Table 5 shows results of the primary analysis of time to cessation of otorrhea in the CITT population. Findings were consistent across both trials. When comparing treatments in Trials 02 & 04 respectively, the median number of days at which cessation of otorrhea was achieved was 3.8 & 4.9 days for the CIPRO+FLUO arm and 7.7 & 6.8 days for the CIPRO arm. The median number of days was not estimable in the FLUO arm in either of the studies due to the majority (i.e. 51.8% & 56.5%) of patients being censored, however, the lower 95% confidence limit of the median in the FLUO arm was estimated at 7.4 & 13.9 days which was considerably longer than the lower 95% confidence limit in the CIPRO+FLUO arm at 3.0 & 3.7 days and the CIPRO arm at 4.8 & 5.5 days. When performing statistical testing using the log rank test, results showed the superiority of CIPRO+FLUO vs. CIPRO (p-value < 0.001 in Trial 02, p-value =0.028 in Trial 04) and the superiority of CIPRO+FLUO vs. FLUO (p-value < 0.001 in both trials). Similar findings were observed when using Wilcoxon test.

Cessation rates in Trials 02 & 04, respectively, showed similar trends in efficacy across the treatment arms at 78.6% & 78.4% in the CIPRO+FLUO arm, 67.0% & 68.8% in the CIPRO arm and 48.2% to 43.5% in the FLUO arm. The results of these analyses supported the Sponsor's primary objective of demonstrating the contribution of both the CIPRO component and the FLUO component in the combination drug product (CIPRO+FLUO).

Reviewer Comment: *No adjustment for multiplicity is needed in these analyses since the Applicant must show the contribution of both components in order to satisfy the primary objective.*

Table 5: Primary Analysis: Time to Cessation of Otorrhea (CITT)

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 110)**
Number (%) of patients with cessation of otorrhea	88 (78.6%)	73 (67.0%)	53 (48.2%)
Number (%) of patients censored at Day 22 (no cessation of otorrhea)	24 (21.4%)	36 (33.0%)	57 (51.8%)
Time to cessation of otorrhea (days): Mean (SE) Median (95% CI)	 6.9 (0.61) 3.8 (3.0, 4.4)	 10.8 (0.78) 7.7 (4.8, 11.4)	 12.6 (0.77) NE (7.4, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Number of patients with cessation of otorrhea	87 (78.4%)	77 (68.8%)	47 (43.5%)
Number of patients censored (no cessation of otorrhea)	24 (21.6%)	35 (31.3%)	61 (56.5%)

Time to cessation of otorrhea (days): Mean (SE) Median (95% CI)	 7.6 (0.63) 4.9 (3.7, 5.5)	 10.5 (0.78) 6.8 (5.5, 7.7)	 13.7 (0.70) NE (13.9, NE)
Log rank test p-value[1]		0.028	< 0.001
Wilcoxon test p-value[2]		0.018	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Reviewer Comment: *Kaplan-Meier methods were used in the primary analysis with the assumption that patients who did not achieve cessation would be censored at Day 22 (i.e. end of study). Using this methodology, time to cessation based on the median number of days (with 95% confidence limits) and the mean number of days (with standard error) could be estimated. However, since the time variable may not follow a normal distribution, estimates made using the median number of days was considered to be more informative. Therefore, Reviewer sensitivity and subgroup analyses do not report mean changes in time to cessation of otorrhea but rather median changes with the corresponding 95% CI.*

Figure 1 shows the cumulative percentage patients in each treatment arm of Trial 02 achieving cessation of otorrhea over the study period (22 days). The CIPRO+FLUO arm showed the highest rates of cessation over the study period after 2 days (or by start of Day 3) through Day 22. The difference in cessation rates between CIPRO+FLUO and the other arms appeared to be substantial throughout most of the trial. The CIPRO arm showed cessation rates that were higher than in the FLUO arm and tended to widen after 4 days (or by the start of Day 5) through Day 22. Overall, patients tended to achieve their cessation within the first 10 days of the trial with only a few subjects achieving cessation after 10 days.

Figure 1: Comparison of the Percentage of Patients in Each Study Arm Achieving Cessation of Otorrhea Over Time, Trial 02

