CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22428Orig1s000

SUMMARY REVIEW

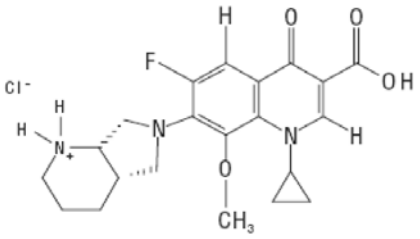
Division Director Review of NDA 22-428

Date	November 19, 2010
From	Wiley A. Chambers, M.D.
NDA #	22-428
Applicant	Alcon Pharmaceuticals, Ltd.
Date of Re-Submission	May 21, 2010
Type of Application	505(b)(1)
Name	Moxeza (moxifloxacin hydrochloride ophthalmic solution) 0.5%
Dosage forms / Strength	Topical ophthalmic solution, 0.5% as base
Proposed Indication(s)	Indicated for the treatment of bacterial conjunctivitis
Action:	Approval

1. Introduction

Moxifloxacin is a fluoroquinolone that was originally developed and approved for the treatment of various systemic bacterial infections. Alcon developed a topical ophthalmic formulation of moxifloxacin marketed as Vigamox for the treatment of bacterial conjunctivitis. The approved dosage and administration for Vigamox is one drop in the affected eye 3 times a day for 7 days. The current application is for an alternate formulation of moxifloxacin for the treatment of bacterial conjunctivitis. This application is for an alternate formulation containing a xanthan gum- (b) (4) The objective of this formulation change is to maintain the same efficacy as the marketed Vigamox with only twice a day dosing.

Moxifloxacin hydrochloride was approved in Alcon's NDA 21-598 for Vigamox and is currently being marketed in the United States. Moxifloxacin hydrochloride is manufactured by Bayer AG in Wuppertal, Germany.



$C_{21}H_{24}FN_3O_4 \cdot HCl$ Mol Wt 437.9

Comparison of Compositions of Moxifloxacin AF and Vigamox

Component	% Composition	
	Moxifloxacin AF	**Vigamox**
Moxifloxacin hydrochloride	0.545	Same
Xanthan gum	(b) (4)	(b) (4)
Sodium chloride		
Boric acid		
Sorbitol		
Tyloxapol		
Hydrochloric acid and/or sodium hydroxide	Adjust pH to 7.4	Adjust to pH 6.8
Purified water	(b) (4)	(b) (4)

The formulation of moxifloxacin used in the clinical studies is the same as the one intended for marketing.

2. Background

Alcon's proposed Phase 3 development program for moxifloxacin AF ophthalmic solution was discussed with the Agency in a Pre-IND/End of Phase 2 meeting on March 3, 2005. Alcon subsequently submitted Special Protocol Assessment requests for study C-04-38 and C-04-40, to which the Agency responded with comments on June 22, 2005. Comments on both studies were provided to Alcon. A Pre-NDA meeting package containing a summary of efficacy results from these studies was submitted to the Agency and comments were discussed at the Pre-NDA meeting on April 8, 2008. The new formulation of moxifloxacin is not marketed in any other country.

