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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number: 22,428
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Indication(s): Treatment of bacterial conjunctivitis
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1. EXECUTIVE SUMMARY

Alcon Pharmaceuticals Ltd., referred hereafter as Applicant, attempts to completely address the deficiency described in FDA's Complete Response letter dated 07 October, 2009. In that letter, FDA requested an additional adequate and well-controlled study be conducted to support the approval of Moxifloxacin AF for treating bacterial conjunctivitis. Herein, the Applicant submits the results of the additional vehicle-controlled trial, Study C-07-40. This study is a prospective, multi-center, double masked, parallel group, randomized (1:1), vehicle-controlled trial designed to evaluate efficacy and safety of topical ocular Moxifloxacin AF Ophthalmic Solution compared to Moxifloxacin AF vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. The primary clinical efficacy variable was the clinical cure rate attained when the sum of the two cardinal ocular signs (bulbar conjunctival injection and conjunctival discharge/exudate) was zero at Day 4 (EOT)/Exit Visit in the microbiological intent-to-treat (MBITT) population which includes all patients who received study drug, are culture-positive at Day 1 and had at least one on-therapy visit.

1.1 Conclusions and Recommendations

The clinical cure rate for Moxifloxacin AF was 62.50% (265/424) vs. 50.59% (214/423) for Vehicle. The treatment difference is 11.91% [95% CI: (5.07, 18.60)] and is statistically significant (p-value = 0.0005). In addition, the microbiological success rate for Moxifloxacin AF was 74.5% (316/424) compared to 56.0% (237/423) for the Vehicle. The difference in microbiological success is 18.5% (12.2, 24.8) and is statistically significant (p < 0.0001). The results are robust and are also demonstrated in other efficacy populations.

The results of this study are also consistent with the results of the previously submitted Study C-04-38, which was a prospective, multi-center (32 US sites), double masked, parallel group, randomized, vehicle-controlled trial designed to evaluate efficacy and safety of topical ocular Moxifloxacin AF Ophthalmic Solution compared to vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. In this Study, the clinical cure rate for Moxifloxacin AF in a similarly defined population was 58.4% (104/178) vs. 46.7% (78/169) for Vehicle at Day 4 (EOT) Visit and the treatment difference is 12.3% [95% CI(1.4, 22.8)]. This result is also consistent with the results of the other efficacy datasets.

This review concludes that Study C-07-40 has established efficacy of Moxifloxacin AF for the treatment of bacterial conjunctivitis and completely addresses FDA's request for an additional adequate and well-controlled study to support the approval of Moxifloxacin AF in the said indication.

1.2 Brief Overview of Clinical Studies

Study C-07-40 was a prospective, multi-center, double masked, parallel group, randomized (1:1), vehicle-controlled trial designed to evaluate efficacy and safety of topical ocular Moxifloxacin AF Ophthalmic Solution compared to Moxifloxacin AF vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. There were 1180 patients enrolled with clinical diagnosis of bacterial conjunctivitis and achieved 847 bacterial pathogen positive patients (424 on Moxifloxacin AF Ophthalmic Solution and 423 on Vehicle). The study is 4 days

in duration with visits at Day 1 (Screening/Baseline), Day 3 (- 1), and Day 4/Exit (EOT, 12- 48 hours after the last dose).

The primary clinical efficacy variable was the clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection including bulbar conjunctival injection and conjunctival discharge/exudate at Day 4 (EOT)/Exit visit (12-48 hours after the last dose) in the study eyes. Clinical cure was attained when the sum of the two cardinal ocular signs was zero. The key secondary efficacy variable was the microbiological success at the Day 4 (EOT)/Exit Visit in the study eyes. Microbiological success was attained if the pre-therapy bacterial pathogens were eradicated.

Analyses were conducted on all data sets, but primary inference was based on the microbiological intent-to-treat (MBITT) data set.

1.3 Statistical Issues and Findings

The reviewer did not identify any statistical issues that would preclude finding that Moxifloxacin AF is efficacious in the treatment of bacterial conjunctivitis. For the treatment difference in proportions for the primary endpoint and key secondary endpoints, the reviewer calculated the 95% CI using the Wilson's procedure with continuity correction. This procedure yielded slightly different results from those of the asymptotic (Wald) confidence limits reported in the submission. The conclusions are the same regardless of the analysis methods.

In the MBITT data set, the primary efficacy endpoint of clinical cure rate for Moxifloxacin AF was 62.50% (265/424) and 50.59% (214/423) for Vehicle at Day 4 (EOT)/Exit Visit. The treatment difference between Moxifloxacin AF and Vehicle is 11.91% (5.07, 18.60) which statistically significantly favors Moxifloxacin AF. A similar result can also be obtained from the remaining efficacy populations.

Table 1.1 Cure Rate for Studies C-04-38 and C-07-40 at Day 4 Visit

	C-04-38		C-07-40	
	Moxifloxacin AF	Vehicle	Moxifloxacin AF	Vehicle
MBITT				
Clinical cure, (n%)	104/178 (58.4)	78/169 (46.7)	265/424(62.5)	214/423 (50.6)
Treatment difference (Moxi AF – Vehicle) and 95% CI	12.3 (1.4, 22.8)		11.91 (5.07, 18.60)	
MITT				
Clinical cure, (n%)	103/177 (58.2)	77/165 (46.7)	261/415 (62.9)	207/414 (50.0)
Treatment difference (Moxi AF – Vehicle) and 95% CI	11.5 (0.5, 22.2)		12.89 (5.97, 19.64)	
PP				
Clinical cure, (n%)	146/247 (59.1)	99/236 (41.1)	342/539 (63.5)	285/529 (53.9)
Treatment difference (Moxi AF – Vehicle) and 95% CI	17.2 (8.0, 26.0)		9.52 (3.59, 15.35)	
MPP				
Clinical cure, (n%)	80/132 (60.6)	54/122 (44.3)	243/383 (63.4)	194/380 (51.1)
Treatment difference (Moxi AF – Vehicle) and 95% CI	16.3 (3.5, 28.5)		12.3 (5.28, 19.16)	

95% Confidence Interval is based on Wilson's procedure with continuity correction

Moxifloxacin AF is also superior to Vehicle for microbiological success (the key secondary efficacy endpoint), defined as the eradication of pre-therapy pathogen(s), at the Day 4 (EOT)/Exit Visit. The microbiological success rate for Moxifloxacin AF was 74.5% (316/424) compared to 56.0% (237/423) for Vehicle in the MBITT population. A similar result can also be obtained from the other remaining analysis populations.

The treatment effect of Moxifloxacin AF is also supported by the results of the secondary efficacy endpoints. The secondary efficacy endpoints include clinical outcome at the Day 3 visit and the eight individual ocular sign and symptom cure rates (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia) at the Day 3 and Day 4 (EOT)/Exit visits. A cure for an individual ocular sign or symptom is attained if the score is zero (i.e. absent or normal).

The results of the primary efficacy endpoint are also consistent with the results of Study C-04-38 (see Table 1.1), which was a prospective, multi-center, double masked, parallel group, randomized, vehicle-controlled trial designed to evaluate efficacy and safety of topical ocular Moxifloxacin AF Ophthalmic Solution compared to vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. Although the primary efficacy parameter assessed in this study was the clinical cure rate at Day 7 visit, the clinical cure rate at Day 4 (EOT) Visit was assessed as one of the secondary efficacy endpoints. In this visit, the clinical cure rate for Moxifloxacin AF was 58.4% (104/178) vs. 46.7% (78/169) for Vehicle. This result is also consistent with the results of the other efficacy datasets and by the microbiological eradication rate.

Reviewer remark: The primary efficacy endpoint (defined as the clinical cure rate at Day 7) in Study C-04-38 did not show superiority of Moxifloxacin AF versus Vehicle. That is why the secondary endpoint which is the clinical cure at Day 4 (EOT) Visit cannot be tested. Nevertheless, the data is being used here as supporting information that the treatment effect of Moxifloxacin over Vehicle is reliable and is not due to chance.

2. INTRODUCTION

2.1 Overview

Moxifloxacin is a broad spectrum, fourth generation fluoroquinolone, active against both Gram-positive and Gram-negative bacteria. Moxifloxacin hydrochloride was developed by Bayer HealthCare AG as AVELOX in tablet (NDA 21-085) and intravenous (NDA 21-277) formulation for a variety of bacterial infections (community acquired pneumonia, acute bacterial sinusitis, complicated skin and skin structure infections, etc.). The mechanism of antibacterial action of moxifloxacin resides in its ability to inhibit two important enzymes involved in DNA replication, transcription, repair and recombination (i.e., DNA gyrase and DNA topoisomerase IV).

Because moxifloxacin is particularly active against *staphylococci*, *pneumococci*, and community acquired respiratory pathogens, Alcon licensed moxifloxacin hydrochloride from Bayer and developed VIGAMOX (moxifloxacin hydrochloride ophthalmic solution 0.5% as base, for the treatment of bacterial conjunctivitis (NDA 21-598). The approved dosage is one drop in the affected eye three times a day for seven days. Recently, Alcon developed a moxifloxacin-based ophthalmic solution (0.5% active concentration) containing (b) (4) - (b) (4) (b) (4) (xanthan gum) that is expected to provide similar efficacy and safety to VIGAMOX (t.i.d for 7 days) with a reduced dosing regimen. This formulation, referred to as Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution, is developed for the same indication but with a dosing regimen of one drop administered two times a day for 7 days.

2.1.1 Regulatory history of Moxifloxacin AF drug development

The Applicant submitted the original NDA 22428 on December 12, 2008. FDA issued a Complete Response letter on October 7, 2009, identifying lack of substantial evidence of efficacy as the reason for the action and recommending the conduct of at least one additional adequate and well-controlled clinical study.

With this resubmission, the Applicant attempts to completely address the deficiency described in the Complete Response letter. Results of the additional vehicle-controlled pivotal trial (C-07-40) have been included herein.

2.1.2 Clinical Studies Reviewed

Only one clinical study, C-07-40, is submitted and reviewed. This study is a randomized, double-masked, multi-center, parallel group study.

Table 2.1 Study parameters of C-07-40

Protocol	C-07-40 Safety/Efficacy study
Study Design	Prospective, multi-center, randomized, vehicle-controlled, double-masked
Study Objective	Evaluate the safety/efficacy of Moxifloxacin AF 0.5% compared to Moxifloxacin AF vehicle in the treatment of bacterial conjunctivitis in patients 1 months or older
Treatment Groups	Moxifloxacin AF ophthalmic 0.5% solution and vehicle
Subject/Patient population	Adults and children (≥ 1 month of age) with bacterial conjunctivitis
Dosing Regimen	1 drop BID OU vs 1 drop BID OU
Dosing Duration	3 days
Patients Enrolled	1180 (847 microbiologically evaluable)
Primary Efficacy	Clinical cure (sum of scores for bulbar conjunctival injection and conjunctival discharge/exudate = 0) at Day 4 (EOT)/Exit Visit
Secondary Efficacy	Microbiological success (eradication of pre-therapy pathogens) at Day 4 (EOT)/Exit Visit
Safety Variables	Visual acuity, ocular signs, dilated fundus exam, adverse events
Study Visits	Day 1 (Baseline/Screening); Day 3; Day 4 (EOT: 12-48 hrs after last dose)
Primary Efficacy Dataset	Microbiological Intent-To-Treat (MBITT)

2.2 Data Sources

The clinical study reports were provided in a paper submission. Datasets and SAS codes for analysis of primary and secondary endpoints are provided in EDR: \\FDSWA150\NONECTD\N22428\N_000\2010-07-13. Overall, the data sets were adequately documented.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study C-07-40 was a prospective, multi-center, double masked, parallel group, randomized (1:1), vehicle-controlled trial designed to evaluate efficacy and safety of topical ocular Moxifloxacin AF Ophthalmic Solution compared to Moxifloxacin AF vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. There were 1180 patients enrolled with clinical diagnosis of bacterial conjunctivitis and achieved 847 bacterial pathogen positive patients (424 on Moxifloxacin AF Ophthalmic Solution and 423 on Vehicle).

The study consisted of 3 visits conducted over a period of 4 days: Day 1 (Screening/Baseline) Visit, an interim visit at Day 3, and study exit visit at Day 4 (12-48 hours following the last study dose). Patients were instructed to dose the study medication in both eyes 1 drop twice daily (BID) for 3 days. Patients of any race and either sex, 1 month of age and older, diagnosed with bacterial conjunctivitis in 1 or both eyes were enrolled. A diagnosis of bacterial conjunctivitis at Day 1 (Screening/Baseline) Visit was based upon all of the following clinical observations occurring in at least one eye:

- a rating ≥ 1 for bulbar conjunctival injection and
- a rating ≥ 1 for conjunctival discharge/exudate, and
- evidence of matting or history of matting upon waking

As bacterial conjunctivitis is a self-limiting infection, patients were included in the study if signs/symptoms were present in at least 1 eye for 4 days or less.

3.1.2 Endpoints and Analysis Populations

The primary clinical efficacy variable was the clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection including bulbar conjunctival injection and conjunctival discharge/exudate at Day 4 (EOT)/Exit Visit in the study eyes. Clinical cure was attained when the sum of the two cardinal ocular signs was zero.

Table 3.1 Evaluability Criteria in Analysis Populations

Analysis data set	Patient-level Evaluability Criteria					
	Received drug	Pathogen Positive at day 1	At least one on-therapy visit	Meet pre-randomization inclusion/exclusion criteria	No major protocol violations	Baseline and Day 4 (EOT)/Exit Visit data
Safety	✓					
ITT	✓		✓			
MBITT	✓	✓	✓			
MITT	✓	✓	✓	✓		
PP	✓		✓	✓	✓	✓
MPP	✓	✓	✓	✓	✓	✓

The key secondary efficacy variable was the microbiological bacterial eradication rate at Day 4 (EOT)/Exit Visit in the study eyes. Microbiological success was attained if the pre-therapy bacterial pathogens were eradicated.