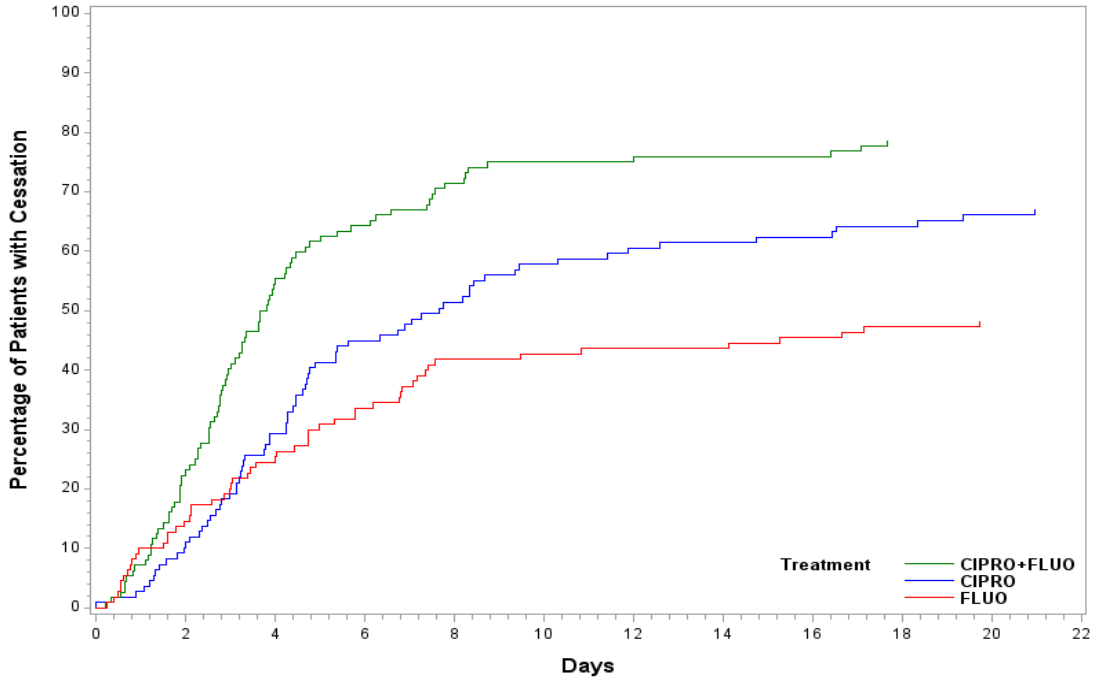
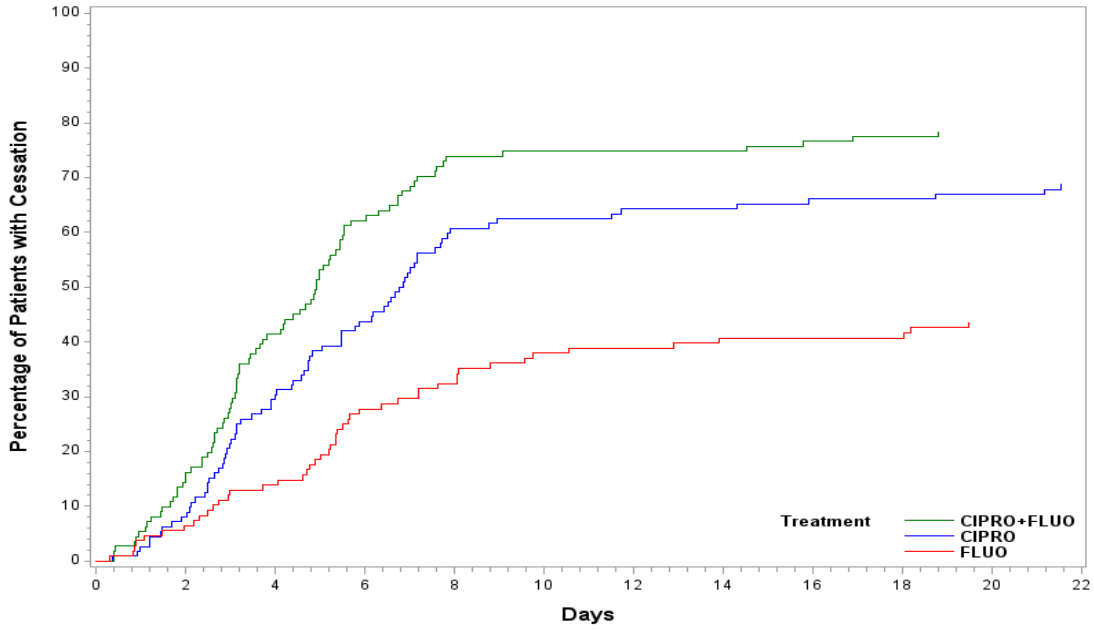


Figure 2 shows the percentage patients in each treatment arm of Trial 04 achieving cessation of otorrhea over the study period (22 days). The CIPRO+FLUO arm showed the highest rates of cessation after 1 day (or by the start of Day 2) through Day 22. The difference in cessation rates between CIPRO+FLUO and the other arms appeared to be substantial throughout most of the study period. The CIPRO arm showed cessation rates that were higher than in the FLUO arm after 2 days (or by the start of Day 3) through Day 22. The CIPRO arm was observed to perform relatively better against the other arms in Trial 04 compared to Trial 02. Similar to Trial 02, patients in Trial 04 tended to achieve their cessation within the first 10 days of the trial with only a few subjects achieving cessation after 10 days.

Figure 2: Comparison of the Percentage of Patients in Each Study Arm Achieving Cessation of Otorrhea Over Time, Trial 04



Source: Reviewer Figure

Principal Secondary Analysis

The Principal Secondary Analysis was considered by the Applicant to be the only confirmatory secondary analysis with all other secondary analyses being considered as supportive. The principal secondary endpoint considered in this analysis was sustained microbiological cure. Sustained microbiological cure was defined as Eradication or Presumed Eradication in the per-patient microbiological response at both Visit 3 and Visit 4. The primary analysis of sustained microbiological cure was performed on the MITT population.

As shown in **Table 6**, the MITT analysis in Trial 02 showed sustained microbiological cure rates of 47/61 (77.0%) of patients in the CIPRO+FLUO group, 41/63 (65.1%) in the CIPRO group, and 23/52 (44.2%) of patients in the FLUO group. Pairwise comparisons of the CMH test, stratified by age showed a statistically significant difference in sustained microbiological cure between the CIPRO+FLUO group compared with the FLUO group ($p < 0.001$) and for the CIPRO group compared with the FLUO group ($p = 0.017$).

In Trial 04, microbiological cure rates were 47/57 (82.5%) in the CIPRO+FLUO group, 43/61 patients (70.5%) in the CIPRO group, and 18/57 patients (31.6%) in the FLUO group. Pairwise comparisons showed a significant difference in sustained microbiological cure between the CIPRO+FLUO group compared with the FLUO group ($p < 0.001$) and for the CIPRO group compared with the FLUO group ($p < 0.001$).