3. CMC

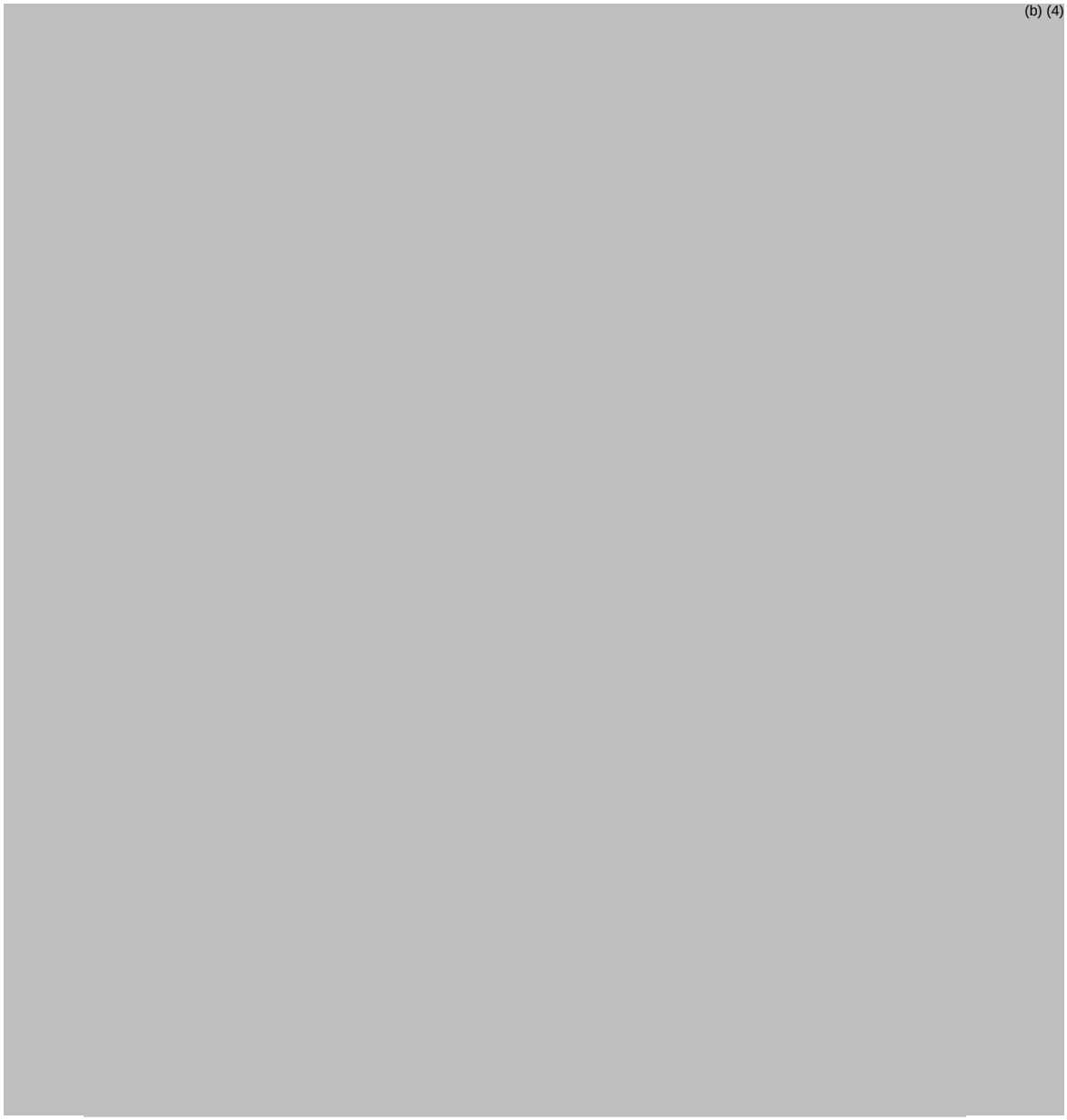
DRUG SUBSTANCE:

The applicant holds an approved NDA 21-598 on Vigamox, an ophthalmic solution containing the same drug substance. The drug substance information provided in NDA 21-598 is acceptable for the current application.

DRUG PRODUCT:

Moxifloxacin alternative formulation ophthalmic solution, 0.5% (Moxifloxacin AF) is a sterile, ophthalmic solution containing 0.545% w/v moxifloxacin hydrochloride, equivalent to 0.5% moxifloxacin. The proposed formulation has been modified (b) (4) with similar efficacy to Vigamox but with a less frequent dosing regimen from TID to BID. The product will be packaged in a natural, low density polyethylene (LDPE) bottle with a polyethylene (LDPE) natural dispensing plug and a tan polypropylene (PP) closure.

(b) (4) is used in the proposed formulation. As with the marketed Vigamox product, the applicant has stated that the new formulation of moxifloxacin ophthalmic solution maintains adequate (b) (4) to meet USP (b) (4) effectiveness requirements in the absence of a (b) (4) agent.



