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:21 May 2010; Filing date: 18 June, 2010; PDUFA goal date: 19 November 2010
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Keywords: superiority, Moxifloxacin hydrochloride ophthalmic solution, bacterial conjunctivitis, bulbar conjunctival injection, conjunctival discharge/exudate

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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, l2- 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) (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 walking

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.

Table3.11 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

	Moxi AF		Vehicle	
Coded Adverse Event	**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.

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/s/

MARK A GAMALO
10/01/2010

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