Table 6: Principal Secondary Endpoint Analysis: Sustained Microbiological Cure Rate in Observed Subjects (MITT)

Trial 02	CIPRO+FLUO (N = 65)	CIPRO (N = 70)	FLUO (N = 60)
Sustained Cure, n/N_{obs} (%)	47/61 (77.0)	41/63 (65.1)	23/52 (44.2)
No Sustained Cure, n/N_{obs} (%)	14/61 (23.0)	22/63 (34.9)	29/52 (55.8)
Missing, n/N_{MITT} (%)	4/65 (6.2)	7/70 (10.0)	8/60 (13.3)
p-value[1] vs. CIPRO+FLUO		0.173	< 0.001
p-value[2] vs. CIPRO			0.017
Trial 04	**CIPRO+FLUO (N = 60)**	**CIPRO (N = 65)**	**FLUO (N = 62)**
Sustained Cure, n/N_{obs} (%)	47/57 (82.5)	43/61 (70.5)	18/57 (31.6)
No Sustained Cure, n/N_{obs} (%)	10/57 (17.5)	18/61 (29.5)	39/57 (68.4)
Missing, n/N_{MITT} (%)	3/60 (5.0)	4/65 (6.2)	5/57 (8.1)
p-value[1] vs. CIPRO+FLUO		0.129	< 0.001
p-value[2] vs. CIPRO			< 0.001

Source: Reviewer Table
Analysis is based on observed cases (excluding missing data) which may be conservative given the relatively low rates of missing data in the CIPRO+FLUO arm.
[1]Pairwise comparisons versus CIPRO+FLUO using CMH test stratified by age (< 3 yrs vs. ≥ 3yrs)
[2]Pairwise comparisons versus CIPRO using CMH test stratified by age (< 3 yrs vs. ≥ 3yrs)

3.2.4.2 Additional Reviewer Analyses

Primary Endpoint

The Reviewer conducted several additional exploratory/sensitivity analyses of the primary endpoint. These analyses were conducted in the CITT population under a variety of different assumptions. These analyses aimed to assess the robustness of primary analysis results by controlling for potential confounding variables. Findings from Reviewer exploratory/sensitivity analyses were generally supportive of findings reported for the primary analysis.

Exploratory/sensitivity analyses of the primary endpoint considered various changes of assumptions in the primary analysis:

- Analysis of rates of cessation of ottorhea (rather than time to cessation of otorrhea)
- Analysis without stratification (rather than with stratification by age group, < 3yrs and ≥ 3 yrs)
- Analysis including only uncensored patients (rather than all CITT patients)
- Analysis censoring discontinued patients at Day 1 (rather than censoring at Day 22)
- Analysis including only the MITT population (rather than the CITT population)
- Analysis including only unshared study sites (rather than all study sites)

Additional Reviewer exploratory/sensitivity analyses are shown in the **Appendix.** These analyses considered the following groups of patients:

- Per protocol patients
- Patients not using effective prior antibacterial therapies
- Patients not using prohibited concomitant antibacterial therapies
- Patients not using titanium tubes
- Patients not using out of specification study medication

Secondary Endpoint

The Reviewer conducted the following exploratory/sensitivity analyses related to the secondary endpoint:

- Microbiological outcomes at Visit 3 and Visit 4 separately
- Microbiological outcomes at Visit 3 and Visit 4 by target pathogen.

Sensitivity Analysis: Rates of Cessation of Otorrhea by Day 22

Sensitivity/exploratory analyses were performed to observe the rates of cessation of otorrhea by Day 22. These analyses assessed whether the contribution of the components observed in the primary analysis is being driven more by faster times to cessation of otorrhea or by higher rates of cessation of otorrhea by Day 22. **Table 7** and **Figure 3** shows that patients in the CIPRO+FLUO arm had the highest rates of cessation by Day 22. The rates across in Trials 02 & 04, respectively, were 78.6% & 78.4% for the CIPRO+FLUO arm, 67.0% & 68.8% for the CIPRO arm and 48.2% & 43.5% for the FLUO arm.

In both studies, statistical comparisons of CIPRO+FLUO vs. FLUO using Fisher's exact test were significant ($p < 0.001$) indicating that findings of superiority in the primary analysis were highly robust and did not depend upon whether a time component is factored in. When comparing CIPRO+FLUO vs. CIPRO, rates of cessation consistently favored CIPRO+FLUO, however, the treatment differences in Trials 02 & 04 of 11.6% & 9.6% were not significant ($p=.069$ & $p=.129$). This indicated that findings of superiority for CIPRO+FLUO vs. CIPRO in the primary analysis were less robust and were dependent upon whether a time component is factored in.

Table 7: Sensitivity Analysis: Rates of Cessation of Otorrhea by Day 22 (CITT)

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 110)**
Number (%) of patients with cessation of otorrhea	88 (78.6%)	73 (67.0%)	53 (48.2%)
Treatment Difference (95% CI)[1]		11.6% (-0.1%, 23.2%)	30.4% (18.4%, 42.4%)
Binomial test, p-value[2]		0.069	<0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Number (%) of patients with cessation of otorrhea	87 (78.4%)	77 (68.8%)	47 (43.5%)

Treatment Difference (95% CI)[1]		9.6% (-1.9%, 21.1%)	34.9% (22.8%, 47.0%)
Binomial test, p-value[2]		0.129	<0.001

Source: Reviewer Table

[1] Treatment difference (95% CI) of 'CIPRO+FLUO – Component'

[2] Pairwise comparisons versus CIPRO+FLUO using Fisher's exact test

Sensitivity Analysis: Primary Analysis without Stratification

Sensitivity analyses were conducted to assess the potential impact of stratification on primary analysis findings. The statistical tests used in the primary analyses, log rank test and Wilcoxon test, were stratified according the patient's age group at baseline (patients less than 3 years old and patients 3 years and older). The sensitivity analyses shown in **Table 8** consider these statistical tests without using any stratification. Findings in these analyses appeared be similar to the findings observed in the primary analysis and were not meaningfully affected by assumptions regarding stratification by age.