All facilities were found acceptable for NDA 22-428 by Compliance as of September 1, 2010.

4. Nonclinical Pharmacology/Toxicology

Daily topical application of the drug product to rabbits for up to one month was not associated with ocular inflammation, irritation, or toxicity. Higher concentrations of moxifloxacin (1%, 1.5%) in the same AF vehicle did not cause inflammation, but microscopic evaluation indicated signs of minor irritation in the lower conjunctiva and third eyelid. Ophthalmic examination (biomicroscopy/slit lamp, indirect ophthalmoscopy) did not reveal any changes associated with Moxifloxacin AF treatment at concentrations up to 1.5%. Moxifloxacin AF, 0.5%, did not impede wound healing in rabbits when applied following a keratectomy.

Systemic availability of moxifloxacin was very low in human subjects when the drug product was applied to both eyes twice daily for 4 days, then once on Day 5 (Cmax 0.977 $\pm$0.673 ng/mL; AUC 8.17 $\pm$ 5.31 ng·hr/mL).

The genotoxic profile of moxifloxacin is comparable to other fluoroquinolones. It was mutagenic in one of 5 bacterial strains used for the Ames test (TA 102) and clastogenic in a chromosome aberration assay using cultured cells. It did not induce unscheduled DNA synthesis in vitro and was negative in a mouse micronucleus test *in vivo*. Moxifloxacin had no effect on fertility in rats at systemic doses far above those that can be achieved using a topical ophthalmic route. It was not teratogenic in rats and monkeys given oral doses far above the highest recommended total daily human ophthalmic dose.

5. Clinical Pharmacology/Biopharmaceutics

The extent of systemic exposure to moxifloxacin following topical ophthalmic administration of the new formulation of moxifloxacin was evaluated in a double-masked, vehicle-controlled, parallel-group, multiple-dose pharmacokinetic (PK) study in healthy adults (Study C-05-15). The clinical pharmacology findings from this study are summarized as follows:

- Following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days, a mean peak plasma concentration of 0.977 ± 0.673 ng/mL (range: 0.267 to 3.19 ng/mL) was observed within approximately one hour.
- Moxifloxacin concentrations declined in a monophasic manner with terminal half-lives ranging from 7.6 to 27.3 hours (mean half life: 16.6 ± 5.5 hours) in healthy subjects.
- Steady-state following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% was achieved between 3 to 4 days. The estimated accumulation ratio was 2.5.
- Cmax and AUC_{0-8} for moxifloxacin following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days were approximately 36% and 45%, respectively, of the Cmax and AUC_{0-8} observed following TID dosing for 5 days with the previously approved moxifloxacin ophthalmic formulation VIGAMOX.
- Moxifloxacin Cmax following twice-daily bilateral ophthalmic administration of Moxifloxacin AF 0.5% for 5 days is approximately 0.02% of that achieved with the oral formulation of moxifloxacin hydrochloride (Cmax values: Moxifloxacin AF, 0.977 ± 0.88 ng/mL versus AVELOX, 4.5 ± 0.5 μg/mL). These findings suggest a wide margin of safety for Moxifloxacin AF ophthalmic solution.

Based on the assessment of systemic exposure information for the drug product from a multiple-dose PK study in healthy adult male and female volunteers, the regulatory requirement for submission of in vivo

bioavailability data has been adequately addressed. The clinical pharmacology information provided by the applicant in the resubmission was considered acceptable, but the data from Study C-07-12 was consided to be for informational purposes only and was not included in the labeling.

6. Sterility Assurance

The integrity of the container/closure system for stability samples was demonstrated by successful sterility testing of each of the three primary stability lots of each of the (b) (4) 3ml fill sizes (lot numbers SLN-0363, SLN-0365, SLN-0366, SLN-0368, SLN-0369, SLN-0371).

