CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214965Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	214965
Priority or standard	Standard
Submit date(s)	8/26/2020
Received date(s)	8/26/2020
PDUFA goal date	6/26/2021
Division/office	Division of Ophthalmology (DO)
Review completion date	6/23/2021
Established/proper name	Verkazia
(Proposed) proprietary name	cyclosporine ophthalmic emulsion, 0.1%
Pharmacologic class	calcineurin inhibitor
Code name	NOVA22007
Applicant	Santen Incorporated
Dosage form(s)/formulation(s)	ophthalmic emulsion
Dosing regimen	Instill 1 drop of Verkazia ophthalmic emulsion 4 times daily to each affected eye
Applicant proposed indication(s)/ population(s)	Treatment of (b) (4) vernal keratoconjunctivitis for children from 4 through 18 years of age
Proposed SNOMED indication	Vernal keratoconjunctivitis
Regulatory action	Approval
Approved dosage (if applicable)	Instill 1 drop of Verkazia ophthalmic emulsion 4 times daily to each affected eye
Approved indication(s)/ population(s) (if applicable)	Treatment of vernal keratoconjunctivitis in children and adults
Approved SNOMED term for indication (if applicable)	Vernal Keratoconjunctivitis (317349009)

Abbreviations: NDA, new drug application; PDUFA, Prescription Drug User Fee Act; SNOMED, systemized nomenclature of medicine; VKC, vernal keratoconjunctivitis

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Glossary

AE	adverse event
BID	twice daily
CFS	corneal fluorescein staining
CsA	cyclosporine A
D	day
EW	early withdrawal
F	filial generation
FDA	Food and Drug Administration
GLP	good laboratory practices
HD	high dose
IND	investigational new drug
LD	low dose
LLNA	local lymph node assay
LLOQ	lower limit of quantification
NDA	new drug application
NOVATIVE	Study NVG05L101
PSUR	periodic safety update report
QID	four times daily
ULOQ	upper limit of quantification
VEKTIS	Study NVG09B113
VKC	vernal keratoconjunctivitis

I. Executive Summary

1. Summary of Regulatory Action

This new drug application (NDA 214965) for Verkazia (cyclosporine ophthalmic emulsion) 0.1%, was submitted in accordance with Section 505(b)(2) of the Federal Food Drug and Cosmetic Act and 21 CFR 314.50 of the United States Code of Federal Regulations by Santen, Inc. for the treatment of vernal keratoconjunctivitis (VKC) in children and adults.

Orphan-drug designation of Verkazia (cyclosporine ophthalmic emulsion) 0.1% (Designation #07-2399) was granted on May 4, 2007, for the treatment of VKC. NDA 214965 was reviewed by a multidisciplinary team as a Standard Review and was not presented at an Advisory Committee.

The review disciplines (i.e., Clinical, Clinical Pharmacology, Pharmacology/Toxicology, Statistics, Chemistry/Manufacturing and Regulatory) did not identify any issues that preclude approval. I, the signatory authority, agree that the benefit-risk assessment favors approval.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Vernal keratoconjunctivitis (VKC) is an anterior segment eye disease, characterized by chronic ocular surface inflammation. • VKC age of onset is usually between 5 and 12 years, occurring before age 10 in 80% of patients. Boys are affected 2 to 4 times more frequently than girls. • VKC is an orphan disease with an estimated annual incidence in the United States of 0.30 to 0.40 per 10,000.	• The goal of treatment of VKC is the alleviation of the severe ocular signs and symptoms.
Current treatment options	• Cromolyn sodium ophthalmic solution and lodoxamide ophthalmic solution are currently approved in the United States for the alleviation of symptoms of VKC.	• Verkazia 0.1% dosed four times daily (QID) demonstrated safety and efficacy compared to placebo. Verkazia will provide practitioners with an additional treatment option.
Benefit	• VEKTIS (Study NVG09B113) demonstrated that Verkazia 0.1% dosed QID was superior to placebo through Month 4 in the change from baseline in corneal fluorescein staining (CFS) score and in itching in patients with VKC. • NOVATIVE (Study NVG05L101) demonstrated that Verkazia was superior to placebo at Month 1 in the change from baseline in CFS in patients with VKC. • In both trials, CFS was measured on a 0 to 5 scale (0: no stain, 5: more stain). For itching, NOVATIVE assessed itching with a 0 to 3 scale (0: no symptom, 3: severe symptom) and VEKTIS used a 0 to 100 visual analogue scale (0: no pain, 100: maximal pain). No statistically significant improvement in itching was observed compared to placebo in the NOVATIVE study. • Four administrative splits to evaluate the robustness of the VEKTIS study findings provided numerically supportive demonstrations of efficacy for CFS and itching. The administrative splits were conducted by region (European	• VEKTIS was an adequate and well-controlled study with appropriate endpoints and study duration which provides evidence of efficacy for the treatment of VKC. • Supportive demonstration of the efficacy for Verkazia was provided by the NOVATIVE study and the administrative split of the VEKTIS study. • Taken together, the VEKTIS and NOVATIVE studies demonstrate the efficacy of Verkazia 0.1% dosed QID for the treatment of VKC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Union versus rest of the world), latitude group (<39 versus ≥39), longitude group (<15 versus ≥15), and randomization order.	
Risk and risk management	• In the VEKTIS and NOVATIVE studies, Verkazia demonstrated a safety profile that was similar to the known safety profile for topically administered cyclosporine ophthalmic solution and emulsion. • Verkazia is marketed in Canada, Denmark, Austria, and the United Kingdom. Post-marketing data has not revealed any safety issues.	• Routine monitoring and reporting of all adverse events are expected to be adequate to monitor for potential new adverse reactions.