Reviewer Comments: *Since the initial randomization was already stratified by age group (patients less than 3 years old and patients 3 years and older), the use of statistical tests stratified by age group vs. not stratified had a minimal impact on findings.*

Table 8: Sensitivity Analysis: Time to Cessation of Otorrhea without Stratification (CITT)

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 110)**
Number (%) of patients with cessation of otorrhea	88 (78.6%)	73 (67.0%)	53 (48.2%)
Time to cessation of otorrhea (days): Median (95% CI)	3.8 (3.0, 4.4)	7.7 (4.8, 11.4)	NE (7.4, NE)
Log rank test p-value[1]		0.003	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Number (%) of patients with cessation of otorrhea	87 (78.4%)	77 (68.8%)	47 (43.5%)
Time to cessation of otorrhea (days): Median (95% CI)	4.9 (3.7, 5.5)	6.8 (5.5, 7.7)	NE (13.9, NE)
Log rank test p-value		0.028	< 0.001
Wilcoxon test p-value		0.019	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test without stratification

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test without stratification

Sensitivity Analysis: Uncensored Patients Only

Exploratory/sensitivity analyses were conducted to compare treatment arms with respect to reductions in time to cessation of otorrhea among only uncensored patients (i.e. those patients achieving cessation by Day 22). Although these analyses involve some clear

biases since only the patients with the most favorable outcomes are being compared and there are differences in the proportions of patients selected from each of the treatment groups, they may provide insight into the ability of the components to reduce time to cessation of otorrhea. **Table 9** shows that patients in the CIPRO+FLUO arm had the shortest time to cessation and that comparisons for CIPRO and FLUO varied across trials, showing FLUO with a shorter median time to cessation than CIPRO in Trial 02 and CIPRO as having the shorter median time to cessation than FLUO in Trial 04. These analyses indicate that the addition of either of the components may lead to modest reductions in the time to cessation in uncensored patients but it is not clear as to which component is resulting in larger reductions.

Table 9: Sensitivity Analysis: Time to Cessation of Otorrhea Using Uncensored Patients Only (CITT)

Trial 02	**CIPRO+FLUO (N = 88)**	**CIPRO (N = 73)**	**FLUO (N = 53)**
Time to cessation of otorrhea (days): Median (95% CI)	2.9 (2.6, 3.6)	4.4 (3.3, 4.9)	3.6 (2.1, 5.0)
Log rank test p-value[1]		0.003	0.207
Wilcoxon test p-value[2]		0.002	0.361
Trial 04	**CIPRO+FLUO (N = 87)**	**CIPRO (N = 77)**	**FLUO (N = 47)**
Time to cessation of otorrhea (days): Median (95% CI)	3.7 (3.1, 4.8)	4.6 (3.5, 5.5)	5.4 (4.6, 5.9)
Log rank test p-value[1]		0.062	0.016
Wilcoxon test p-value[2]		0.088	0.018

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using CMH test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO using CMH test stratified by age (< 3 yrs vs. ≥ 3yrs)

Sensitivity Analysis: Censoring All Discontinued Patients at Day 1

In order to assess the effect of censoring on primary analysis results, sensitivity analyses were conducted where all discontinued patients were censored at Day 1. While this sensitivity analysis may not be useful by itself, a comparison of findings from the primary analysis which censored patients at Day 22 (essentially considering them as having no cessation) and this sensitivity analysis which censored patients at Day 1 (essentially excluding them from the analysis) can help to determine whether primary analysis findings are robust to assumptions regarding censoring. As shown in **Table 10**, there is a significant contribution of each of the components of CIPRO+FLUO which shows that primary analysis findings (shown earlier in **Table 5)** are likely to be robust to the assumptions used for censoring discontinued patients.

Table 10: Sensitivity Analysis: Time to Cessation of Otorrhea Censoring All Discontinued Patients at Day 1 (CITT)

Trial 02	CIPRO+FLUO (N = 112)	CIPRO (N = 109)	FLUO (N = 110)
Number (%) of patients with cessation of otorrhea	88 (78.6%)	73 (67.0%)	53 (48.2%)
Time to cessation of otorrhea (days): Median (95% CI)	3.6 (2.9, 4.3)	7.1 (4.8, 9.4)	17.1 (7.1, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 108)**
Number of patients with cessation of otorrhea	87 (78.4%)	77 (68.8%)	47 (43.5%)
Time to cessation of otorrhea (days): Median (95% CI)	4.9 (3.7, 5.5)	6.7 (5.0, 7.7)	NE (NE, NE)
Log rank test p-value		0.023	< 0.001
Wilcoxon test p-value		0.015	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Sensitivity Analysis: Analysis of MITT Population Only

In **Table 11**, sensitivity analyses were conducted in an analysis population of MITT patients only. These analyses determine whether the inclusion of patients without a baseline pathogen in the primary analysis could have potentially influenced treatment comparisons. Although there is a loss in statistical power associated with using the smaller MITT population (58.9% & 56.1% of CITT patients in Trials 02 & 04 were included in the MITT, **Table 3**), statistical comparisons showed similar degrees of significance. This indicates that primary analysis results were robust to assumptions regarding the analysis population considered (i.e. CITT or MITT).

Table 11: Sensitivity Analysis: Time to Cessation of Otorrhea (MITT)

Trial 02	CIPRO+FLUO (N = 65)	CIPRO (N = 70)	FLUO (N = 60)
Number (%) of patients with cessation of otorrhea	51 (88.5)	45 (64.3)	26 (43.3)
Time to cessation of otorrhea (days): Median (95% CI)	4.3 (3.3, 6.3)	8.1 (4.9, 16.4)	NE (9.5, NE)
Log rank test p-value[1]		0.009	< 0.001
Wilcoxon test p-value[2]		0.008	< 0.001
Trial 04	**CIPRO+FLUO (N = 60)**	**CIPRO (N = 65)**	**FLUO (N = 62)**
Number of patients with cessation of	48 (80.0)	43 (66.1)	23 (37.1)

otorrhea			
Time to cessation of otorrhea (days): Median (95% CI)	4.6 (3.2, 6.8)	7.0 (5.9, 11.8)	NE (19.5, NE)
Log rank test p-value[1]		0.030	< 0.001
Wilcoxon test p-value[2]		0.029	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