In addition, microbial ingress tests were conducted. For each of three validation runs, the challenged units were negative for growth. Positive controls were confirmed for E. coli growth, and negative controls showed no growth. Acceptable TSB growth promotion testing (< 100 CFU/ml E. coli) was performed. Plate counts were used to confirm the pre- and post-exposure microbial challenge (pre = 8.5 to 9.7 x 107 CFU/ml; post = 7.5 to 9.2 x 107 CFU/ml).

The drug product does not contain any traditional (b) (4) and the Applicant describes it as (b) (4) (b) (4) effectiveness testing was conducted on the six stability batches (3 lots of each fill size - lot numbers SLN-0363, SLN-0365, SLN-0366, SLN-0368, SLN-0369, SLN-0371).

Test data indicated that the drug product met or exceeded the USP <51> acceptance criteria for antimicrobial effectiveness. For the six lots tested at the three time periods, the drug product exhibited the following ranges for the reduction of organism counts:

Organism	Log10 unit reduction of microorganisms after		
	7 days	14 days	28 days
S. aureus (ATCC 65338)	4.8-5.4	4.8-5.4	4.8-5.4
P. aeruginosa (ATCC 9027)	4.6-5.4	4.6-5.4	4.6-5.4
E. coli (ATCC 8739)	4.9-5.4	4.9-5.4	4.9-5.4
C. albicans (ATCC 10231)	1.3-2.8	2.3-4.2	4.1-5.5
A. niger (ATCC 16404)	0.8-1.7	2.1-4.4	3.9-4.4

These results indicate the (b) (4)- (b) (4) nature of the drug product formulation. Such product development study results mitigate the lack of a routine release assay for (b) (4) effectiveness.

7. Clinical/Statistical - Efficacy

This application contained three safety and efficacy trials. Study C-04-38 was a two-arm superiority trial comparing moxifloxacin to vehicle; C-04-40 was a non-inferiority trial which compared the new formulation to the currently marketed Vigamox. Study C-07-40 was a two-arm superiority trial comparing moxifloxacin to vehicle using a significantly larger number of patients than C-04-38.

The primary clinical efficacy variable in all three studies was the clinical cure rate of the two cardinal ocular signs of bacterial conjunctival infection (bulbar conjunctival injection and conjunctival discharge/exudate). Clinical cure was attained when the sum of the two cardinal ocular signs was zero (i.e., normal or absent) at Day 7 for studies C-04-38 and C-04-40 and at Day 4 for C-07-40. The primary microbiological efficacy variable was the bacterial eradication rate at the Exit visit.

Analyses of Endpoints

Study C-04-38

	Clinical Cure at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	**129 (72.5%)**	128 (72.3%)	105 (75%)
Vehicle	**113 (67.7%)**	111 (67.3%)	88 (66.2%)
p-value	**0.3295**	0.3097	0.1089
	Microbiological Success at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	**150 (84.3%)**	149 (84.2%)	115 (82.7%)
Vehicle	**110 (65.9%)**	109 (66.1%)	90 (67.7%)
p-value	**< 0.0001**	0.0001	0.0039

Study C-04-40

	Clinical Cure at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	**152 (80.4%)**	150 (80.2%)	103 (84.4%)
Vigamox	**163 (84.5%)**	161 (84.3%)	108 (85.7%)
p-value	**0.30**	0.3	0.78
Delta	**-4.1**	-4.1	-1.3
LCL	**-11.65**	-11.78	-10.16
UCL	**3.62**	3.62	7.59
	Microbiological Success at Day 7		
	MBITT	MITT	MPP
Moxifloxacin AF	**165 (87.3%)**	163 (87.2%)	112 (92.6%)
Vigamox	**173 (89.6%)**	171 (89.5%)	115 (92%)
p-value	**0.48**	0.47	0.87
Delta	**-2.3**	-2.3	0.6
LCL	**-8.74**	-8.8	-6.11
UCL	**4.07**	4.1	7.23