2.2. Conclusions Regarding Benefit-Risk

The data contained in this submission establishes the efficacy of Verkazia (cyclosporine ophthalmic emulsion) 0.1 % dosed four times daily (QID) in each affected eye for the treatment of VKC in children from age 4 and up and adults.

The benefit of Verkazia is based on improvement in corneal fluorescein staining score and in itching from 168 patients with VKC enrolled in Study NVG09B113 (VEKTIS) and from 118 patients with VKC enrolled in Study NVG05L101 (NOVATIVE). The VEKTIS Study demonstrated improvement in corneal fluorescein staining and itching in patients treated with Verkazia 0.1% compared to placebo. The NOVATIVE Study provided supportive efficacy information for this indication.

To date, no long-term consequences of cyclosporine ophthalmic emulsion administration have been identified. The most common ocular adverse event for cyclosporine ophthalmic emulsion was eye pain, eye pruritus, and ocular discomfort.

There is a favorable benefit-risk ratio of cyclosporine ophthalmic emulsion 0.1% in the treatment of vernal keratoconjunctivitis.

II. Interdisciplinary Assessment

3. Introduction

Verkazia is a topical, ocular formulation of cyclosporine A (CsA). CsA is a lipophilic cyclic polypeptide that has been approved as a calcineurin inhibitor immunosuppressant agent for the prevention of specific tissue graft rejections following organ/tissue transplantation. Cyclosporine (new drug application [NDA] 50573 Sandimmune) was originally approved in 1983 for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Following ocular administration, cyclosporine is thought to act by blocking the release of pro-inflammatory cytokines such as IL-2. The exact mechanism of action in the treatment of VKC is not known.

Santen Inc. (Applicant) seeks approval of Verkazia (cyclosporine ophthalmic emulsion) 0.1% for the treatment of vernal keratoconjunctivitis (VKC) in children and adults. Verkazia is currently marketed in Canada, Denmark, Austria, and the United Kingdom.

VKC is a potentially sight-threatening disease due to corneal damage. VKC is characterized by chronic ocular surface inflammation in children, typically in hot, arid environments. The age of onset is usually between 5 to 12 years of age. Eighty percent of cases occur in boys. VKC is an orphan disease with an average duration of 4 to 8 years and is estimated to have an annual incidence of 0.3 to 0.4 per 10,000 in the United States.

The Food and Drug Administration (FDA) has approved two drug products for the treatment of VKC.

- NDA 18-155, Opticrom (cromolyn sodium ophthalmic solution) 4% was approved for the treatment of VKC in 1984. While NDA 18-155 was withdrawn in 2014, multiple ANDAs for cromolyn sodium ophthalmic solution continue to be marketed. NDA 18-155 was not withdrawn for reasons of safety or efficacy.
- NDA 20-191, Alomide (lodoxamide tromethamine ophthalmic solution) 0.1% was approved in 1993 for the treatment of VKC and is currently marketed.