The secondary efficacy variables were clinical outcome at the Day 3 visit and the eight individual ocular sign and symptom cure rates (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia) at the Day 3 and Day 4 (EOT)/Exit visits. A cure for an individual ocular sign or symptom was attained if the score was zero (i.e. absent or normal).

The primary analysis population is the microbiological intent-to-treat (MBITT) dataset for study C-07-40. All secondary efficacy conclusions will also be based on this population. However, analyses will also be conducted on the ITT, MITT, PP and MPP data sets, wherever applicable, as well.

Table 3.2 Number of Patients per Analysis Population

Analysis data set	C-07-40			
	Data Set (# Evaluable)		Exclusions (# Evaluable)	
	Moxifloxacin AF	Vehicle	Moxifloxacin AF	Vehicle
Safety	593	586	0	1
ITT	593	586	0	1
MBITT	424	423	169	164
MITT	415	414	178	172
PP	567	561	26	25
MPP	406	408	161	153

3.1.3 Patient Disposition

There were 1180 patients who were randomized to treatment. One patient did not receive study drug and therefore was not evaluable in all data sets. A total of 1179 patients were considered evaluable for the safety and intent-to-treat analyses. Of the patients randomized in the study, 847 were culture positive at the baseline visit and thus evaluable for the MBITT data set. A total of 333 were excluded from the MBITT data set. Of the 847 culture positive patients, 829 were evaluable for and 18 were excluded from the MITT data set. Of the 1179 patients who were evaluable for the ITT data set, 1128 were evaluable for and 51 were excluded from the PP data set. Of the patients who were evaluable for the PP data set, 814 were evaluable for and 314 were excluded from the MPP data set. The number of patients randomized to each treatment and included in the safety, ITT, MBITT, MITT, PP and MPP data sets are shown below

Table 3.3 Summary of Reasons for Discontinuation

Reasons for Discontinuation	Moxi AF	Vehicle	Total
Adverse Event	1	6	7
Lost to Follow-up	3	9	12
Patient's Decision Unrelated to an Adverse Event	3	7	10
Treatment Failure	6	10	16
Other	1	1	2
Total	14	33	47

Sponsor's Table 10.1.-12

Of the 1180 patients randomized in this study, 47 discontinued from the study for the following reasons: adverse event (7), lost to follow-up (12), patient's decision unrelated to an adverse event (10), treatment failure (16), and other (2). Table 3.3, lists the number of discontinued patients by reason for discontinuation and by treatment group.

3.1.4 Demographics

In the MBITT data set, results were similar between the Moxifloxacin AF and Vehicle treatment groups for each of the following demographic characteristics: mean age, age range, age range > 64 years, sex, ethnicity, iris color, affected eye, study eye and mean duration of current bacterial conjunctivitis episode.

Table 3.4 MBITT - Demographics by Treatment

	Moxi AF		Vehicle	
	N	%	N	%
Age				
28 days – 23 months	44	10.4	43	10.2
2 – 11 years	129	30.4	134	31.7
12 – 17 years	43	10.1	45	10.6
18 – 64 years	175	41.3	159	37.6
> 65 years	33	7.8	42	9.9
Age (> 65 years)				
65 – 74 years	16	3.8	22	5.2
75 – 84 years	14	3.3	15	3.5
85 – 94 years	3	0.7	5	1.2
Sex				
Male	172	40.6	179	42.3
Female	252	59.4	244	57.7
Race				
White	329	77.6	350	82.7
Black	64	15.1	37	8.7
Asian	14	3.3	6	1.4
Native Hawaiian	2	0.5	1	0.2
American Indian	3	0.7	6	1.4
Other	8	1.9	16	3.8
Multi-Racial	4	0.9	7	1.7
Ethnicity				
Hispanic, Latino, or Spanish	102	24.1	108	25.5
Not Hispanic, Latino, or Spanish	322	75.9	315	74.5
Iris Color				
Brown	241	56.8	225	53.2
Hazel	54	12.7	52	12.3
Green	30	7.1	31	7.3
Blue	97	22.9	113	26.7
Grey	2	0.5	2	0.5

3.1.5 Baseline Characteristics

There were no substantial differences in distribution of baseline characteristics between Moxifloxacin AF and Vehicle. The minor differences that were noted would not affect the efficacy or safety results of this study (in favor of either treatment group). The distributions of the 5 ocular signs (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling and palpebral conjunctiva) and 3 ocular symptoms (foreign body sensation, tearing and photophobia) at the Day 1 (Screening/Baseline) Visit for the MBITT data set are shown in the following tables. Similar results were observed in the remaining efficacy data sets.

Table 3.5 MBITT - Baseline Ocular Signs by Treatment

	Total		Moxi AF		Vehicle	
	N	%	N	%	N	%
Bulbar Conjunctival Injection						
Normal			0			
Mild	308	27.52	158	28.16	150	26.88
Moderate	724	64.70	350	62.39	374	67.03
Severe	87	7.77	53	9.45	34	6.09
Conjunctival Discharge/Exudate						
Absent	3	0.27	2	0.36	1	0.18
Mild	585	52.28	284	50.62	301	53.94
Moderate	467	41.73	240	42.78	227	40.68
Severe	64	5.72	35	6.24	29	5.20
Eyelid Erythema						
Absent	316	28.24	149	26.56	167	29.93
Mild	523	46.74	274	48.84	249	44.62
Moderate	253	22.61	124	22.10	129	23.12
Severe	27	2.41	14	2.50	13	2.33
Eyelid Swelling						
Absent	387	34.58	191	34.05	196	35.13
Mild	487	43.52	247	44.03	240	43.01
Moderate	218	19.48	107	19.07	111	19.89
Severe	27	2.41	16	2.85	11	1.97
Palpebral Conjunctiva						
Normal	139	12.42	74	13.19	65	11.65
Mild	431	38.52	207	36.90	224	40.14
Moderate	497	44.41	249	44.39	248	44.44
Severe	52	4.65	31	5.53	21	3.76

3.1.6 Statistical Methodology

This study was designed to demonstrate statistical superiority of Moxifloxacin AF Ophthalmic Solution dosed 2 times a day for 3 days relative to Vehicle dosed 2 times a day for 3 days in the treatment of bacterial conjunctivitis as evidenced by the clinical cure rate and microbiological success rate at the Day 4 (EOT)/Exit Visit. Clinical cure, the primary efficacy variable, was attained if the sum of the 2 cardinal ocular signs of bacterial conjunctivitis (bulbar conjunctival injection and conjunctival discharge/exudate) was zero (i.e., normal or absent). Microbiological

success, the key secondary efficacy variable, was attained if the pre-therapy bacterial pathogens were eradicated. Chi-square tests of independence were used to compare proportions between the two treatment groups for both the primary efficacy and key secondary variables. Statistical superiority was declared when $p < 0.05$. Primary conclusions for these variables were based on the MBITT data set with supportive information based on the remaining data sets.

Table 3.6 MBITT- Baseline Ocular Symptoms by Treatment

	Total		Moxi AF		Vehicle	
	N	%	N	%	N	%
Foreign Body Sensation						
Absent	208	20.59	106	20.91	102	20.28
Mild	362	35.84	184	36.29	178	35.39
Moderate	371	36.73	181	35.70	190	37.77
Severe	69	6.83	36	7.10	33	6.56
Tearing						
Absent	154	15.22	76	14.93	78	15.51
Mild	391	38.64	190	37.33	201	39.96
Moderate	354	34.98	179	35.17	175	34.79
Severe	113	11.17	64	12.57	49	9.74
Photophobia						
Absent	405	40.06	201	39.57	204	40.56
Mild	350	34.62	168	33.07	182	36.18
Moderate	197	19.49	106	20.87	91	18.09
Severe	59	5.84	33	6.50	26	5.17

The secondary efficacy variables provide supportive efficacy for the primary and key secondary variables for this study. The secondary efficacy variables are the 8 individual ocular sign and symptom cure rates (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia) at the Day 3 and Day 4 (EOT)/Exit Visits and clinical cure at the Day 3 Visit. A cure for an individual ocular sign or symptom was attained if the score was zero (i.e., absent or normal) and remained zero (for Day 3 findings) throughout the rest of the study. Clinical cure was attained if the sum of the 2 cardinal ocular signs of bacterial conjunctivitis was zero (i.e., normal or absent) and remained zero throughout the course of the study. A chi-square test of independence (or Fisher's exact test if one or more expected cell frequencies were < 5) was used to assess differences between Moxifloxacin AF and Vehicle for each of the secondary efficacy variables. Primary conclusions for the secondary efficacy variables are based on the MBITT data set but supportive results for the remaining data sets are also presented.

Reviewer remark: The study protocol did not pre-specified method for controlling overall type I error at alpha level of 5% for the secondary efficacy endpoints. The study protocol considered the analyses of the secondary endpoints as supportive analyses only. For the treatment difference in proportions for the primary endpoint and key secondary endpoints, the reviewer calculated the 95% CI using the Wilson's procedure with continuity correction. This procedure yielded slightly different results from those of the asymptotic (Wald) confidence limits reported in the submission; consequently the conclusions are the same regardless of the analysis methods.

3.1.7 Results and Conclusions

In the MBITT data set, the primary efficacy endpoint of clinical cure rate for Moxifloxacin AF was 62.50% (265/424) and 50.59% (214/423) for Vehicle at Day 4 (EOT)/Exit Visit. The treatment difference between Moxifloxacin AF and Vehicle is 11.91% (5.07, 18.60) which statistically significantly favors Moxifloxacin AF. A similar result can also be obtained from the remaining efficacy populations ITT, MITT, PP and MPP (see Table 3.7).

Table 3.7 Clinical Cure Rate at Day 4 (EOT/Exit) Visit

Population	Moxifloxacin AF	Vehicle	Difference ^a
ITT	62.73% (372/593)	52.90% (310/586)	9.83% (4.07, 15.50)
MITT	62.89% (261/415)	50.00% (207/414)	12.89% (5.97, 19.64)
MBITT	62.50% (265/424)	50.59% (214/423)	11.91% (5.07, 18.60)
PP	60.32% (342/567)	50.80% (285/561)	9.52% (3.59, 15.35)
MPP	59.85% (243/406)	47.55% (194/408)	12.3% (5.28, 19.16)

^a 95% confidence interval based on Wilson's procedure with continuity correction

26 patients had missing bulbar conjunctival injection and/or conjunctival discharge/exudate data at the Day 4 (EOT)/Exit Visit for PP.

23 patients had missing bulbar conjunctival injection and/or conjunctival discharge/exudate data at the Day 4 (EOT)/Exit Visit for MPP.

Reviewer remark: Missing data were considered as failures.

As shown in Table 3.8, Moxifloxacin AF is also numerically better than Vehicle for the clinical cure rate at Day 3. It should be noted that these results are different from those presented in Table 11.4.1.3.-10 and Table 14.2.3.1.-1 to -4 of the Applicant's clinical study report (CSR). The explanation given by the Applicant is that the results from the CSR are for the sustained clinical cure rate at Day 3. A sustained clinical cure is achieved if there is a cure at Day 3 that continues for the remainder of the study.

Table 3.8 Clinical Cure Rate at Day 3 Visit

Population	Moxifloxacin AF	Vehicle	Difference ^a
ITT	20.24% (120/593)	18.60% (109/586)	1.64% (-2.89, 6.15)
MITT	20.48% (85/415)	15.94% (66/414)	4.54% (-0.72, 9.78)
MBITT	20.05% (85/424)	16.55% (70/423)	3.50% (-1.72, 8.70)
PP	20.28% (115/567)	18.36% (103/561)	1.92% (-2.69, 6.53)
MPP	20.69% (84/406)	16.18% (66/408)	4.51% (-0.82, 9.83)

Table 3.9 Sustained Clinical Cure Rate at Day 3 Visit (from Tables 11.4.1.3.-10, 14.2.3.1.-1 to -4 in the Applicant's CSR)

Population	Moxifloxacin AF	Vehicle	Difference ^a
ITT	17.0% (101/593)	15.0% (88/586)	2.0% (-2.2, 6.2)
MITT	17.1% (71/415)	12.8% (53/414)	4.3% (-0.5, 9.2)
MBITT	10.04 % (71/424)	8.26% (56/423)	3.5% (-1.72, 8.70)
PP	17.6% (99/561)	15.2% (84/551)	2.4% (-2.0, 6.8)
MPP	18.0% (72/401)	13.3% (53/398)	4.6% (-0.4, 9.7)

Moxifloxacin AF is also superior to Vehicle for microbiological success, defined as the eradication of pre-therapy pathogen(s), at the Day 4 (EOT)/Exit Visit. The microbiological success rate for Moxifloxacin AF was 74.5% (316/424) compared to 56.0% (237/423) for Vehicle in the MBITT population. A similar result can also be obtained from the other remaining analysis populations (see Table 3.10).