Study C-07-40

	Clinical Cure at Day 4				
	MBITT	ITT	MITT	PP	MPP
Moxifloxacin AF	265/424 (62.5%)	372/593 (62.7%)	261/415 (62.9%)	342/539 (63.5%)	243/383 (63.4%)
Vehicle	214/423 (50.6%)	310/586 (52.9%)	207/414 (50.0%)	285/529 (53.9%)	194/380 (51.1%)
p-value	0.0005	0.0006	0.0002	0.0015	0.0005

	Microbiological Success at Day 4		
	MBITT	MITT	MPP
Moxifloxacin AF	316/424 (74.5%)	308/415 (74.2%)	285/385 (74.0%)
Vehicle	237/423 (56.0%)	231/414 (55.8%)	220/384 (57.3%)
p-value	< 0.0001	< 0.0001	< 0.0001

Clinical Cure by Organism for patients Treated with Moxifloxacin AF Studies C-04-38, C-04-40, and C-07-40 Combined (MBITT Population)

Organism	Total (N)	Clinical Cure (n)	Clinical Failure (n)	Eradication Rate (%)
Gram - positive				
Aerococcus viridans*	6	6	0	100
Corynebacterium macginleyi*	7	7	0	100
Enterococcus faecalis*	6	6	0	100
Micrococcus luteus*	6	6	0	100
Staphylococcus arlettae*	8	8	0	100
Staphylococcus aureus	38	36	2	95
Staphylococcus capitis[1]	25	24	1	96
Staphylococcus epidermidis	156	145	11	93
Staphylococcus haemolyticus	13	10	3	77
Staphylococcus hominis[2]	10	10	0	100
Staphylococcus saprophyticus*	6	6	0	100
Staphylococcus warneri*	10	8	2	80
Streptococcus mitis*	11	9	2	82
Streptococcus pneumoniae	43	39	4	91
Streptococcus parasanguinis*	5	5	0	100
Gram – negative				
Escherichia coli*	6	5	1	83
Haemophilus influenzae	109	100	9	92
Klebsiella pneumoniae*	8	8	0	100
Anaerobe				
Propionibacterium acnes	152	139	13	91
Other bacteria				
Chlamydia trachomatis*	5	5	0	100

* Efficacy for this organism was found in fewer than 10 infections.
[1] Includes *Staphylococcus capitis subspecies capitis* (3), *S. capitis* (22); eradication rate 100% and 96 % respectively.
[2] Includes *Staphylococcus hominis ss. novobiosepticus* (4), *S. hominis* (6); eradication rate 100%.

Clinical Microbiology Review

Data from the three Phase 3 clinical trials submitted in support of the Application suggest that the new formulation of moxifloxacin ophthalmic solution, 0.5% is effective in eradicating the principle pathogens associated with bacterial conjunctivitis.

In in vitro studies, using systemic interpretation criteria for antimicrobial activity, moxifloxacin has demonstrated activity against bacteria commonly associated with bacterial conjunctivitis, including *Staphylococcus aureus*, *S. epidermidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Propionibacterium acne*. These organisms, as well as others listed in the proposed label, should be susceptible to moxifloxacin at the concentration that is available per drop of solution (0.25 mg/drop). Data from in vitro susceptibility testing of isolates collected during Phase 3 clinical trials supports the inclusion of these and the other bacteria listed in the proposed indications for Moxifloxacin AF Ophthalmic Solution.

8. Safety

Studies C-04-38, Study C-04-40 and C-07-40 were used in the safety analysis.

Exposure to Study Drug by Protocol

Protocol Number	Safety N	Moxifloxacin AF	Vigamox	Vehicle
C-07-40	1177	593		586
C-07-12	130	65	65	
C-04-38	661	331		330
C-04-40	695	346	349	
C-05-15	30	20		10

Exposure to Study Drug by Age Group

Age group	Number exposed
Infants (≥1 to <2 months)	1
Infants (≥2 to <3 months)	3
Infants (≥3 to <4 months)	3
Infants (≥4 to <5 months)	10
Infants (≥5 to 12 months)	41
Toddlers (≥12 to 23 months)	59
2 to 11 years	317
12 to 17 years	110
18 to 64 years	646
65 years or older	80