Santen has submitted the results from two adequate and well-controlled studies in support of the proposed indication.

- VEKTIS (Study NVG09B113) was a 12-month, multicenter, randomized, double-masked, placebo-controlled study consisting of two parts: a 4-month efficacy and safety evaluation period and an 8-month safety follow-up period. Two dosing regimens of Verkazia 0.1% were administered, twice daily (BID, low dose [LD]) and QID (high dose [HD]), in pediatric patients with VKC.
- NOVATIVE (Study NVG05L101) was a 4-month, multicenter, randomized, double-masked, placebo-controlled study consisting of two parts: a 1-month efficacy and safety evaluation period and a 3-month safety follow-up period. Verkazia, 0.5% and 1%, was administered QID in pediatric patients with VKC.

3.1. Review Issue List

The review team identified the key review issues listed in Section 3.1.1 below relevant to the evaluation of benefit. No key review issues relevant to the evaluation of risk were identified. In depth assessment of these benefit can be found in Section 6.3.

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

- Primary endpoint definition
- Handling Post-Rescue data
- Handling missing data for patients discontinued due to lack of efficacy

3.1.2. Key Review Issues Relevant to Evaluation of Risk

Not applicable.

3.2. Approach to the Review

Table 3 provides an overview of the two clinical trials conducted to support the benefit-risk assessment of Verkazia.

In addition, Verkazia is currently marketed outside the United States. Periodic safety update report (PSUR) #10 was submitted with the original NDA submission. On December 17, 2020, Santen submitted the periodic safety update report (PSUR) #11 (covering March 20, 2020 to September 19, 2020) and a summary statement in lieu of the 120-day Safety Update Report. No new information was identified and there was no alteration of the safety profile.

Table 3. Clinical Trials Submitted[1] in Support of Efficacy and Safety Determinations

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Patients Randomized	Number of Trial Sites
VEKTIS NVG09B113	Patients with VKC	Control Type: Placebo concurrent Randomization: standardized randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug (established name): Verkazia Dose: 0.1% QID or 0.1%, BID Number treated: 169 Duration (quantity and units): 4 months efficacy evaluation period plus 8 months safety follow-up period	Planned Primary[2]: Composite efficacy score Secondary: Use of rescue medication, keratitis assessment, 100 mm VAS, responder, objective signs, questionnaire, Investigator global assessment, and artificial tear use.	Planned: 179 Actual: 169	Centers: 51 Countries: 11
NOVATIVE NVG05L101	Patients with VKC	Control Type: Placebo concurrent Randomization: standardized randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug (established name): Verkazia Dose: 0.1% QID or 0.05%, QID Number treated: 118 Duration (quantity and units): 1 month plus 3 months follow-up	Planned Primary[2]: Rating of subjective symptoms Secondary: Rating of subjective symptoms, rating of objective symptoms, corneal fluorescein staining, oculo-palpebral examination, global response to treatment, and tear substitute installation	Planned: 118 Actual: 118	Centers: 18 Countries: 6

Source: Clinical Study Report and adsl.xpt
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.
[2]Agency did not agree with Planned Primary Endpoint. Agency considered corneal staining and itching to be relevant endpoints for evaluating efficacy.
Abbreviations: BID, twice daily; QID, four times daily; VAS, visual analogue scale; VKC, vernal keratoconjunctivitis

4. Patient Experience Data

For the VEKTIS and NOVATIVE studies, the primary efficacy outcome measures analyzed were corneal fluorescein staining score, a clinician-reported outcome, and itching score, a patient-reported outcome.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		**(Section 6 – Study Endpoints)**
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Recommendations

This NDA is recommended for approval from a Clinical Pharmacology perspective. The systemic concentrations of cyclosporine following BID or QID topical administration of CsA ophthalmic emulsion 0.1% in humans were either not detectable (below the lower limit of quantification [LLOQ] of 0.1 ng/mL) or above the LLOQ with the maximum blood level observed not greater than 0.67 ng/mL.

Summary and Review

The dosing regimen in the VEKTIS was one drop of CsA ophthalmic emulsion, 0.1%, BID or QID (morning, noon, afternoon, and evening) to each affected eye. Blood samples were collected

for detection of CsA in 166 patients (55 patients who were in the QID group, 53 in the BID group, and 58 in the vehicle group). Blood samples were collected at Baseline (Day 0), Month 2 (Week 8 ± 3 days), Month 4 (Week 16 ± 3 days/early discontinuation), and Month 12 (Week 48 ± 14 days/early discontinuation) visits. A 4 mL sample of whole blood was collected from patients at these visits.