Table 3.10 Microbiological cure at Day 4 (EOT/Exit) Visit

Population	Moxifloxacin AF	Vehicle	Difference ^a
MITT	74.2% (308/415)	55.8% (231/414)	18.4% (12.0, 24.8)
MBITT	74.5% (316/424)	56.0% (237/423)	18.5% (12.2, 24.8)
MPP	74.0% (285/385)	57.3% (220/384)	16.7% (10.1, 23.3)

Moxifloxacin AF is also superior compared to the Vehicle in majority of the secondary efficacy parameters in the MBITT, ITT and MITT populations and in 4 of the 8 ocular signs and symptoms in the PP and MPP populations at Day 4 (EOT)/Exit Visit (see Table 3.11). Furthermore, the bulbar conjunctival injection, conjunctival discharge/exudate, and eyelid erythema cure rates for Moxifloxacin AF were superior compared to the Vehicle cure rates at the Day 4 (EOT)/Exit Visit in all five efficacy data sets (ITT, MBITT, MITT, PP, and MPP). The palpebral conjunctiva and tearing cure rates for Moxifloxacin AF were superior at the Day 4 (EOT)/Exit Visit compared to the Vehicle cure rates in 4 of the data sets. The eyelid swelling cure rate for Moxifloxacin AF was superior compared to the Vehicle cure rate at the Day 4 (EOT)/Exit Visit in 3 of the data sets. In addition, foreign body sensation and photophobia cure rate for Moxifloxacin AF is numerically higher to Vehicle.

Table 3.11 Treatment Difference and Statistical Significance of Secondary Efficacy Parameters

	Day 4 (EOT)/Exit Visit				
	P-value				
	MBITT	ITT	MITT	PP	MPP
Bulbar Conjunctival Injection	11.9% (0.0003)	9.4% (0.0008)	12.6% (0.0002)	8.7% (0.0030)	11.8% (0.0007)
Conjunctival Discharge/Exudate	9.3% (0.0015)	8.6% (0.0004)	9.7% (0.0010)	7.3% (0.0031)	7.8% (0.0097)
Eyelid Erythema	6.9% (0.0022)	5.7% (0.0021)	7.3% (0.0013)	3.9% (0.0355)	4.8% (0.0304)
Eyelid Swelling	5.5% (0.0103)	3.5% (0.0475)	5.8% (0.0066)	2.0% (0.2472)	3.7% (0.0734)
Palpebral Conjunctiva	8.1% (0.0115)	5.8% (0.0315)	8.3% (0.0107)	4.7% (0.0950)	7.1% (0.0349)
Foreign Body Sensation	4.3% (0.1341)	3.8% (0.1212)	5.3% (0.0704)	2.2% (0.3782)	3.0% (0.3179)
Tearing	7.1% (0.0188)	7.2% (0.0047)	8.2% (0.0077)	5.8% (0.0260)	5.2% (0.0955)
Photophobia	1.8% (0.4286)	0.7% (0.7211)	2.7% (0.2435)	0.1% (0.9611)	1.7% (0.4620)

3.2 Evaluation of Safety

3.2.1 Extent of Exposure

A total of 1179 male and female patients (ages 1 month to 92 years) with a diagnosis of bacterial conjunctivitis were randomized to treatment with either Moxifloxacin AF or Vehicle. Patients were to administer 1 drop of study medication into the conjunctival sac of both eyes 2 times per day for 3 days. Exposure data for the overall safety population shows that 593/1179 randomized patients received twice daily Moxifloxacin AF while 586/1179 received twice daily Vehicle for 3 days. No clinically relevant differences in duration of exposure were noted between the overall treatment groups.

Table 3.12 All Adverse Drug Reactions - Safety Population

Coded Adverse Event	Moxi AF		Vehicle	
	N	(%)	N	(%)
Eye disorder				
Eye irritation	4	0.7	3	0.5
Eye Pain	3	0.5	2	0.3
Eye Pruritus	1	0.2		
Ocular hyperaemia	1	0.2		
Vision blurred			1	0.2
Asthenopia			1	0.2
Nervous system disorders				
Headache	1	0.1		

Sponsor Table 12.2.3.1.-2

3.2.2 Adverse Events

No deaths or serious adverse events were reported during the study. Seven patients (0.6%) discontinued study participation due to an adverse event which included 1 patient receiving Moxifloxacin AF (0.2%) (eye irritation) and 6 patients receiving Vehicle (1.0%) (3 reports of otitis media, and single reports of generalized rash, lip swelling, pharyngitis, and ulcerative keratitis). All of these events were assessed as not related to the study drug by the investigators.

The most frequently reported adverse drug reactions (treatment-related adverse events) in the Moxifloxacin AF and the Vehicle groups were eye irritation (0.7% vs. 0.5%, respectively) and eye pain (0.5% vs. 0.3%, respectively). All other adverse drug reactions in the Moxifloxacin AF (eye pruritus, ocular hyperaemia, and headache) and Vehicle (asthenopia and blurred vision) treatment groups were single occurrences.

Reviewer remark: Please see Medical Officer's review for details on serious adverse events (SAEs) and treatment emergent adverse events (TEAEs).

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Age and Sex does not seem to be a factor in cure rate. Notice that cure rate is consistent across sex categories.

It is quite difficult to assess the effect of race on clinical cure since the bulk of the study is predominantly Caucasians (e.g. study C-07-40).

Table 4.1MBITT - Clinical Cure at TOC Visit Stratified by Age, Sex, and Race

	C-07-40			
	Moxi AF		Vehicle	
	n	(%)	n	(%)
Age				
28 days -23 Months	33/44	75.0	24/43	55.8
2-11 yrs	96/129	74.4	75/134	56.0
12-17 yrs	24/43	55.8	24/45	53.3
18-64 yrs	95/175	54.3	77/159	48.4
65 and older	17/33	51.5	14/42	33.3
Sex				
Male	109/172	63.4	75/179	41.9
Female	156/252	61.9	139/244	57.0
Race				
White	205/329	62.3	171/350	48.9
Black or African American	40/64	62.5	24/37	64.9
Asian	8/14	57.1	1/6	16.7
Native Hawaiian	2/2	100	1/1	100
American Indian	1/3	33.3	5/6	83.3
Other	5/8	62.5	7/16	43.8
Multi-racial	4/4	100	5/7	71.4
Iris Color				
Brown	154/241	63.9	120/255	53.3
Hazel	30/54	55.6	31/52	59.6
Green	12/30	40.0	14/31	45.2
Blue	68/97	70.1	47/113	41.6
Grey	1/2	50.0	2/2	100.0

Summarized from Sponsor's tables 11.4.2.8.2.-1 to 11.4.2.8.4.-1 and 11.4.2.8.7.-1

In all subgroups with reasonable sample sizes, the clinical cure rates for Moxifloxacin AF were similar to (or higher than) the cure rate observed overall. The clinical cure rate for Vehicle was larger in some subgroups than in the overall study sample. These subgroups tended to be ones with smaller sample size. Similar results were noted in the remaining efficacy data sets.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In the MBITT data set, the clinical cure rate at the Day 4 (EOT)/Exit Visit for Moxifloxacin AF was 62.50% (265/424) vs. 50.59% (214/423) for Vehicle. The treatment difference is 11.91% [95% CI: (5.07, 18.60)] and is statistically significant. A similar result can be obtained using the other efficacy datasets and implies that the observed treatment effect of Moxifloxacin AF compared to Vehicle is robust.

Moxifloxacin AF is superior to Vehicle for microbiological success at the Day 4 (EOT)/Exit Visit. The microbiological success rate for Moxifloxacin AF was 74.5% (316/424) compared to 56.0% (237/423) for the Vehicle in the MBITT population. The difference in microbiological success is 18.5% [95% CI: (12.2, 24.8)] and is statistically significant ($p < 0.0001$). Robustness of this finding was demonstrated in the two other culture positive data sets, MITT and MPP.

The superiority of Moxifloxacin AF compared to the Vehicle in the secondary efficacy parameters demonstrates the consistency of the results observed in the primary and key secondary analyses at Day 4 (EOT)/Exit Visit. The observed Moxifloxacin AF cure rate was higher than the cure rate of Vehicle at the Day 4 (EOT)/Exit Visit for every ocular signs and numerically higher than the cure rate of Vehicle at the Day 4 (EOT)/Exit Visit for every ocular symptoms in all efficacy data sets.

The results of this study are also consistent with the results of Study C-04-38, which was a prospective, multi-center (32 US sites), double masked, parallel group, randomized, vehicle-controlled trial designed to evaluate efficacy and safety of topical ocular Moxifloxacin AF Ophthalmic Solution compared to vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. Although the primary efficacy parameter assessed in this study was the clinical cure rate at Day 7 visit, the same company also evaluated the clinical cure rate at Day 4 (EOT) Visit. In this visit, the clinical cure rate for Moxifloxacin AF was 58.4% (104/178) vs. 46.7% (78/169) for Vehicle. This result is also consistent with the results of the other efficacy datasets and by the microbiological eradication rate.

5.2 Conclusions and Recommendations

This review concludes that Study C-07-40 has established efficacy of Moxifloxacin AF for the treatment of bacterial conjunctivitis.

SIGNATURES/DISTRIBUTION LIST

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/s/

MARK A GAMALO
10/01/2010

YAN WANG
10/01/2010
Concur with the primary review.

STATISTICS FILING CHECKLIST FOR A NEW NDA 22428 (SD#11)

NDA Number:

22428 (SD#11)

Applicant:

Alcon Laboratories, Inc.

Stamp Date:

21 May, 2010

Drug Name:Moxifloxacin AF Ophthalmic
Solution**NDA/BLA Type:**

NDA, Standard Review

On **initial** overview of the NDA/BLA application for refuse to file (RTF):

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	✓			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	✓			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

In your datasets c0740_outcomes_, please differentiate the definition of the variables “clin_cure_vlmls” and “clin_cure_vls”. Moreover, please specify the primary efficacy endpoint and define the Test-of-Cure Visit in contradistinction with the End-of-Therapy Visit.

STATISTICS FILING CHECKLIST FOR A NEW NDA 22428 (SD#11)

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	✓			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			

STATISTICS FILING CHECKLIST FOR A NEW NDA 22428 (SD#11)

Brief summary of controlled clinical trials

The following table contains information on the relevant trials contained in the submission.

Study number	Design/Formulation	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
C-07-40	<p>Name of Product: Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution 0.5%</p> <p>Name of Active Ingredient: Moxifloxacin Hydrochloride 0.5% (5 mg/mL)</p> <p>Methodology: Structure: Multi-center, randomized (1:1), parallel group, 4 day, double-masked trial</p> <p>Visit Schedule: Day 1 (Screening/Baseline), Day 3 interim visit, Day 4 study exit visit (12-48 hours following the last study dose)</p>	<p>Moxifloxacin AF: 424 patients</p> <p>Vehicle: 423 patients</p>	<p>Primary endpoint: clinical cure at Day 4 (EOT)/Exit Visit (12-48 hours after last dose)</p> <p>Analysis: A chi-square test of independence (or Fisher's exact test if one or more expected cell frequencies were <5) was used to assess clinical cure rate in the MBITT population. Statistical superiority was declared when $p < 0.05$.</p>	<p>The results of the study demonstrate that 3 day BID dosing of Moxifloxacin AF Ophthalmic Solution 0.5% is superior to Moxifloxacin AF Vehicle in the treatment of bacterial conjunctivitis. The clinical cure rate for Moxifloxacin AF (62.5%) was statistically significantly higher than the Vehicle cure rate (50.6%) at Day 4 (EOT)/Exit Visit ($p = 0.0005$, MBITT data set). This statistically superior result was confirmed in the ITT, MITT, PP and MPP data sets.</p>

Clinical Cure Rate at End-of-Therapy Visit (MBITT Population)

Population	Moxifloxacin AF	Vehicle	Difference ^a
ITT	10.18% (120/593)	9.25% (109/586)	1.64% (-2.89, 6.15)
MITT	10.25% (85/415)	7.96% (66/414)	4.54% (-0.72, 9.78)
MBITT	10.04 % (85/424)	8.26% (70/423)	3.5% (-1.72, 8.70)
PP	10.20% (115/567)	9.13% (103/561)	1.92% (-2.69, 6.53)
MPP	10.32% (84/406)	8.11% (66/408)	4.51% (-0.82, 9.83)

Clinical Cure Rate at Test-of-Cure Visit (MBITT Population)

Population	Moxifloxacin AF	Vehicle	Difference ^a
ITT	62.73% (372/593)	52.90% (310/586)	9.83% (4.19, 15.38)
MITT	62.89% (261/415)	50.00% (207/414)	12.89% (6.15, 19.47)
MBITT	62.50% (265/424)	50.59% (214/423)	11.91% (5.23, 18.43)
PP	60.32% (342/567)	50.80% (285/561)	9.52% (3.72, 15.23)
MPP	59.85% (243/406)	47.55% (194/408)	12.3% (5.45, 18.99)

^a 95% confidence interval with non continuity correction

26 patients had missing bulbar conjunctival injection and/or conjunctival discharge/exudate data at the Day 4 (EOT)/Exit Visit for PP.

23 patients had missing bulbar conjunctival injection and/or conjunctival discharge/exudate data at the Day 4 (EOT)/Exit Visit for MPP.