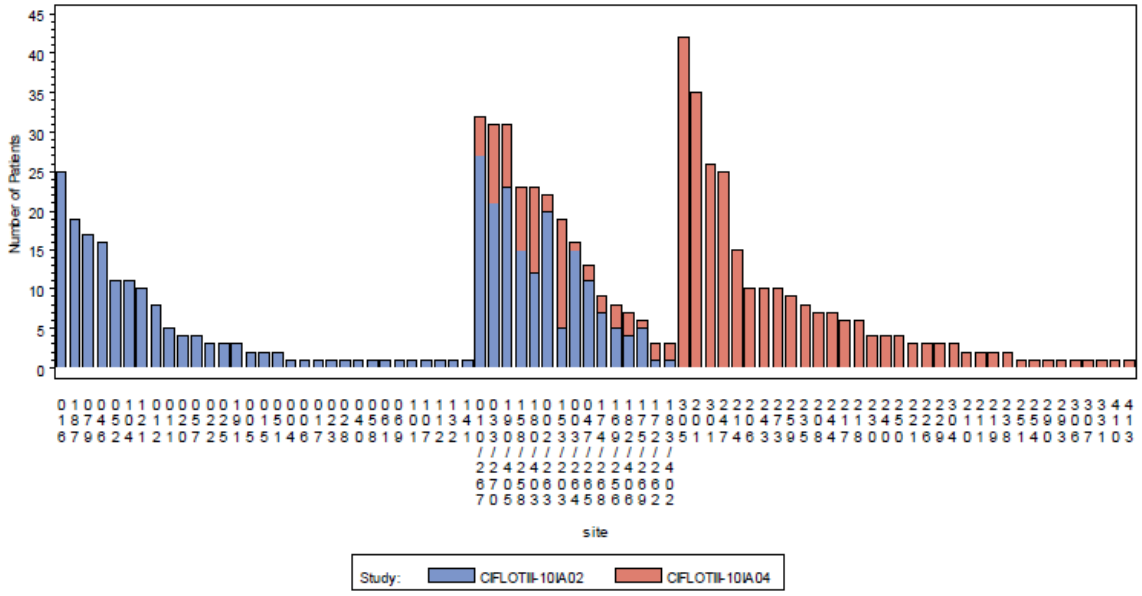
[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Sensitivity Analysis: Patients from Sites Not Shared Across Trials 02 & 04

In this submission, the Applicant provided **Figure 4** which shows all the study sites used in Studies 02 and 04, including those sites used in Study 02 only, those sites used in Study 04 only and those sites used in both Study 02 and Study 04. Reviewer sensitivity analyses assessed the influence of the sharing of study sites on primary analysis findings. From **Table 12**, treatment comparisons did not meaningfully change when excluding all shared sites.

Reviewer Comments: *Some sites that completed participation in the 02 study were also selected to participate in the identical clinical study, Study 04. However, based on Agency recommendations, the rollover of sites would be minimized and high enrolling sites from Study 04 were not permitted to continue and/or be initiated in Study 02. In addition, Study 04 would remain blinded until Study 02 was completed.*

Figure 3: Distribution of Patients Enrolled in each Study Site, Trials 02 & 04 (CITT)



Source: Applicant Figure 14.2.1.13 in SCE

Table 19: Sensitivity Analysis: Time to Cessation of Otorrhea (Per Protocol Population), Trials 02 & 04

Trial 02	CIPRO+FLUO (N = 82)	CIPRO (N = 80)	FLUO (N = 83)
Number (%) of patients with cessation of otorrhea	67 (81.7)	55 (68.8)	41 (49.4)
Time to cessation of otorrhea (days): Median (95% CI)	3.7 (2.8, 4.4)	8.0 (4.7, 11.4)	NE (6.8, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 77)**	**CIPRO (N = 89)**	**FLUO (N = 73)**
Number of patients with cessation of otorrhea	61 (79.2)	61 (68.5)	28 (38.4)
Time to cessation of otorrhea (days): Median (95% CI)	5.0 (3.7, 5.5)	6.5 (4.8, 7.2)	NE (19.5, NE)
Log rank test p-value[1]		0.076	< 0.001
Wilcoxon test p-value[2]		0.123	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Reviewer Comments: *In Trial 02, the Sponsor reported slightly different findings, identifying 83 rather than 82 patients in the CIPRO+FLUO group and 82 rather than 83 patients in the FLUO group. However, Reviewer calculations of p-values for the log rank and Wilcoxon tests as well as calculations for the median (95% CI) were not altered despite this difference. There was only a slight disparity in findings regarding the number (%) of patients with cessation of otorrhea.*

Table 20 considers patients with prior antibiotic use as well as patients with prior antibiotic use within 48 hours of initiation of study drug. These patients are of primary concern in potentially influencing study outcomes. Since the number of patients with prior antibiotic use within 48 hours was observed to be very small, only one subject per study, prior antibiotic use was not considered to be a factor in the primary analysis and no further analyses were considered.

Table 20: Number (%) of Patients with Prior Antibiotic Use (CITT)

	CIPRO+FLUO	CIPRO	FLUO	Total
Trial 02	**N=112**	**N=109**	**N=110**	**N=331**
Patients with Prior Antibiotic Use	6 (5.4%)	4 (3.7%)	6 (5.5%)	16 (4.8%)
Patients with Prior Antibiotic Use within 48 hours of initiation of study drug	1 (0.9%)	0	0	1 (0.3%)
Trial 04	**N=111**	**N=112**	**N=108**	**N=331**
Patients with Prior Antibiotic Use	10 (9.0%)	5 (4.5%)	2 (1.9%)	17 (5.1%)
Patients with Prior Antibiotic Use within	0	1 (0.9%)	0	1 (0.3%)

48 hours of initiation of study drug				

Source: Reviewer Table

Tables 21 & 22 explore the potential influence that use of prohibited concomitant antibacterial medications may have on the primary outcome. As shown in **Table 21**, such use was rather limited at 6.0% in Trial 02 and 8.5% in Trial 04.

