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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22134
Drug Name:	(b) (4) (alcaftadine ophthalmic solution) 0.25%
Indication(s):	Prevention of itching associated with allergic conjunctivitis
Applicant:	Vistakon Pharmaceuticals
Date(s):	Submitted: September 29, 2009
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Review Priority:	Standard
Biometrics Division:	IV
Statistical Reviewer:	Dongliang Zhuang, PhD
Concurring Reviewer:	Yan Wang, PhD
Medical Division:	Anti-infectives/Ophthalmology
Clinical Team:	Martin Nevitt, MD; William Boyd, MD; Wiley Chambers, MD
Project Manager:	Raphael Rodriguez

Keywords: allergic conjunctivitis, conjunctival allergen challenge (CAC) model, ocular itching, conjunctival redness

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This new drug application (NDA) seeks the marketing approval of (b) (4) (alcaftadine ophthalmic solution) 0.25% for a once daily dosing regimen in the prevention of itching associated with allergic conjunctivitis.

The efficacy of alcaftadine in preventing itching associated with allergic conjunctivitis was supported by three efficacy studies using the conjunctival allergen challenge (CAC) model. In these Phase 3 CAC studies, treatment with alcaftadine led to approximately one unit or greater than one unit improvement in the ocular itching score for alcaftadine-treated eyes compared with vehicle-treated eyes at all post-allergen challenge time points at Visits 3 and 4. These improvements are clinically meaningful, as well as statistically significant ($p<0.001$).

The clinical development program for alcaftadine had intended to demonstrate superiority of alcaftadine to vehicle for both ocular itching and conjunctival redness. However, alcaftadine was unable to demonstrate clinical significance compared to vehicle in preventing conjunctival redness. Therefore, alcaftadine is recommended only for the approval for the prevention of the itching associated with allergic conjunctivitis.

1.2 Brief Overview of Clinical Studies

The Phase 3 clinical development program to support the NDA filing is comprised of a 6-week safety study (05-003-10) and three efficacy CAC studies (05-003-11, 05-003-13, and 09-003-05). The numbers of subjects enrolled in these studies were 909, 126, 88, and 60, respectively.

The CAC studies were double-masked, vehicle-controlled trials designed to evaluate the efficacy of alcaftadine compared to vehicle in preventing the signs and symptoms of CAC-induced allergic conjunctivitis at 15 minutes (onset of action) and 16 hours (duration of action) following medication instillation. Eligible subjects were 10 years of age or older and had a history of allergic conjunctivitis or allergic rhinoconjunctivitis. In studies 05-003-11 and 05-003-13, subjects were randomly assigned to receive alcaftadine bilaterally, alcaftadine in one eye and vehicle in the fellow eye (contralaterally), or vehicle bilaterally. Subjects in study 09-003-05 were randomly assigned to receive alcaftadine or vehicle bilaterally.

The co-primary efficacy endpoints in the study protocols were ocular itching and conjunctival redness. Ocular itching was evaluated by the subjects at 3, 5, and 7 minutes post allergen challenge on a 0 to 4 scale, allowing half unit increments, at Visit 3 (Day 0) and Visit 4 (Day 14). Conjunctival redness was evaluated by the investigators at 7, 15, and 20 minutes post

allergen challenge, on a 0 to 4 scale, allowing half unit increments, at Visit 3 (Day 0) and Visit 4 (Day 14). The success of a CAC trial with respect to efficacy was evaluated as follows:

- A statistically significant improvement in ocular itching and conjunctival redness is demonstrated for alcaftadine over the vehicle at all time points at the specified significance level of 5%.
- In addition, meaningful clinical benefits of alcaftadine over vehicle require that the mean score difference (active minus vehicle-treated eye) must be greater than 0.5 unit at all time points, with two of three time points demonstrating at least 1 unit difference for ocular itching and conjunctival redness assessment.

1.3 Statistical Issues and Findings

According to the study protocol and the statistical analysis plan, the Applicant analyzed each of the primary efficacy variables using the Wilcoxon rank-sum test without adjusting for centers. The results were considered statistically significant if primary endpoints were significant at an alpha level of 0.05 (i.e. type 1 error rate $\alpha = 0.05$) from a two-sided test. No adjustment for multiplicity was done. Two statistical issues are raised and discussed for this submission.

1.3.1 Multiplicity

The clinical development program for alcaftadine intended to demonstrate superiority of alcaftadine to vehicle for both ocular itching and conjunctival redness, which was defined as the co-primary endpoint in the study protocols. However, the CAC trials met the success criteria for ocular itching, but not for conjunctival redness. As a result, the Applicant is only seeking the indication for the prevention of itching associated with allergic conjunctivitis.

Multiplicity problems arise when the individual components of a co-primary endpoint are intended as separate claims. The probability of the Type 1 error was specified at 5% in the protocols for the testing of the co-primary endpoint, including both ocular itching and conjunctival redness. However, if the success of the trial can be claimed based on either ocular itching or conjunctival redness as the Applicant intended to, the components of the co-primary efficacy endpoint are treated as independent to support separate claims. As a result, multiplicity arises and it should be adequately adjusted. To do that, each endpoint should be tested at an appropriate significance level to control the overall Type 1 error at the desired level of 5%. Hence, in the review of efficacy based on ocular itching, a significance level of 2.5% (two-sided) is used to determine the statistical significance, assuming equal importance of the two components of the original co-primary endpoint.

In the CAC studies, the treatment comparisons with respect to the ocular itching score had a p-values of <0.001 at all post-allergen challenge time points at Visits 3 and 4. Therefore, the results are significant at a two-sided significance level of 2.5%.

1.3.2 Handling of Correlated Data

The ocular itching scores for the right eye and the left eye of the same subject are expected to be correlated. In two CAC studies (Protocols 05-003-11 and 05-003-13), eye was unit of analysis. The primary analysis treated the scores for the right eye and the left eye from the same subject as independent. As a sensitivity analysis, the Applicant conducted a repeated-measure analysis. The Applicant claimed that overall the results of the repeated-measure analysis were consistent with the primary analysis. However, the Applicant's repeated-measure analysis employed an independent correlation structure, which failed to take into account of the dependence between the right eye score and the left eye score from the same subject.

In order to adequately model the dependence between the scores from the right eye and the left eye from the same subject, the Reviewer performed a repeated-measure analysis using an unstructured correlation structure. The results from this analysis are comparable to those from the Applicant's primary analysis.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Ocular allergic disorders, including seasonal allergic conjunctivitis and perennial allergic conjunctivitis, affect over 20% of the general population aged 3 years and older. The conditions reflect IgE-dependent (Type 1) hypersensitivity inflammatory responses. In susceptible individuals, ocular exposure to an allergen triggers mast cell degranulation and the release of a host of mediators including histamine. This inflammatory cascade culminates in the characteristic signs and symptoms of ocular allergy disorders, including itching, redness, swelling of the eyelid, chemosis, and tearing.

As histamine plays a central role in the pathogenesis of ocular allergic reactions, antihistamines remain the cornerstone of treatment. Several of the currently available therapies for ocular allergic reactions have a limited duration of action, requiring dosing two to four times daily. A therapy with a longer duration of action (>12 hours) would be advantageous as it could be instilled once daily to provide day-long relief.

(b) (4) (alcaftadine) is a potent H1, H2, and H4 histamine receptor antagonist with anti-inflammatory properties. (b) (4) is a clear, sterile ophthalmic solution containing alcaftadine 2.5mg/mL (0.25%) intended for topical administration to the eye.

This application seeks the marketing approval of (b) (4) (alcaftadine) for a once daily dosing regimen in the prevention of itching associated with allergic conjunctivitis. With its once-a-day dosing regimen, (b) (4) (alcaftadine) is expected to offer the patient advantages in terms of convenience which could lead to enhanced treatment compliance, and be a valuable addition to the currently available therapies for the treatment of allergic conjunctivitis.

2.1.2 History of Drug Development

The clinical program for alcaftadine included three Phase 1 tolerability (comfort) studies, one Phase 1 pharmacokinetic (PK) study, one Phase 2 proof-of-concept (POC) study, one Phase 2 pilot relief study, three Phase 3 efficacy studies, one Phase 3 safety study, and one Phase 3b environmental study (multi-center CAC).

It was agreed upon at the pre-NDA meeting (April 26, 2006) that the Phase 3 clinical program for alcaftadine, which consisted of a 6-week safety study (Protocol 05-003-10), one Multi-Center CAC study (Protocol 05-003-11) and one single-center CAC study (Protocol 05-003-13), was considered adequate to support an NDA filing. These studies were conducted using formulation

PD-F-3730. Subsequent to the meeting, changes were made to the formulation for the purpose of improving the overall comfort of the drug product and additional development work was conducted. The new formulation PD-F-5525, targeted for commercial use, was tested in a Phase 3 multi-center CAC (Protocol 09-003-05) to confirm that the commercial formulation has efficacy similar to that observed with the old formulation.

2.1.3 Specific Studies Reviewed

Three efficacy CAC studies (multi-center CAC [Protocol 05-003-11], single-center CAC [Protocol 05-003-13], and multi-center CAC study [Protocol 09-003-05]) were included in the submission. These studies were double-masked, randomized, vehicle-controlled trials to evaluate the onset and duration of action of alcaftadine in the CAC model of acute allergic conjunctivitis in adult and pediatric subjects 10 years of age and older with a history of allergic conjunctivitis or allergic rhinoconjunctivitis. In each study, there were four study visits (Day -21, -14, 0, and 14) and the total duration was approximately five weeks. The duration of action was measured at Visit 3 (Day 0) with CAC conducted 16 hours after study medication instillation at this visit. The onset of action was measured at Visit 4 (Day 14) with CAC conducted 15 minutes after study medication instillation at this visit.

In studies 05-003-11 and 05-003-13, subjects were randomly assigned to one of the following treatment arms:

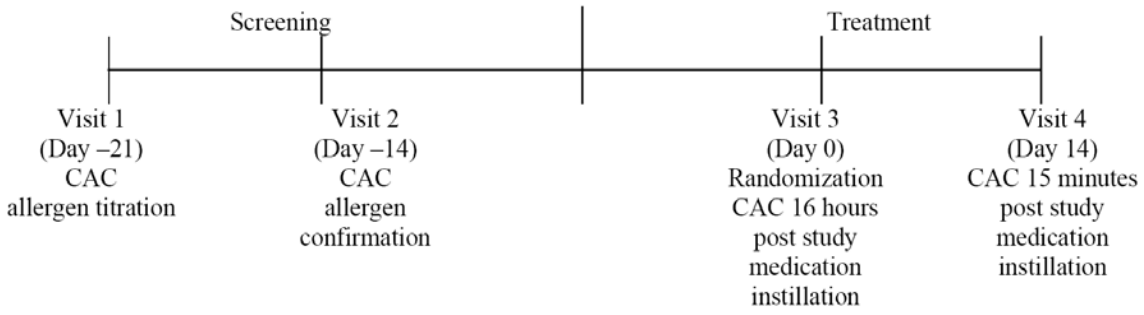
- Alcaftadine administered bilaterally.
- Alcaftadine in one eye and vehicle in the fellow eye (contralaterally).
- Vehicle administered bilaterally.

In study 09-003-05, subjects were randomly assigned to one of the following treatment arms:

- Alcaftadine administered bilaterally.
- Vehicle administered bilaterally.

The CAC studies have same study designs. A summary of the study visits is presented in Figure 1.

Figure 1: Study Design Schematic
(Protocols 05-003-11, 09-003-05, 05-003-13)



A brief summary of the three CAC studies and the safety study is provided in Table 1.

Table 1: Brief Summary of Phase 3 Controlled Studies

Study	Design	Treatment arms/Sample size	Primary endpoint
05-003-11 Phase 3, Multi-center CAC 5 US centers	Multi-center, double-masked, randomized, vehicle (placebo)-controlled, CAC study in subjects aged ≥10 years with a history of allergic conjunctivitis or allergic rhinoconjunctivitis. Visits at Visit 1 (Day -21), Visit 2 (Day -14), Visit 3 (Day 0; CAC conducted 16 hours after study medication instillation), and Visit 4 (Day 14; CAC conducted 15 minutes after study medication instillation).	Alcaftadine instilled bilaterally (N=40) Alcaftadine in 1 eye and vehicle in contralateral eye (N=42) Vehicle instilled bilaterally (N=44)	The co-primary efficacy variables include ocular itching evaluated by the subject at 3, 5, and 7 minutes post allergen challenge (0 to 4 scale, allowing half unit increments), and Conjunctival redness evaluated by the investigator at 7, 15, and 20 minutes post allergen challenge (0 to 4 scale, allowing half unit increments).
05-003-13 Phase 3, Single-center CAC 1 US center	Single-center, double-masked, randomized, vehicle (placebo) controlled, CAC study in subjects aged ≥10 years with a history of allergic conjunctivitis or allergic rhinoconjunctivitis. Visits on Days -21, -14, 0, and 14.	Alcaftadine instilled bilaterally (N=30) Alcaftadine in 1 eye and vehicle in contralateral eye (N=29) Vehicle instilled bilaterally (N=29)	The co-primary efficacy variables include ocular itching evaluated by the subject at 3, 5, and 7 minutes post allergen challenge (0 to 4 scale, allowing half unit increments), and Conjunctival redness evaluated by the investigator at 7, 15, and 20 minutes post allergen challenge (0 to 4 scale, allowing half unit increments).
09-003-05 Phase 3, Multi-center CAC 2 US centers	Multi-center, double-masked, randomized, vehicle (placebo)-controlled, CAC study in adult and pediatric subjects with a history of acute allergic conjunctivitis. Visits on Days -21, -14, 0 and 14.	Alcaftadine instilled bilaterally (N=30) Vehicle instilled bilaterally (N=30)	The co-primary efficacy variables are ocular itching (at 3, 5, and 7 minutes following CAC) and conjunctival redness (at 7, 15, and 20 minutes following CAC) at Visits 3 and 4. The average of both eyes for each subject for each treatment arm was used for all analyses.
05-003-10 Phase 3, Safety 6 US centers	Multi-center, randomized, double-masked, vehicle (placebo)-controlled, parallel-group study in healthy subjects aged ≥3 years. Visits on Days 0, 7, 21, and 42.	Alcaftadine instilled bilaterally (N=609) Vehicle instilled bilaterally (N=300)	Adverse events

2.2 Data Sources

The NDA submission, including the Applicant's study report and data sets for the clinical studies are available on EDR at "\\CDSESUB1\EVSPROD\NDA022134".

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Endpoints

Three CAC studies were conducted to establish the efficacy of alcaftadine compared to vehicle in alleviating the signs and symptoms of conjunctival allergen challenge-induced allergic conjunctivitis at 15 minutes and 16 hours following medication instillation.

The co-primary efficacy endpoints for these studies were ocular itching and conjunctival redness. Ocular itching was evaluated by the subjects at 3, 5, and 7 minutes post allergen challenge on a 0 to 4 scale, allowing half unit increments, at Visit 3 (Day 0) and Visit 4 (Day 14). Conjunctival redness was evaluated by the investigators at 7, 15, and 20 minutes post allergen challenge, on a 0 to 4 scale, allowing half unit increments, at Visit 3 (Day 0) and Visit 4 (Day 14).

The secondary efficacy endpoints included:

- Ciliary and episcleral redness and chemosis evaluated by the investigator at 7, 15, and 20 minutes post allergen challenge (0 to 4 scale, allowing half unit increments)
- Lid swelling evaluated by the subject at 7, 15, and 20 minutes post allergen challenge (0 to 3 scale)
- Tearing evaluated by the subject at 7, 15, and 20 minutes post allergen challenge (absent or present)
- Ocular mucous discharge evaluated by the investigator at 7, 15, and 20 minutes post allergen challenge (absent or present)
- Rhinorrhea, nasal congestion, nasal pruritus, and ear or palate pruritus evaluated by the subject at 7, 15, and 20 minutes post allergen challenge (0 to 4 scale)
- A composite score of rhinorrhea, nasal congestion, nasal pruritus, and ear or palate pruritus evaluated by the subject at 7, 15, and 20 minutes (0 to 16 scale)
- A composite score of presence or absence of at least 1 nasal symptom evaluated by the subject at 7, 15 and 20 minutes (0 to 1 scale).

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Subject disposition and completion status are summarized in Table 2 by treatment for the three efficacy studies. Of all randomized subjects, the number of subjects who discontinued from the study was 3, 1, and 2 for the three studies (05-003-11, 05-003-13, and 09-003-05), respectively.

Table 2: Subject Disposition and Completion Status
(All randomized subjects; Protocols 05-003-11, 05-003-13, and 09-003-05)

Study	Category	Vehicle/ Vehicle N (%)	Alcaftadine /Vehicle N (%)	Alcaftadine / Alcaftadine N (%)
05-003-11 (multi-center CAC)	**Intent-to-Treat Population**	44 (100)	42 (100)	40 (100)
	Safety Population	44 (100)	42 (100)	40 (100)
	Per-Protocol Population	43 (97.7)	39 (92.9)	38 (95.0)
	Completed	44 (100)	39 (92.9)	40 (100)
	Discontinued	0 (0.0)	3 (7.1)	0 (0.0)
	Subject Choice	0 (0.0)	2 (4.8)	0 (0.0)
	Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)
	Adverse Event	0 (0.0)	0 (0.0)	0 (0.0)
	Death	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	1 (2.4)	0 (0.0)
05-003-13 (single-center CAC)	**Intent-to-Treat Population**	29 (100)	29 (100)	30 (100)
	Safety Population	29 (100)	29 (100)	30 (100)
	Per-Protocol Population	28 (96.6)	28 (96.6)	30 (100)
	Completed	29 (100)	28 (96.6)	30 (100)
	Discontinued	0 (0.0)	1 (3.4)	0 (0.0)
	Subject Choice	0 (0.0)	0 (0.0)	0 (0.0)
	Lost to Follow-up	0 (0.0)	0 (0.0)	0 (0.0)
	Adverse Event	0 (0.0)	1 (3.4)	0 (0.0)
	Death	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)
09-003-05 (multi-center CAC)	**Intent-to-Treat Population**	30 (100)	--	30 (100)
	Safety Population	30 (100)	--	30 (100)
	Per-Protocol Population	28 (93.3)	--	28 (93.3)
	Completed	29 (96.7)	--	29 (96.7)
	Discontinued	1 (3.3)	--	1 (3.3)
	Subject Choice	1 (3.3)	--	1 (3.3)
	Lost to Follow-up	0 (0.0)	--	0 (0.0)
	Adverse Event	0 (0.0)	--	1 (3.3)
	Death	0 (0.0)	--	0 (0.0)
	Other	0 (0.0)	--	0 (0.0)

Source: Applicant's CSRs 05-003-11, 05-003-13 and 09-003-05; Table 2.

Demographic and baseline characteristics (including ocular characteristics) are summarized in Table 3.1.1, Table 3.1.2, Table 3.2.1, Table 3.2.2, Table 3.3.1, and Table 3.3.2. The treatment arms were evenly balanced with regard to demographic and baseline characteristics. The majority of subjects enrolled in these studies was White and in the age group of 18-64 years. More than half of the subjects did not require visual correction. Normal slit lamp examinations

were noted for the majority of eyes; none of the abnormalities reported were considered by the investigator as being clinically relevant and therefore did not impact participation in the study.

