsey 1999, Oermann 2010, EAGER and COLO/DPI/06) presents data at 20 weeks. Furthermore, it is more clinically sound to compare at 20 weeks instead of 24 weeks. A cycle of tobramycin treatment consists of 28 days on-treatment followed by 28 days off-treatment. Colobreathe (and all colistimethate sodium therapies for the treatment of Pa) is a continuous, daily treatment. Therefore, the 20-week time point is a more clinically relevant time point as then a comparison between active treatments will be taking place rather than a comparison of an active treatment (Colobreathe) versus the off-treatment part of the tobramycin cycle. The FEV_1 data for TOBI Podhaler at 20 weeks and 24 weeks both show a higher numerical point estimate compared to TOBI. Unlike the assertion within the TAR (page 55), the point estimate for TOBI Podhaler is even larger at 24 weeks than 20 weeks in comparison to TOBI nebuliser solution. For Colobreathe the point estimate of effect appears to be even lower at 20 weeks than the data reported at 24 weeks.

(6) Benefits of TOBI Podhaler are not adequately presented within the TAR

TOBI Podhaler offers convenience and reduced administration time in comparison to TOBI nebuliser solution. The TAR does not adequately highlight that approximately 60% of nebulisers face contamination issues. Furthermore, the benefits of TOBI Podhaler extend beyond faster administration times; advantages such as lack of requirement for cold storage and electricity are not discussed within the TAR. These benefits are either not discussed or are discounted throughout the TAR by inappropriately highlighting the unproven benefits of off-label use of alternative nebulisers.

(7) Factual inaccuracies

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A number of factual inaccuracies and misleading statements within the TAR are listed below.

- 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 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]
- Page 5 presents the FEV1 transition strata (99-70%, 69-40%, <40%) which is of questionable relevance given the labelling for 25-75% predicted.
- Page 13 discussions regarding renal transplant should also note that colistin is also nephrotoxic.
- Page 14, figure 2 lacks the legend for gender.
- 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.
- 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.
- 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.
- 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.
- Page 26 does not clearly state that the post marketing events listed are for TOBI nebuliser solution and not TOBI Podhaler.
- 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-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.
- 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%.

- 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."*
- Page 48, Table 10 should include that Knudson 1976 was used to calculate $FEV_{1\%}$ predicted.
- 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).
- 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.

Conclusion

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.

Once again, we are grateful for the opportunity to comment on the TAR and look forward to continued dialogue with NICE regarding the issues raised in this response.

Regards,

[redacted]

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