During the 4-month randomized period, the highest proportion of patients with quantifiable CsA amounts was 14 patients (28%) in the QID group at Month 4/early termination, and 6 patients (13.3%) in the BID group at Month 2. The maximum concentration of CsA in the blood was 0.670 ng/mL in the QID group and 0.336 ng/mL in the BID group. No CsA was detected in the blood of patients on placebo. At Month 12/early termination, quantifiable amounts were reported for 12 patients (17.6%) in the QID total group and 5 patients (8.2%) in the BID total group. The maximum blood levels of CsA after the 4-month randomized period were 0.291 ng/mL in the QID group and 0.180 ng/mL in the BID group.

Reviewer's comment:
***Blood concentrations of cyclosporine after BID or QID topical administration of CsA ophthalmic emulsion, 0.1%, in humans were either not detectable (below the LLOQ of 0.1 ng/mL) or slightly above the LLOQ in a small proportion of patients post-treatment. The maximum blood level observed for CsA was not greater than 0.67 ng/mL following administration of 1 drop of CsA ophthalmic emulsion, 0.1%, QID. This value is about 1000-fold lower than the maximum plasma concentration of cyclosporine (655 to 1802 ng/mL) after oral administration of Neoral as per Neoral USPI, 2015 and this supports the establishment of a pharmacokinetic bridge between these two products from a clinical pharmacology safety perspective. In addition, the information provided by the Applicant in Table 5 (safety margin for bilateral QID instillations of CsA ophthalmic emulsion, 0.1%, when compared to systemic doses of CsA used to prevent graft rejections in renal transplant pediatric patients: total daily dose 8.26 mg/kg and the trough level 115 to 120 ng/mL) further provides support of the* systemic safety assessment for CsA ophthalmic emulsion, 0.1% (Wigger et al. 2003).**

Table 5. Safety Margin Calculation for Bilateral QID Instillations of CsA Ophthalmic Emulsion, 0.1%

	VKC	Graft rejection	Safety margin
Daily dose (mg/kg)[a,b]	(b) (4) (mg/kg)	8.26 (mg/kg)[c]	> (b) (4) fold
CsA level (ng/mL)	0.670 ng/mL and below[d] (when detectable & quantifiable)	~115-120 (ng/mL)[c]	>172 fold

(b) (4)

Source: NDA 214965, Module 2.5, Page 39
Abbreviations: CsA, cyclosporine A; QID, four times daily, VKC, vernal keratoconjunctivitis

Bioanalytical

Cyclosporine was quantified in blood using a validated liquid chromatography tandem mass spectrometry method. The LLOQ and ULOQ for blood CsA were 0.1 ng/mL and 5 ng/mL,

respectively. Review summary of the information from the submitted bioanalytical information is provided in Table 6.

Table 6. Summary of the Bioanalytical Method

	Yes/No
Validation report provided	☒ Yes ☐ No
Validation report acceptable	☒ Yes ☐ No
Quality control samples range acceptable	☒ Yes ☐ No
Samples analyzed within the established stability period	☒ Yes ☐ No
Sample chromatograms provided	☒ Yes ☐ No
Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
Overall performance acceptable	☒ Yes ☐ No

5.1. Nonclinical Assessment of Potential Effectiveness

No nonclinical pharmacology studies were included in this NDA.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

The Applicant's proposed dose, 0.1%, dosed QID in the affected eye(s), was evaluated in both the VEKTIS and NOVATIVE trials. This proposed dose is acceptable for approval.