Table 21: Number (%) of Patients with Use of Prohibited Concomitant Antibacterial Medications (CITT)

	CIPRO+FLUO	CIPRO	FLUO	Total
Trial 02	**N=112**	**N=109**	**N=110**	**N=331**
Patients with use of effective concomitant antibiotic medication	7 (6.3%)	5 (4.6%)	8 (7.3%)	20 (6.0%)
Trial 04	**N=111**	**N=112**	**N=108**	**N=331**
Patients with use of effective concomitant antibiotic medication	8 (7.2%)	9 (8.0%)	11 (10.2%)	28 (8.5%)

Source: Reviewer Table

Reviewer Comments: *The use of prohibited concomitant antibacterial medications can lead to potential confounding of the primary analysis. Note that patients may improve their primary outcome with such antibacterial use. This would tend to reduce the median time to cessation of otorrhea across the treatment arms and make it more difficult to show superiority. However, if large disparities exist across treatment arms with respect to such antibacterial use then this can lead to potential biases.*

*In **Table 22,** a sensitivity analysis is conducted removing all CITT patients using effective concomitant antibacterial medications. Results in this analysis population appeared to be similar to those of the primary analysis indicating that any impact from such concomitant use is likely to be minimal.*

Table 22: Sensitivity Analysis: Time to Cessation of Otorrhea in CITT Patients not Using Prohibited Concomitant Antibacterial Medications (CITT), Trials 02 & 04

Trial 02	**CIPRO+FLUO (N = 105)**	**CIPRO (N = 104)**	**FLUO (N = 102)**
Number (%) of patients with cessation of otorrhea	83 (79.0)	70 (67.3)	51 (50.0)
Time to cessation of otorrhea (days): Median (95% CI)	3.7 (3.0, 4.5)	7.7 (4.9, 11.4)	NE (7.1, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 103)**	**CIPRO (N = 103)**	**FLUO (N = 97)**
Number of patients with cessation of otorrhea	83 (80.6)	72 (69.9)	44 (45.4)
Time to cessation of otorrhea (days):			

Median (95% CI)	5.0 (3.8, 5.6)	6.6 (4.9, 7.6)	NE (9.8, NE)
Log rank test p-value[1]		0.024	< 0.001
Wilcoxon test p-value[2]		0.020	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

In **Table 23**, a sensitivity analysis was conducted in CITT patients not using titanium tubes. The use of titanium tubes can have an antibacterial effect which can confound analyses. These analyses did not indicate that the use of titanium tubes is likely to influence the primary outcome.

Table 23: Sensitivity Analysis: Time to Cessation of Otorrhea in CITT Patients not Using Titanium Tubes, Trials 02 & 04

Trial 02	**CIPRO+FLUO (N = 101)**	**CIPRO (N = 100)**	**FLUO (N = 104)**
Number (%) of patients with cessation of otorrhea	79 (78.2)	67 (67.0)	51 (49.0)
Time to cessation of otorrhea (days): Median (95% CI)	3.7 (3.0, 4.7)	7.7 (4.8, 11.4)	NE (7.4, NE)
Log rank test p-value[1]		0.003	< 0.001
Wilcoxon test p-value[2]		0.002	< 0.001
Trial 04	**CIPRO+FLUO (N = 106)**	**CIPRO (N = 100)**	**FLUO (N = 99)**
Number of patients with cessation of otorrhea	82 (77.4)	66 (66.0)	45 (45.5)
Time to cessation of otorrhea (days): Median (95% CI)	5.0 (3.8, 5.6)	6.9 (5.8, 9.0)	NE (10.6, NE)
Log rank test p-value[1]		0.025	< 0.001
Wilcoxon test p-value[2]		0.023	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

In **Table 24**, a sensitivity analysis is performed in CITT patients who took no out of specification study medication in order to investigate possible confounding effects. Sensitivity analyses performed in this patient population showed similar findings to primary analyses performed in the CITT population.

Table 24: Sensitivity Analysis: Time to Cessation of Otorrhea in CITT Patients who Took No Out of Specification Study Medication, Trials 02 & 04

Trial 02	**CIPRO+FLUO (N = 112)**	**CIPRO (N = 109)**	**FLUO (N = 93)**
Number (%) of patients with cessation	88 (78.6)	73 (67.0)	47 (50.5)

of otorrhea			
Time to cessation of otorrhea (days): Median (95% CI)	3.8 (3.0, 4.4)	7.7 (4.8, 11.4)	19.7 (7.1, NE)
Log rank test p-value[1]		< 0.001	< 0.001
Wilcoxon test p-value[2]		< 0.001	< 0.001
Trial 04	**CIPRO+FLUO (N = 111)**	**CIPRO (N = 112)**	**FLUO (N = 84)**
Number of patients with cessation of otorrhea	87 (77.7)	77 (68.8)	38 (45.2)
Time to cessation of otorrhea (days): Median (95% CI)	4.9 (3.7, 5.5)	6.8 (5.5, 7.7)	NE (10.6, NE)
Log rank test p-value[1]		0.028	< 0.001
Wilcoxon test p-value[2]		0.018	< 0.001

Source: Reviewer Table

[1]Pairwise comparisons versus CIPRO+FLUO using the log-rank test stratified by age (< 3 yrs vs. ≥ 3yrs)

[2]Pairwise comparisons versus CIPRO+FLUO using the wilcoxon test stratified by age (< 3 yrs vs. ≥ 3yrs)

Reviewer Exploratory/Sensitivity Analyses of the Principal Secondary Endpoint

Further exploratory/sensitivity analyses for the principal secondary endpoint were conducted. **Tables 25, 26, 27 and 28** show the microbiological success rates for Visits 3 and 4, both overall and by target pathogen. In **Table 25** (Visit 3) and **Table 26** (Visit 4), the percentage of patients with each microbiological response was summarized at Visit 3 and Visit 4 and compared between the CIPRO+FLUO and CIPRO groups, the CIPRO+FLUO and FLUO groups and the CIPRO and FLUO groups using a CMH test at Visit 3 and Visit 4.