Table 3.1.1: Demographic and Baseline Characteristics
(Intent-to-Treat Population; Protocol 05-003-11)

	Vehicle/ Vehicle (N=44)	Alcaftadine /Vehicle (N=42)	Alcaftadine / Alcaftadine (N=40)	Total (N=126)
Age (Years)				
Mean (SD)	32.9 (12.37)	35.8 (15.02)	33.5 (14.07)	34.0 (13.78)
Age Group, n (%)				
≤ 17 years	1 (2.3)	3 (7.1)	7 (17.5)	11 (8.7)
18-64 years	43 (97.7)	38 (90.5)	33 (82.5)	114 (90.5)
≥ 65 years	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.8)
Sex, n (%)				
Male	15 (34.1)	14 (33.3)	14 (35.0)	43 (34.1)
Female	29 (65.9)	28 (66.7)	26 (65.0)	83 (65.9)
Race, n (%)				
American Indian/Alaska native	0 (0.0)	1 (2.4)	1 (2.5)	2 (1.6)
Black/African American	3 (6.8)	3 (7.1)	6 (15.0)	12 (9.5)
White	39 (88.6)	35 (83.3)	32 (80.0)	106 (84.1)
Other	2 (4.5)	3 (7.1)	1 (2.5)	6 (4.8)
Ethnicity, n (%)				
Hispanic/Latino	3 (6.8)	3 (7.1)	1 (2.5)	7 (5.6)
Not Hispanic/Latino	41 (93.2)	39 (92.9)	39 (97.5)	119 (94.4)
Iris Color, n (%)				
Blue	17 (38.6)	12 (28.6)	11 (27.5)	40 (31.7)
Brown	12 (27.3)	19 (45.2)	18 (45.0)	49 (38.9)
Green	5 (11.4)	5 (11.9)	5 (12.5)	15 (11.9)
Hazel	9 (20.5)	4 (9.5)	6 (15.0)	19 (15.1)
Other	1 (2.3)	2 (4.8)	0 (0.0)	3 (2.4)

Note: Demographic and baseline characteristics obtained at Visit 1 (Day -21); N represents number of subjects.
Source: Applicant's CSR 05-003-11; Table 5.

Table 3.1.2: Baseline Ocular Characteristics (Intent-to-Treat Population; Protocol 05-003-11)

	Vehicle (N=130)	Alcaftadine (N=122)	Total (N=252)
LogMAR Visual Acuity			
Mean (SD)	0.005 (0.1605)	0.025 (0.1517)	0.014 (0.1563)
Best Visual Correction, n (%)			
With Correction and Without Using Pinhole	42 (32.3)	42 (34.4)	84 (33.3)
With Correction and Using Pinhole	0 (0.0)	0 (0.0)	0 (0.0)
Without Correction and Without Using Pinhole	85 (65.4)	74 (60.7)	159 (63.1)
Without Correction and Using Pinhole	3 (2.3)	6 (4.9)	9 (3.6)
Slit lamp Biomicroscopy, n (%)			
Any Abnormal Findings	1 (0.8)	8 (6.6)	9 (3.6)
No Abnormal Finding	129 (99.2)	114 (93.4)	143 (96.4)

Note: Baseline ocular characteristics assessed at Visit 1 (Day -21); N represents number of eyes treated.
Source: Applicant's CSR 05-003-11; Table 6.

Table 3.2.1: Demographic and Baseline Characteristics
(Intent-to-Treat Population; Protocol 05-003-13)

	Vehicle/ Vehicle (N=29)	Alcaftadine /Vehicle (N=29)	Alcaftadine / Alcaftadine (N=30)	Total (N=88)
Age (Years)				
Mean (SD)	37.2 (15.04)	38.8 (14.38)	36.0 (14.20)	37.3 (14.42)
Age Group, n (%)				
≤ 17 years	2 (6.9)	2 (6.9)	2 (6.7)	6 (6.8)
18-64 years	25 (86.2)	27 (93.1)	27 (90.0)	79 (89.8)
≥ 65 years	2 (6.9)	0 (0.0)	1 (3.3)	3 (3.4)
Sex, n (%)				
Male	10 (34.5)	16 (55.2)	20 (66.7)	46 (52.3)
Female	19 (65.5)	13 (44.8)	10 (33.3)	42 (47.7)
Race, n (%)				
American Indian/Alaska native	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.1)
Asian	0 (0.0)	1 (3.4)	0 (0.)	1 (1.1)
Black/African American	1 (3.4)	1 (3.4)	0 (0.0)	2 (2.3)
White	28 (96.6)	26 (88.7)	29 (96.7)	83 (94.3)
Other	0 (0.0)	1 (3.4)	0 (0.0)	1 (1.1)
Ethnicity, n (%)				
Hispanic/Latino	2 (6.9)	1 (3.4)	0 (0.0)	3 (3.4)
Not Hispanic/Latino	27 (39.1)	28 (96.6)	30 (100)	85 (96.6)
Iris Color, n (%)				
Blue	8 (27.6)	8 (27.6)	7 (23.3)	23 (26.1)
Brown	16 (55.2)	13 (44.8)	13 (43.3)	42 (47.7)
Green	2 (6.9)	2 (6.9)	4 (13.3)	8 (9.1)
Hazel	3 (10.3)	5 (17.2)	6 (20.0)	14 (15.9)
Other	0 (0.0)	1 (3.4)	0 (0.0)	1 (1.1)

Note: Demographic and baseline characteristics obtained at Visit 1 (Day -21); N represents number of subjects.
Source: Applicant's CSR 05-003-13; Table 4.

Table 3.2.2: Baseline Ocular Characteristics (Intent-to-Treat Population; Protocol 05-003-13)

	Vehicle (N=87)	Alcaftadine (N=89)	Total (N=176)
LogMAR Visual Acuity			
Mean (SD)	0.066 (0.1340)	0.046 (0.1319)	0.056 (0.1329)
Best Visual Correction, n (%)			
With Correction and Without Using Pinhole	29 (33.3)	23 (25.8)	52 (29.5)
With Correction and Using Pinhole	1 (1.1)	3 (3.4)	4 (2.3)
Without Correction and Without Using Pinhole	50 (57.5)	58 (65.2)	108 (61.4)
Without Correction and Using Pinhole	7 (8.0)	5 (5.6)	12 (6.8)
Slit lamp Biomicroscopy, n (%)			
Any Abnormal Findings	6 (6.9)	8 (9.0)	14 (8.0)
No Abnormal Finding	81 (93.1)	81 (91.0)	162 (92.0)

Note: Baseline ocular characteristics assessed at Visit 1 (Day -21); N represents number of eyes treated.
Source: Applicant's CSR 05-003-13; Table 5.

Table 3.3.1: Demographic and Baseline Characteristics
(Intent-to-Treat Population; Protocol 09-003-05)

	Vehicle/Vehicle (N=30)	Alcaftadine / Alcaftadine (N=30)	Total (N=60)
Age (Years)			
Mean (SD)	34.3 (15.64)	37.8 (13.52)	36.1 (14.61)
Age Group, n (%)			
≤ 17 years	7 (23.3)	2 (6.7)	9 (15.0)
18-64 years	23 (76.7)	27 (90.0)	50 (83.3)
≥ 65 years	0 (0.0)	1 (3.3)	1 (1.7)
Sex, n (%)			
Male	15 (50.0)	9 (30.0)	24 (40.0)
Female	15 (50.0)	21 (70.0)	36 (60.0)
Race, n (%)			
Asian	0 (0.0)	1 (3.3)	1 (1.7)
White	30 (100)	29 (96.7.0)	59 (98.3)
Ethnicity, n (%)			
Hispanic/Latino	0 (0.0)	0 (0.0)	0 (0.0)
Not Hispanic/Latino	30 (100)	30 (100)	60 (100)
Iris Color, n (%)			
Blue	11 (36.7)	12 (40.0)	23 (38.3)
Brown	9 (30.0)	7 (23.3)	16 (26.7)
Green	4 (13.3)	4 (13.3)	8 (13.3)
Hazel	6 (20.0)	7 (23.3)	13 (21.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Note: Demographic and baseline characteristics obtained at Visit 1 (Day -21); N represents number of subjects.
Source: Applicant's CSR 09-003-05; Table 4.

Table 3.3.2: Baseline Ocular Characteristics (Intent-to-Treat Population; Protocol 09-003-05)

	Vehicle (N=60)	Alcaftadine (N=60)	Total (N=120)
LogMAR Visual Acuity			
Mean (SD)	-0.034 (0.1078)	-0.039 (0.1246)	-0.036 (0.1160)
Best Visual Correction, n (%)			
With Correction and Without Using Pinhole	26 (43.3)	24 (40.0)	50 (41.7)
With Correction and Using Pinhole	0 (0.0)	0 (0.0)	0 (0.0)
Without Correction and Without Using Pinhole	32 (53.3)	36 (60.0)	68 (56.7)
Without Correction and Using Pinhole	2 (3.3)	0 (0.0)	2 (1.7)
Slit lamp Biomicroscopy, n (%)			
Any Abnormal Findings	0 (0.0)	0 (0.0)	0 (0.0)
No Abnormal Finding	60 (100)	60 (100)	120 (100)

Note: Baseline ocular characteristics assessed at Visit 1 (Day -21); N represents number of eyes treated.
Source: Applicant's CSR 09-003-05; Table 5.

3.1.3 Statistical Methodologies

Three populations were defined for the purpose of analyses. The Intent-to-Treat (ITT) population included all randomized subjects. The Per-Protocol (PP) population included all ITT subjects who did not have any significant protocol deviations and had complete data for the primary efficacy analyses. Exclusion of subjects from the Per-Protocol population was determined prior to database lock. The Safety population consisted of all randomized subjects who received at least one dose of study medication.

According to the statistical analysis plan, the primary efficacy variables, ocular itching and conjunctival redness, were analyzed by using the non-parametric Wilcoxon rank-sum test without adjusting for centers. The results were considered statistically significant if both primary endpoints were significant at an alpha level of 0.05 (i.e., type 1 error rate $\alpha = 0.05$) from the 2-sided test. However, since the Applicant is only seeking the indication for the prevention of itching associated with allergic conjunctivitis, the components of the co-primary efficacy endpoint are treated as independent to support separate claims. As a result, multiplicity arises and it should be addressed. In order to control the overall Type 1 error at the desired level of 5%, each efficacy endpoint should be tested at an appropriate significance level. Therefore, in the review of efficacy based on ocular itching, a significance level of 2.5% (two-sided) is used to determine the statistical significance, assuming equal importance of two components in the co-primary endpoint.

The Agency recommended at the pre-NDA meeting that the primary analyses not stratified by center and a sensitivity analysis using parametric methods (e.g. two sample t-test) be conducted to confirm the results from the non-parametric tests (e.g. Wilcoxon Rank-Sum test).

In studies 05-003-11 and 05-003-13, eye was the unit of the analyses. In study 09-003-05, Subject was the unit of the analyses after averaging the scores of both eyes.

Missing data were imputed by the last observation carried forward (LOCF) within the same study visit for Visit 3 (Day 0) and Visit 4 (Day 14) only. Data were not carried forward from the previous visit. All three studies had good retention. Of all randomized subjects, the number of subjects who discontinued from the study was 3, 1, and 2 for the three studies (05-003-11, 05-003-13, and 09-003-05), respectively.

3.1.4 Results and Conclusions

3.1.4.1 Ocular Itching

Ocular itching was evaluated by the subjects at 3, 5, and 7 minutes post allergen challenge at Visit 3 (Day 0) and Visit 4 (Day 14) on a 0 to 4 scale, allowing half unit increments, where 0 indicates no itching and 4 indicates severe itching.

Overall Treatment Comparison

Treatment with alcaftadine led to less ocular itching compared with vehicle-treated eyes. Except that a difference of -0.865 in the mean ocular itching score was achieved at 3-minute post allergen challenge at Visit 3 in Protocol 05-003-11, a difference of approximately one unit or greater in the mean ocular itching score was achieved for eyes treated with alcaftadine compared with vehicle-treated eyes at all post allergen challenge time points at Visit 3 and Visit 4 in all CAC studies. The improvement in ocular itching for alcaftadine-treated subjects over the vehicle-treated subjects is statistically significant (p-value<0.001) at all time points.

The comparison of differences in ocular itching scores based on the Intent-to-Treat population is presented in Table 4.

Table 4: Comparison of Differences in Ocular Itching Scores at Visit 3 (Day 0) and Visit 4 (Day 14) (Intent-to-Treat Population; Protocols 05-003-11, 09-003-05, and 05-003-13)

Visit **Time Point**	**Protocol 05-003-11** (Vehicle N=130; Alcaftadine N=122)[a]	**Protocol 09-003-05** (Vehicle N=30; Alcaftadine N=30)[b]	**Protocol 05-003-13** (Vehicle N=87; Alcaftadine N=89)[a]
Visit 3 (Day 0); 16-hr post study medication instillation			
3 Min Post-CAC	-0.865 (-1.078, -0.653)	-1.731 (-2.145, -1.317)	-1.094 (-1.359, -0.830)
5 Min Post-CAC	-0.963 (-1.191, -0.735)	-1.687 (-2.095, -1.280)	-1.219 (-1.478, -0.961)
7 Min Post-CAC	-0.957 (-1.197, -0.718)	-1.576 (-2.014, -1.138)	-1.109 (-1.361, -0.858)
Visit 4 (Day 14); 15-min post study medication instillation			
3 Min Post-CAC	-1.345 (-1.552, -1.137)	-1.500 (-1.861, -1.139)	-1.321 (-1.597, -1.045)
5 Min Post-CAC	-1.319 (-1.540, -1.098)	-1.491 (-1.895, -1.088)	-1.255 (-1.555, -0.956)
7 Min Post-CAC	-1.240 (-1.478, -1.002)	-1.474 (-1.911, -1.038)	-1.170 (-1.471, -0.870)

a. N represents the number of eyes treated.
b. N represents the number of subjects treated.
Last observation carried forward to impute missing values within a visit.
Difference was calculated as mean of alcaftadine minus mean of vehicle; a negative difference favors alcaftadine.
P-value<0.001 for all comparisons. P-value was based on Wilcoxon Rank Sum test for comparing alcaftadine to vehicle.
Source: Applicant's CSRs and analysis by the primary reviewer.

In addition to the point estimates and p-values from the Applicant's analyses, the table includes the 95% confidence intervals for the differences from the Reviewer's analyses. As specified in the statistical analysis plan, the p-values for the treatment comparison were derived from the Wilcoxon Rank Sum test. The sensitivity analyses found that the p-values from two sample t-test are consistent with those from the Wilcoxon Rank Sum test.

Different from other two studies, in Study 09-003-05, the Applicant adjusted for centers in the Wilcoxon Rank Sum test to derive the p-value for the treatment comparison. The reviewer's unadjusted analyses yield similar p-values.

The analyses based on the Per Protocol Population yielded comparable results.

The Applicant showed that ocular itching scores by investigator were comparable to those noted for the overall study population. This is consistent with Reviewer's analyses that demonstrated the treatment by investigator interaction was not statistically significant (α=10%) at the majority of time points. The exceptions include 3-min Post-CAC at Visits 3 and 4 in Study 05-003-11 (p-value=0.0384 and 0.0133, respectively), and 5-min Post-CAC at Visit 3 in Study 09-003-05 (p-value=0.0922).

Distribution of Ocular Itching Scores

In addition to subjects who received alcaftadine or vehicle instillation bilaterally, Studies 03-005-11 and 03-005-13 included subjects who received alcaftadine instillation in one eye and vehicle instillation in the contralateral eye. The Applicant's analyses for these two studies treated eyes as the independent units of analysis. It was thus assumed that the ocular itching score distributions would be the same for the eyes that received the same treatment, regardless of the study medication administration method (bilateral versus contralateral). However, the Applicant didn't examine the validity of this assumption.

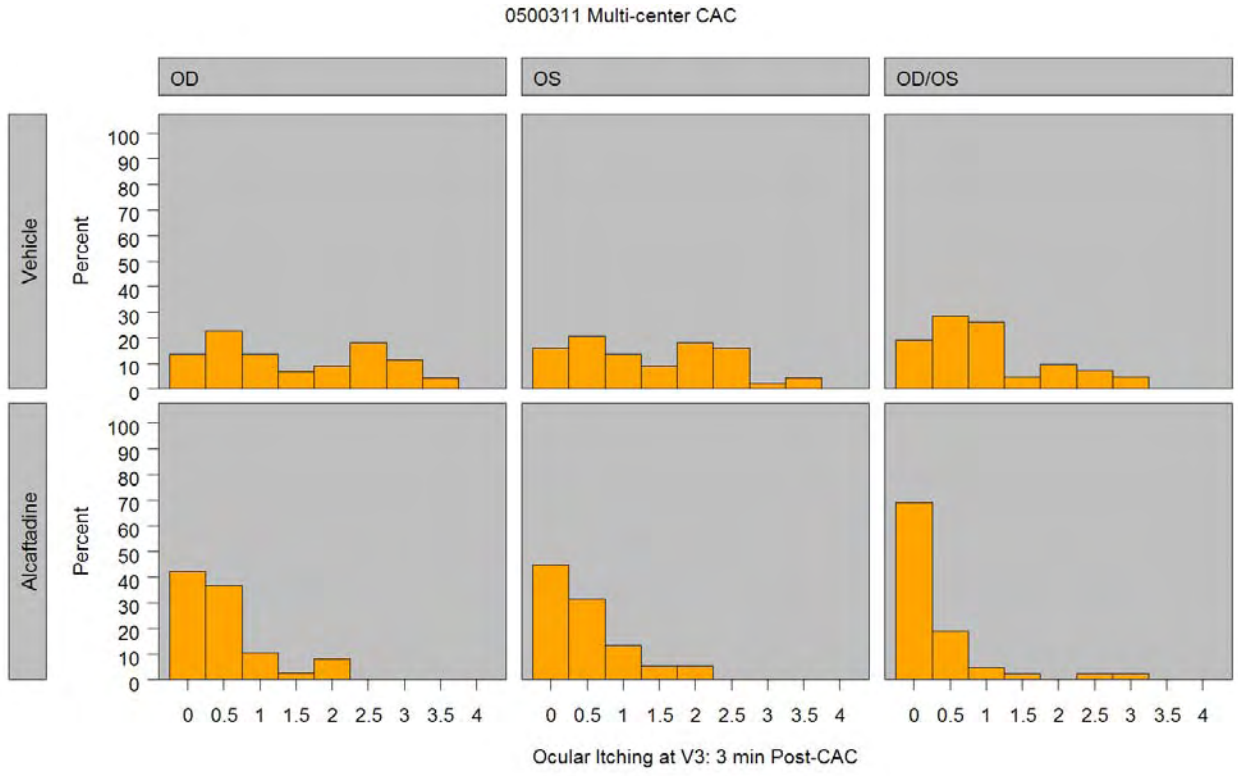
For the purpose of illustration, Figure 2 displays the histograms of the ocular itching scores at Visit 3 and 3 minutes post allergen challenge by treatment and eye for subjects in Studies 03-005-11. For subjects treated bilaterally with either alcaftadine or vehicle, the itching scores are displayed in 'OD' and 'OS' panels for right eye and left eye. For subjects treated contralaterally, the itching scores could be obtained from right eye or left eye. They are indicated as 'OD/OS'.