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial Design

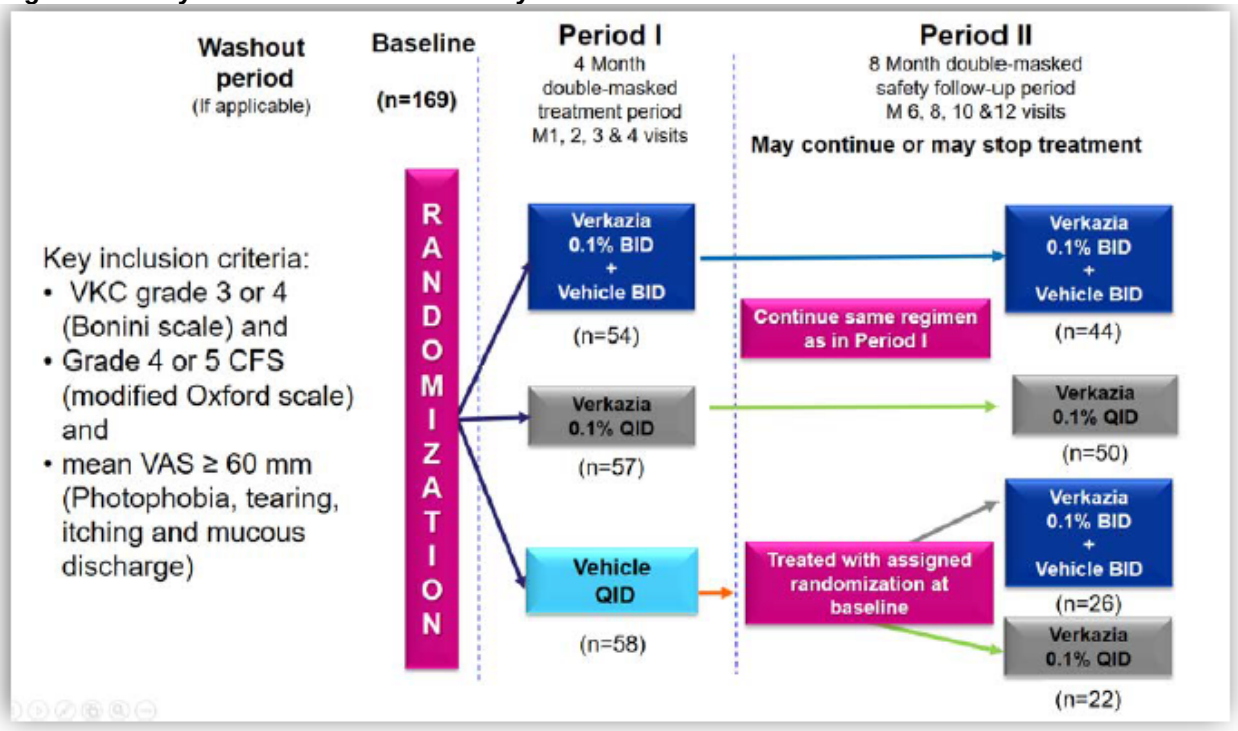
Support for the clinical benefit of Verkazia for the treatment of VKC in children and adults was based on data from a Phase 3 study (VEKTIS) and a supporting Phase 2/3 dose ranging study (NOVATIVE).

VEKTIS was a 12-month, multicenter, randomized, double-masked, placebo-controlled study. The study duration was divided in two parts: a 4-month efficacy and safety evaluation period and an 8-month safety follow-up period. The first 4-month period was a randomized, double-masked study treatment period designed as a superiority trial in which a total of 169 children and adolescents with VKC were randomized in a 1:1:1 ratio from 11 countries (Croatia, France, Germany, Greece, Hungary, India, Israel, Italy, Portugal, Spain, and the United States) and received the following treatments:

- Verkazia 1 mg administered one drop QID (in the morning, at noon, in the afternoon, and evening) (N=56), or
- Verkazia 1 mg administered one drop BID (in the morning and evening and placebo BID for matching at noon and in the afternoon) (N=56), or
- Placebo administered one drop QID (in the morning, at noon, in the afternoon, and evening) (N=57)

During the 8-month safety follow-up period, all patients received one of the two active dosing regimens. Patients enrolled in the VKC season and randomized to the placebo group were allowed to switch to one of the Verkazia study arms in a 1:1 ratio and received treatment up to the end of the VKC season or to the end of the follow-up period, whichever occurred first. The VEKTIS study was initiated on April 29, 2013, and completed on February 1, 2016 (Figure 1).

