Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of chronic *Pseudomonas aeruginosa* lung infection in cystic fibrosis

Summary of non-inferiority analysis in Forest submission to NICE

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This document should be read with reference to the Forest submission to NICE for further details where necessary.

1.1 Section 6.2.9 in Forest submission to NICE states

> "The primary efficacy analysis was done using last observation carried forward (LOCF) imputation to Week 24 for missing data. Analysis populations included both ITT and PP populations. Both populations were of equal importance. An analysis of covariance (ANCOVA) was performed using main effects of treatment and centre. The treatment-by-centre interaction was explored as a secondary analysis.
>
> A 95% two-sided CI was computed for the difference in Colobreathe® minus TOBI®. If the lower limit was no lower than -3.0% for both the PP and ITT populations it was concluded that Colobreathe® was non-inferior to TOBI®.
>
> The LOCF values of this variable were summarised at each visit using descriptive statistics.
>
> The normality of the residuals and homogeneity of variances were investigated using the Shapiro-Wilk test.
>
> The proportion of patients with early withdrawal in each treatment group was compared using the Cochran-Mantel-Haenszel (CMH) method, stratified by age and pooled centre. If there were significant differences ($p<0.05$), then the effect of the differential drop-out rate on the primary efficacy analysis (FEV_1 % predicted) was to be explored using sensitivity analysis methods."

1.2 Potential issues with statistical plan for consideration by statisticians.

1. LOCF may overestimate treatment effects; as patients with cystic fibrosis are generally on a slow decline, carrying the last observation forward may be an overestimate of expected FEV1% values. Would another method of imputation have been better?
2. Was it appropriate to test the normality of the data, when this is not done as standard for analysis of cystic fibrosis patient FEV1% data? i.e. on what basis is skew in data expected? Previous studies do not appear to use this approach.
3. If testing for normality is considered unusual, should we instead look at the data analysed on the original scale and disregard the logarithmic and non-parametric analyses? Or given the fact that the distribution was non-normal, is this approach acceptable?
4. Note that a completers analysis is not mentioned in section 6.2.9.

2.1 Explanation of statistical analyses in results section of Forest submission to NICE (sections reproduced from Forest submission to NICE)

> **"6.2.14.2 Logarithmic transformation**
>
> Based on the ANCOVA, inspection of the Shapiro-Wilk test statistic testing the hypothesis of normality of the studentised residuals, together with normal probability plots of the studentised residuals, indicated departures from normality.
>
> In view of departures from normality, the ANCOVA using the main effects of treatment, baseline FEV_1 % predicted and pooled centre was repeated on logarithmically transformed data. The results are presented in **Error! Reference source not found.** (ITT population) and **Error! Reference source not found.** (PP population). Since data has been logarithmically transformed, comparisons between treatment groups have been presented as ratios. However, the treatment ratios have also been converted to treatment differences using the formula:
>
> Difference (Colobreathe® - TOBI®) = M*(Ratio (Colobreathe®/TOBI®) - 1)
> Where the multiplier M has been chosen in two ways:
>
> - The unadjusted TOBI® geometric mean.
> - The TOBI® geometric mean adjusted for baseline FEV1 % predicted, pooled centre and treatment*pooled centre interaction.
>
> The non-inferiority criterion for the lower limit of the 95% CI of -3% for the treatment difference was equivalent to a lower limit of 0.94 for the treatment ratio. The treatment ratio of 0.94 comes from the fact that as the middle of the inclusion criteria was a predicted FEV_1 % of 50 %, an absolute change of 3 % is a relative change of 6 %."

2.2 Potential issues with analysis for consideration by statisticians

1. Does the adjustment "Difference (Colobreathe® - TOBI®) = M*(Ratio (Colobreathe®/TOBI®) – 1)" provide an estimate of the difference in arithmetic means as required for a comparison against the inferiority margin on the absolute scale?
2. If it does not, should we trust the results that are presented?
3. How would you interpret the results of the logarithmic analysis (see Table below), given that:
   - Section 6.2.9 states that non-inferiority should be demonstrated in both ITT and PP populations
   - The PP population only reaches non-inferiority in the completers analysis. LOCF was designated the primary efficacy analysis in section 6.2.9, and a completers analysis was not mentioned in this section or in the study protocol, and therefore appears to be a post-hoc analysis.
   - There is no statement about whether both LOCF and completer analyses should demonstrate non-inferiority to achieve non-inferiority in section 6.2.9.
   - In every case in the Table below, the completers analysis gives a more favourable estimate of efficacy for the study drug.
4. If the logarithmic analysis does not show non-inferiority, is it correct to apply the -3% criteria to median values presented in the non-parametric analysis, and accept non-inferiority has been demonstrated in this analysis?

Table Estimates of efficacy provided in the Forest submission to NICE to demonstrate non-inferiority[a]

Analysis	Population	Data included in analysis	n CDPI	n TIS	Adjusted[b] mean difference between groups in FEV1% from baseline	Lower limit of 95% CI[c]	Upper limit of 95% CI	Satisfies non-inferiority?	Protocol-defined analysis?	Non-inferiority discussion
ANCOVA analysis on the original absolute scale	ITT	LOCF	183	190	-1.16%	-3.15%	0.84%	No	yes	Non-inferiority not met.
		Completers	153	171	-0.43%	-2.59%	1.72%	Yes	no	
	PP	LOCF	141	157	-1.49	-3.79%	0.81%	No	yes	
		Completers	120	141	-0.99	-3.48%	1.51%	No	no	
Logarithmic analysis	ITT	LOCF	183	190	-0.98%	-2.74%	0.86%	yes	yes	Unclear. Non-inferiority met in ITT population and PP completers analysis but "marginally missed" in PP population with LOCF analysis. Protocol definition of non-inferiority requires both populations to demonstrate non-inferiority, but is not clear whether this needs to be demonstrated in both LOCF and completers analyses. LOCF is the protocol-defined primary analysis and the completers analysis appears to be a non-protocol-defined post-hoc analysis.
		Completers	153	171	-0.29%	-2.20%	1.70%	yes	no	
	PP	LOCF	141	157	-1.10%	-3.08%	0.97%	no	yes	
		Completers	120	141	-0.56%	-2.71%	1.70%	yes	no	
Non-parametric analysis	ITT	LOCF	183	190	-0.56%[d]	-2.16%[d]	1.00%	yes	yes	Non-inferiority met in both populations
		Completers	153	171	0.05%[d]	-1.61%[d]	1.67%	yes	no	
	PP	LOCF	141	157	-0.67%[d]	-2.57%[d]	1.16%	yes	yes	
		Completers	120	141	-0.15%[d]	-2.14%[d]	1.17%	yes	no	

CDPI, colistimethate sodium dry powder for inhalation; TIS, tobramycin inhaled solution; CI, confidence interval; ANCOVA, analysis of covariance; ITT, intention to treat; LOCF, last observation carried forward; PP, per protocol

[a] Grey shading denotes protocol-defined analyses.

[b] Adjusted for baseline FEV1% and pooled centre

[c] Lower limit of the 95% CI should no lower than -3% to satisfy non-inferiority criteria

[d] Median difference, CI determined using distribution-free methods based on the Wilcoxon Rank Sum Test, without adjustment for pooled centre. Unclear if adjusted for baseline FEV1%