Figure A.1, Figure A.2, and Figure A.3 in the Appendix display the histograms of the ocular itching scores by treatment, eye, visit and timepoint for three CAC Studies. Overall, the itching scores from right eyes and left eyes had similar distributions for subjects treated bilaterally. The itching scores for eyes treated contralaterally generally follow similar distributions as those for eyes treated bilaterally. Nevertheless, in Study 03-005-11, a higher percentage of eyes receiving

alcaftadine contralaterally had 0 itching score compared to eyes receiving alcaftadine bilaterally, whereas a higher percentage of eyes receiving vehicle contralaterally tended to have low itching scores (0, 0.5, and 1.0) compared to eyes receiving vehicle bilaterally.

Among subjects treated contralaterally in Study 03-005-13, it was noted at Visit 4 (Day 14) that a higher percentage of eyes receiving alcaftadine had 0 itching score compared to eyes receiving alcaftadine bilaterally, and a greater percentage of eyes receiving vehicle had higher itching scores (2.0, 2.5 and 3.0) compared to eyes receiving vehicle bilaterally.

Figure 2: Histogram of Ocular Itching Score by Treatment and Eye (Intent-to-Treat Population; Protocol 05-003-11)

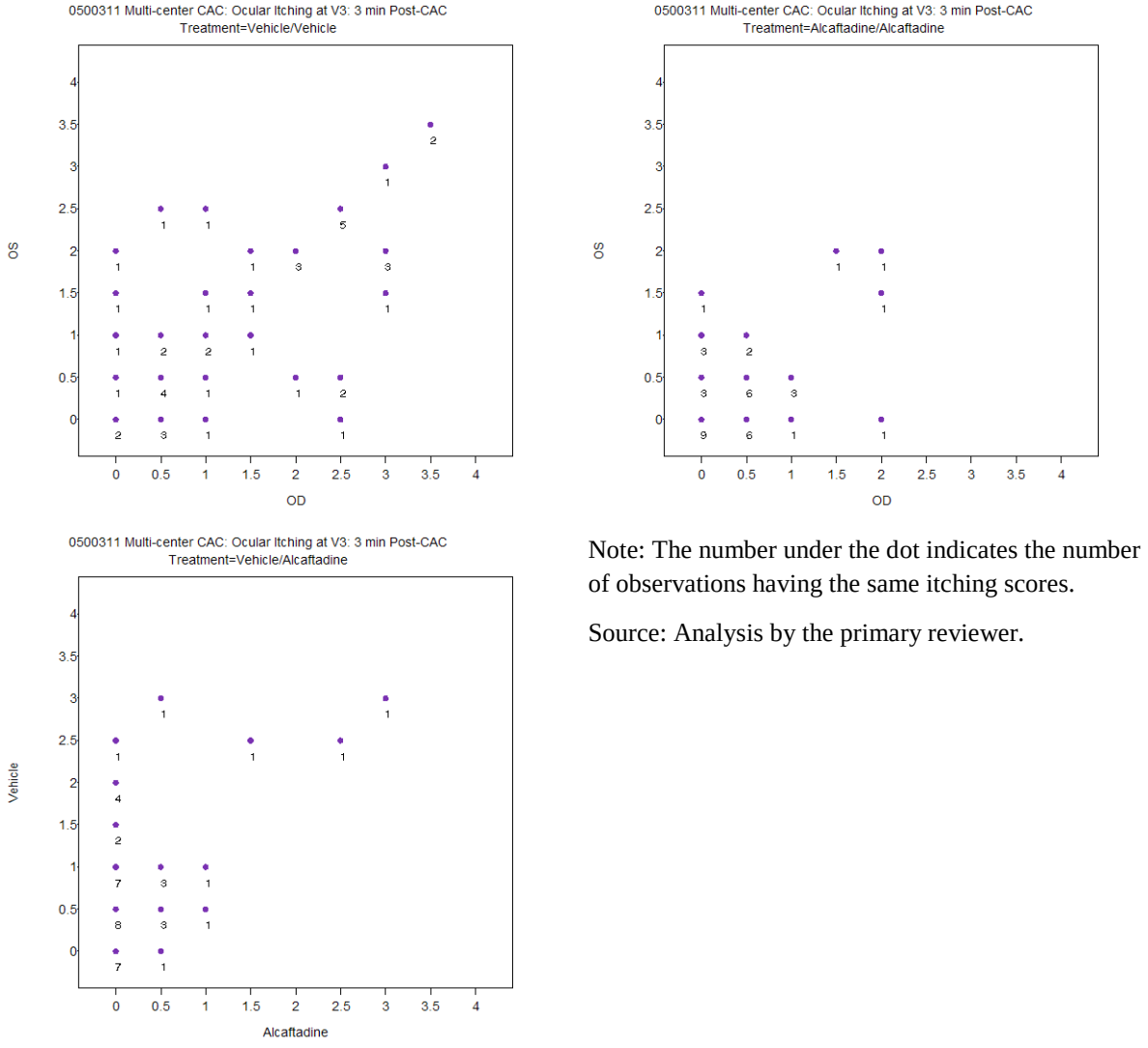


Source: Analysis by the primary reviewer.

Repeated-Measure Analyses of Ocular Itching

The ocular itching scores for the right eye and the left eye of the same subject are expected to be correlated. A scatterplot as in Figure 3 provides visual examination of the data. For the purpose of illustration, the ocular itching scores at Visit 3 and 3 minutes post allergen challenge are plotted by treatment and eye for subjects in Studies 03-005-11. For subjects treated bilaterally with either alcaftadine or vehicle, the itching scores are displayed in 'OD' and 'OS' for right eye and left eye. For subjects treated contralaterally, the itching scores could be obtained from right eye or left eye. They are indicated as 'Vehicle' or 'Alcaftadine' according to treatment received.

Figure 3: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye (Intent-to-Treat Population; Protocol 05-003-11)



Note: The number under the dot indicates the number of observations having the same itching scores.

Source: Analysis by the primary reviewer.

A complete display of the data in scatterplot for three CAC Studies is provided in Figure A.4, Figure A.5, and Figure A.6 in the Appendix by treatment, eye, visit and timepoint. For subjects treated bilaterally with either vehicle or alcaftadine, the itching scores from the left eye and right eye fall around the diagonal. Of note, in Study 09-003-05, data are concentrated in a narrower band along the diagonal compared to the other two CAC studies. This seems to indicate that subjects tended to report similar scores when it was made aware that they could receive either vehicle or alcaftadine in both eyes. For subjects treated contralaterally in studies 05-003-11 and 05-003-13, the itching scores falls above the diagonal, indicating that treatment with alcaftadine resulted in a lower itching score compared to vehicle.

Table 5 presents the correlation coefficients between the ocular itching scores for the right eye and the left eye of the same subject by treatment, visit and timepoint. For example, 3 minutes post allergen challenge at Visit 3 in Study 05-003-11, the correlation coefficient between the ocular itching scores for the right eye and the left eye was 0.614 for subjects treated with vehicle bilaterally, 0.424 for subjects treated with alcaftadine bilaterally, and 0.496 for subjects treated contralaterally. At most of the timepoints, the correlation was moderate. Stronger correlation is observed in Study 09-003-05.

Table 5: Correlation Coefficients between the Ocular Itching Scores for Right Eye and Left Eye of the Same Subject by Treatment, Visit and Timepoint (Intent-to-Treat Population; Protocols 05-003-11, 09-003-05, and 05-003-13)

Visit **Time Point**	**Protocol 05-003-11** (Vehicle N=44; Alcaftadine N=40; Veh./Alcaftadine N=42)[a]	**Protocol 09-003-05** (Vehicle N=30; Alcaftadine N=30)[a]	**Protocol 05-003-13** (Vehicle N=29; Alcaftadine N=30; Veh./Alcaftadine N=29)[a]
Visit 3 (Day 0); **16-hr post study** **medication instillation**			
3 Min Post-CAC	0.614; 0.424; 0.496	0.962; 0.778	0.734; 0.703; 0.245
5 Min Post-CAC	0.696; 0.414; 0.335	0.896; 0.814	0.673; 0.684; 0.341
7 Min Post-CAC	0.564; 0.461; 0.316	0.951; 0.872	0.688; 0.758; 0.329
Visit 4 (Day 14); **15-min post study** **medication instillation**			
3 Min Post-CAC	0.805; 0.319; 0.278	0.897; 0.777	0.687; 0.654; -0.112
5 Min Post-CAC	0.720; 0.615; 0.437	0.969; 0.838	0.771; 0.745; -0.268
7 Min Post-CAC	0.740; 0.558; 0.503	0.977; 0.776	0.779; 0.682; 0.053

a. N represents the number of subjects.
Source: Analysis by the primary reviewer.

In the Applicant's primary analyses for 05-003-11 and 05-003-13, eye was the unit of analysis. The itching scores for the right eye and the left eye from the same subject were treated as

independent. As a sensitivity analysis, the Applicant conducted a repeated-measure analysis. The Applicant claimed that overall the results of the repeated-measure analysis were consistent with the primary analysis. However, the Applicant's repeated-measure analysis employed an independent correlation structure, which failed to take into account of the dependence between the right eye score and the left eye score from the same subject.

In the Reviewer's repeated-measure analysis, an unstructured correlation structure was used to model the correlation between the right eye score and the left eye score from the same subject. As Table 5 indicated, the dependence between the right eye score and the left eye score from the same subject differs among treatment groups. Therefore, a different correlation structure is used for different treatment groups. The results from this analysis are presented in Table 6. Overall, the results are comparable to those from the Applicant's primary analysis.

Table 6: Repeated-Measure Analysis of Differences in Ocular Itching Scores at Visit 3 (Day 0) and Visit 4 (Day 14)
(Intent-to-Treat Population; Protocols 05-003-11, 09-003-05, and 05-003-13)

Visit Time Point	**Protocol 05-003-11** (Vehicle N=44; Alcaftadine N=40; Veh./Alcaftadine N=42)[a]	**Protocol 09-003-05** (Vehicle N=30; Alcaftadine N=30)[a]	**Protocol 05-003-13** (Vehicle N=29; Alcaftadine N=30; Veh./Alcaftadine N=29)[a]
Visit 3 (Day 0); 16-hr post study medication instillation			
3 Min Post-CAC	-0.736 (-0.927, -0.545)	-1.685 (-2.096, -1.273)	-1.184 (-1.474, -0.894)
5 Min Post-CAC	-0.879 (-1.113, -0.645)	-1.695 (-2.085, -1.304)	-1.254 (-1.527, -0.981)
7 Min Post-CAC	-0.898 (-1.146, -0.650)	-1.651 (-2.080, -1.221)	-1.189 (-1.461, -0.916)
Visit 4 (Day 14); 15-min post study medication instillation			
3 Min Post-CAC	-1.362 (-1.582, -1.143)	-1.503 (-1.864, -1.143)	-1.439 (-1.758, -1.120)
5 Min Post-CAC	-1.293 (-1.528, -1.059)	-1.501 (-1.903, -1.100)	-1.317 (-1.694, -0.940)
7 Min Post-CAC	-1.273 (-1.515, -1.032)	-1.474 (-1.909, -1.038)	-1.428 (-1.775, -1.081)

b. N represents the number of subjects.
Difference was calculated as mean of alcaftadine minus mean of vehicle; a negative difference favors alcaftadine.
The difference and its 95% confidence interval were derived from a mixed model including treatment in the model and using an unstructured variance-covariance structure.
Source: Analysis by the primary reviewer.

Additional Analyses for Ocular Itching

Studies 03-005-11 and 03-005-13 included a subset of subjects who received alcaftadine instillation in one eye and vehicle instillation in the contralateral eye. It is of interest to examine whether the treatment comparison of difference in ocular itching scores from this group of

subjects is consistent with the overall treatment comparison. Table 7 presents the treatment comparison of difference in ocular itching scores for subjects who received alcaftadine instillation in one eye and vehicle instillation in contralateral eye in Studies 05-003-11 and 05-003-13. The eye, as the unit of analysis, was treated as independent.

Table 7: Comparison of Differences in Ocular Itching Scores at Visit 3 (Day 0) and Visit 4 (Day 14) (Intent-to-Treat Subjects Who Received alcaftadine in One Eye and Vehicle in Contralateral Eye; Protocols 05-003-11 and 05-003-13)

Visit **Time Point**	**Protocol 05-003-11** (Vehicle N=42; (b) (4) N=42)[a]	**Protocol 05-003-13** (Vehicle N=29; (b) (4) N=29)[a]
Visit 3 (Day 0); **16-hr post study medication instillation**		
3 Min Post-CAC	-0.679 (-1.010, -0.347)	-1.161 (-1.617, -0.705)
5 Min Post-CAC	-0.845 (-1.225, -0.466)	-1.196 (-1.638, -0.755)
7 Min Post-CAC	-0.821 (-1.232, -0.411)	-1.268 (-1.697, -0.839)
Visit 4 (Day 14); **15-min post study medication instillation**		
3 Min Post-CAC	-1.218 (-1.632, -0.804)	-1.661 (-2.091, -1.231)
5 Min Post-CAC	-1.269 (-1.707, -0.832)	-1.607 (-2.086, -1.128)
7 Min Post-CAC	-1.269 (-1.728, -0.811)	-1.839 (-2.282, -1.397)

a. N represents the number of eyes treated.
Last observation carried forward to impute missing values within a visit.
Difference was calculated as mean of alcaftadine minus mean of vehicle; a negative difference favors alcaftadine.
P-value<0.001 for all comparisons. P-value was based on Wilcoxon Rank Sum test for comparing alcaftadine to vehicle.
Source: Analysis by the primary reviewer.

Similar to the results from the analysis using all data, the difference in ocular itching scores between the eyes treated with alcaftadine compared to the eyes treated with vehicle from the same subjects is statistically significant (P-value<0.001) at all time points. However, the differences appear more pronounced at all time points at Visit 4 (Day 14) in Study 05-003-13. Using all the data, the difference is less than 1.3; but with the subset of the subjects, the difference is greater than 1.6. The bigger difference in ocular itching scores between alcaftadine and vehicle at this visit is consistent with the observations made from examining the distributions of the data.

Data were handled differently in the analyses for these three CAC efficacy studies. In studies 05-003-11 and 05-003-13, eyes were treated as the independent units in the analyses. In study 09-003-05, however, subjects were the units of the analyses after averaging the scores of both eyes. To examine the robustness of these two different methods, the Reviewer conducted one

additional analysis for Study 09-003-05, in which eye was treated as the independent unit of analysis.

When eye was the independent unit of analysis, the differences in itching score between the alcaftadine-treated eyes and vehicle-treated eyes are the same as those observed when subject is the unit of analysis at all but one time-point, Visit 4 (Day 14) 3 minutes post-CAC (-1.491 vs -1.500). The minor difference was a result of the missing scores in the left eyes (OS) of two subjects (02027 and 01011). When subject was the unit of analysis, the right eye scores were used for the average scores of the subjects.

In general, if the scores are missing for both eyes, treating eye as the unit of analysis and treating subject as the unit of analysis will yield the same estimate for treatment difference. However, as the number of observations is halved when scores from both eyes are averaged to generate the subject's score, the analysis treating subject as the unit of analysis will result in wider confidence intervals and bigger p-values than the analysis using eye as the unit of analysis. If the scores are missing for only one eye of a subject, these two analyses may produce different results.

3.1.4.2 Conjunctival Redness

Conjunctival redness was evaluated by the investigators at 7, 15, and 20 minutes post allergen challenge at Visit 3 (Day 0) and Visit 4 (Day 14) on a 0 to 4 scale, allowing half unit increments, where 0 indicates no redness and 4 indicates severe redness. The comparison of differences in conjunctival redness scores at 16 hours (Visits 3) and 15 minutes (Visit 4) post medication instillation for the three Phase 3 studies are presented in Table 8.

According to the Applicant's analyses, single-center CAC Study 05-003-13 didn't show statistically significant improvement compared to a significance level of 5% in conjunctival redness for alcaftadine-treated eyes versus vehicle-treated eyes at all time points. For Multi-Center CAC Studies 05-003-11 and 09-003-05, statistically significant differences ($p<0.05$) in conjunctival redness scores were noted in favor of alcaftadine versus vehicle at all post-challenge time points at Visit 3 and Visit 4. However, the mean score difference (alcaftadine minus vehicle-treated eye) was less than 0.5 unit at all time points of Visit 3 in Study 05-003-11, and less than 1 unit at all the time points in both studies. Therefore, the pre-specified criteria of achieving mean difference scores (alcaftadine minus vehicle-treated eye) of greater than 0.5 units differences at all time points, with two of three time points demonstrating at least 1 unit difference, was not accomplished in the Phase 3 CAC studies.

The Applicant noted that the Phase 3 CAC studies didn't replicate the results from a Phase 2 proof-of-concept (POC) study (Protocol 04-003-10), in which an improvement of approximate one unit or greater in conjunctival redness was achieved. It was then suggested by the Applicant

that differences in the study design (e.g., bilateral versus contralateral instillation of study medication) or inter-study variability might have contributed to this difference. The reviewer conducted two additional analyses for Studies 03-005-11 and 03-005-13. The first analysis used the data from subjects who received alcaftadine or vehicle instillation bilaterally. The second one included subjects who received alcaftadine instillation in one eye and vehicle instillation in contralateral eye. The results from these analyses (Table A.1 and Table A.2 in the Appendix) are consistent with the overall results. Thus, it is unlikely that the differences in study design or inter-study variability contributed to the lack of efficacy in improving the conjunctival redness.

Table 8: Comparison of Differences in Conjunctival Redness Scores at Visit 3 (Day 0) and Visit 4 (Day 14) (Intent-to-Treat Population; Protocols 05-003-11, 09-003-05, and 05-003-13)

Visit **Time Point**	**Protocol 05-003-11** (Vehicle N=130; Alcaftadine N=122)[a]	**Protocol 09--003-05** (Vehicle N=30; Alcaftadine N=30)[b]	**Protocol 05-003-13** (Vehicle N=87; Alcaftadine N=89)[a]
Visit 3 (Day 0); 16-hr post study medication instillation			
7 Min Post-CAC	-0.410 (-0.616, -0.203)	-0.952 (-1.278, -0.626)	-0.369 (-0.627, -0.111)
15 Min Post-CAC	-0.398 (-0.627, -0.168)	-0.542 (-0.918,-0.166)	-0.243 (-0.495, 0.010)
20 Min Post-CAC	-0.372 (-0.603, -0.142)	-0.542 (-0.921, -0.163)	-0.185 (-0.432, 0.063)
Visit 4 (Day 14); 15-min post study medication instillation			
7 Min Post-CAC	-0.797 (-0.983, -0.612)	-0.879 (-1.270, -0.489)	-0.526 (-0.726, -0.327)
15 Min Post-CAC	-0.696 (-0.900, -0.492)	-0.612 (-1.022, -0.202)	-0.139 (-0.356, 0.078)
20 Min Post-CAC	-0.585 (-0.798, -0.371)	-0.578 (-1.021, -0.134)	-0.092 (-0.316, 0.133)

a. N represents the number of eyes treated.
b. N represents the number of subjects treated.
Last observation carried forward to impute missing values within a visit.
Difference was calculated as mean of alcaftadine minus mean of vehicle; a negative difference favors alcaftadine.
Source: Applicant's CSRs and analysis by the primary reviewer.

3.1.4.3 Secondary Efficacy Endpoints

Overall, at some or all post allergen challenge time points at Visits 3 and 4, treatment with alcaftadine led to improvement in most of ocular symptoms included as secondary efficacy parameters (i.e., ciliary redness, episcleral redness, chemosis, lid swelling, and tearing); subjects treated with alcaftadine had a lower incidence of rhinorrhea, nasal congestion, and nasal composite symptom scores compared with vehicle-treated subjects.