ITT: All patients who receive drug and have at least one on-therapy visit

MITT: All patients who received drug, have at least one on-therapy visit, met the inclusion exclusion criteria (pre randomization requirements only), and were pathogen positive for bacteria on Day 1

STATISTICS FILING CHECKLIST FOR A NEW NDA 22428 (SD#11)

MBITT: All patients who received drug, have at least one on-therapy visit, and were pathogen positive for bacteria on day 1

PP: All patients who received drug, met pre-randomization inclusion and exclusion criteria and had baseline and end of therapy (or exit if the patient exited from the study early) visits, and had no major protocol violations

MPP: All patients who received drug, met pre-randomization inclusion and exclusion criteria and had baseline and end of therapy (or exit if the patient exited from the study early) visits, had no major protocol violations, and were pathogen positive for bacteria at Day 1

Mark A. Gamalo, PhD

15 June, 2010

Reviewing Statistician

Date

Yan Wang, PhD

Supervisor/Team Leader

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22428	ORIG-1	ALCON PHARMACEUTICA LS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

MARK A GAMALO
06/18/2010

YAN WANG
06/18/2010



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number: 22,428
Drug Name: Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5%
Indication(s): Treatment of bacterial conjunctivitis
Applicant: Alcon Pharmaceuticals, Ltd.
Date(s): Letter date: 12-Dec-2008; Filing date: 13-Feb-2009; 74-day date: 27-Feb-2009; PDUFA goal date: 15-Oct-2009
Review Priority: Standard
Biometrics Division: Anti-infective and Ophthalmology Products
Statistical Reviewer: Mark. A. Gamalo, Ph.D.
Concurring Reviewers: Yan Wang, Ph.D.
Medical Division: Anti-infective and Ophthalmology Products
Clinical Reviewer: Jennifer Harris, M.D.
Project Manager: Lori Gorski

Keywords: superiority, non-inferiority, non-inferiority margin

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1. EXECUTIVE SUMMARY

The current submission initiated by Alcon Pharmaceuticals Ltd. seeks the approval of a new drug Moxifloxacin alternative formulation (AF) indicated for the treatment of bacterial conjunctivitis. The proposed dosage is one drop instilled twice daily. To support this request, two pivotal Phase 3 clinical studies, namely, C-04-38 and C-04-40 were performed and enrolled patients were evaluated for the clinical cure rates at test-of-cure (TOC) visit (60–96 hours or Day 7 after the 3-day treatment) in the microbiological intent-to-treat (MITT) population. The first study, C-04-38, was conducted to support the hypothesis that Moxifloxacin AF is superior to placebo in the treatment of the said disease; while, the second study, C-04-40, is to demonstrate that moxifloxacin is non-inferior to VIGAMOX, the original formulation, in the treatment of bacterial conjunctivitis. The remaining trial parameters in both of these studies are identical.

The executive summary is broken as follows. Results of primary analysis will be highlighted together with the reviewer's conclusion and recommendation. A summary of the clinical studies including study objectives, endpoints, populations, and baseline characteristics will also be discussed to give a background of the ensuing results. Finally, statistical issues that affect overall accuracy of results and conclusions for the approvability of the new drug are discussed.

1.1 Conclusions and Recommendations

The superiority Study C-04-38 failed to demonstrate superiority of Moxifloxacin AF over vehicle in the treatment of bacterial conjunctivitis. In the primary efficacy analysis, the clinical cure rate at TOC visit (Day 7) in Moxifloxacin AF treated patients was 129/178 (72.5%) compared to 113/167 (67.7%) in the vehicle group with a treatment difference of 4.8% (95% CI: -5.2%, 14.8%).

The non-inferiority Study C-04-40 demonstrated non-inferiority of Moxifloxacin AF to VIGAMOX when evaluated using the protocol-defined non-inferiority margin of 15%. In the primary efficacy analysis, the clinical cure rate at TOC visit (Day 7) in Moxifloxacin AF treated patients was 103/122 (84.4%) compared to 108/126 (85.7%) in VIGAMOX treated patients with a treatment difference of -1.3% (95% CI: -10.16%, 7.58%). However, the results of this study is not informative and cannot be used to infer efficacy of Moxifloxacin AF treatment because a non-inferiority margin of 15% cannot be scientifically justified. In fact, the reviewer identified only one historical placebo-control trial of VIGAMOX for the treatment of bacterial conjunctivitis. The results of this historical trial indicated that the treatment effect of VIGAMOX over vehicle could be as small as 4% at Day 5 visit and no improvement over vehicle at Day 9. Thus, the treatment effect of VIGAMOX over vehicle at Day 7 could be as small as 4% or no improvement at all.

This review concludes that neither of the two pivotal studies has established effectiveness of Moxifloxacin AF treatment. As a result, the reviewer does not recommend approval of this NDA. It is recommended that additional adequate and well-controlled studies be conducted to support the approval of Moxifloxacin AF for treating bacterial conjunctivitis.

1.2 Brief Overview of Clinical Studies

Moxifloxacin AF Ophthalmic Solution is an alternative formulation of VIGAMOX, which is based on a fluoroquinolone, moxifloxacin, approved as AVELOX. The current formulation moxifloxacin-based ophthalmic solution (0.5% active concentration) contains (b) (4) that is expected to provide similar efficacy and safety to VIGAMOX. This formulation is being developed for the *treatment of bacterial conjunctivitis* with a dosing regimen of one drop administered two times a day for 7 days.

There were two completed Phase 3 clinical trials, C-04-38 and C-04-40, conducted with Moxifloxacin AF Ophthalmic Solution which is relevant for the evaluation of efficacy. The specific objectives of these two studies were: (1) to evaluate the safety and efficacy of Moxifloxacin AF ophthalmic solution compared to vehicle for the treatment of bacterial conjunctivitis in patients one month of age and older (C-04-38); (2) to evaluate the safety and efficacy of Moxifloxacin AF Ophthalmic Solution compared to VIGAMOX for the treatment of bacterial conjunctivitis in patients one month of age and older (C-04-40). In study C-04-38, patients in both treatment groups are dosed with either Moxifloxacin AF ophthalmic solution or vehicle one drop two times daily for 3 days. In study C-04-40, patients in the Moxifloxacin AF group are given Moxifloxacin AF ophthalmic solution one drop two times a day (morning and bedtime) and one drop of vehicle once a day (midday) and patients in the VIGAMOX group are given VIGAMOX one drop, three times a day (morning, midday, and bedtime) for 3 days.

The primary efficacy endpoint assessed in this study were the cardinal ocular signs of bacterial conjunctivitis including bulbar conjunctival injection and conjunctival discharge/exudate as well as the bacterial eradication rate of the baseline ocular pathogens. Clinical cure was attained when the sum of the two cardinal ocular signs was zero (i.e., normal or absent). The primary microbiological efficacy variable was the bacterial eradication rate at the Exit visit (a specimen was obtained from the affected eye(s) at the visit).

All patients who receive the drug will be evaluable for safety analysis. All patients who receive drug and have at least one on-therapy visit were evaluable for intent-to-treat (ITT) analysis. All patients who received drug, have at least one on-therapy visit, and were pathogen positive for bacteria on day 1 (baseline) were evaluable for the microbiological intent-to-treat (MBITT) analysis. All patients who received drug, have at least one on-therapy visit, met the inclusion exclusion criteria (pre randomization requirements only), and were pathogen positive for bacteria on Day 1 were evaluable for the modified intent-to-treat (MITT) analysis. For the ITT, MBITT and MITT data sets, patients who had no measurements after baseline were included as treatment failures. All patients who received drug, met inclusion and exclusion criteria and had baseline and test-of-cure (or exit if patient exited from the study early) visits will be available for the per protocol (PP) analysis. All per protocol patients who are pathogen positive for bacteria on Day 1 will be evaluable for the modified per protocol (MPP) analysis. Evaluability may also be performed on a by visit basis for all patients with one or more on-therapy visits.

In study C-04-38, 661 patients were randomized and evaluable for the intent-to treat (ITT) data set. The average age was 16.8 years with a minimum age of 1 month and a maximum age of 89 years. Caucasians form the majority of the patients enrolled, with other races combined only

constitute less than 15% of the patient population. Of the 661 patients, 342 were evaluable for the MITT analysis and 345 were evaluable for the MBITT analysis. As the Sponsor confirms, there was a statistically significant difference between treatments for the distribution of race; however, this difference appears to be due to the distribution of patients who were Asian or of other races and with small number of patients in these two categories, it is unlikely that this would adversely affect the results. The rest of the results between treatment groups and for each demographic characteristic: mean age, age range, age range >64, sex, ethnicity, iris color, affected eye, study eye and duration of current episode are similar.

In study C-04-40, 695 patients were randomized and were considered evaluable for the intent-to-treat data (ITT) set. The average age was 37.2 years with a minimum age of 1 month and a maximum age of 87 years. Majority of the patients are Asian males (66.3%) and all were Asian. Of the 695 patients, 378 (54.4%) were evaluable for the MITT analysis and 382 (55.0%) were evaluable for the MBITT analysis. The rest of the following demographic characteristics between the two treatment groups are similar, e.g. mean age range, age range >64, sex race, ethnicity, iris, color, affected eye, study eye and duration of current episode.

1.3 Statistical Issues and Findings

The major concerns include but not limited to inability of Moxifloxacin AF to be superior to vehicle in Study C-04-38 and the choice of the NI margin used in Study C-04-40.

Not superior to vehicle. Based on the primary efficacy endpoint of clinical cure rate of the MITT population at TOC (Day 7) visit Moxifloxacin AF Ophthalmic Solution is not superior over Vehicle. Clinical cure rate for Moxifloxacin AF is at 72.3% compared to 67.3% for Vehicle. The 95% confidence interval about the treatment difference, 5.0%, is (-5.1%, 15.1%). Since the interval crosses zero, Moxifloxacin AF Ophthalmic Solution cannot be declared statistically superior to vehicle. Notice that this is slightly different from what is reported in the conclusion, in section 1.1, because the Agency recommends the use of MBITT as primary analysis population.

Choice of Non-inferiority margin. In study C-04-40, the clinical cure rate of Moxifloxacin AF at Day 7 (TOC) visit in the MPP population is 84.4% while the clinical cure rate of VIGAMOX at Day 7 (TOC) visit in the MPP data set is 85.7%. The upper and lower limits of the 95% confidence interval on the difference -1.3% were (95% CI: -10.16, 7.58). Since the lower bound of this margin is not smaller than the protocol defined margin of -15%, the Sponsor concluded that Moxifloxacin AF ophthalmic solution is non-inferior to VIGAMOX.

This review argues that the Sponsor's justification of the protocol defined non-inferiority margin is not valid. In their justification, the Sponsor did not quantify M1 (treatment effect of active drug over placebo) and M2 (acceptable loss of effect relative to control while preserving some portion of the effect of the control drug) while controlling for the variability. Without knowledge of M1, there can be no meaningful M2. Determining M1 requires searching through historical trials quantifying the effect of VIGAMOX vis-a-vis vehicle in the treatment of bacterial conjunctivitis.

In an extensive literature search, there is only one study that directly compares the treatment effect of Moxifloxacin and vehicle in bacterial conjunctivitis. This is given by Study C-00-55 from the Sponsor's previous submission NDA 21598. In this study, patients were randomized to receive either Moxifloxacin ophthalmic solution (VIGAMOX) or vehicle and were instructed to instill one drop of masked study medication in both eyes three times a day while awake for 4 days. The primary analysis population was defined as all patients who received treatment, had at least one on-therapy visit, met inclusion/exclusion criteria, and were culture positive for bacteria at Day 1. The primary efficacy variable was the clinical cure (i.e., the sum of the ratings for bulbar conjunctival injection and conjunctival discharge/exudate is zero) at the test-of-cure visit (Day 9). The results of the study are given in the table below.

1.1 Cure rates for VIGAMOX in Study C-00-55 of NDA 21598

Study Day	Outcome	VIGAMOX	Vehicle	P-value	Delta	LCL	UCL
MITT							
EOT (Day 5)	Clinical cure	66% (95/143)	51% (74/144)	0.0096	15.04	3.66	25.89
TOC (Day 9)	Clinical cure	83% (113/137)	74% (101/136)	0.0991	8.21	-1.58	17.85
	Microbiological eradication	82% (111/136)	67% (93/138)	0.0069	14.23	3.90	24.16
ITT							
EOT (Day 5)	Clinical cure	62% (167/270)	52% (142/274)	0.0182	10.03	1.70	18.15
TOC (Day 9)	Clinical cure	77% (201/260)	72% (187/259)	0.1805	5.11	-2.37	12.51

Study C-00-55 of NDA 21598 and Study C-04-40 have similar primary analysis population. The only distinction is with the treatment duration of VIGAMOX. In Study C-00-55, VIGAMOX is instilled thrice daily for 4 days while in Study C-04-40, VIGAMOX is instilled thrice daily for 3 days. The primary efficacy parameter in C-00-55 and C-04-40 is assessed on Day 9 and Day 7, respectively. From table 1.1, the minimum treatment effect of VIGAMOX over vehicle at Day 5 is 3.66% and diminishes at Day 9. Due to the self-limiting nature of bacterial conjunctivitis, the minimum treatment effect of VIGAMOX over vehicle could be no more than 3.66% at Day 7. Therefore, a non-inferiority margin of more than this amount cannot be justified.

2. INTRODUCTION

2.1 Overview

Moxifloxacin is a broad spectrum, fourth generation fluoroquinolone, active against both Gram-positive and Gram-negative bacteria. Moxifloxacin hydrochloride was developed by Bayer HealthCare AG as AVELOX in tablet (NDA 21-085) and intravenous (NDA 21-277) formulation for a variety of bacterial infections (community acquired pneumonia, acute bacterial sinusitis, complicated skin and skin structure infections, etc.). The mechanism of antibacterial action of moxifloxacin resides in its ability to inhibit two important enzymes involved in DNA replication, transcription, repair and recombination (i.e., DNA gyrase and DNA topoisomerase IV).

Because moxifloxacin is particularly active against *staphylococci*, *pneumococci*, and community acquired respiratory pathogens, Alcon licensed moxifloxacin hydrochloride from Bayer and developed VIGAMOX (moxifloxacin hydrochloride ophthalmic solution 0.5% as base, for the treatment of bacterial conjunctivitis (NDA 21-598). The approved dosage is one drop in the affected eye three times a day for seven days. Recently, Alcon developed a moxifloxacin-based ophthalmic solution (0.5% active concentration) containing (b) (4) - (b) (4) (b) (4) (xanthan gum) that is expected to provide similar efficacy and safety to VIGAMOX (t.i.d for 7 days) with a reduced dosing regimen. This formulation, referred to as Moxifloxacin Alternative Formulation (AF) Ophthalmic Solution, is developed for the same indication but with a dosing regimen of one drop administered two times a day for 7 days.