Dropouts/Discontinuations

Reason	C-07-40	C-04-38	C-04-40
Adverse Event	1	5	3
Lost to follow-up	3	3	24
Patient decision	3	5	2
Noncompliance	0	1	0
Treatment failure	6	7	7
Other	1	1	0

Common Adverse Events (rate ≥ 1%) – Safety Population
(Studies C-04-38, C-04-408, C-05-15, C-07-12, C-07-40 Pooled)

Adverse Event	Moxifloxacin AF N=1355		Vigamox N=414		Vehicle N=926	
	N	%	N	%	N	%
Eye disorder						
Eye irritation	16	1.2	5	1.2	6	0.6
Conjunctivitis	14	1.0	2	0.5	13	1.4
Eye Pain	14	1.0	7	1.7	5	0.5
Eye pruritis	5	0.4	5	1.2	2	0.2
Punctate keratitis	5	0.4	5	1.2	2	0.2
Pyrexia	16	1.2	7	1.7	6	0.6
Conjunctivitis bacterial	8	0.6			22	2.4
Otitis media	4	0.3			10	1.1
Headache	8	0.6	2	0.5	10	1.1

The most common adverse reactions reported in 1-2% of patients were eye irritation, pyrexia, and conjunctivitis.

POSTMARKETING EXPERIENCE
This drug product is not marketed in any country. Other formulations of moxifloxacin hydrochloride ophthalmic solution, 0.5% base are approved in more than 50 countries including the US (approved in 2003). Alcon has received 471 spontaneous adverse event reports worldwide associated with moxifloxacin. Thirty-five (35) were considered serious. The spontaneous postmarketing reports for moxifloxacin are consistent with its known safety profile. A review of the postmarketing reports does not raise concern that there is a new unknown safety risk associated with moxifloxacin.

9. Advisory Committee Meeting

No Advisory Committee Meeting was necessary for moxifloxacin hydrochloride ophthalmic solution 0.5%.

10. Pediatrics

On February 25, 2009, Alcon submitted a request for a partial pediatric waiver to this application. This application was presented at the Pediatric Review Committee (PeRC) on November 17, 2010. The pediatric study requirements for ages 0 to 1 month were waived because the disease does not exist in that age group (i.e. neonatal conjunctivitis as opposed to bacterial conjunctivitis). Alcon has fulfilled the pediatric study requirement for all other relevant pediatric age groups for this application.

The safety and effectiveness of Moxez solution in infants below 4 months of age have not been established. The safety and effectiveness of the currently marketed Viagmox in infants below one year of age have not been established.

There is no evidence that the ophthalmic administration of quinolones has any effect on weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

11. Other Relevant Regulatory Issues

DSI

Per the DSI Clinical Inspection Summary dated 7/8/09, In general, Protocol C-04-38 appears to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the Clinical Investigator inspection of Dr. Watson is No Action Indicated (NAI). The preliminary classification of the Clinical Investigator inspection of Dr. Christensen is VAI. While regulatory violations occurred at this site, the primary safety and efficacy data from this site are considered reliable.

FINANCIAL DISCLOSURE

Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided by Alcon for clinical studies C-04-38, C-04-40, and C-05-15 submitted in this application.

Alcon has adequately disclosed financial arrangements with the clinical investigators who participated in the clinical development program for the new formulation of moxifloxacin ophthalmic solution. There are two investigators and two subinvestigators who participated in the phase 3 safety and efficacy trials who have disclosed financial ties to the sponsor.

Investigators with Financial Interests or Arrangements

Clinical Study	Investigators
(b) (6)	(b) (6)
C-04-40	None
C-05-15	None
(b) (6)	(b) (6)

There is no evidence to suggest that the results of the study were impacted by any financial payments.

DMEPA

The proprietary name Moxeza was proposed for this application and accepted by the Division of Medication Error Prevention and Analysis (DMEPA).

BIOSTATISTICS

The primary analysis population is the microbiological intent-to-treat (MBITT) dataset for study C-07-40. 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 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.