3.1.4.4 Efficacy Conclusions

Treatment with alcaftadine led to less ocular itching compared with vehicle-treated eyes when CAC was conducted 16 hours post study medication instillation at Visit 3 (Day 0) to assess duration of action, and 15 minutes post study medication instillation at Visit 4 (Day 14) to assess onset of action. Treatment with alcaftadine led to approximately one unit or greater than one unit improvement in the ocular itching score for alcaftadine-treated eyes compared with vehicle-treated eyes at all post-allergen challenge time points at Visits 3 and 4. These improvements are clinically meaningful, as well as statistically significant ($p<0.001$). However, alcaftadine was unable to clearly demonstrate meaningful clinical benefits compared to vehicle in preventing conjunctival redness in the Phase 3 studies using the CAC model.

3.2 Evaluation of Safety

A total of eleven clinical studies provided safety data for this NDA. Phase 3 Safety Study 05-003-10 was intended to derive the bulk of the safety data to fulfill the exposure requirement of the application.

Study 05-003-10 was a multi-center, randomized, double-masked, vehicle-controlled, parallel-group study designed to evaluate the safety of alcaftadine in healthy subjects three years of age or older when administered one drop of study solution into each eye, once daily for six weeks. Subjects were randomized at a ratio of 2:1 to receive alcaftadine or vehicle. A total of 909 subjects were enrolled, including 795 adults and 114 pediatric subjects (71 were 3 to 10 years of age; and 43 were 11 to 17 years old). The major findings from the study are summarized below. A comprehensive review of the safety can be found in Medical Review.

In Study 05-003-10, 190 (31.2%) of subjects treated with alcaftadine and 72 (24.0%) of subjects treated with vehicle reported at least one treatment-emergent adverse event (TEAE). Within each treatment group, the percentage of subjects reporting any individual AE was less than <5%.

Overall, 31 subjects (3.4%) were withdrawn from the study early due to TEAEs; 23 (3.8%) treated with alcaftadine and 8 (2.7%) treated with vehicle. Among the 31 subjects, adverse events leading to early discontinuation were ocular in nature for 20 subjects, nonocular in nature for 9 subjects, and both ocular and nonocular for 2 subjects. The incidence of ocular adverse events resulting in study discontinuation was greater among subjects treated with alcaftadine (3.0%) as compared with subjects who received vehicle (1.3%).

A higher percentage of subjects treated with alcaftadine than with vehicle experienced ocular AEs (20.0% versus 13.3%). The most common ocular TEAEs (reported in at least one eye), including eye irritation, eye redness, eye pruritus, and instillation site burning, occurred in approximately 3% to 5% of alcaftadinetreated subjects, compared to approximately 1% to 3% of vehicle-treated subjects.

A total of four serious adverse events, including one ocular adverse event and three non-ocular adverse events occurred in 2 subjects in each group (alcaftadine and vehicle); none were considered treatment related.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The efficacy was further evaluated for the following subgroups:

- Male versus Female
- White versus Non-white

- Age groups: ≤17 years; 18-64 years; and >64 years

For this review, the focus of the subgroup analyses will on the ocular itching.

4.1 Gender, Race and Age

Overall, 66%, 48%, and 60% of the intent-to-treat subjects in Studies 05-003-11, 05-003-13, and 09-003-05 were females. The improvements in the ocular itching favoring alcaftadine versus vehicle for both genders are consistent with those in the overall population.

Due to small number of non-White subjects, the subjects were regrouped as 'White' and 'Non-White' for the purpose of analyses. More than 80% of subjects in these studies were White. Ocular itching scores for the subpopulation of White subjects were consistent with those noted for the overall population in each study. In Study 05-003-11, for non-Whites, a general trend towards a decrease in ocular itching favored alcaftadine versus vehicle treatment as noted in the overall population at all post-challenge time points. No consistent trends with respect to the improvement in ocular itching were seen in Studies 05-003-13 and 09-003-05, possibly due to small number of non-White subjects.

Over 80% of subjects enrolled in each of the Phase 3 CAC studies were 18-64 years of age. The ocular itching scores in the 18 to 64 years subpopulation were consistent with those noted for the overall population in each study. The other age subgroups with small number of subjects showed consistent trends towards improvement in ocular itching as observed in the overall population.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Multiplicity is one statistical issue discussed in this review. The Phase 3 CAC studies included a co-primary efficacy endpoint based on ocular itching and conjunctival redness. Therefore, the plan was to demonstrate the superiority of alcaftadine to vehicle for this endpoint. However, the CAC trials met the success criteria for ocular itching, but not for conjunctival redness. As a result, the Applicant is only seeking the indication for the prevention of itching associated with allergic conjunctivitis. Multiplicity problems can arise when the individual components of a co-primary endpoint are intended as separate claims and need to be addressed. The probability of the Type 1 error was specified at 5% in the protocol for the testing of both ocular itching and conjunctival redness. However, if the trial had been designed to meet the success criterion for either ocular itching or conjunctival redness, the two endpoints would have been treated as

independent. To adequately adjust for multiplicity, each endpoint should be tested at an appropriate significance level to control the overall Type 1 error at the desired level of 5%.

In the review of efficacy based on ocular itching, a significance level of 2.5% is used to determine the statistical significance, assuming equal importance of the two components of the original co-primary endpoint. The three CAC studies had p-values less than 0.001 at all time points, well below the threshold of significance level of 2.5%.

Correlated data is another statistical issue discussed in the review. This refers to the ocular itching scores for the right eye and the left eye of the same subject, which are expected to be correlated. In two CAC studies (Protocols 05-003-11 and 05-003-13), eye was unit of analysis. The primary analysis treated the scores for the right eye and the left eye from the same subject as independent. As a sensitivity analysis, the Applicant conducted a repeated-measure analysis. The Applicant claimed that overall the results of the repeated-measure analysis were consistent with the primary analysis. However, the Applicant's repeated-measure analysis employed an independent correlation structure, which failed to take into account of the dependence between the right eye score and the left eye score from the same subject.

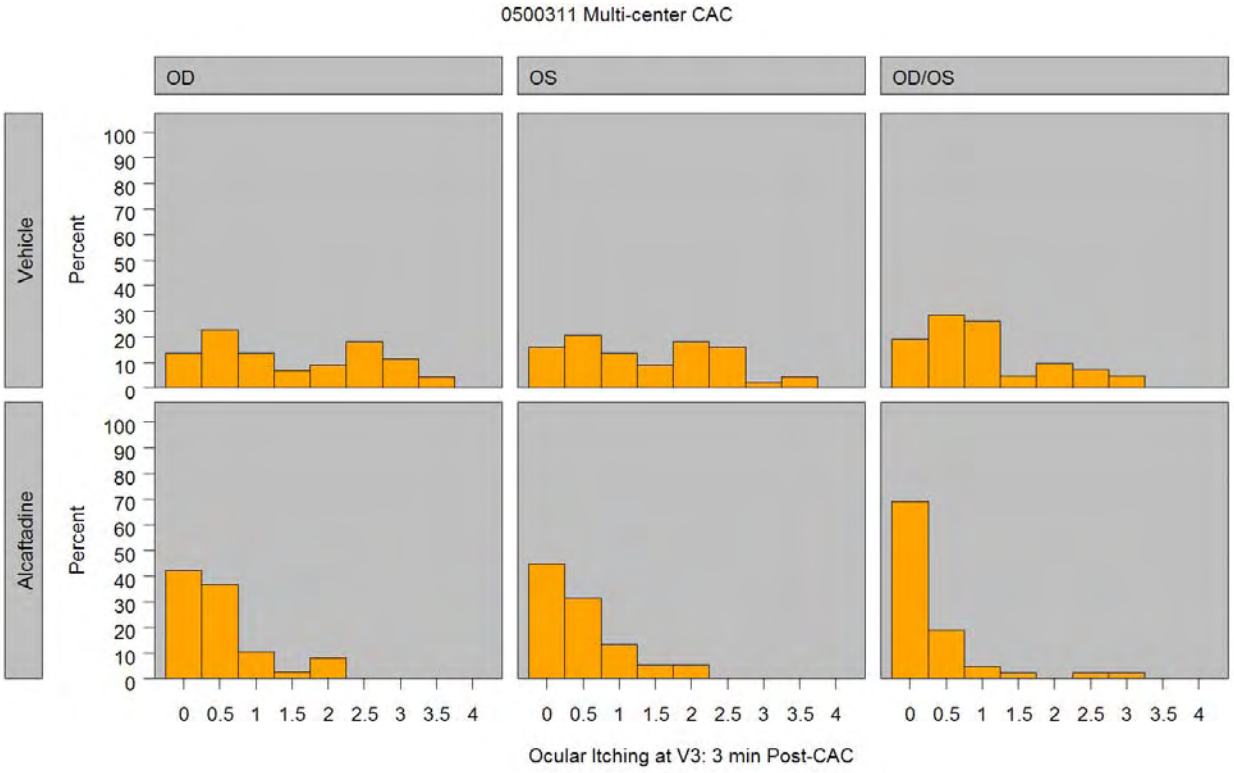
In the Reviewer's repeated-measure analysis, an unstructured correlation structure was used to model the correlation between the right eye score and the left eye score from the same subject. The results from this analysis are comparable to those from the Applicant's analysis.

5.2 Conclusions and Recommendations

Treatment with alcaftadine resulted in less ocular itching compared with vehicle-treated eyes when CAC was conducted 16 hours post study medication instillation at Visit 3 (Day 0) to assess duration of action, and 15 minutes post study medication instillation at Visit 4 (Day 14) to assess onset of action. Approximately one unit or greater than one unit improvement in the ocular itching score for alcaftadine-treated eyes compared with vehicle-treated eyes was observed at all post-allergen challenge time points at Visits 3 and 4. These improvements are clinically meaningful, as well as statistically significant ($p<0.001$). However, alcaftadine was unable to demonstrate clinical significance compared to vehicle in preventing conjunctival redness in the Phase 3 studies using the CAC model. Various sensitivity analyses conducted by the Reviewer concluded that the lack of efficacy in improving the conjunctival redness is unlikely due to the differences in study design or inter-study variability. Therefore, alcaftadine is only recommended for the approval of indication of preventing itching associated with allergic conjunctivitis.

6. Appendix

Figure A.1: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 05-003-11)



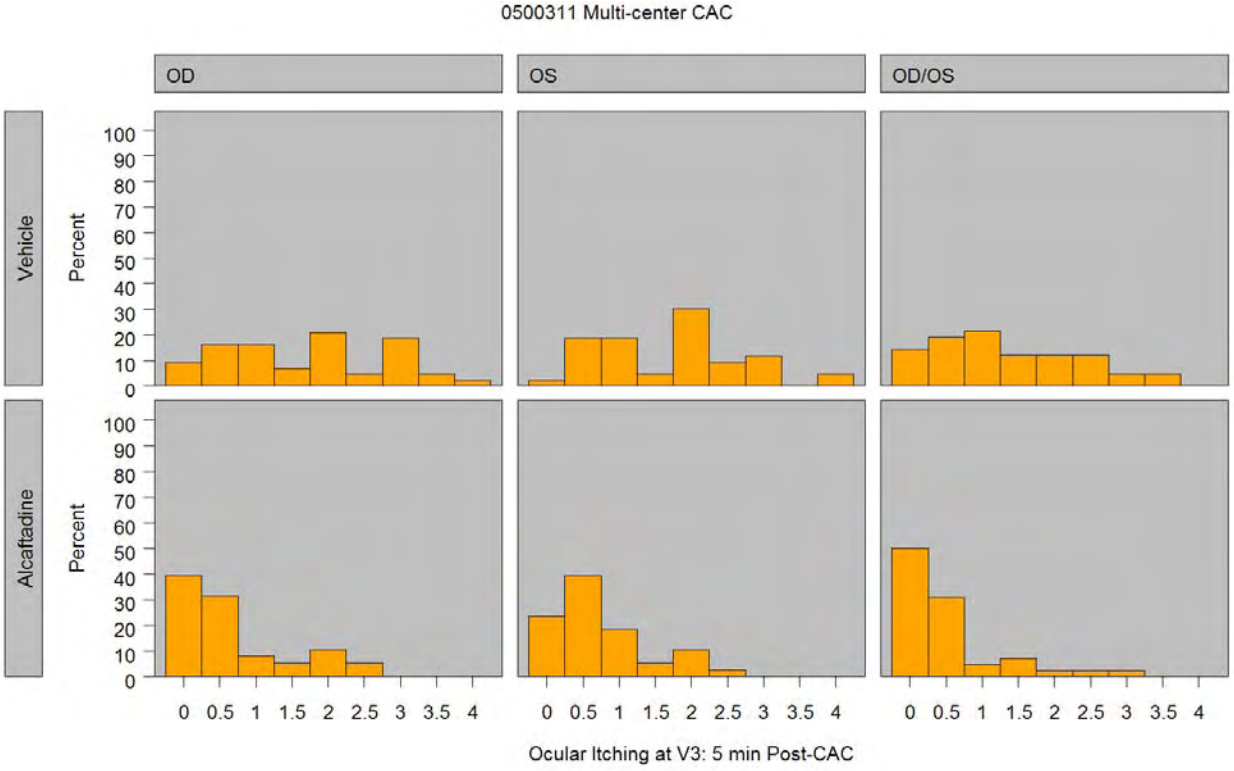


Figure A.1: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 05-003-11)-Continued

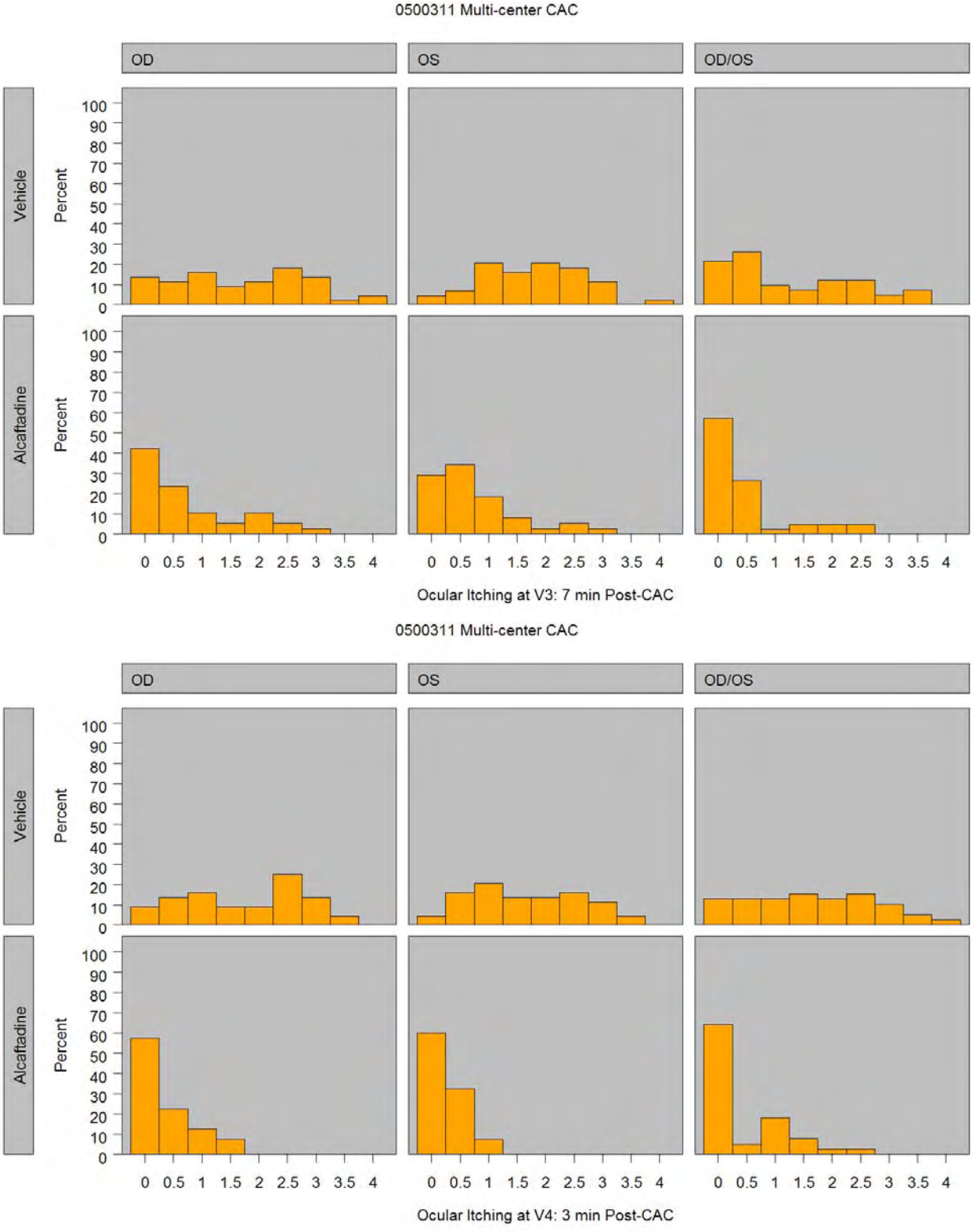


Figure A.1: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 05-003-11)-Continued