Table 25 shows that for Trials 02 & 04, respectively, microbiological response rates at the end of treatment visit (Visit 3) were highest in the CIPRO+FLUO arm at 81.5% & 84.7%, next highest in the CIPRO arm at 64.7% & 73.4% and lowest in the FLUO arm at 44.8% & 36.1%. Post-hoc comparisons using a CMH test (stratified by age group) were also performed for CIPRO+FLUO vs. FLUO (p-values of < 0.001 & < 0.001), CIPRO vs. FLUO (p-values of 0.023 & < 0.001) and for CIPRO + FLUO vs. CIPRO (p-values of 0.046 & 0.187). However, as these are post-hoc comparisons where the overall type I error rate is not controlled, the interpretation of these findings is extremely limited. However, findings from these sensitivity/exploratory analyses appear to be generally consistent with secondary analyses based on the sustained microbiological cure rate.

Table 25: Microbiological Response at Visit 3 (End of Treatment)

Trial 02	**CIPRO+FLUO (N = 65)**	**CIPRO (N = 70)**	**FLUO (N = 60)**
Favorable	53 (81.5)	44 (64.7)	26 (44.8)
Unfavorable	7 (10.8)	19 (27.9)	30 (51.7)
Indeterminate	5 (7.7)	5 (7.4)	2 (3.4)
Total	65 (100)	68 (100)	58 (100)

Missing	0	2	2
CMH test p-value vs. CIPRO+FLUO		0.046	< 0.001
CMH test p-value vs. CIPRO			0.023
Trial 04	**CIPRO+FLUO (N = 60)**	**CIPRO (N = 65)**	**FLUO (N = 62)**
Favorable	50 (84.7)	47 (73.4)	22 (36.1)
Unfavorable	5 (8.5)	13 (20.3)	36 (59.0)
Indeterminate	4 (6.8)	4 (6.3)	3 (4.9)
Total	59 (100)	64 (100)	61 (100)
Missing	1	1	1
CMH test p-value vs. CIPRO+FLUO		0.187	< 0.001
CMH test p-value vs. CIPRO			< 0.001

[1] Missing data at Visit 4 were imputed as "unfavorable". Missing data after receiving rescue medication are not replaced.

Source: Partially adapted from Sponsor Table 14.2.2.1

Table 26 shows that for Trials 02 & 04, respectively, microbiological response rates at the test of cure visit (Visit 4) were highest in the CIPRO and CIPRO+FLUO arms at 84.6% & 89.8% (CIPRO) and 83.1% & 88.7% (CIPRO+FLUO) and lowest in the FLUO arm at 71.4% and 73.3%. Post-hoc comparisons using a CMH test (stratified by age group) were also performed for CIPRO+FLUO vs. CIPRO, CIPRO vs. FLUO and CIPRO + FLUO vs. CIPRO, however all of the estimated p-values were not significant.

These analyses were limited by the substantial amount of missing data for the test-of-cure visit which was due to patients who did not have a favorable response at Visit 3 being counted as 'Missing' at Visit 4. As a result, missing data occurred much less frequently in the CIPRO+FLUO arm and much more frequently in the FLUO arm. In these analyses, patients who received rescue medication were counted as 'Missing' and patients with no exudate in their ear at Visit 4 were also counted as 'Missing'. However, patients with missing data due to having withdrawn consent were imputed as "Unfavorable."

Reviewer Comments: *The Reviewer considers this methodology for handling missing data as being conservative since the CIPRO+FLUO arm had the least missing data. These analyses show that treatment differences in sustained microbiological cure rates in the principal secondary analyses appear to be driven primarily by the treatment differences observed at the end of treatment visit (Visit 3).*

Table 26: Microbiological Response at Visit 4 (Test of Cure)

Trial 02	**CIPRO+FLUO (N = 65)**	**CIPRO (N = 70)**	**FLUO (N = 60)**
Favorable	49 (83.1)	44 (84.6)	25 (71.4)
Unfavorable	5 (8.5)	5 (9.6)	9 (25.7)
Indeterminate	5 (8.5)	3 (5.8)	1 (2.9)
Total	59 (100)	52 (100)	35 (100)
Missing	6	18	25
CMH test p-value vs. CIPRO+FLUO		0.835	0.057

CMH test p-value vs. CIPRO			0.139
Trial 04	**CIPRO+FLUO (N = 60)**	**CIPRO (N = 65)**	**FLUO (N = 62)**
Favorable	47 (88.7)	44 (89.8)	22 (73.3)
Unfavorable	4 (7.5)	4 (8.2)	6 (20.0)
Indeterminate	2 (3.8)	1 (2.0)	2 (6.7)
Total	53 (100)	49 (100)	30 (100)
Missing	7	16	32
CMH test p-value vs. CIPRO+FLUO		0.876	0.280
CMH test p-value vs. CIPRO			0.310

Source: Partially adapted from Sponsor Table 14.2.2.2.1

Additional analyses were conducted to explore microbiological response rates by pathogen in the MITT population at Visits 3 and 4. Findings in these analyses are shown in **Table 27** (Trial 02) and **Table 28** (Trial 04). However, comparisons by pathogen were generally limited by the small number of isolates presented.