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.

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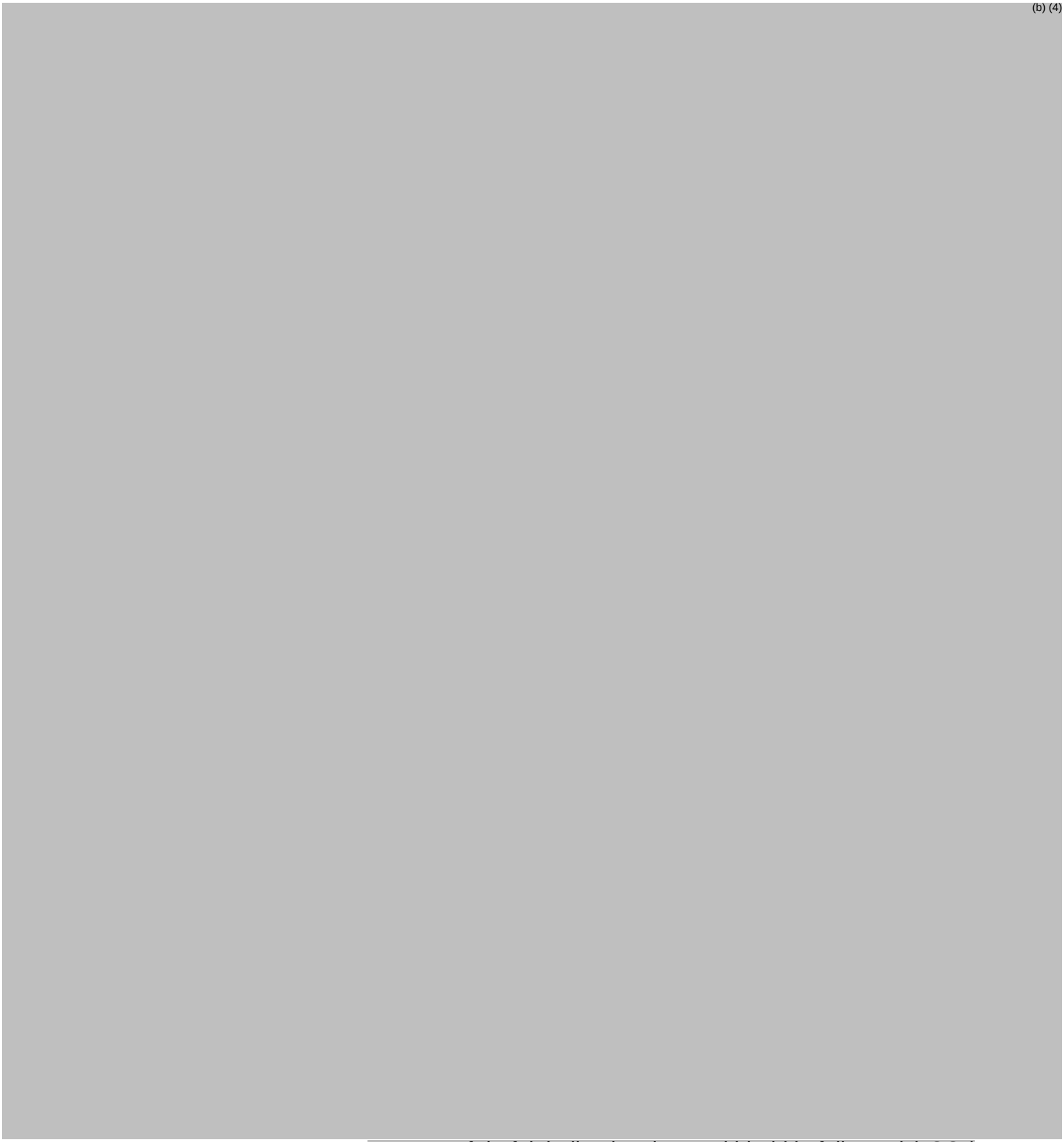

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WILEY A CHAMBERS
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