Figure 1. Study Schema for VEKTIS Study



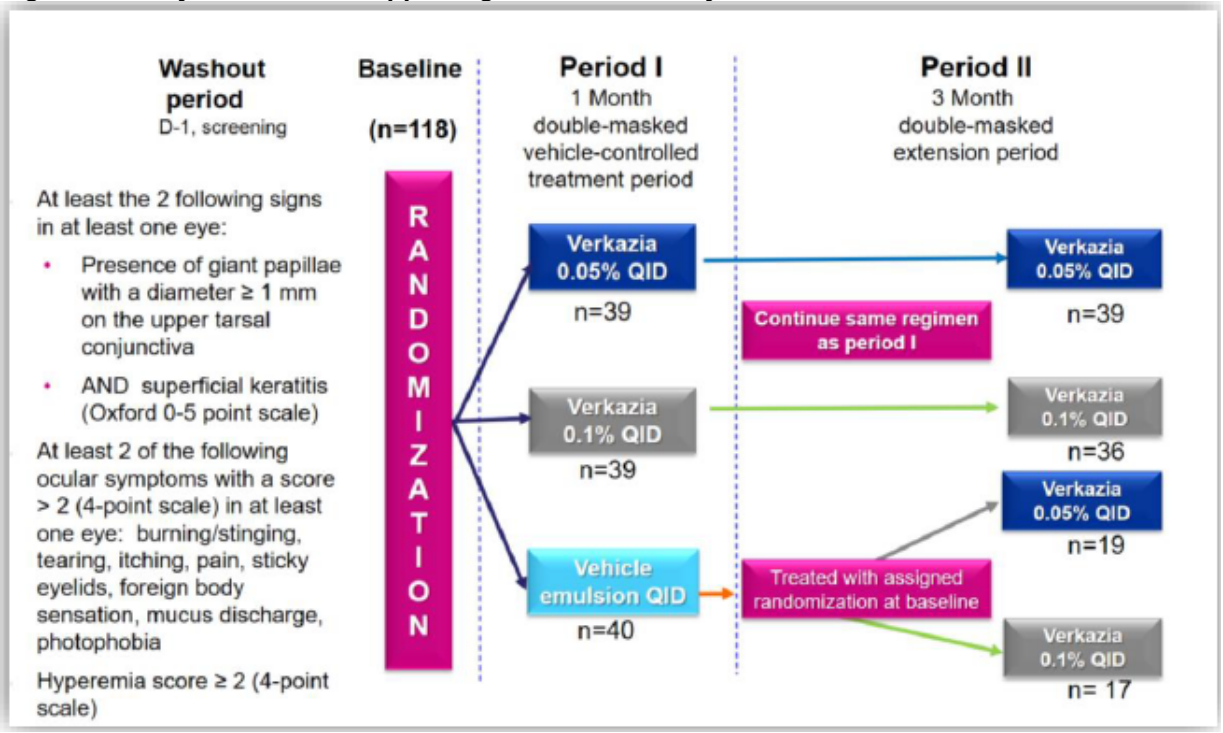
Source: Section 4.3 of Applicant's Clinical Overview Document
Abbreviations: BID, twice daily; QID, four times daily; VAS, visual analogue scale; VKC, vernal keratoconjunctivitis

NOVATIVE was a 4-month, multicenter, randomized, double-masked, placebo-controlled study. The study duration was divided in two parts: a 1-month efficacy and safety evaluation period and a 3-month safety follow-up period. In the first month of the study, a total of 118 patients with VKC were randomized in a 1:1:1 ratio from six countries (France, Italy, Israel, Morocco, Spain, and Turkey) and received:

- Verkazia 0.5 mg/mL administered one drop QID (N=39), or
- Verkazia 1 mg/mL administered one drop QID (N=39), or
- Placebo QID (N=40)

During the 3-month safety follow-up period, all patients received one of the two active dosing regimens; patients randomized to the vehicle group switched to a Verkazia study arm in a 1:1 ratio. The NOVATIVE study was initiated on May 19, 2006 and completed on February 22, 2007 (Figure 2).

Figure 2. Study Schema for Supporting NOVATIVE Study



Source: Section 4.3 of Applicant's Clinical Overview Document
Abbreviations: D, day; n, number of patients; QID, four times daily

In the VEKTIS study, patients had scheduled visits at Months 1, 2, 3, and 4 through the first 4-month treatment period and at Months 6, 8, 10, and 12 during the safety follow-up period. Similarly, patients in the NOVATIVE study had scheduled visits at Days 7, 14, and 28 during the first 1-month treatment period and at Months 2 and 4 during the safety follow-up period.