Regulatory history of Moxifloxacin AF drug development

In a letter received on January 5, 2005, Alcon requested a t-con with the Division to discuss a new formulation for moxifloxacin alternate formulation (AF) ophthalmic solution for the treatment of bacterial conjunctivitis (b) (4) (IND #59,944). The request was granted and the meeting was scheduled on Thursday March 3, 2005. In this meeting, the Division recommended that both clinical cure and microbiologic success be the primary endpoints. Clinical cure is defined as the resolution of signs and symptoms (i.e. a score of 0, normal conjunctiva and no discharge) for the patients who meet the inclusion criteria of the protocol. On the other hand, the microbiological outcome is achieved when the pre-therapy microbiological pathogens are eradicated at the Test-of-Cure (Day 6) visit.

In May 6, 2005 Alcon Pharmaceuticals submitted protocols to conduct Phase 3 studies (C-04-38 and C-04-40) in an alternate formulation in moxifloxacin ophthalmic solution and requested for a special protocol assessment. Review of the protocols was sent on June 22, 2005 recommending an additional analysis is needed to support approval for C-04-38. This analysis involves demonstration that Moxifloxacin AF is not inferior to vehicle in the intent-to-treat (ITT) population. For C-04-40, on the other hand, the Division finds the single masked study design is inadequate to meet the stated objectives of the study due to the differing dosing regimens (Moxifloxacin AF b.i.d. vs. VIGAMOX t.i.d.) of the treatment arms. An alternate proposal for masking the dosing should be made before the protocol is initiated.

Another request was received July 20, 2005 for a clinical follow-up t-con with the Division to discuss the SPA response dated June 22, 2005, in which the Division provided comments on 2 Phase 3 protocols. This discussion is to give additional clarification on the Division's comments. A meeting was scheduled for Thursday August 18, 2005. In this meeting Alcon agrees with the Agency's comment and plan to demonstrate that Moxifloxacin AF is superior to vehicle in the modified intent-to-treat analysis and to confirm in the intent-to-treat analysis that Moxifloxacin AF is not worse than vehicle. The intent-to-treat analysis was included as part of the original analysis plan and will be included in the Clinical Study Report. The Division agrees with the Alcon's proposed plan but noted, however, that the submitted protocol (C-04-38) does not include an intent-to-treat (ITT) analysis. Only modified intent-to-treat (MITT), microbiological intent-to-treat (MBITT) and modified per-protocol (MPP) analyses are included. A true ITT analysis would be all patients randomized. Furthermore, the Division warned that there is a potential for bias when using MITT population since it excludes patients who meet any exclusion criteria. Some of these criteria: such as #13 (preserved topical ocular medication use), #14 (topical ocular antibacterial use), #15 (oral antibacterial use), #17 (NSAIDS use) exclude patients who use these products during the study. Use of these products during the study is a post-baseline event so this violates the ITT principle.

In the same t-con, Alcon also asked if it would be acceptable to use VIGAMOX as the 7-day comparator, or would it be necessary to use Moxifloxacin AF as the 7-day comparator. The Division recommended that VIGAMOX, the approved drug, should be the 7-day comparator. In addition the Division also agrees that the non-inferiority criteria of 95% confidence limit for difference $< [\text{minimum}(1-P_c \text{ or } 15\%)]$ is acceptable contrary to the recommendation of the reviewing statistician. The statistician, writing in his review, argued that the use of this method violates the principles laid out in ICH E10 which states that "The margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial." Use of this method does not provide any confidence that the test article could have beat placebo if a placebo arm had been in the trial since the treatment effect of the active control relative to placebo is not considered.

A Pre-NDA meeting was held on April 8, 2008. Alcon asked if the results of Study C-04-38 represent sufficient demonstration of efficacy to qualify C-04-38 as one of the two pivotal studies for Moxifloxacin AF for the treatment of bacterial conjunctivitis. The Division responded that Study C-04-38 as presented in the meeting package appears to be an adequate and well controlled study. However the Division does not agree with the primary clinical efficacy variable and expects to use the assessment of the clinical cure rate at Day 5 as the primary clinical efficacy variable in evaluating this new NDA. The assessment of the clinical cure rate at Day 5 as the primary clinical efficacy variable in the evaluation of the NDA was not communicated prior to the conduct of the trial. However, the previous NDA (NDA 21,598), referenced in the current submission, was evaluated at Day 5. Alcon, furthermore, asked if the results of Study C-04-40 represent sufficient demonstration of efficacy to qualify C-04-40 as one of the two pivotal studies for Moxifloxacin AF for the treatment of bacterial conjunctivitis. The Division replied that over the past two years, the Office of Antimicrobial Products has not been accepting non-inferiority margins such as the one demonstrated in study C-04-40. Study C-04-40 is unlikely to

mathematically support an extrapolation of efficacy over the product's vehicle; the need for additional efficacy support beyond that demonstrated by Study C-04-38 will be a review issue.

Clinical Studies Reviewed

There were two completed clinical trials conducted with Moxifloxacin AF Ophthalmic Solution which are relevant for the evaluation of efficacy, C-04-38 and C-04-40. The specific objectives of these two studies were: (1) to evaluate the safety and efficacy of Moxifloxacin AF ophthalmic solution compared to vehicle for the treatment of bacterial conjunctivitis in patients one month of age and older (C-04-38); (2) to evaluate the safety and efficacy of Moxifloxacin AF Ophthalmic Solution compared to VIGAMOX for the treatment of bacterial conjunctivitis in patients one month of age and older (C-04-40). A comparison of the two study parameters are given in the following table.

2.1 Study parameters of C-04-38 and C-04-40

Protocol	C-04-38 Safety/Efficacy study	C-04-40 Safety/Efficacy study
Study Design	Prospective, randomized, vehicle-controlled, double-masked	Prospective, randomized, active-controlled, double-masked
Study Objective	Demonstration of the superiority of Moxifloxacin AF to vehicle for the treatment of bacterial conjunctivitis	Demonstration of the non-inferiority of Moxifloxacin AF to VIGAMOX for the treatment of bacterial conjunctivitis
Treatment Groups	Moxifloxacin AF ophthalmic solution and vehicle	Moxifloxacin AF ophthalmic solution and VIGAMOX
Subject/Patient population	Adults and children (≥ 1 month of age) with bacterial conjunctivitis	
Treatment groups	Moxifloxacin AF Ophthalmic Solution vs. Vehicle	Moxifloxacin AF Ophthalmic Solution and Vehicle vs. VIGAMOX
Dosing Regimen	1 drop BID OU vs 1 drop BID OU	1 drop BID OU + 1 drop QD OU (vehicle dose at mid-day) vs 1 drop TID
Dosing Duration	3 days	3 days
Total number Subjects/Patients Enrolled	661 (345 culture positive diagnosed eye)	695 (382 culture positive diagnosed eye)
Primary Efficacy	Clinical cure (sum of scores for bulbar conjunctival injection and conjunctival discharge/exudate = 0) and microbiological success (eradication of pre-therapy pathogens) at TOC visit.	
Secondary Efficacy	Eight individual signs and symptoms of bacterial conjunctivitis: bulbar conjunctival injection, conjunctival discharge/exudate, lid erythema, lid swelling, palpebral conjunctiva, foreign body sensation, tearing, photophobia.	
Safety Variables	Visual acuity, cornea and iris/anterior chamber, dilated fundus exam, adverse events	
Study Visits	Day 1 (Baseline/Screening); Day 3 Day 4 (EOT: 12-48 hrs after last dose) Day 7 (TOC: 60-96 hours after last dose)	
Primary Efficacy Dataset	Modified Intent-To-Treat (MITT) Microbiological Intent-To-Treat (MBITT)	Modified Per Protocol

Sponsor's table 2.7.3.2.-1

2.2 Data Sources

The clinical study reports were provided in a 68-volume paper submission. Datasets and SAS codes for analysis of primary and secondary endpoints are provided in a separate soft copy version. Overall, the data sets (including the requested analysis set) were adequately documented.

3. STATISTICAL EVALUATION

As stated in the earlier sections, there were two Phase 3 studies conducted to evaluate the efficacy and safety of Moxifloxacin AF in the treatment of bacterial conjunctivitis. One is a clinical study comparing Moxifloxacin AF versus vehicle (C-04-38) and the other is a clinical study comparing Moxifloxacin AF versus VIGAMOX (C-04-40). In study C-04-38 adults and pediatric patients one month of age and older with suspected bacterial conjunctivitis were centrally randomized to receive either Moxifloxacin AF or vehicle for 3 days while in study C-04-40, adults and pediatric patients one month of age and older with suspected bacterial conjunctivitis were centrally randomized to receive either Moxifloxacin AF + vehicle or VIGAMOX for 3 days.

3.1 Evaluation of Efficacy

The primary clinical efficacy variable was the clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection including bulbar conjunctival injection and conjunctival discharge/exudate at Day 7 (TOC visit). Clinical cure was attained when the sum of the two cardinal ocular signs was zero. The primary microbiological efficacy variable was the bacterial eradication rate at the Exit visit.

The secondary efficacy variables were the eight individual signs and symptoms of bacterial conjunctivitis at each visit, e.g., bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia.

Reviewer Remark: Endpoints are acceptable and reflects current thinking of medical reviewer's view. See Medical review.

Primary time of assessment was specified to be Day 7 (TOC visit). Conclusion based on data collected at Day 4 (EOT visit) will only be used as supportive information.

Reviewer remark: During the Pre-NDA meeting, the Agency expressed that it plans to use the assessment of the clinical cure rate at Day 5 as the primary clinical efficacy variable in evaluating this new NDA. This, however, cannot be accomplished since there is no data at Day 5.

The primary analysis population is the modified intent-to-treat (MITT) dataset for study C-04-38. The microbiological intent-to-treat (MBITT) population will be used as supportive information. All secondary efficacy conclusions will also be based on this population. In study C-04-40, the modified per protocol population was the primary analysis population. Key secondary conclusions were also based on this population. The characteristics of the analysis populations are given in the table below.

Reviewer remark: The Agency prefers using the MBITT as the primary efficacy data set in both studies (see Agency response to special protocol assessment dated June 4, 2008). All subsequent discussions will be primarily based on the MBITT and or the MITT population

3.1 Evaluability Criteria in Analysis Populations

Analysis data set	Patient-level Evaluability Criteria					
	Received drug	Pathogen Positive at day 1	At least one on-therapy visit	Meet pre-randomization inclusion/exclusion criteria	No major protocol violations	Baseline and Test of cure/exit data
Safety	✓					
ITT	✓		✓			
MBITT	✓	✓	✓			
MITT	✓	✓	✓	✓		
PP	✓		✓	✓	✓	✓
MPP	✓	✓	✓	✓	✓	✓

Sponsor's table 2.7.3.1.-1.

All patients who receive the drug will be evaluable for safety analysis. All patients who receive drug and have at least one on-therapy visit were evaluable for intent-to-treat (ITT) analysis. All patients who received drug, have at least one on-therapy visit, and were pathogen positive for bacteria on day 1 were evaluable for the microbiological intent-to-treat (MBITT) analysis. All patients who received drug, have at least one on-therapy visit, met the inclusion exclusion criteria (pre randomization requirements only), and were pathogen positive for bacteria on Day 1 were evaluable for the modified intent-to-treat (MITT) analysis. For the ITT, MBITT and MITT data sets, patients who had no measurements after baseline were included as treatment failures. All patients who received drug, met inclusion and exclusion criteria and had baseline and test-of-cure (or exit if patient exited from the study early) visits will be available for the per protocol (PP) analysis. All per protocol patients who are pathogen positive for bacteria on Day 1 will be evaluable for the modified per protocol (MPP) analysis. Evaluability may also be performed on a by visit basis for all patients with one or more on-therapy visits.

Study Design and Endpoints

Study C-04-38 was a prospective, multi-center (32 US sites), double masked, parallel group, randomized, placebo-controlled trial designed to evaluate efficacy and safety of topical ocular Moxifloxacin AF Ophthalmic Solution compared to vehicle in the treatment of bacterial conjunctivitis in patients one month of age or older. There were 661 patients enrolled with clinical diagnosis of bacterial conjunctivitis and achieved 345 bacterial pathogen positive patients. Enrollment in the study included patients one month of age or older and excluded all considerations of race, occupation, socioeconomic status, or gender. On Day 1, eligible patients who met inclusion criteria were randomized into one of two groups, Moxifloxacin AF Ophthalmic Solution or Vehicle. Both groups were dosed with one drop two times per day. Treatment continued for 3 days with a test-of-cure follow-up visit at 60 to 96 hours after the last dose of medication.

Study C-04-40 was a prospective, multi-center (India sites), randomized, double masked, and parallel group study. Approximately 675 patients with a clinical diagnosis of bacterial conjunctivitis are targeted for enrollment to achieve at least 370 (185 on Moxifloxacin AF and 185 on VIGAMOX) bacterial pathogen positive patients. If the pathogen positive rate is lower than the expected rate of 55%, additional patients will be enrolled to reach the target number of

patients. This study is designed as a two-arm, active-controlled, non-inferiority comparison of Moxifloxacin AF ophthalmic solution to VIGAMOX.

Post-randomization evaluation times of Day 3 and 4 were considered sufficient to monitor patient safety. The Day 4 visit provided an End of Therapy (EOT) evaluation of the patient 12 to 48 hours after the last dose of medication. The Exit Test-of-Cure (TOC) evaluation 60 to 96 hours after the last dose of medication was considered sufficient to monitor for recurrence of infection and to obtain a test-of-cure microbiological specimen.