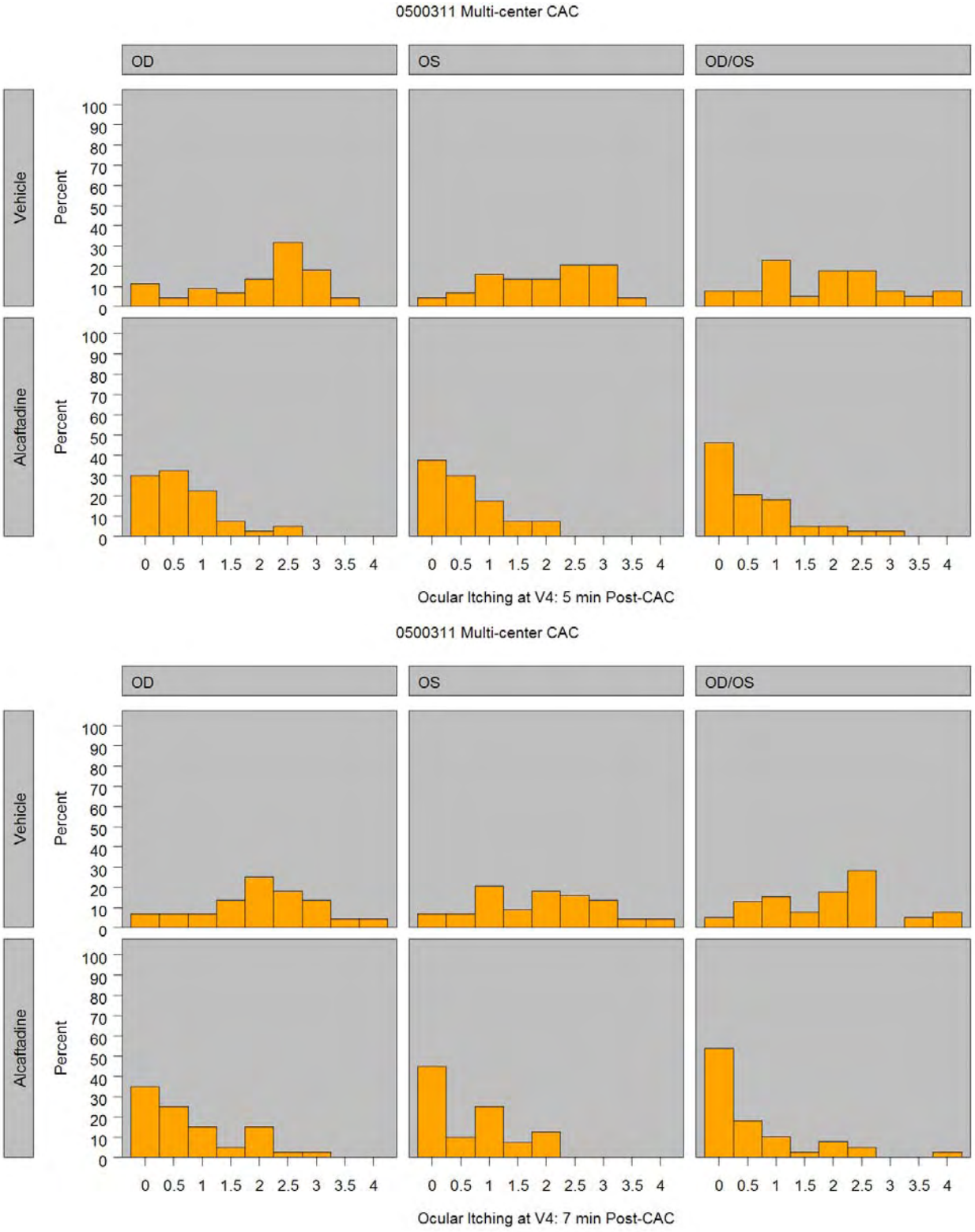
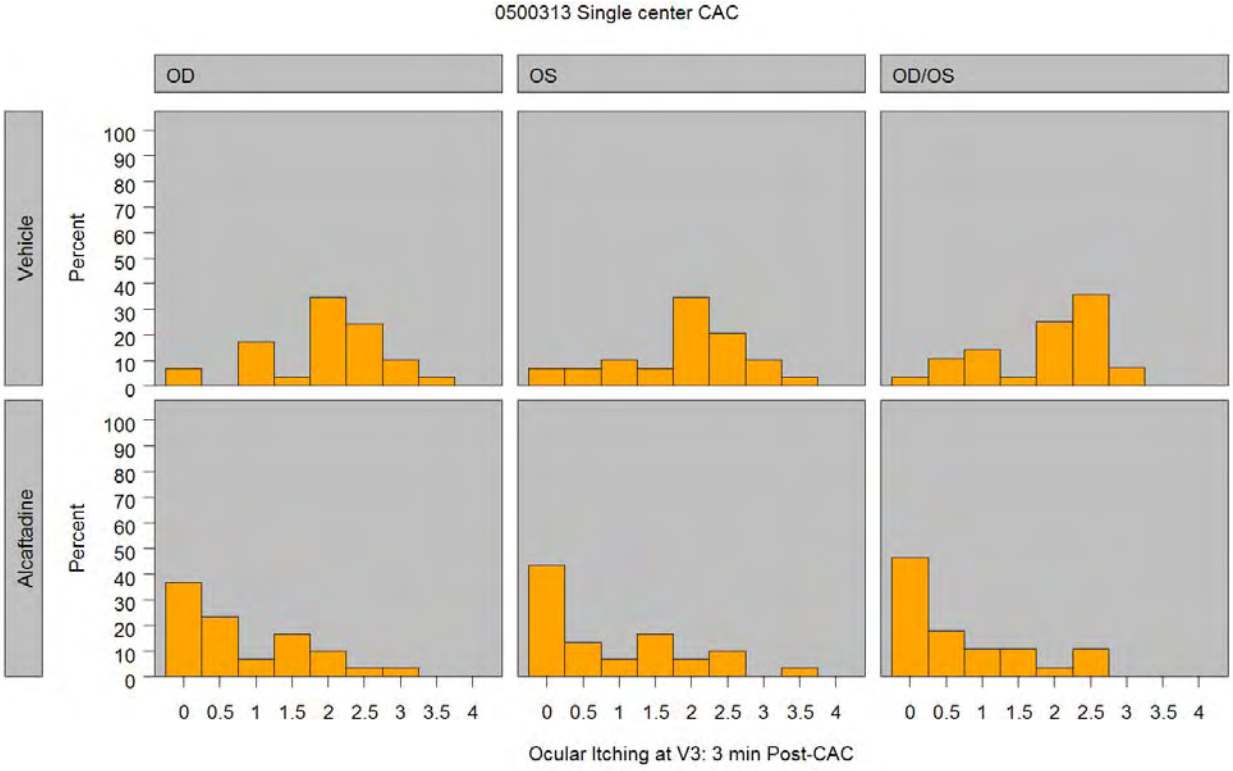


Figure A.2: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 05-003-13)



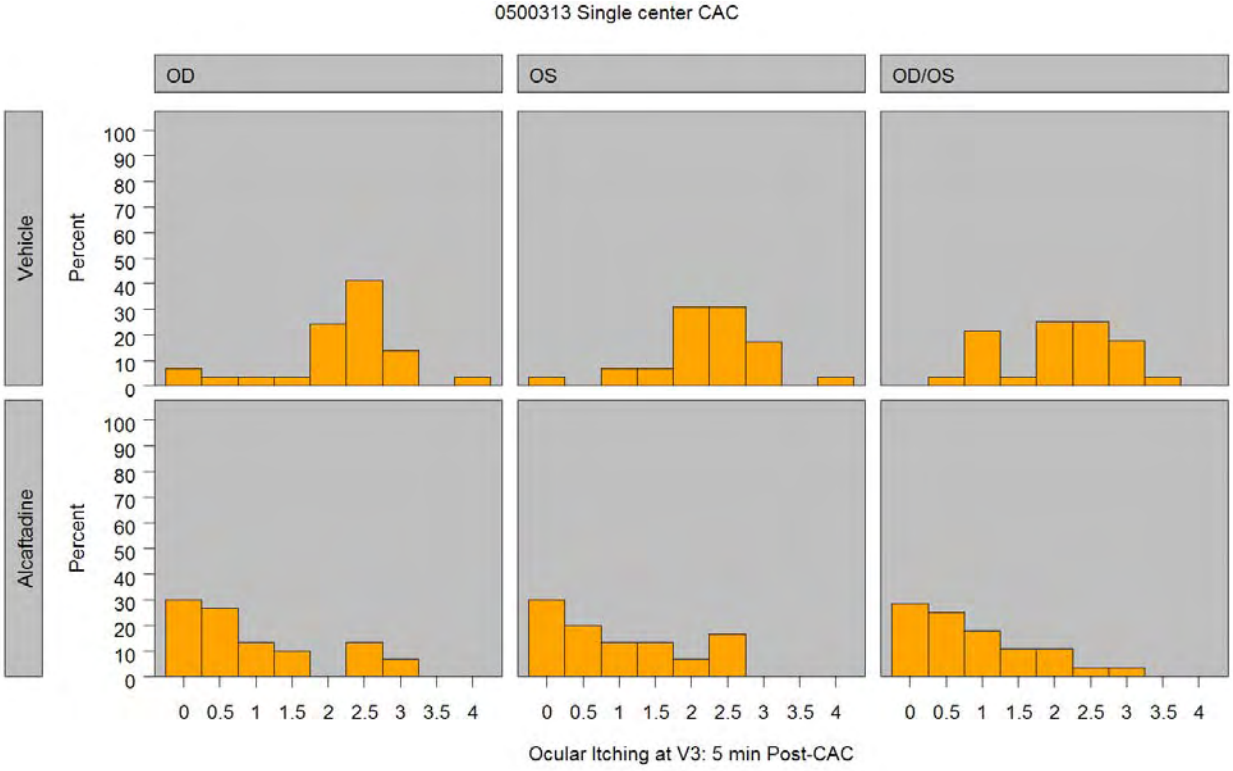
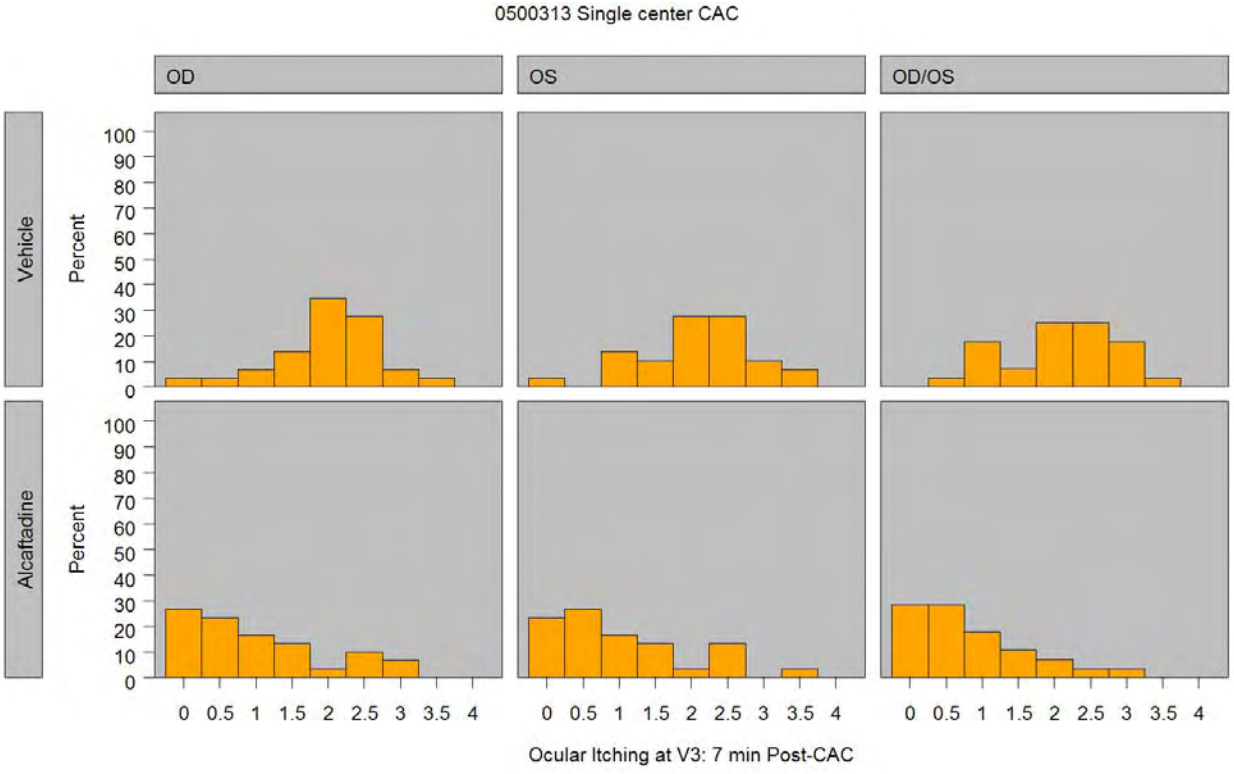


Figure A.2: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 05-003-13)-Continued



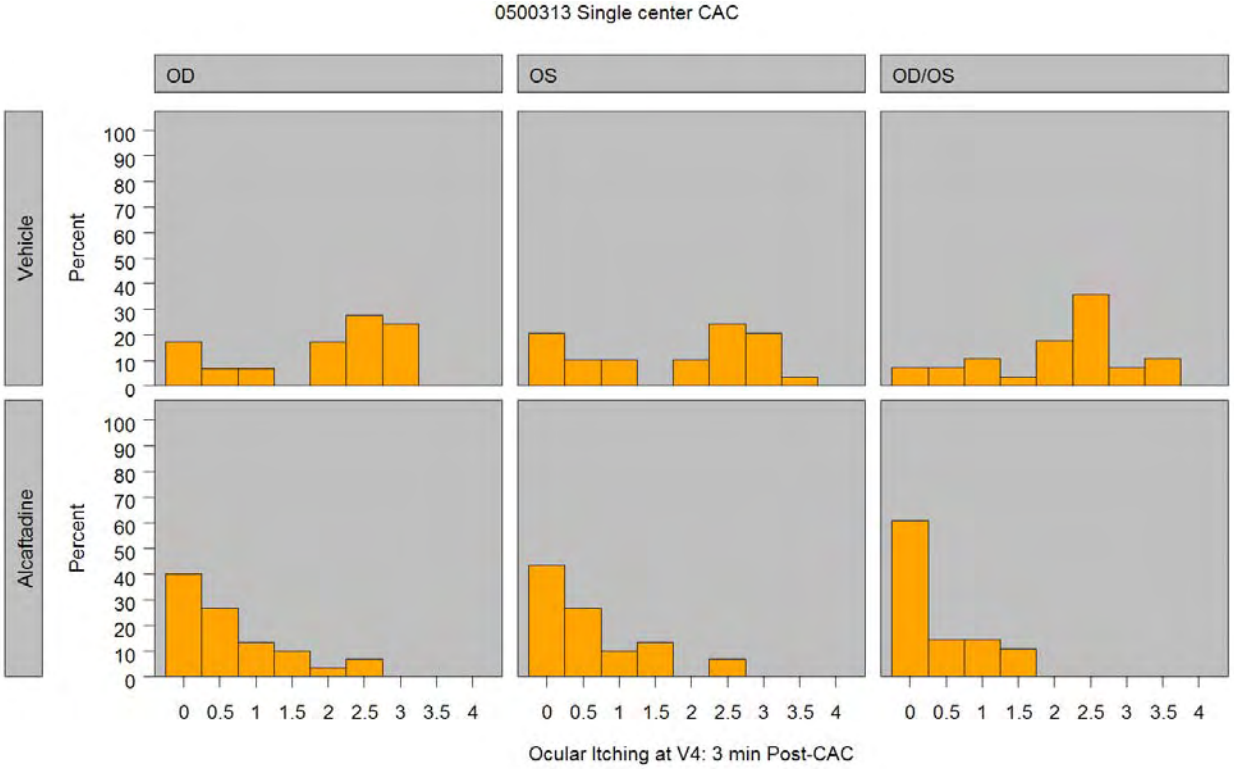
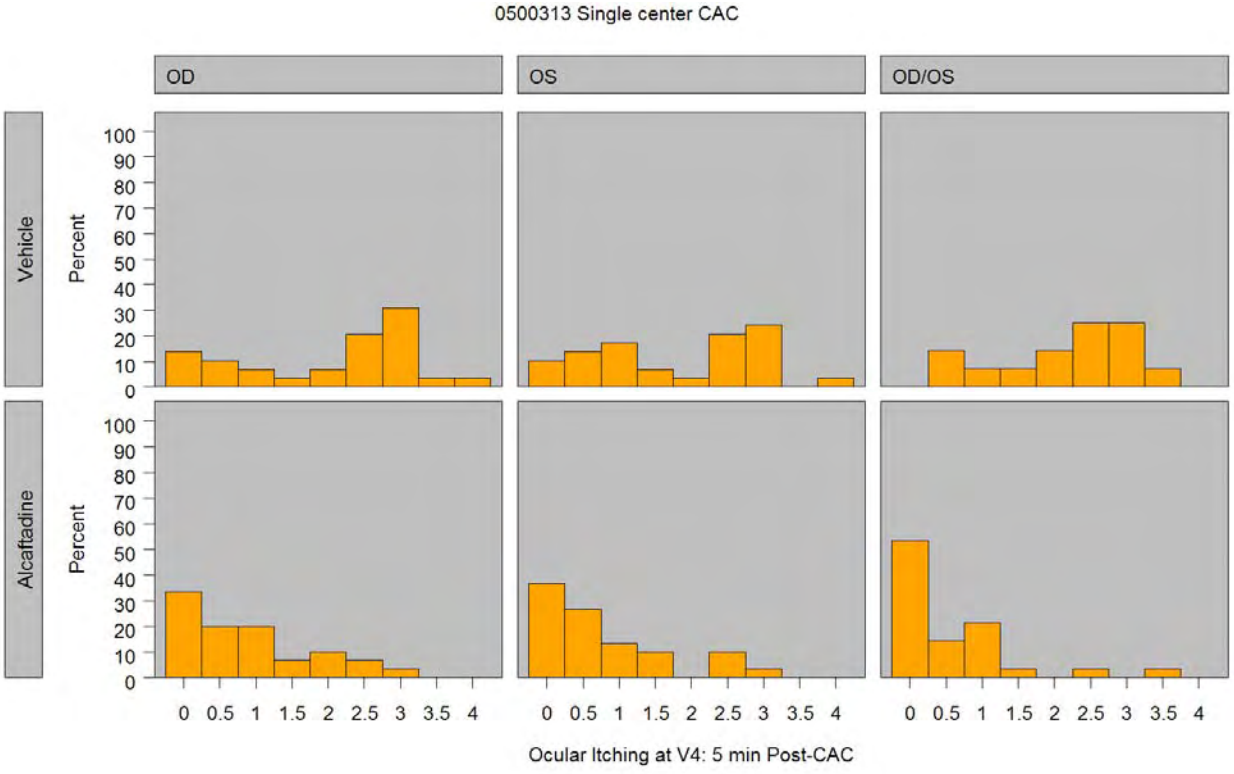


Figure A.2: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 05-003-13)-Continued