Table 27: Microbiological Response Rates by Pathogen (Visits 3 & 4), Trial 02

Trial 04	**CIPRO+FLUO (N = 65)**		**CIPRO (N = 70)**		**FLUO (N = 60)**	
Pathogen Isolated Response	**Visit 3**	**Visit 4**	**Visit 3**	**Visit 4**	**Visit 3**	**Visit 4**
Pseudomonas aeruginosa, n (%)						
n	11	11	12	12	12	12
Favorable	10 (90.9)	10 (90.9)	6 (50.0)	8 (66.7)	2 (16.7)	2 (16.7)
Unfavorable	1 (9.1)	0	4 (33.3)	0	8 (66.7)	2 (16.7)
Indeterminate	0	0	1 (8.3)	0	1 (11.1)	0
Missing	0	1 (9.1)	1 (8.3)	4 (33.3)	2 (16.7)	8 (66.7)
Staphylococcus aureus, n (%)						
n	26	26	25	25	23	23
Favorable	22 (84.6)	18 (69.2)	15 (60.0)	15 (60.0)	8 (34.8)	7 (30.4)
Unfavorable	2 (7.7)	2 (7.7)	8 (32.0)	0	10 (43.5)	4 (17.4)
Indeterminate	2 (7.7)	2 (7.7)	0	0	2 (8.7)	1 (4.3)
Missing	0	4 (15.4)	2 (8.0)	10 (40.0)	3 (13.0)	11 (47.8)
Moraxella catarrhalis, n (%)						
n	6	6	7	7	1	1
Favorable	6 (100)	5 (83.3)	4 (57.1)	6 (85.7)	1 (100)	1 (100)
Unfavorable	0	0	3 (42.9)	0	0	0
Indeterminate	0	0	0	0	0	0
Missing	0	1 (16.7)	0	1 (14.3)	0	0
Haemophilus influenzae, n (%)						
n	18	18	22	22	16	16
Favorable	13 (72.2)	9 (50.0)	15 (68.2)	15 (68.2)	7 (43.8)	8(50.0)
Unfavorable	2 (11.1)	1 (5.6)	3 (13.6)	0	8 (50.0)	0
Indeterminate	3 (16.7)	2 (11.1)	3 (13.6)	2 (9.1)	1 (6.3)	0
Missing	0	6 (33.3)	1 (4.5)	5 (22.7)	0	8(50.0)
Streptococcus pneumoniae, n (%)						
n	6	6	10	10	6	6
Favorable	3 (50.0)	3 (50.0)	7 (70.0)	8 (80.0)	2 (33.3)	2 (33.3)

Unfavorable	3 (50.0)	0	2 (20.0)	0	1 (16.7)	0
Indeterminate	0	0	1 (10.0)	1 (10.0)	1 (16.7)	0
Missing	0	3 (50.0)	0	1 (10.0)	1 (16.7)	4 (66.7)

Notes: n is the number of patients who had the pathogen alone or in combination with other pathogens at Visit 1 (each patient may have appeared in multiple rows). n (%) is the number (percentage of n) of patients with each microbiological outcome.

Source: Partially adapted from Sponsor Table 14.2.2.5

Table 28: Microbiological Response Rates by Pathogen (Visits 3 & 4), Trial 04

Trial 04	**CIPRO+FLUO (N = 60)**		**CIPRO (N = 65)**		**FLUO (N = 62)**	
Pathogen Isolated Response	**Visit 3**	**Visit 4**	**Visit 3**	**Visit 4**	**Visit 3**	**Visit 4**
Pseudomonas aeruginosa, n (%)						
n	10	10	6	6	9	9
Favorable	9 (90.0)	8 (80.0)	5 (83.3)	5 (83.3)	1 (11.1)	2 (22.2)
Unfavorable	0	1 (10.0)	0	0	7 (77.8)	0
Indeterminate	1 (10.0)	0	0	0	1 (11.1)	0
Missing	0	1 (10.0)	1 (16.7)	1 (16.7)	0	7 (77.8)
Staphylococcus aureus, n (%)						
n	18	18	28	28	21	21
Favorable	15 (83.3)	15 (83.3)	15 (53.6)	14 (50.0)	9 (42.9)	8 (38.1)
Unfavorable	1 (5.6)	0	11 (39.3)	1 (3.6)	8 (38.1)	1 (4.8)
Indeterminate	1 (5.6)	0	1 (3.6)	0	3 (14.3)	1 (4.8)
Missing	1 (5.6)	3 (16.7)	1 (3.6)	13 (46.4)	1 (4.8)	11 (52.4)
Moraxella catarrhalis, n (%)						
n	9	9	9	9	6	6
Favorable	8 (88.9)	8 (88.9)	6 (66.7)	6 (66.7)	4 (66.7)	4 (66.7)
Unfavorable	0	0	1 (11.1)	0	1 (16.7)	1 (16.7)
Indeterminate	1 (11.1)	0	2 (22.2)	0	0	0
Missing	0	1 (11.1)	0	3 (33.3)	1 (16.7)	1 (16.7)
Haemophilus influenzae, n (%)						
n	15	15	19	19	25	25
Favorable	13 (86.7)	12 (80.0)	17 (89.5)	15 (78.9)	7 (28.0)	7 (28.0)
Unfavorable	1 (6.7)	1 (6.7)	0	2 (10.5)	16 (64.0)	3 (12.0)
Indeterminate	1 (6.7)	1 (6.7)	1 (5.3)	0	1 (4.0)	0
Missing	0	1 (6.7)	1 (5.3)	2 (10.5)	1 (4.0)	15 (60.0)
Streptococcus pneumoniae, n (%)						
n	7	7	6	6	10	10
Favorable	6 (85.7)	6 (85.7)	6 (100)	6 (100)	5 (50.0)	6 (60.0)
Unfavorable	1 (14.3)	0	0	0	5 (50.0)	0
Indeterminate	0	0	0	0	0	0
Missing	0	1 (14.3)	0	0	0	4 (40.0)

Notes: n is the number of patients who had the pathogen alone or in combination with other pathogens at Visit 1 (each patient may have appeared in multiple rows). n (%) is the number (percentage of n) of patients with each microbiological outcome.

Source: Partially adapted from Sponsor Table 14.2.2.5

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Christopher Kadoorie, Ph.D.
Date: 4/14/2016

Concurring Reviewer: Karen Higgins, ScD, Statistical Team Leader

cc:
Carmen DeBellas, RPh, PharmD Project Manager
Dmitri Iarikov, MD, PhD, Medical Team Leader
Mayurika Ghosh, MD, Medical Reviewer
Sumathi Nambiar, MD, Division Director
Christopher Kadoorie, PhD, Primary Statistical Reviewer
Karen Higgins, ScD, Statistical Team Leader
Daphne Lin, PhD, Biometrics Deputy Division Director
Dionne Price, PhD, Biometrics Division Director
Lillian Patrician MS, MBA, Mathematical Statistician

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER E KADOORIE
04/14/2016

KAREN M HIGGINS
04/14/2016
I concur.