The primary efficacy parameters assessed in this study were the cardinal ocular signs of bacterial conjunctivitis including bulbar conjunctival injection and conjunctival discharge/exudate as well as the bacterial eradication rate of the baseline ocular pathogens at Day 7 visit. Clinical cure was attained when the sum of the two cardinal ocular signs was zero (i.e., normal or absent). The primary microbiological efficacy variable was the bacterial eradication rate at the Exit visit (a specimen was obtained from the affected eye(s) at the visit). The secondary efficacy variables were the eight individual signs and symptoms of bacterial conjunctivitis at each visit (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia).

Enrollment continued in the study until at least 150 culture positive patients in each treatment group in the MITT data set were enrolled. With 150 culture positive patients per treatment group, the study had greater than 97% power to detect a treatment difference of 20 percentage points in either the clinical cure or microbiological success rate at Exit visit for Moxifloxacin AF relative to Vehicle.

Reviewer remark: Based on the results of the current study, in retrospect, the sponsor over-estimated treatment effect of Moxifloxacin AF Ophthalmic solution in the design of the current trials.

For patients presenting with bilateral symptomatic and bilateral pathogen positive bacterial conjunctivitis at time of enrollment, the eye with the higher score for the cardinal signs at Day 1 visit was declared the study eye. If both eyes were rated equally by the investigator, the right eye was declared the study eye. For patients presenting with bilateral asymptomatic and unilateral pathogen positive bacterial conjunctivitis at time of enrollment, the pathogen positive eye was designated the study eye. For patients presenting with unilateral symptomatic and unilateral pathogen positive bacterial conjunctivitis at time of enrollment, the enrolled eye was followed, regardless if the opposite eye became involved at any time during the study.

Patient Disposition

In study C-04-38, there were 661 patients who were randomized to treatment and received study drug. All 661 randomized patients were considered evaluable for safety and intent-to-treat (ITT) analysis. Of the patients randomized in the study, 345 were culture positive at baseline visit and thus evaluable for while 316 were excluded from the MBITT dataset. Of the 345 culture positive patients, 342 were evaluable for and 3 were excluded from the MITT dataset. Of the 661 patients who were evaluable for the ITT dataset, 622 were evaluable for and 39 were excluded from the

PP set. Of the patients who were evaluable for the PP data set, 328 were evaluable for and 294 were excluded from the MPP data set.

3.2 Number of Patients per Analysis Population

Analysis data set	C-04-38				C-04-40			
	Data Set (# Evaluable)		Exclusions (# Evaluable)		Data Set (# Evaluable)		Exclusions (# Evaluable)	
	Moxi AF	Vehicle	Moxi AF	Vehicle	Moxi AF	VIGAMOX	Moxi AF	VIGAMOX
Safety	331	330	0	0	346	349	0	0
ITT	331	330	0	0	346	349	0	0
MBITT	178	167	153	163	189	193	157	156
MITT	177	165	154	165	187	191	159	158
PP	317	305	14	25	315	310	31	39
MPP	173	155	158	175	164	172	182	177

Summarized from Figure 11.1.-1 from CSR C-04-38 and C-04-40

In study C-04-40, there were 695 patients who were randomized to treatment and received study drug. All 695 randomized patients were considered evaluable for the safety and intent-to-treat (ITT) analyses. Of the patients randomized in the study, 382 were culture positive at the baseline visit and thus evaluable for, while 313 were excluded, from MBITT data set. Of the 382 culture positive patients, 378 were evaluable for and 4 were excluded from, the MITT data set. Of the 695 patients who were evaluable for ITT data set, 625 were evaluable for and 70 were excluded from, the PP data set. Of the patients who were evaluable for the PP data set, 336 were evaluable for and 289 were excluded from, the MPP data set.

3.3 Summary of Discontinuations

Reason for Discontinuation	C-04-38			C-04-40		
	Moxi AF	Vehicle	Total	Moxi AF	VIGAMOX	Total
Adverse event	5	5	10	3	1	4
Lost to follow-up	3	6	9	24	25	49
Decision unrelated to an adverse event	5	5	10	2	2	4
Noncompliance	1	8	9	0	1	1
Treatment failure	7	32	39	7	13	20
Other	1	4	5	0	0	0
Total	22	60	82	36	42	78

Sponsor's table 10.1.-11 from CSR C-04-38 and C-04-40

A summary of all important protocol deviations related to study inclusion/exclusion criteria, conduct of trial, patient management or patient assessment which resulted in the exclusion from the MITT, PP and/or MPP data sets are described in the following table.

3.4 Protocol Deviations

	Protocol Deviation	Number of Patients	
		C-04-38	C-04-40
Inclusion Criteria	Ocular Signs Ratings	5	1
Visit Procedure	Other – No exit or TOC	35	20
	Other	3	0
	Visual Acuity	5	0
General	Non-compliance with Dosing Regimen	4	9
	Use of Disallowed Concomitant Medications	9	0
	Visit Outside Visit Window	108	0
	Other	4	0
Exclusion Criteria	Disallowed Medications or Period Use	4	3
	Visual Acuity	2	0

Sponsor's table 10.2.-1 from CSR C-04-38 and C-04-40

Reviewer remark: There is imbalance in protocol deviations in the two studies. Protocol deviations are prevalent among patients in the US study sites.

Demographics

In study C-04-38, of the 345 patients evaluable for the MBITT population, the minimum age is 1 month and a maximum age is 89 years. Caucasians form the majority of the patients enrolled, with other races combined only constitute less than 15% of the patient population. As the Sponsor confirms, there was a statistically significant difference between treatments for the distribution of race; however, this difference appears to be due to the distribution of patients who were Asian or of other races and with small number of patients in these two categories, it is unlikely that this would adversely affect the results. The rest of the results between treatment groups and for each demographic characteristic: mean age, age range, age range >64, sex, ethnicity, iris color, affected eye, study eye and duration of current episode are similar.

In study C-04-40, there were similar results between the treatment groups for each of the following demographic characteristics: mean age range, age range >64, sex race, ethnicity, iris, color, affected eye, study eye and duration of current episode. This information is summarized the following table. Similar results were obtained from the MITT, PP, and MPP data sets for all demographic variables

3.5 Demographic characteristics - MBITT Population

	C-04-38		C-04-40	
	Moxifloxacin AF N = 178	Vehicle N = 167	Moxifloxacin AF N = 189	VIGAMOX N = 193
Age , (n%)				
28 Days – 23 Months	45 (25.3%)	43 (25.7%)	3 (1.6%)	5 (2.6%)
2 – 11 years	71 (39.9%)	70 (41.9%)	16 (8.5%)	16 (8.3%)
12 – 17 years	11 (6.2%)	9 (5.4%)	2 (1.1%)	8 (4.1%)
18 – 64 years	46 (25.8%)	39 (23.4%)	150 (79.4%)	145 (75.1%)
≥ 65 years	5 (2.8%)	6 (3.6%)	18 (9.5%)	19 (9.8%)
Age, (n%)				
65 – 74 years	2 (40.0%)	3 (50.0%)	11 (61.1%)	12 (63.2%)
75 – 84 years	3 (60.0%)	2 (33.3%)	5 (27.8%)	7 (36.8%)
≥ 65 years	0 (0.0%)	1 (16.7%)	2 (11.1%)	0 (0.0%)
Sex, (n%)				
Male	79 (44.4%)	85 (50.9%)	138 (73.0%)	125 (64.8%)
Female	99 (55.6%)	82 (49.1%)	51 (27.0%)	68 (35.2%)
Race, (n%)				
Caucasian	152 (85.4%)	139 (83.2%)		
Black	9 (5.1%)	12 (7.2%)		
Asian	8 (4.5%)	1 (0.6%)	189 (100.0%)	193 (100.0%)
Native Hawaiian	0 (0.0%)	0 (0.0%)		
American Indian	0 (0.0%)	0 (0.0%)		
Other	8 (4.5%)	15 (9.0%)		
Multi-Racial	1 (0.6%)	0 (0.0%)		
Iris Color				
Brown	95 (53.4%)	105 (62.9%)	189 (100.0%)	193 (100.0%)
Hazel	20 (11.2%)	19 (11.4%)		
Green	3 (1.7%)	4 (2.4%)		
Blue	59 (33.1%)	38 (22.8%)		
Grey	1 (0.6%)	1 (0.6%)		
Affected Eye				
Right	29 (16.3%)	22 (13.2%)	49 (25.9%)	43 (22.3%)
Left	41 (23.0%)	32 (19.2%)	39 (20.6%)	46 (23.8%)
Both Eyes	108 (60.7%)	113 (67.7%)	101 (53.4%)	104 (53.9%)
Study Eye				
Right	101 (56.7%)	93 (55.7%)	116 (61.4%)	104 (53.9%)
Left	77 (43.3%)	74 (44.3%)	73 (38.6%)	89 (46.1%)

Sponsor's table 10.2.1-7 from CSR C-04-38 and table 10.2.1-6 from CSR C-04-40

Reviewer remarks: Enrollment of pediatric patients in C-04-40 is less than in C-04-38. Majority of patients in C-04-40 are adults. 2. Males are predominant in C-04-40. 3. In general, patient population is dissimilar in the two studies. The second study does not represent patient population found in the US. It is preferable that patient populations somehow mimic patient population in the targeted market of the new drug.

Baseline Characteristics

There were 5 ocular signs (bulbar conjunctival injection, conjunctival discharge/exudate, eyelid erythema, eyelid swelling and palpebral conjunctiva) and 3 ocular symptoms (foreign body sensation, tearing and photophobia) at the screening visit. There were no statistically significant differences between Moxifloxacin AF and Vehicle for the distribution of any 5 ocular signs and 3 ocular symptoms at the screening visit in the MBITT population as seen in the succeeding 2 tables. The same result can also be concluded from the other populations ITT, MITT, PP and MPP. There were also no statistically significant differences between Moxifloxacin AF and VIGAMOX for the distribution of any 5 ocular signs and 3 ocular symptoms at the screening visit in the MBITT population as seen in the succeeding 2 tables. The same result can also be concluded from the other populations ITT, MITT, PP and MPP.

3.6 Baseline Ocular Signs by Treatment in the MBITT population

	C-04-38				C-04-40			
	Moxi AF		Vehicle		Moxi AF		VIGAMOX	
Bulbar Conjunctival Injection	p-value 0.8625				p-value 0.6337			
Normal	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Mild	59	(33.1%)	54	(32.3%)	35	(18.5%)	31	(16.1%)
Moderate	99	(55.6%)	93	(55.7%)	101	(53.4%)	118	(61.1%)
Severe	20	(11.2%)	20	(12.0%)	53	(28.0%)	44	(22.8%)
Conjunctival Discharge/Exudate	p-value 0.1473				p-value 0.7853			
Normal	0	(0.0%)	2	(1.2%)	1	(0.5%)	1	(0.5%)
Mild	64	(36.0%)	75	(44.9%)	75	(39.7%)	76	(39.4%)
Moderate	102	(57.3%)	74	(44.3%)	83	(43.9%)	91	(47.2%)
Severe	12	(6.7%)	16	(9.6%)	30	(15.9%)	25	(13.0%)
Eyelid Erythema	p-value 0.0567				p-value 0.0577			
Normal	32	(18.0%)	42	(25.1%)	97	(51.6%)	118	(61.5%)
Mild	93	(52.2%)	87	(52.1%)	53	(28.2%)	44	(22.9%)
Moderate	47	(26.4%)	34	(20.4%)	32	(17.0%)	25	(13.0%)
Severe	6	(3.4%)	4	(2.4%)	6	(3.2%)	5	(2.6%)
Eyelid Swelling	p-value 0.2143				p-value 0.1754			
Normal	46	(25.8%)	54	(32.3%)	73	(38.6%)	85	(44.0%)
Mild	94	(52.8%)	82	(49.1%)	52	(27.5%)	55	(28.5%)
Moderate	34	(19.1%)	27	(16.2%)	54	(28.6%)	45	(23.3%)
Severe	4	(2.2%)	4	(2.4%)	10	(5.3%)	8	(4.1%)
Palpebral Conjunctiva	p-value 0.9137				p-value 0.0977			
Normal	3	(1.7%)	5	(3.0%)	12	(6.3%)	15	(7.8%)
Mild	62	(34.8%)	56	(33.5%)	26	(13.8%)	34	(17.6%)
Moderate	99	(55.6%)	90	(53.9%)	103	(54.5%)	107	(55.4%)
Severe	14	(7.9%)	16	(9.6%)	48	(25.4%)	37	(19.2%)

Sponsor's table 14.1.2-1 from CSR C-04-38 and C-04-40

3.7 Baseline Ocular Symptoms by Treatment

	C-04-38		C-04-40	
	Moxi AF	Vehicle	Moxi AF	VIGAMOX
Foreign body sensation	p-value 0.4222		p-value 0.7069	
Normal	25 (14.3%)	26 (16.3%)	30 (16.2%)	32 (17.2%)
Mild	69 (39.4%)	65 (40.6%)	65 (35.1%)	59 (31.7%)
Moderate	64 (36.6%)	58 (36.3%)	77 (41.6%)	79 (42.5%)
Severe	17 (9.7%)	11 (6.9%)	1 (7.0%)	16 (8.6%)
Tearing	p-value 0.6159		p-value 0.4741	
Normal	18 (10.3%)	18 (11.2%)	12 (6.5%)	11 (5.8%)
Mild	63 (36.0%)	61 (37.9%)	70 (37.6%)	67 (35.3%)
Moderate	72 (41.1%)	63 (39.1%)	87 (46.8%)	91 (47.9%)
Severe	22 (12.6%)	19 (11.8%)	17 (9.1%)	21 (11.1%)
Photophobia	p-value 0.1570		p-value 0.9662	
Normal	54 (30.9%)	41 (25.6%)	101 (54.6%)	95 (51.1%)
Mild	86 (49.1%)	77 (48.1%)	53 (28.6%)	70 (37.6%)
Moderate	26 (14.9%)	33 (20.6%)	23 (12.4%)	18 (9.7%)
Severe	9 (5.1%)	9 (5.6%)	8 (4.3%)	3 (1.6%)

Sponsor's table 14.1.2-2 from CSR C-04-38 and C-04-40

Statistical Methodologies

Hypothesis: The hypothesis being tested in study C-04-38 is

$$H_0: \pi_m = \pi_v$$

$$H_1: \pi_m \neq \pi_v$$

where π_m denotes the probability of clinical cure for Moxifloxacin AF patients at Day 7/Exit visit and π_v denotes the probability of clinical cure for Vehicle patients at the Day 7/Exit visit. A chi-square test of independence (or Fisher's exact test if one or more expected cell frequencies are < 5) will be used to assess differences for Moxifloxacin AF compared to Vehicle for Day 7 clinical cure rate. Analyses will be conducted on all data sets, but primary inference will be based on the microbiological intent-to-treat data set.