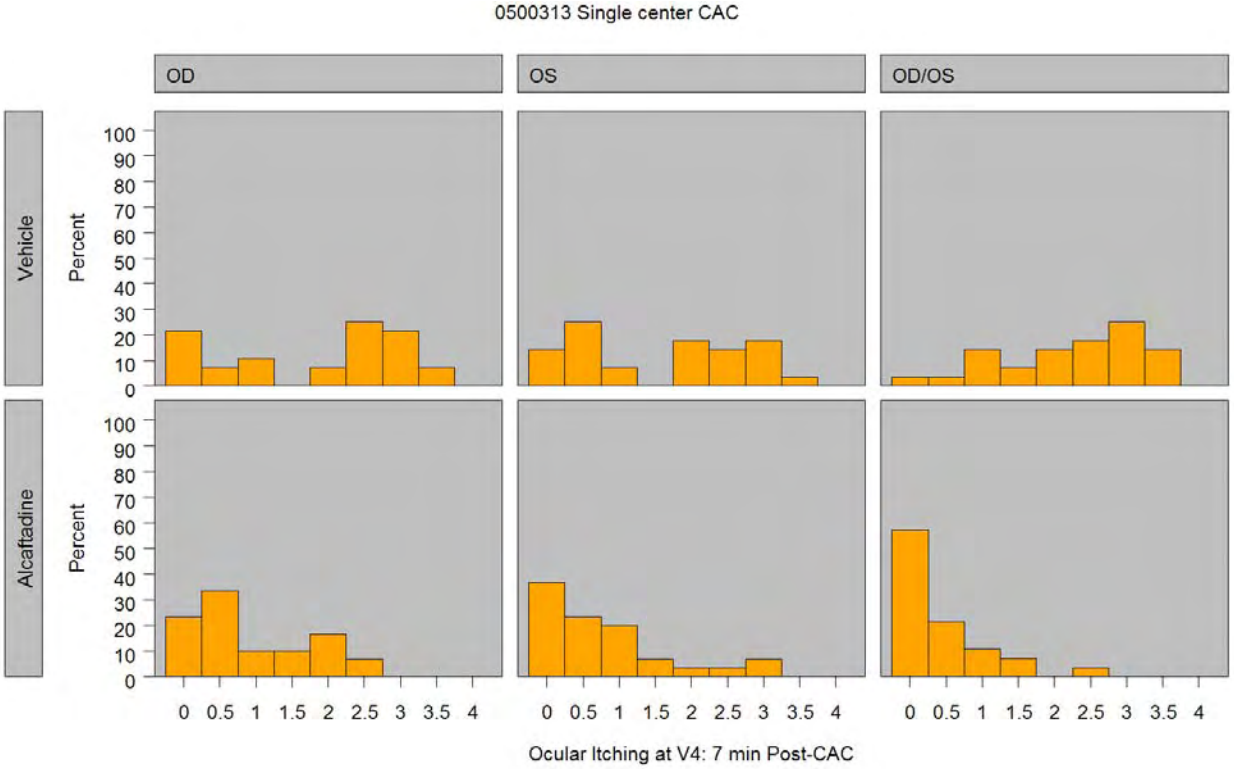
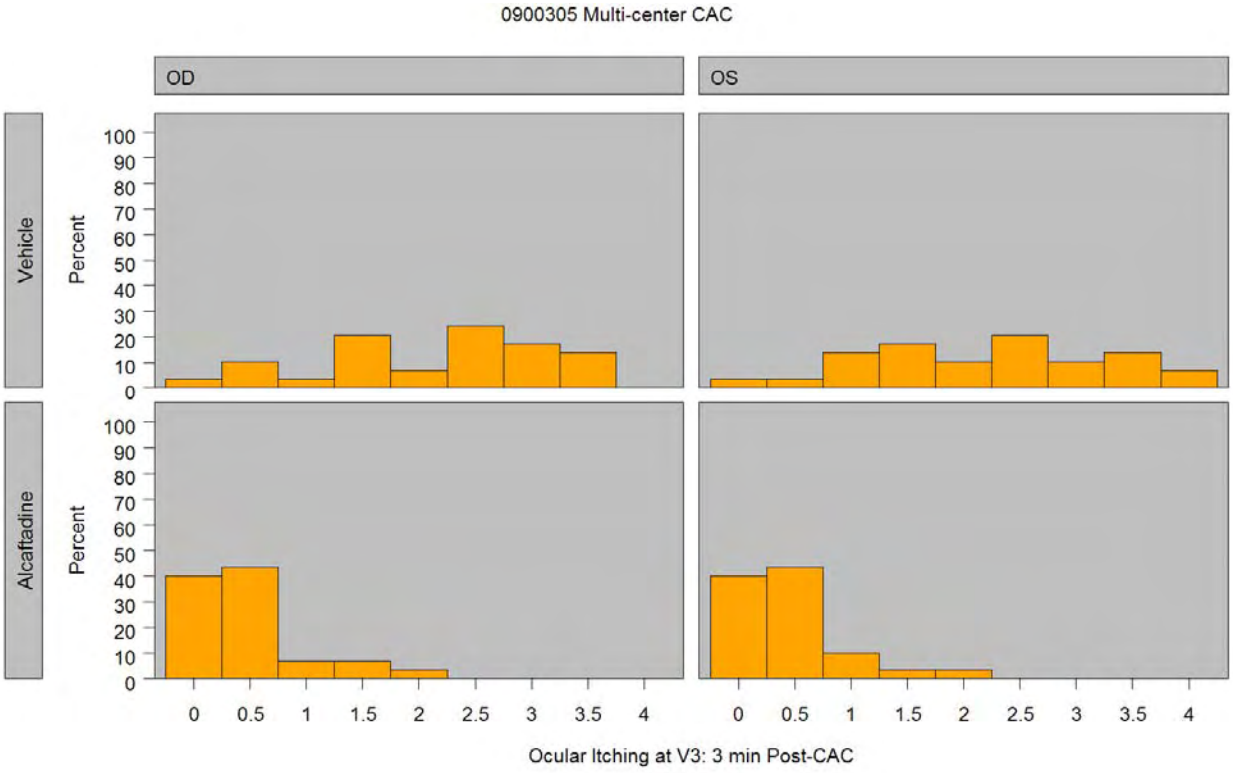


Figure A.3: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 09-003-05)



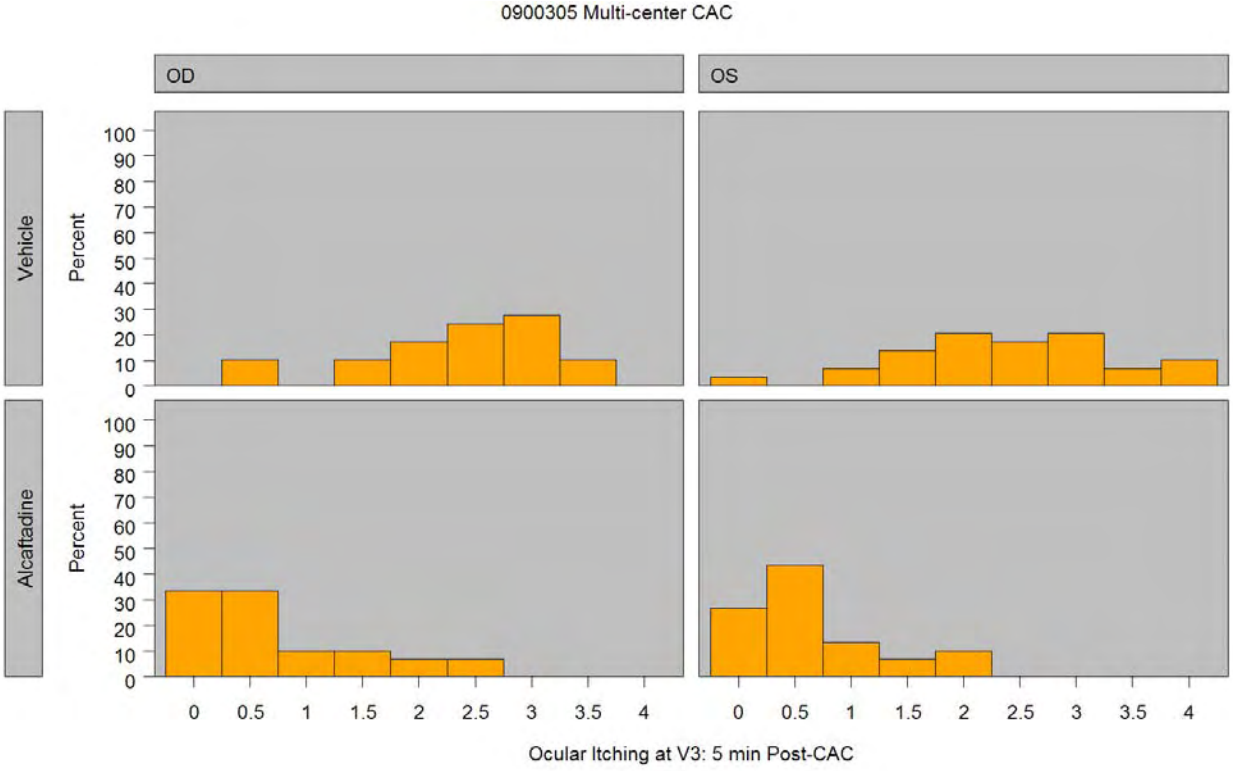
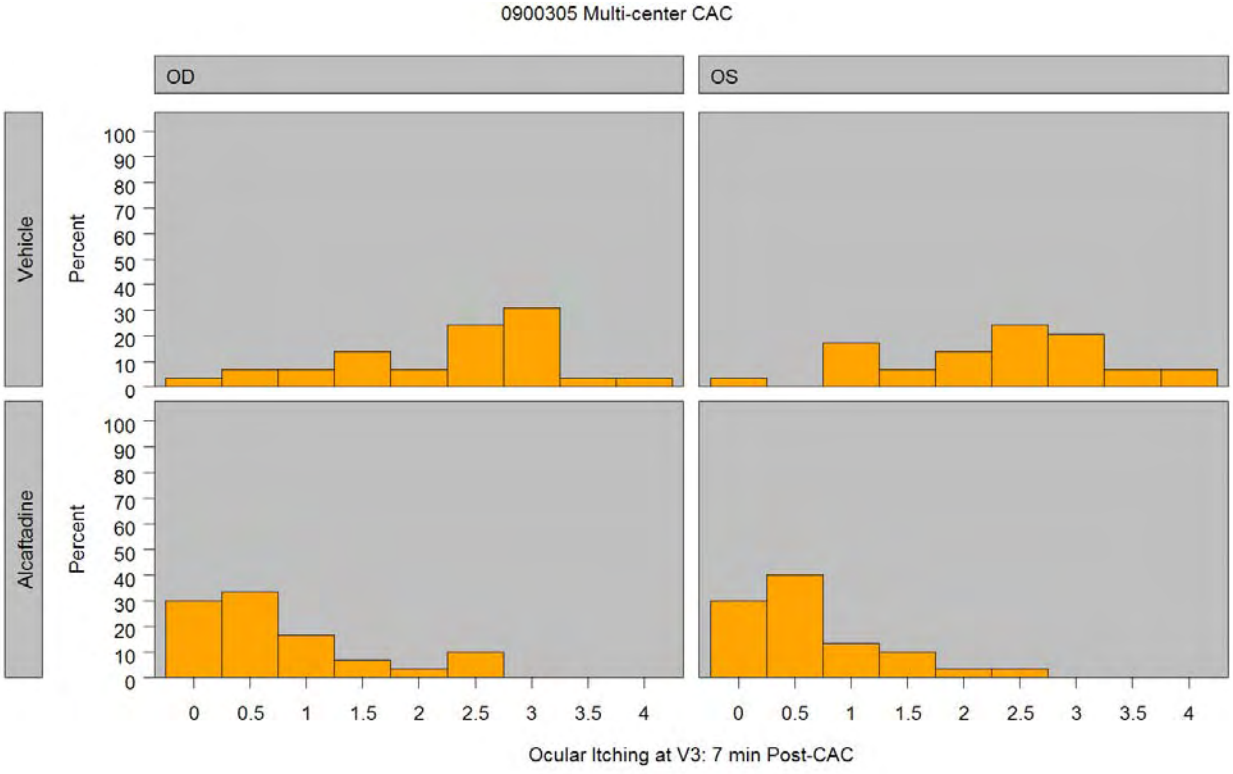


Figure A.3: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 09-003-05)-Continued



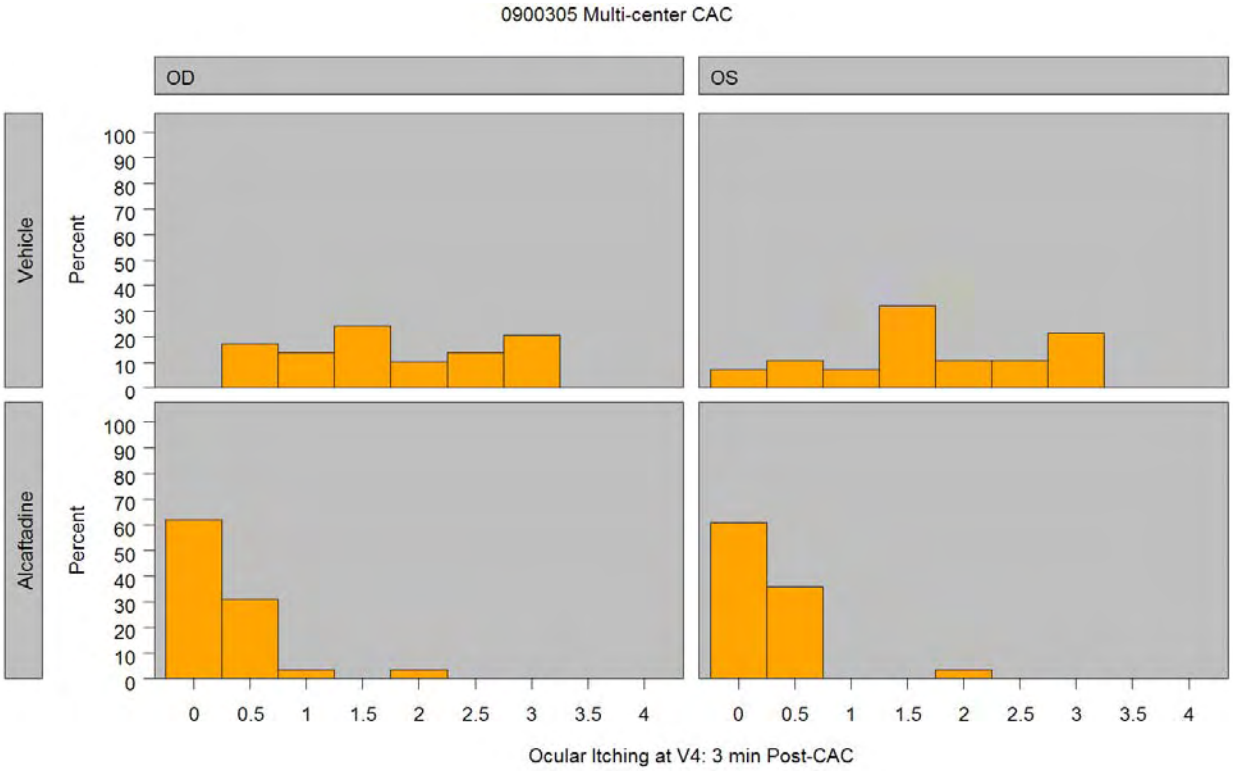
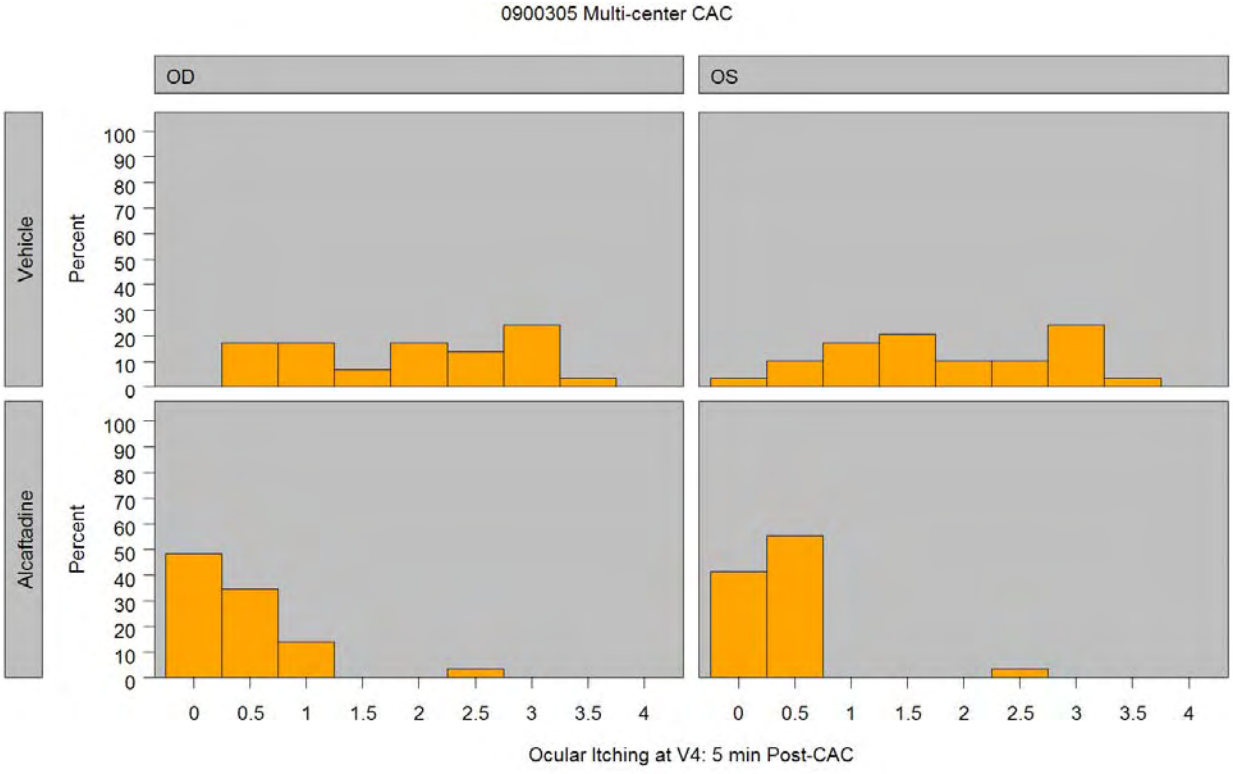


Figure A.3: Histogram of Ocular Itching Score by Treatment and Eye
(Intent-to-Treat Population; Protocol 09-003-05)-Continued