In both studies, treatment efficacy (primary and key secondary endpoints) was assessed during the efficacy evaluation period (through Month 4 in VEKTIS and through Month 1 in NOVATIVE).

Efficacy assessment in both studies was based on improvement in the key sign and symptom variables of VKC from baseline. The key sign variable was based on improvement in corneal keratitis as measured by the modified Oxford Corneal Fluorescein Staining (CFS) 5-point scale (0 [no stain], 0.5, and 1 to 5 [more stain]) at each visit during the 4-month efficacy evaluation period (hereafter referred to as CFS score). A grade of 0 represents complete corneal clearing, and a negative change from baseline indicates an improvement in the CFS score. The key symptom variables were based on improvement in itching, photophobia, tearing, and mucous discharge score each measured using a Visual Analogue Scale (0 [no pain] to 100 [maximal pain]) through Month 4. A decrease in the Visual Analogue Scale score from baseline indicates an improvement.

The protocol-defined primary efficacy endpoint for the sign of VKC in the VEKTIS study was penalty-adjusted change in CFS score (for corneal keratitis) from each month (Month 1 to Month 4) to baseline averaged over the four-month visits. Penalty adjustment was made for receipt of rescue therapy and/or occurrence of corneal ulceration during the 4-month efficacy evaluation period. Patients whose keratitis worsened by ≥1-grade or was maintained for 2 months and/or

whose symptoms worsened by ≥1 centimeter on at least 1 of the 4 symptoms were allowed rescue therapy using Dexamethasone 0.1% 1 drop QID for 5 days for a maximum of 2 courses between 2 scheduled visits during the 4-month treatment period and a maximum of 4 courses between 2 scheduled visits during the follow-up period.

The change in CFS score from baseline, the use of rescue medication, and occurrence of ulcer at each monthly visit during the 4-month efficacy evaluation period were defined as secondary efficacy endpoints. The change in the symptom variables of itching, photophobia, tearing, and mucous discharge from baseline at each visit through Month 4 were additional secondary symptom endpoints in the VEKTIS study. Additionally, presence of the related signs of VKC such as hyperemia, conjunctival discharge, papillae, and limbal infiltrates were assessed at each visit as additional secondary sign efficacy variables.

A responder analysis, defined as the mean CFS score of the last 3 months of treatment ≤50% of baseline who did not (i) withdraw from the study (for a reason possibly due to treatment), (ii) experience an ulceration, and (iii) use rescue medication in the last 3 months of treatment in the 4-month randomized period was also defined as an additional secondary endpoint. A more stringent responder analysis defined as the proportion of patients with corneal clearing at Month 4 or early withdrawal (EW) who had not experienced a corneal ulceration or had not used rescue medication in the last 3 months of treatment was also performed.

For the VEKTIS study, the Applicant discussed the selection of the primary and secondary endpoints with the Agency in a Type B meeting held on December 18, 2018. During the meeting, the Agency recommended that treatment efficacy of Verkazia for the intended indication be assessed using a subjective evaluation of ocular itching by the patient and an objective evaluation of staining by the examining physician. The Agency disagreed with the penalty-adjusted assessment of the CFS score for corneal keratitis because the applied penalties for rescue medication use were arbitrary. The effect of rescue medication and the timing may have affected the score significantly more or less than the penalty assigned. Accordingly, the Agency suggested that nonpenalized CFS scores as a sign and itching as a symptom should be assessed, without averaging the scores over several months to be able to determine the onset of action and the duration of effect of the product.

Thus, per the Agency's recommendation, the primary sign and symptom endpoints for the efficacy evaluation of Verkazia for the treatment of VKC in this review are based on:

- The change in CFS score from baseline at each visit through Month 4 for sign and
- The change in the ocular itching from baseline at each visit for symptom.

The change in CFS score and itching score from baseline at Month 1 in the NOVATIVE study were assessed as supporting evidence. It should be noted that no rescue medication was administered during the conduct of the NOVATIVE study.

6.2.2. Statistical Analysis Plan

Primary Efficacy Analysis

The Applicant's primary efficacy analysis in the VEKTIS study was an evaluation of superiority of each dose of Verkazia to placebo in the primary sign efficacy variable of penalty-adjusted change in CFS score from each month (Month 1 to Month 4) to baseline averaged over the

four-month visits. The change in itching score from baseline at each month was assessed similarly, without averaging.