Reviewer remark: A chi-square test evaluates whether or not variables within a contingency table are independent, or that there is no association between them. In this example, independence would mean that the proportion of individuals that were cured is not dependent on the treatment they are in; thus, the proportion of patients cured would be similar for patients in both experimental groups. Dependence, or association, would mean that the proportion of individuals cured is dependent on the type of treatment they are in, so that cure would be more commonly found in patients with one of the two treatments examined.

The hypothesis in Study C-04-40 for clinical response to therapy addresses a test of non-inferiority. The hypothesis being tested for non-inferiority is:

$$H_0: \pi_m - \pi_v \leq -15\%$$

$$H_1: \pi_m - \pi_v > -15\%$$

where π_m denotes the probability of clinical cure for Moxifloxacin AF patients at Day 7/Exit visit and π_v denotes the probability of clinical cure for VIGAMOX patients at the Day 7/Exit visit. A chi-square test of independence (or Fisher's exact test if one or more expected cell frequencies are < 5) will be used to assess differences for Moxifloxacin AF compared to VIGAMOX Vehicle for Day 7 clinical cure rate.

Non-inferiority margin. Alcon's justification of the non-inferiority margin provided in their NDA is based on the following. "The observed clinical cure rate at TOC visit was approximately 80% for VIGAMOX in the vehicle-controlled study conducted by Alcon Research, Ltd., Protocol C-00-55. In this study, non-inferiority will be declared if the lower 95% confidence limit about the treatment difference lies entirely above -15% which is much less than the observed clinical cure rate of 80% for VIGAMOX."

Reviewer remark: Sponsor's justification of non-inferiority margin is not valid. The justification should include estimation of the treatment effect M1 of active drug over placebo and an acceptable loss of effect relative to control M2 while preserving some portion (usually at least 50%) of the effect of the control drug. Without the information on M1, there is no basis for M2 and consequently of a clinically meaningful non-inferiority margin.

Determining the treatment effect M1 of antibiotics over placebo in the treatment of bacterial conjunctivitis is difficult for many reasons. Historical trials have different parameters, e.g. definition of analysis population, treatment regimen and duration, definition of efficacy endpoints to name a few. The best information that can be used to determine a possible margin for this trial is based on the Sponsor's previous submission in support of VIGAMOX (NDA 21,598). In that NDA, the lower confidence limit of treatment benefit in the MITT population at Day 5 is 3.66% (see table 1.1) and diminishes at Day 9. Since, treatment benefit of antibiotics over placebo in bacterial conjunctivitis diminish as the time to assessment increases, i.e. there is spontaneous resolution of bacterial conjunctivitis, it is not possible to justify a 15% non-inferiority margin for clinical cure at Test-of-Cure (Day 7).

Sample size justification: Enrollment continued in the study C-04-38 until at least 150 culture positive patients in each treatment group in the MITT data set were enrolled. With 150 culture positive patients per treatment group, the study had greater than 97% power to detect a treatment difference of 20 percentage points in either the clinical cure or microbiological success rates at the Exit visit for Moxifloxacin AF relative to Moxifloxacin AF vehicle.

3.8 Expected Clinical Cure and Microbiological Success rates at Exit for C-04-38 Study

Treatment	Clinical Cure (%)	Microbiological Success (5)
Moxifloxacin AF	85.0	85.0
Vehicle	65.0	65.0

In study C-04-40, enrollment continued until at least 370 pathogen positive patients in the MPP data set are enrolled. With approximately 185 pathogen positive patients per group, there is 90%

probability that the lower 95% confidence limit for the difference in proportion for clinical cure (Moxifloxacin AF-VIGAMOX) is greater than -15% assuming an 80% clinical cure rate for both Moxifloxacin AF and VIGAMOX groups.

3.9 Expected Clinical Cure and Microbiological Success rates at Exit for C-04-40 Study

Treatment	Clinical Cure (%)	Microbiological Success (5)
Moxifloxacin AF	80.0	82.0
Vehicle	80.0	82.0

Handling of dropout: All patients who miss a visit will have their data regarding sign and symptoms from the prior visit carried forward and used to replace the missed visit. Patients who have no measurements after baseline are included as treatment failures. All baseline pathogen patients who discontinue the study due to treatment failure will be included as treatment failures in the analysis regardless of evaluability. For these patients, baseline assessments of ocular signs and symptoms will be carried forward into each visit and microbiological outcomes will be set to “failure”. No other data will be imputed.

Results and Conclusions

The Sponsor used two studies as supportive evidence of the efficacy of Moxifloxacin AF Ophthalmic Solution. One is to establish superiority of the latter over vehicle and the second is to establish the non-inferiority of the latter to an established drug with the same active ingredient, VIGAMOX. The results of the corresponding trials used to support these claims will be discussed accordingly.

Study C-04-38. The sponsor concluded that Moxifloxacin AF Ophthalmic Solution dosed a two times a day for 3 days is superior to Vehicle in the treatment of bacterial conjunctivitis based on the following results:

1. The percentage of patients with clinical cures at Day 7 (TOC) visit was significantly higher for Moxifloxacin AF Ophthalmic solution than Vehicle in the ITT data set.
2. The percentage of patients who were microbiological success at Day 7 (TOC) visit was significantly higher for Moxifloxacin AF Ophthalmic Solution than Vehicle in the MBITT and MITT data sets.
3. The percentage of patients with clinical cures at Day 4 (EOT) visit was significantly higher for Moxifloxacin AF Ophthalmic Solution than Vehicle in all data sets.

Although the above observations are true, the reviewer does not agree with the Sponsor that the drug is robustly efficacious for the following reasons. First, based on the primary efficacy endpoint of clinical cure rate of the MITT population at TOC (Day 7) visit Moxifloxacin AF Ophthalmic Solution is not superior over Vehicle. Clinical cure rate for Moxifloxacin AF is at 72.3% compared to 67.3% for Vehicle with a treatment difference of 4.8% (95% CI: -5.2%, 14.8%). A similar conclusion can be reached in the MBITT, MPP and PP population as seen in the following table. Second, the ITT population is not an acceptable primary analysis population because some patients may not necessarily have positive culture to be considered bacterial conjunctivitis. Third, microbiological success is not a clinical endpoint and does not accurately

reflect clinical benefit due to drug. Although clinical cure and microbiological success are correlated, the latter does not always translate to complete resolution of signs and symptoms of bacterial conjunctivitis. Fourth, clinical cure at EOT (Day 4) visit is a secondary endpoint. Testing for significance among secondary endpoints is only applicable if the primary hypothesis has been rejected. This time of assessment does not also completely coincide with what the Agency prefers which is Day 5.

3.10 Study C-04-38: Clinical Cure at Day 7 (TOC) Visit

	C-04-38	
	Moxifloxacin AF	Vehicle
MBITT		
Clinical cure, (n%)	129/178 (72.5%)	113/167 (67.7%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	4.8% (-5.2%, 14.8%)	
MITT		
Clinical cure, (n%)	128/177 (72.3%)	111/165 (67.3%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	5.0% (-5.1%, 15.1%)	
PP		
Clinical cure, (n%)	199/264 (75.4%)	170/258 (65.9%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	7.0% (-0.1%, 14.9%)	
MPP		
Clinical cure, (n%)	105/140 (75.0%)	88/133 (66.2%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	3.9% (-7.1%, 14.9%)	

3.11 Study C-04-38: Microbiological Success at Day 7 (TOC) Visit

	C-04-38	
	Moxifloxacin AF	Vehicle
MBITT		
Microbiological Success, (n%)	150/178 (84.3%)	110/167 (65.9%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	18.4% (8.9%, 27.6%)	
MITT		
Microbiological Success, (n%)	149/177 (84.2%)	109/165 (66.1%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	18.1% (8.6%, 27.4%)	
MPP		
Microbiological Success, (n%)	115/139 (82.7%)	90/133 (67.7%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	15.1%(4.3%, 25.5%)	

3.12 Study C-04-38: Clinical Cure at Day 4 (EOT) Visit

	C-04-38	
	Moxifloxacin AF	Vehicle
MBITT		
Clinical cure, (n%)	104/178 (58.4%)	78/169 (46.7%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	12.3% (1.4%, 22.8%)	
MITT		
Clinical cure, (n%)	103/177 (58.2%)	77/165 (46.7%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	11.5% (0.5%, 22.2%)	
PP		
Clinical cure, (n%)	146/247 (59.1%)	99/236 (41.9%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	17.2% (8.0%, 26.0%)	
MPP		
Clinical cure, (n%)	80/132 (60.6%)	54/122 (44.3%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	16.3% (3.5%, 28.5%)	

Sponsor's table 11.4.1.2.-1

Study C-04-40. The sponsor concluded that Moxifloxacin AF Ophthalmic solution dosed two times for 3 days is non-inferior to VIGAMOX in the treatment of bacterial conjunctivitis based on the following results:

1. Moxifloxacin AF Ophthalmic Solution is non-inferior, at a 15% margin, to VIGAMOX for the clinical cure at Day 7 (TOC) visit. In the MPP data set, the clinical cure rate at Day 7 (TOC) visit was 84.4% for Moxifloxacin AF and 85.7% for VIGAMOX. The upper and lower limits of the 95% confidence interval on the difference (-1.3%) were (Lower CL = -10.1614, Upper CL = 7.5892).
2. Moxifloxacin AF Ophthalmic Solution is non-inferior to VIGAMOX for the microbiological success at Day 7 (TOC) visit. In the MPP data set, the microbiological success rate for Moxifloxacin AF was 92.6% compared to 92.0% for VIGAMOX. The upper and lower limits of the 95% confidence interval on the difference (0.6%) were (Lower CL = -6.1072, Upper CL = 7.2311).
3. Moxifloxacin AF Ophthalmic Solution is non-inferior to VIGAMOX for clinical cure at Day 4 (EOT) visit. In the MPP data set, the clinical cure at Day 4 (EOT) visit for Moxifloxacin AF was 62.4% compared to 65.0% for VIGAMOX. The upper and lower limits of the 95% confidence interval on this difference (-2.6%) were (lower CL = -14.8154, Upper CL = 9.5204).

3.13 Study C-04-40 Clinical Cure at Day 7 (TOC) Visit

	C-04-40	
	Moxifloxacin AF	VIGAMOX
MBITT		
Clinical cure, (n%)	152/189 (80.4%)	163/193 (84.5%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-4.1% (-11.66%, 3.59%)	
MITT		
Clinical cure, (n%)	150/187 (80.2%)	161/191 (84.3%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-4.1% (-11.78%, 3.62%)	
PP		
Clinical cure, (n%)	197/240 (82.1%)	197/229 (86.0%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-3.9% (-10.5%, 2.67%)	
MPP		
Clinical cure, (n%)	103/122 (84.4%)	108/126 (85.7%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-1.3% (-10.16%, 7.58%)	

3.14 Study C-04-40 Microbiological Success at day 7 (TOC) Visit

	C-04-40	
	Moxifloxacin AF	VIGAMOX
MBITT		
Clinical cure, (n%)	165/189 (87.3%)	173/193 (89.6%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-2.3% (-8.74%, 4.07%)	
MITT		
Clinical cure, (n%)	163/187 (87.2%)	171/191 (89.5%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-2.3% (-8.83%, 4.11%)	
PP		
Clinical cure, (n%)	112/121 (92.6%)	115/125 (92.0%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	0.6% (-6.11%, 7.23%)	

3.15 Study C-04-40: Clinical Cure at Day 4 (EOT) Visit

	C-04-38	
	Moxifloxacin AF	VIGAMOX
MBITT		
Clinical cure, (n%)	109/189 (57.7%)	125/193 (64.8%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-7.1% (-16.8%, 2.7%)	
MITT		
Clinical cure, (n%)	108/187 (57.8%)	123/191 (64.4%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-6.6% (-16.5%, 3.2%)	
PP		
Clinical cure, (n%)	136/231 (58.9%)	145/224 (64.7%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-5.8% (-14.8%, 3.1%)	
MPP		
Clinical cure, (n%)	73/117 (62.4%)	80/123 (65.0%)
Treatment difference (Moxi AF – Vehicle) and 95% CI	-2.6% (-14.8%, 9.5%)	

Sponsor's table 11.4.1.2.-1

The reviewer does not find these results meaningful and does not in any way establish efficacy of Moxifloxacin AF Ophthalmic Solution even if all the assumptions of non-inferiority are satisfied, i.e. assay sensitivity, trial constancy, and proper trial conduct. The primary reason is due to incorrect determination of the non-inferiority margin. A non-inferiority margin of 15% is not acceptable because the minimum treatment effect of VIGAMOX at Day 5 is 3.66% and

shows no improvement over vehicle at Day 9. Thus the minimum treatment effect of VIGAMOX over vehicle could be no more than 3.66% at Day 7.