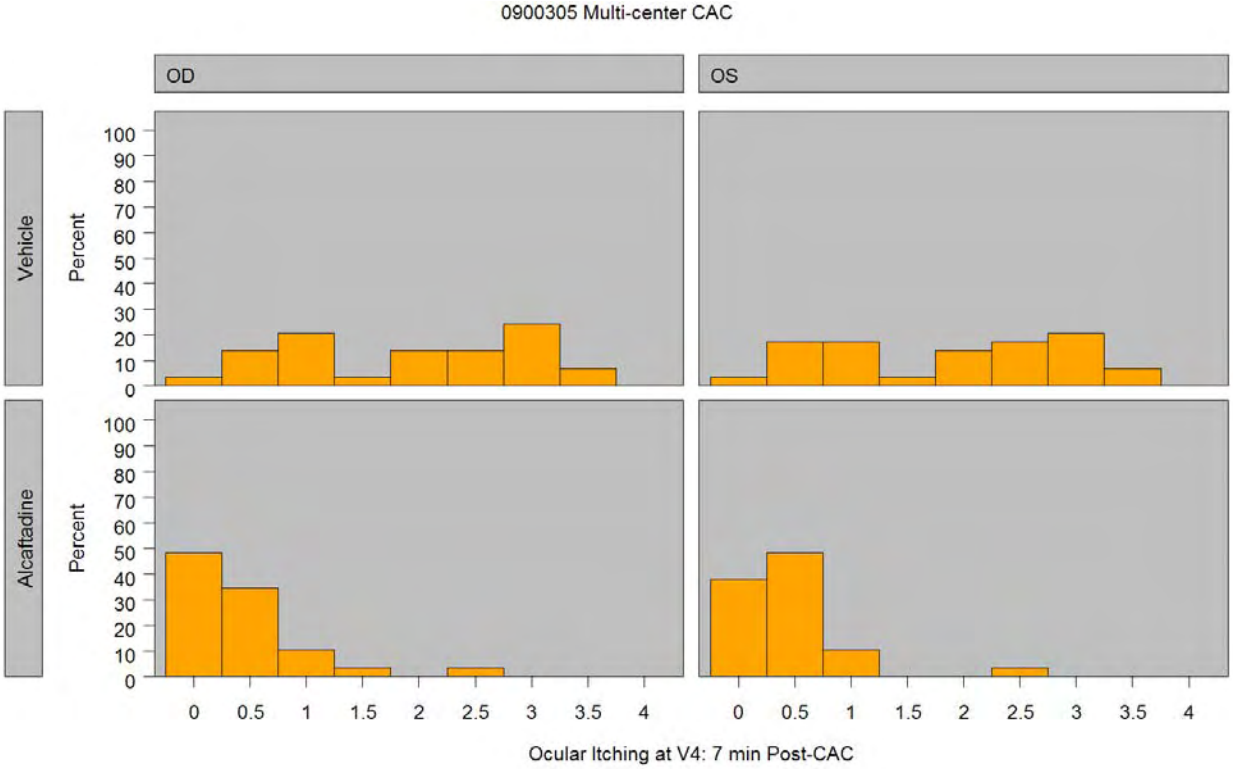
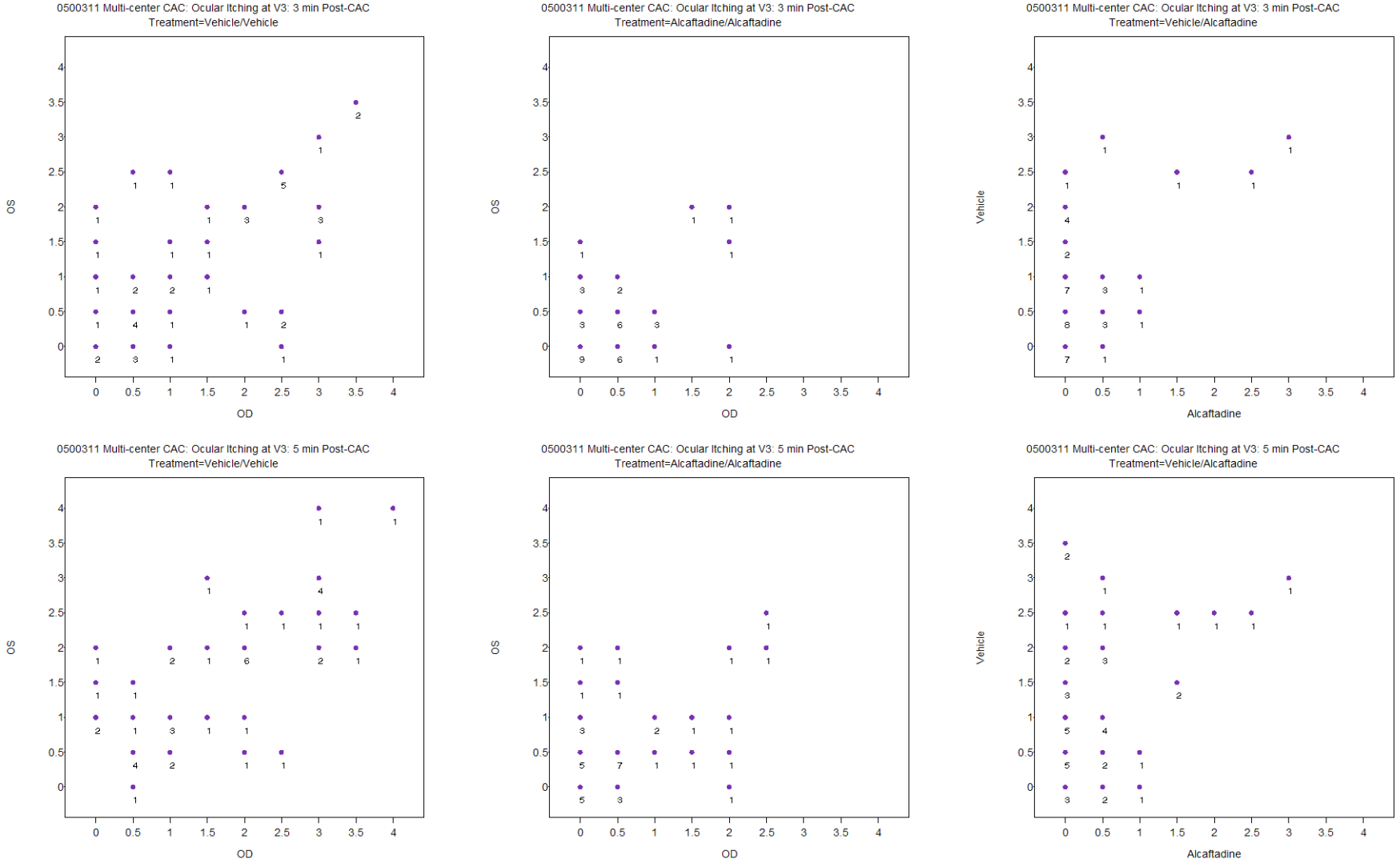
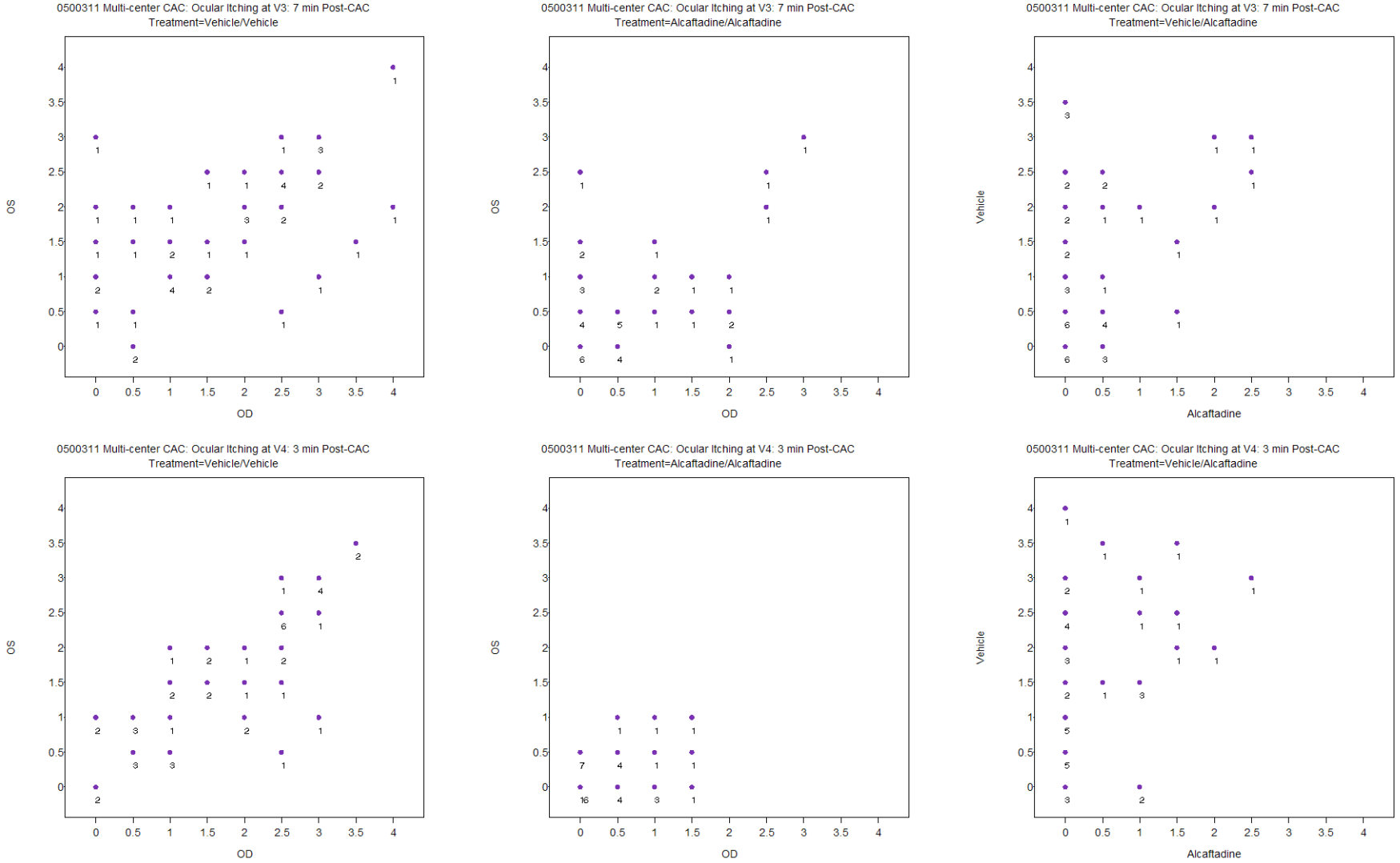


Figure A.4: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye
(Intent-to-Treat Population; Protocol 05-003-11)



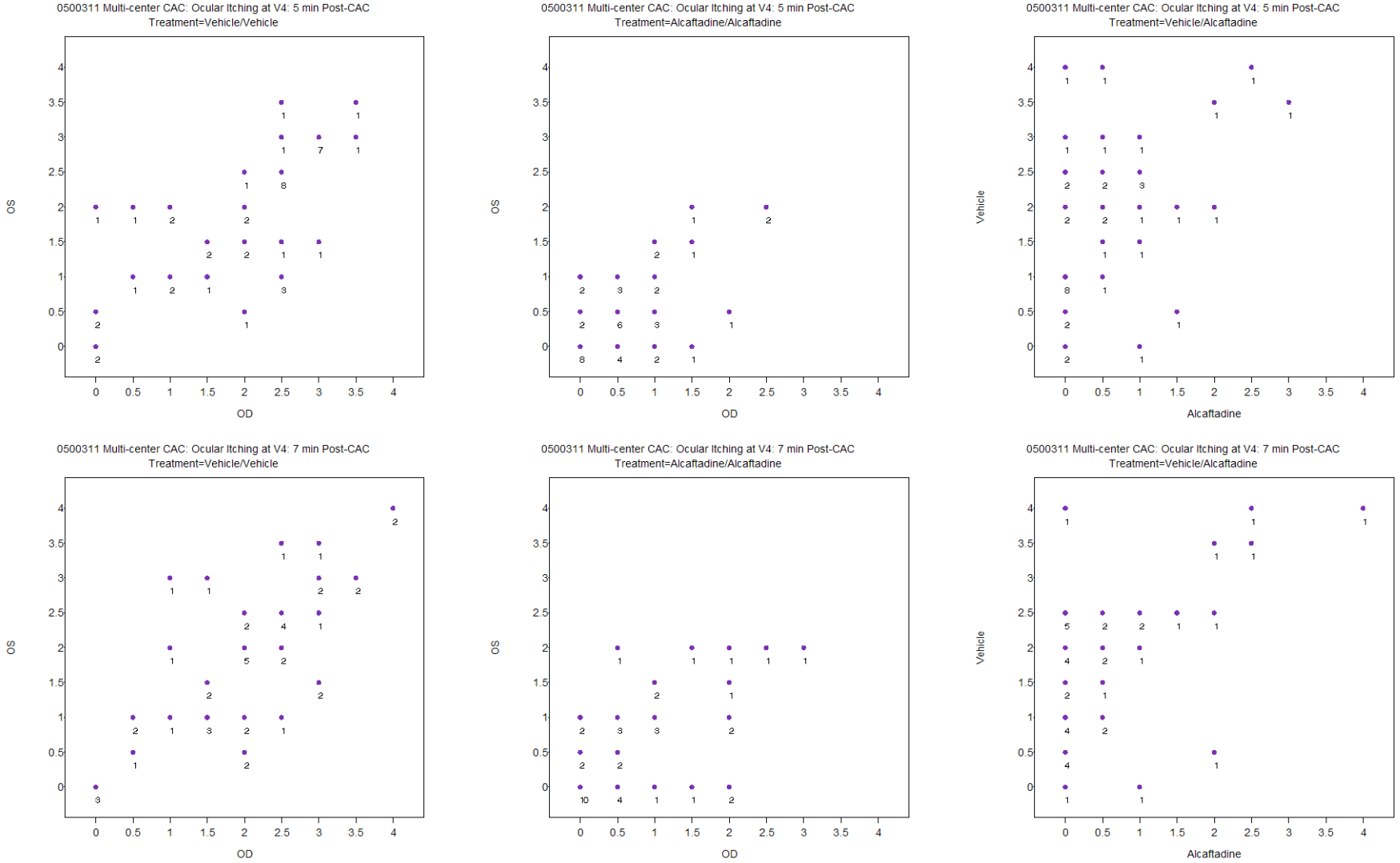
Note: The number under the dot indicates the number of observations having the same itching scores.

Figure A.4: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye (Intent-to-Treat Population; Protocol 05-003-11)-Continued



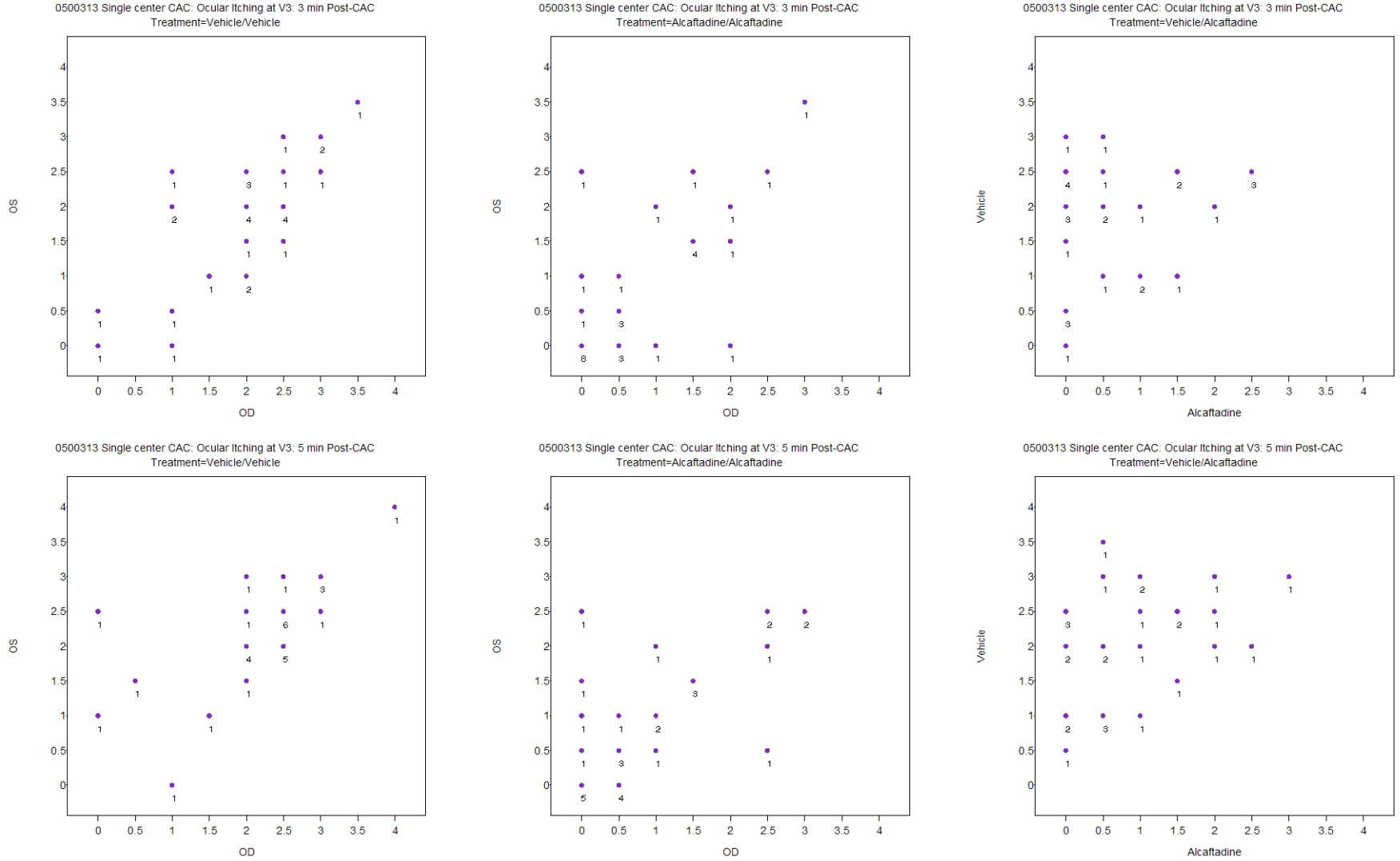
Note: The number under the dot indicates the number of observations having the same itching scores.

Figure A.4: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye (Intent-to-Treat Population; Protocol 05-003-11)-Continued



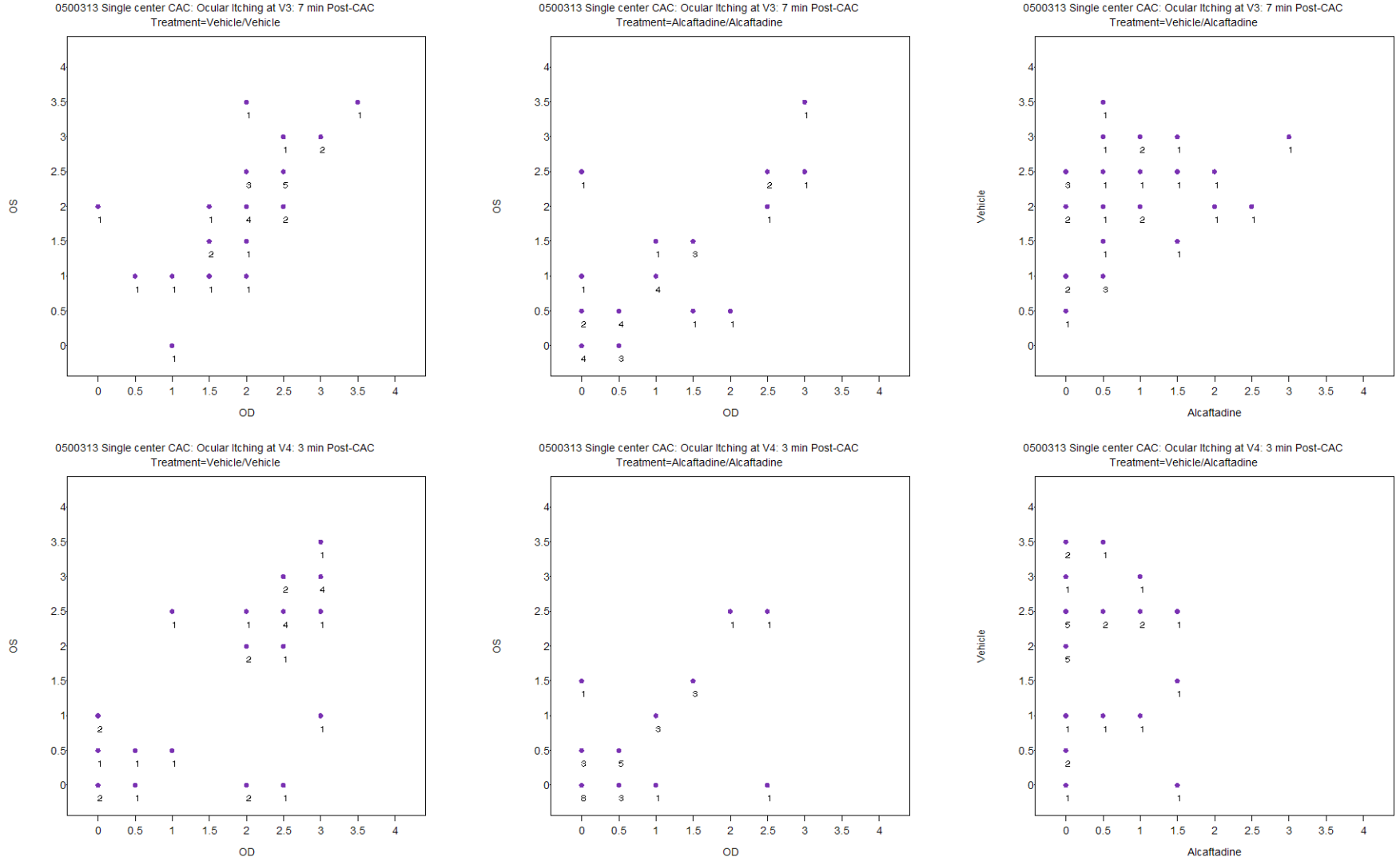
Note: The number under the dot indicates the number of observations having the same itching scores.