Secondary Endpoints. There was no statistically significant difference between Moxifloxacin AF and VIGAMOX in reducing all key secondary endpoints at Day 7 (TOC) visit in the MPP (see table 3.15). These are also replicated in other visits and other data sets. Hommel's method was used to control the Type I error at 0.05 for the secondary efficacy variables. Conclusion in the MPP data set remained the same with the multiplicity correction.

3.16 Secondary Endpoints at Day 7 (TOC)

	C-04-38 (MBITT)				C-04-40 (MPP)			
	Moxi AF		Vehicle		Moxi AF		VIGAMOX	
	n	(%)	n	(%)	n	(%)	n	(%)
Bulbar Conjunctival Injection	p-value 0.1386				p-value 0.9240			
Normal	141	(79.2)	122	(73.1)	104	(85.6)	108	(85.7)
Mild	23	(12.9)	23	(13.8)	7	(5.7)	8	(6.3)
Moderate	12	(6.7)	17	(10.2)	9	(7.4)	6	(4.8)
Severe	2	(1.1)	5	(3.0)	2	(1.6)	4	(3.2)
Conjunctival Discharge/Exudate	p-value 0.0996				p-value 0.9353			
Normal/Absent	146	(82.0)	126	(75.4)	110	(90.2)	114	(90.5)
Mild	23	(12.9)	22	(13.2)	6	(4.9)	7	(5.6)
Moderate	6	(3.4)	15	(9.0)	5	(4.1)	2	(1.6)
Severe	3	(1.7)	4	(2.4)	1	(0.8)	3	(2.4)
Eyelid Erythema	p-value 0.0992				p-value 0.3853			
Normal	155	(87.1)	135	(80.8)	113	(92.6)	120	(95.2)
Mild	18	(10.1)	21	(12.6)	7	(5.7)	5	(4.0)
Moderate	4	(2.2)	10	(6.0)	2	(1.6)	1	(0.8)
Severe	1	(0.6)	1	(0.6)	0	(0.0)	0	(0.0)
Eyelid Swelling	p-value 0.0205				p-value 0.7311			
Normal	161	(90.4)	137	(82.0)	113	(92.6)	118	(93.7)
Mild	13	(7.3)	20	(12.0)	3	(2.5)	4	(3.2)
Moderate	4	(2.2)	9	(5.4)	6	(4.9)	4	(3.2)
Severe	0	(0.0)	1	(0.6)	2	(0.0)	0	(0.0)
Palpebral Conjunctiva	p-value 0.1238				p-value 0.9151			
Normal	123	(69.1)	104	(62.3)	105	(86.1)	109	(86.5)
Mild	39	(21.9)	39	(23.4)	7	(5.7)	8	(6.3)
Moderate	14	(7.9)	18	(10.8)	7	(5.7)	5	(4.0)
Severe	2	(1.1)	6	(3.6)	3	(2.5)	4	(3.2)
Foreign Body Sensation	p-value 0.0084				p-value 0.6401			
Normal	157	(89.7)	129	(80.1)	109	(90.1)	113	(91.9)
Mild	14	(8.0)	15	(9.3)	7	(5.8)	5	(4.1)
Moderate	4	(2.3)	12	(7.5)	4	(3.3)	4	(3.3)
Severe	0	(0.0)	5	(3.1)	1	(0.8)	1	(0.8)
Tearing	p-value 0.0032				p-value 0.7665			
Normal	153	(87.4)	121	(75.2)	109	(90.1)	110	(88.7)
Mild	15	(8.6)	25	(15.5)	4	(3.3)	8	(6.5)
Moderate	7	(4.0)	11	(6.8)	7	(5.8)	4	(3.2)
Severe	0	(0.0)	4	(2.5)	1	(0.8)	2	(1.6)
Photophobia	p-value 0.0910				p-value 0.5869			
Normal	160	(91.4)	138	(85.7)	112	(92.6)	117	(94.4)
Mild	12	(6.9)	16	(9.9)	8	(6.6)	5	(4.0)
Moderate	3	(1.7)	5	(3.1)	1	(0.8)	2	(1.6)
Severe	0	(0.0)	2	(1.2)	0	(0.0)	0	(0.0)

Summarized from Sponsor's tables 11.4.1.3.-1 to 11.4.1.3.-8 from CSR C-04-38 and C-04-40

3.2 Evaluation of Safety

Three clinical studies (C-04-38, C-04-40, and C-05-15) comprise the safety data set used for the analysis of adverse events. Together, accumulated safety evaluation is based on 1386 patients which include 697 patients exposed to Moxifloxacin AF dosed two times a day across the 3 clinical studies, 20 from the pharmacokinetic study (C-05-15) and 677 from the 2 bacterial conjunctivitis studies (C-04-38 and C-04-40).

Overall duration of exposure to drug. The clinical development of Moxifloxacin AF consisted of 3 studies and included an overall total of 1386 patients evaluable for safety. Duration of exposure to the study drug for all 3 studies is summarized the following table.

3.17 Number of Patients exposed to Drug

Treatment	Two times a day		Three times a day	
	N	(%)	N	(%)
Total	1037	(74.8)	349	(25.2)
Moxifloxacin AF	697	(100)	0	(0.0)
VIGAMOX	0	(0.0)	349	(100)
Vehicle	340	(100)	0	(0.0)

Sponsor's table 2.7.4.1.2.-1

Summary of adverse events. No deaths or serious adverse events were reported during the study. A total of 14 patients (1.0%) experience significant adverse events (discontinuation of study participation due to an adverse event; related and unrelated combined). Four of the 14 patients discontinued participation in the study due to treatment-related adverse events, which included 3 patients (0.4%) treated with Moxifloxacin AF (conjunctival oedema, eyelid oedema, and ocular hyperaemia; conjunctival ulcer; foreign body sensation in eyes and lacrimation increased) and 1 patients (0.3%) treated with VIGAMOX (conjunctival oedema, eye pruritus, and eyelid oedema).

The most frequent ocular adverse drug reactions for the Moxifloxacin AF group were eye irritation (1.4%), eye pruritus (0.4%), and eye pain (0.6%). The only non-ocular adverse drug reactions reported were rash (characterized as rash on arms and trunk or rash under left eye, (0.3%) and headache (0.1%).

3.18 Adverse Events

Coded Adverse Event	Moxi AF		Vigamox		Vehicle	
	N	(%)	N	(%)	N	(%)
Nervous System disorders						
Headache	1	(0.1)	1	(0.3)	1	(0.3)
Eye disorder						
Eye irritation	10	(1.3)	5	(1.4)	3	(0.9)
Eye Pain	4	(0.6)	4	(1.1)	1	(0.3)
Eye Pruritus	3	(0.4)	5	(1.4)	2	(0.6)
Cornel Epithelium Disorder	1	(0.1)	1	(0.3)		
Conjunctival oedema	1	(0.1)	1	(0.3)		
Eyelid oedema	1	(0.1)	1	(0.3)		
Conjunctival ulcer	1	(0.1)				
Ocular hyperaemia	1	(0.1)			1	(0.3)
Foreign body sensation in eyes	1	(0.1)				
Lacrimation increased	1	(0.1)				
Asthenopia			1	(0.3)	1	(0.3)
Blepharitis			1	(0.3)	1	(0.3)
Punctuate keratitis			1	(0.3)		
Corneal infiltrates					1	(0.3)
Eye discharge					1	(0.3)
Respiratory, thoracic and mediastinal disorders						
Pharyngolaryngeal pain					1	(0.3)
Skin and subcutaneous tissue disorders						
Rash	2	(0.3)				

Sponsor's table 2.7.4.2.1.1.-2

The most frequently reported common ocular adverse events in the Moxifloxacin AF group were eye irritation (1.6%), conjunctivitis (1.4%), and eye pain (1.1%). These results were comparable to the occurrences among patients in the VIGAMOX and Vehicle treatment. On the other hand, the most frequently reported common non-ocular adverse event in the Moxifloxacin AF treatment group was pyrexia, occurring at an incidence of 1.3%. Pyrexia was reported among patients receiving VIGAMOX or Vehicle at an incidence of 2% and 1.2%, respectively.

3.19 Common Adverse events

Coded Adverse Event	Moxi AF		Vigamox		Vehicle	
	N	(%)	N	(%)	N	%
Infections and infestations						
Upper respiratory tract infection	6	(0.9)			5	(1.5)
Otitis media	2	(0.3)			6	(1.8)
Nervous system disorders						
Headache	4	(0.6)	2	(0.6)	7	(2.1)
Eye disorder						
Eye irritation	11	(1.6)	5	(1.4)	3	(0.9)
Eye Pain	10	(1.4)	2	(0.6)	5	(1.5)
Eye Pruritus	8	(1.1)	7	(2.0)	1	(0.3)
Conjunctivitis	5	(0.7)	5	(1.4)		
Punctate keratitis	3	(0.4)	5	(1.4)	2	(0.6)
General disorders and administration site conditions						
Pyrexia	9	(1.3)	7	(2.0)	4	(1.2)

Sponsor's table 2.7.4.2.1.1.-3

Reviewer remark: See Medical review for more detailed safety analysis.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Gender, Race and Age

The result of C-04-38 stratified by age is not consistent across age groups. In infants, Moxifloxacin AF has a slight advantage over Vehicle but the reverse happens for children and adults less than 65 years of age. On the other hand, result of C-04-40 in all age categories are quite consistent with the overall result.

Sex does not seem to be a factor in cure rate. Notice that cure rate is consistent across sex categories.

It is quite difficult to assess the effect of race on clinical cure since the bulk of the study is either predominantly Caucasians (e.g. study C-04-38) or Asians (study C-040-40).

4.1 Clinical Response at TOC Visit Stratified by Age, Sex, and Race

	C-04-38 (MBITT)		C-04-40 (MPP)	
	Moxi AF	Vehicle	Moxi AF	VIGAMOX
	n (%)	n (%)	n (%)	n (%)
Age				
28 days -23 Months	34 (75.6)	26 (60.5)	2 (100.0)	1 (50)
2-11 yrs	48 (67.6)	50 (71.4)	7 (70.0)	8 (80.0)
12-17 yrs	9 (81.8)	5 (55.6)	2 (100.0)	4 (80.0)
18-64 yrs	34 (73.9)	29 (74.4)	81 (83.5)	82 (86.3)
65 and older	4 (80.0)	3 (50.0)	11 (100.0)	13 (92.9)
Sex				
Male	55 (69.6)	53 (62.4)	75 (83.3)	70 (83.3)
Female	74 (74.7)	60 (73.2)	28 (87.5)	38 (90.5)
Race				
Caucasian	109 (71.7)	93 (66.9)		
Black	4 (44.4)	10 (93.3)		
Asian	7 (87.5)	1 (100)	103 (84.4)	108 (85.7)
Native Hawaiian	0 (0.00)	0 (0.00)		
American Indian	0 (0.00)	0 (0.00)		
Other	8 (100)	9 (60.0)		
Multi-racial	1 (100)	0 (0.00)		

Summarized from Sponsor's tables 11.4.2.8.2.-1 to 11.4.2.8.6.-1 in CSR C-04-38 and tables 11.4.2.8.2.-1 to 11.4.2.8.4.1 in CSR C-04-40

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were two clinical studies submitted in support for Moxifloxacin AF in the treatment of bacterial conjunctivitis. The first study, C-04-38, is a superiority study of Moxifloxacin AF over vehicle while the second study, C-04-40 is a noninferiority study of Moxifloxacin AF compared to VIGAMOX.

In Study C-04-38, the primary efficacy endpoint of clinical cure rate of the MITT population at TOC (Day 7) visit Moxifloxacin AF Ophthalmic Solution is not superior over Vehicle. Clinical cure rate for Moxifloxacin AF is at 72.3% compared to 67.3% for Vehicle with a treatment difference of 4.8% (95% CI: -5.2%, 14.8%). Similar conclusions can be reached in the MBITT, MPP and PP population. It is only in the ITT population where Moxifloxacin AF is found superior over vehicle. However, The ITT population is not an acceptable primary analysis population because some patients may not necessarily have culture positive to be considered bacterial conjunctivitis. Superiority of Moxifloxacin AF over Vehicle cannot also be based on microbiological success since this variable is not a clinical endpoint and does not accurately reflect clinical benefit translated as complete resolution of signs and symptoms of bacterial conjunctivitis. Neither can superiority be based on clinical cure at EOT (Day 4) visit because this is a secondary endpoint. Testing for significance among secondary endpoints is only applicable if the primary hypothesis has been rejected.

In study C-04-40, the reviewer does not find the results of the non-inferiority trial interpretable due to the choice of the non-inferiority margin and does not in any way establish efficacy of Moxifloxacin AF Ophthalmic Solution. Using the results of NDA 21, 598, a submission in support of VIGAMOX (the original formulation of Moxifloxacin) the lower confidence limit of treatment benefit in the MITT population at Day 5 is 3.66%. Since, treatment benefit of antibiotics over placebo in bacterial conjunctivitis diminish as the time to assessment increases, it is not possible to justify a 15% non-inferiority margin.

5.2 Conclusions and Recommendations

The reviewer finds that Moxifloxacin AF has not established itself as an effective therapy. This conclusion relies primarily on the result obtained from the vehicle controlled study where Moxifloxacin failed to establish superiority over vehicle. Additional studies may need to be performed and an appropriate endpoint (time to assessment) needs to be carefully chosen.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22428	ORIG-1	ALCON PHARMACEUTICA LS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

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