Figure A.5: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye
(Intent-to-Treat Population; Protocol 05-003-13)



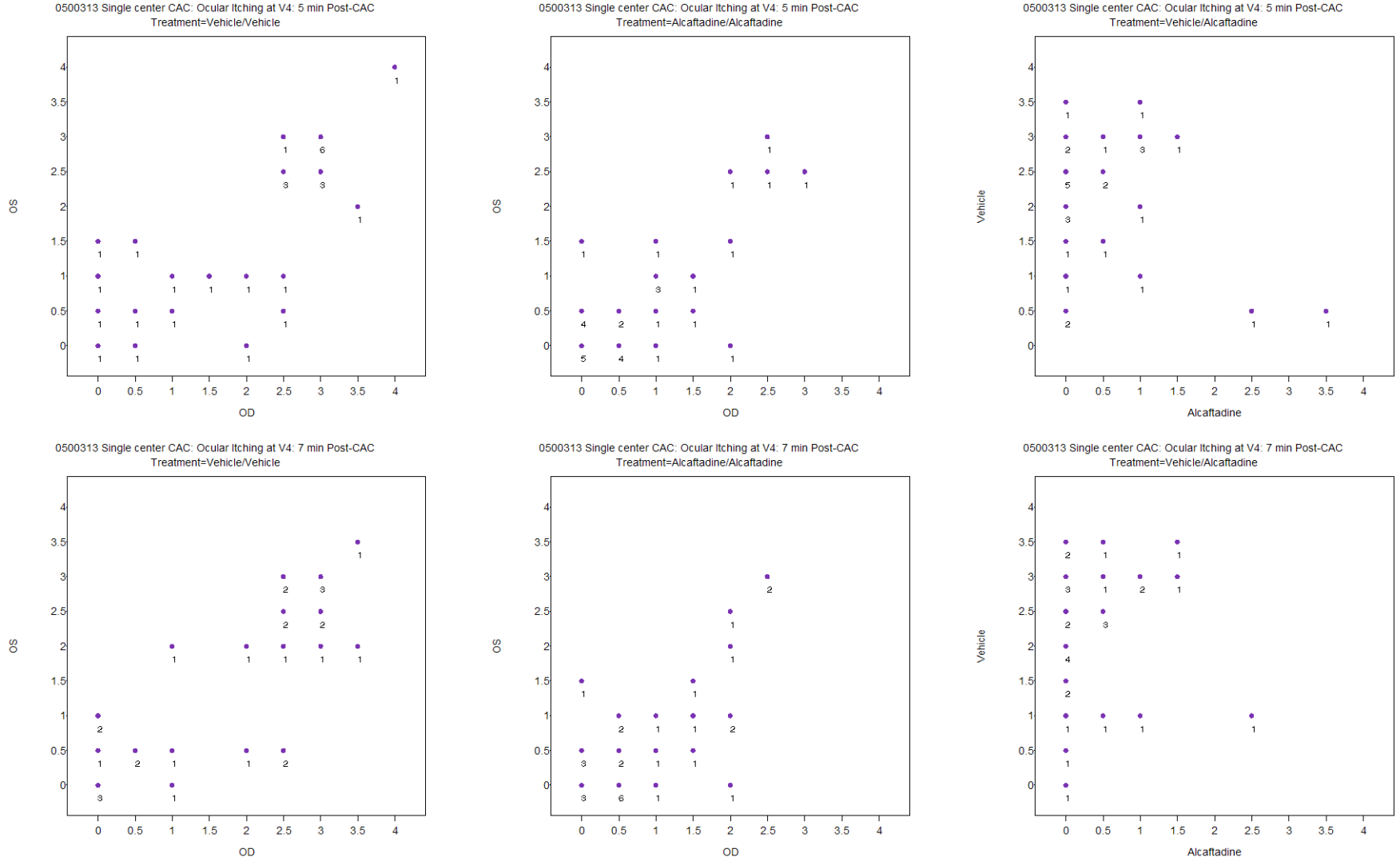
Note: The number under the dot indicates the number of observations having the same itching scores.

Figure A.5: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye (Intent-to-Treat Population; Protocol 05-003-13)-Continued



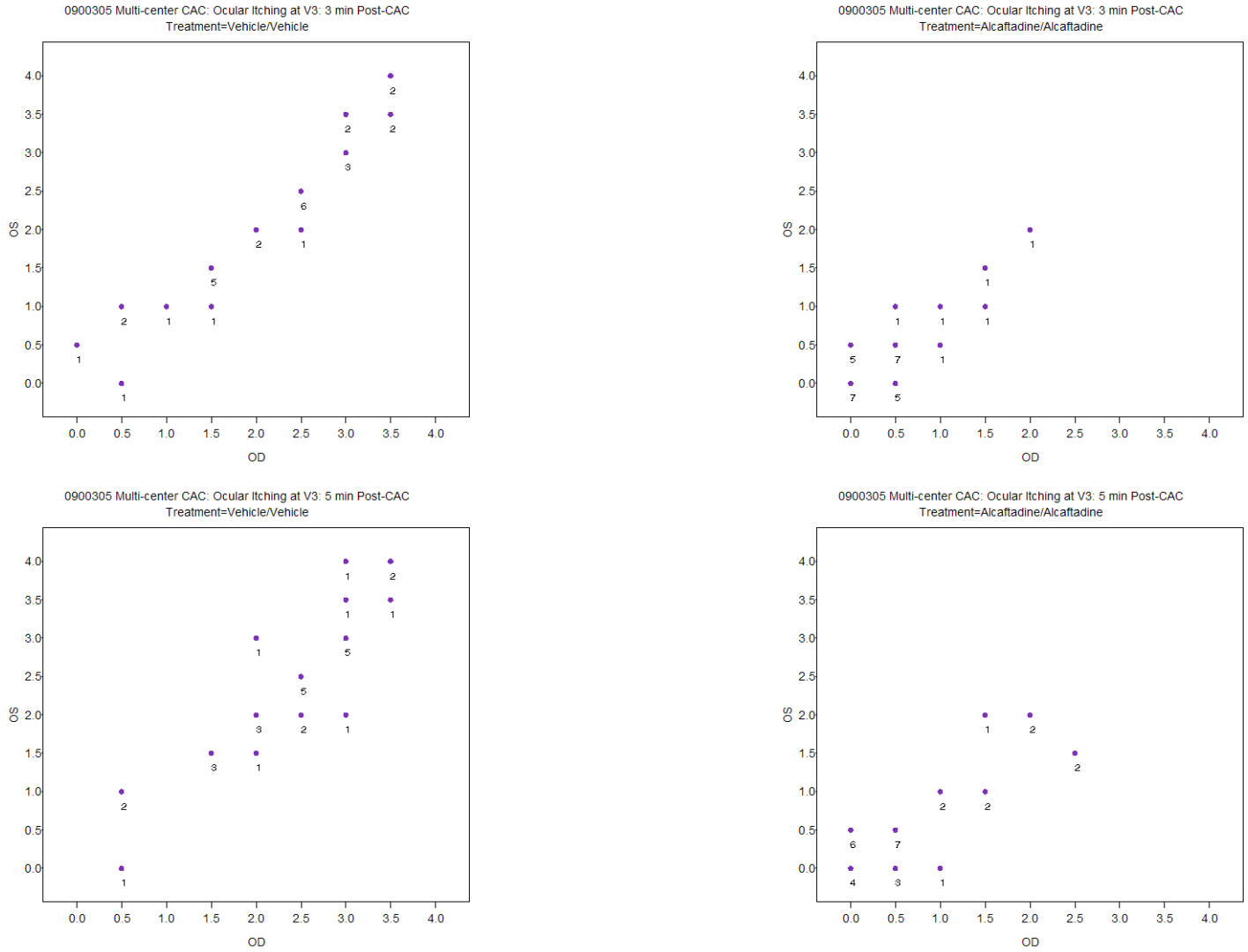
Note: The number under the dot indicates the number of observations having the same itching scores.

Figure A.5: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye (Intent-to-Treat Population; Protocol 05-003-13)-Continued



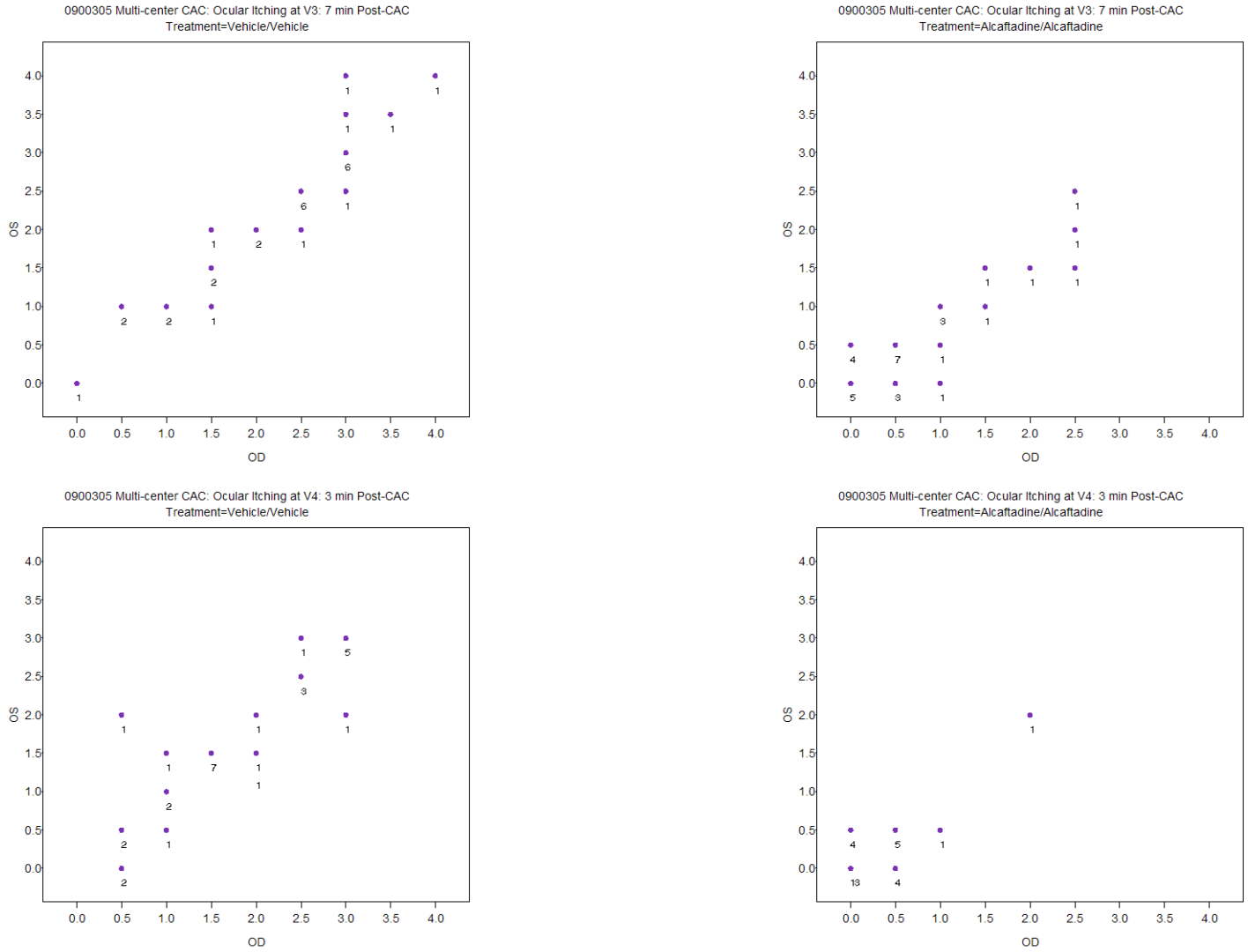
Note: The number under the dot indicates the number of observations having the same itching scores.

Figure A.6: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye (Intent-to-Treat Population; Protocol 09-003-05)



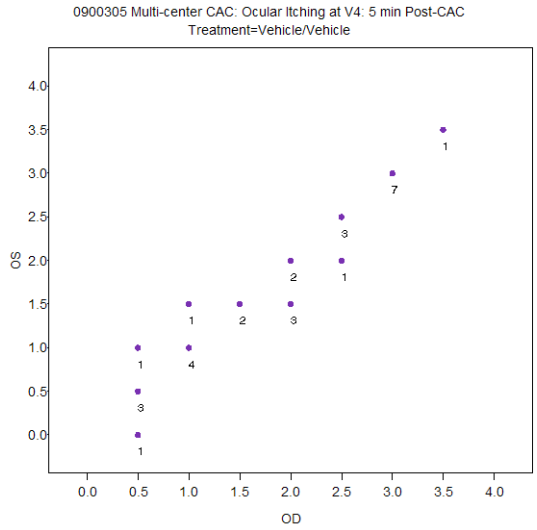
Note: The number under the dot indicates the number of observations having the same itching scores.

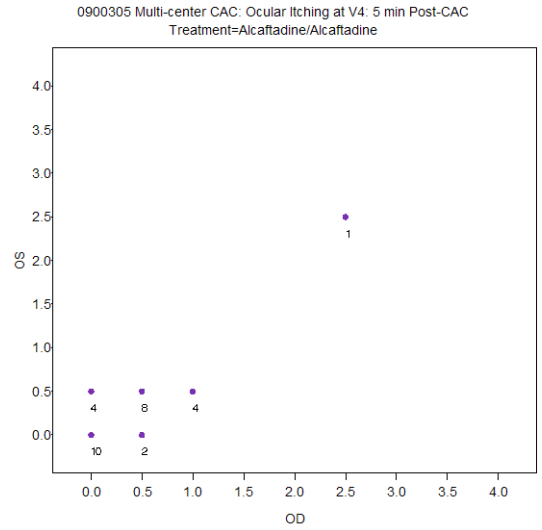
Figure A.6: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye (Intent-to-Treat Population; Protocol 09-003-05)-Continued

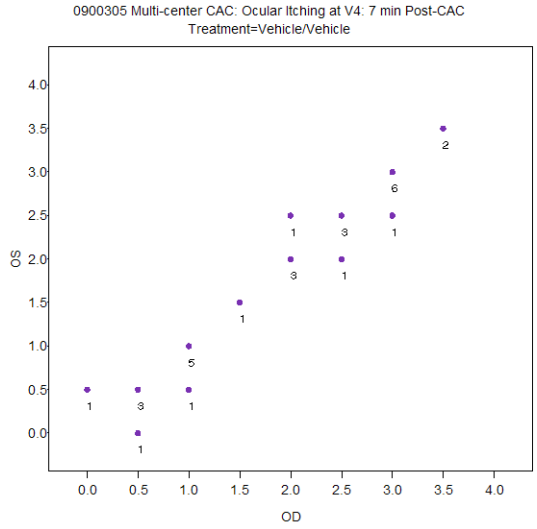


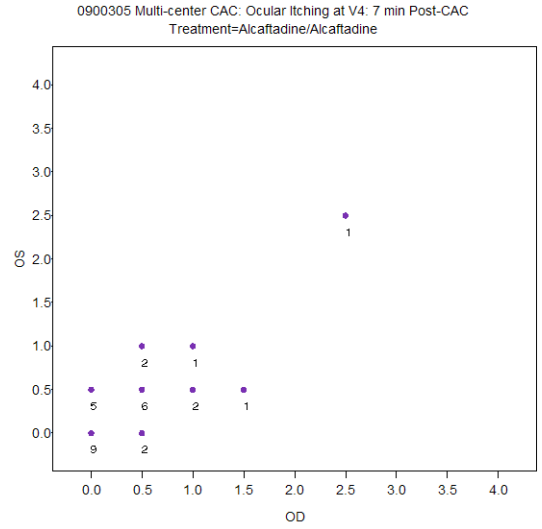
Note: The number under the dot indicates the number of observations having the same itching scores.

Figure A.6: Scatterplot of the Ocular Itching Scores by Treatment and Eye Treatment and Eye (Intent-to-Treat Population; Protocol 09-003-05) -Continued









Note: The number under the dot indicates the number of observations having the same itching scores.

Table A.1: Comparison of Differences in Conjunctival Redness Scores at Visit 3 (Day 0) and Visit 4 (Day 14): (Intent-to-Treat Subjects Who Received Alcaftadine or Vehicle bilaterally; Protocols 05-003-11 and 05-003-13)

Visit **Time Point**	**Protocol 05-003-11** (Vehicle N=88; (b) (4) N=80)[a]	**Protocol 05-003-13** (Vehicle N=58; (b) (4) N=60)[a]
Visit 3 (Day 0); **16-hr post study medication instillation**		
7 Min Post-CAC	-0.485 (-0.746, -0.224)	-0.485 (-0.794, -0.176)
15 Min Post-CAC	-0.500 (-0.792, -0.208)	-0.291 (-0.598, 0.017)
20 Min Post-CAC	-0.468 (-0.756, -0.180)	-0.230 (-0.531, 0.071)
Visit 4 (Day 14); **15-min post study medication instillation**		
7 Min Post-CAC	-0.847 (-1.054, -0.639)	-0.547 (-0.793, -0.302)
15 Min Post-CAC	-0.759 (-0.994, -0.524)	-0.093 (-0.364, 0.177)
20 Min Post-CAC	-0.656 (-0.902, -0.410)	-0.006 (-0.278, 0.265)

a. N represents the number of eyes treated.
Last observation carried forward to impute missing values within a visit.
Difference was calculated as mean of alcaftadine minus mean of vehicle; a negative difference favors alcaftadine.
Source: Analysis by the primary reviewer.

Table A.2: Comparison of Differences in Conjunctival Redness Scores at Visit 3 (Day 0) and Visit 4 (Day 14): (Intent-to-Treat Subjects Who Received Alcaftadine in One Eye and Vehicle in Contralateral Eye; Protocols 05-003-11 and 05-003-13)

Visit **Time Point**	**Protocol 05-003-11** (Vehicle N=42; Alcaftadine N=42)[a]	**Protocol 05-003-13** (Vehicle N=29; Alcaftadine N=29)[a]
Visit 3 (Day 0); **16-hr post study medication instillation**		
7 Min Post-CAC	-0.262 (-0.606, 0.082)	-0.125 (-0.605, 0.355)
15 Min Post-CAC	-0.191 (-0.564, 0.183)	-0.143 (-0.602, 0.317)
20 Min Post-CAC	-0.179 (-0.568, 0.210)	-0.089 (-0.540, 0.361)
Visit 4 (Day 14); **15-min post study medication instillation**		
7 Min Post-CAC	-0.705 (-1.086, -0.325)	-0.482 (-0.837, -0.127)
15 Min Post-CAC	-0.564 (-0.969, -0.160)	-0.232 (-0.606, 0.141)
20 Min Post-CAC	-0.436 (-0.862, -0.010)	-0.268 (-0.670, 0.135)

a. N represents the number of subjects treated.
Last observation carried forward to impute missing values within a visit.
Difference was calculated as mean of alcaftadine minus mean of vehicle; a negative difference favors alcaftadine.
Source: Analysis by the primary reviewer.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Dongliang Zhuang, PhD
Date: March 31, 2010

Statistical Team Leader: Yan Wang, PhD

cc:
HFD-520/Project Manager: Raphael Rodriguez
HFD-520/Medical Officer: Martin Nevitt, MD
HFD-520/Medical Team Leader: William Boyd, MD
HFD-725/Primary Statistical Reviewer: Dongliang Zhuang, PhD
HFD-725/Statistical Team Leader: Yan Wang, PhD
HFD-725/Biometrics Deputy Division Director: Daphne Lin, PhD
HFD-725/Biometrics Division Director: Mohammad Huque, PhD
HFD-700/Office of Biostatistics: Lillian Patrician

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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DONGLIANG ZHUANG
05/07/2010

YAN WANG
05/07/2010