Superiority was assessed using an analysis of covariance model with treatment as a fixed factor, and baseline score and the proportion of time potentially spent in taking study medication during the VKC season as covariates in the model. The primary analysis was based on the full analysis set including all randomized patients who received at least one dose of study medication.

Based on the Agency's recommendation in the meeting held on December 18, 2018, in this review, the treatment efficacy of Verkazia compared to placebo is assessed using nonpenalized CFS score for sign and itching score for symptom at each month (without averaging the scores over several months) using the analysis of covariance model. The Agency recommended the use of nonpenalized scores due to the arbitrary nature of the penalty score and the analyses at each month without averaging over several months to be able to determine the onset of action and the duration of effect of the product.

The change in CFS and itching scores in the NOVATIVE study were analyzed similarly using an analysis of covariance model with treatment as a fixed factor and baseline score as a covariate. The data for the proportion of time potentially spent in taking study medication during the VKC season was not collected in the NOVATIVE study.

The efficacy assessment of the CFS score in the VEKTIS study was based on the worst eligible eye defined as the eye with the highest corneal staining score at baseline; in cases where both eyes had the same level of corneal staining, the right eye was used. The efficacy assessment of the symptom variables was based on both eyes.

Type I Error Control (Plan for Multiplicity Adjustment)

For the superiority testing of each dose of Verkazia to placebo in the primary sign of CFS score, the Applicant used Hochberg's multiple comparison procedure for the Type I error control. In this procedure, the largest p-value is first compared to 0.05 and if this p-value is < 0.05 then both doses will be considered superior to placebo. However, if the largest p-value is > 0.05, and the smallest one is < 0.025, then the dose with $p<0.025$ will be considered superior to placebo. The same procedure was used for testing the superiority of each dose of Verkazia to placebo in the symptom of itching at each month. However, no multiplicity correction was made for the superiority testing of both the CFS score and itching score and for testing each of the scores at each study visit. Therefore, p-values and confidence intervals presented for testing the itching score at each month are intended for descriptive use only.

Handling of Missing Data (Primary Method and Sensitivity Analyses)

For patients who prematurely withdrew from the study during the 4-month efficacy period, the Applicant imputed missing data using the worst observation for patients who dropped out due to lack of efficacy, using the last observation carried forward for patients who dropped out due to lack of safety or lack of tolerance, using the best observation for patients who dropped out due to symptom relief (no subject dropout due to this reason), and using the average of all available data for patients who dropped out due to other reasons. The Applicant did not provide specific reason for the different imputation approach used for the different reasons of discontinuation. In the absence of a specific reason, the Agency considers imputing all post-discontinuation data using the last value observed prior to discontinuation to be reasonable. See Table 7 for the

summary of the reasons for premature withdrawal from the VEKTIS study. Similar missing data handling approach is adopted in the NOVATIVE study.

Handling of Post–Rescue Data in VEKTIS Study

In the efficacy analyses of the CFS and itching scores at each month, the Applicant used all observed data regardless of rescue (including data collected at unscheduled visits) in the analysis (a treatment policy estimand strategy). However, considering the disease condition, the Agency's preference is to assess the treatment effect of Verkazia excluding the impact of rescue medication on the efficacy results. Thus, in the Agency's primary efficacy analyses, all Post-Rescue data are censored and imputed by the last available data observed prior to rescue initiation (a while on treatment estimand strategy). Additionally, data collected at unscheduled visits are excluded in the Agency's efficacy analyses to minimize any potential bias on the treatment effect because most of the data collected at an unscheduled visit were outside the predefined analyses windows.

To assess the robustness of imputing Post-Rescue data with the last available data observed prior to rescue use, the Agency performed the following supporting analyses: (i) impute all Post-Rescue data by baseline data, (ii) use all data regardless of rescue in the analysis by excluding data collected at unscheduled visits, and (iii) impute all Post-Rescue data using control-based multiple imputation for patients who received rescue. See Table 44 and Table 45 for the supporting efficacy analyses results.

6.2.3. Results of Analyses

This section summarizes the subject disposition, baseline demographics, and the main and supporting efficacy analyses results to support the efficacy of Verkazia for the sign and symptom of VKC in the VEKTIS study. Similar analyses results for the supporting NOVATIVE study are presented and discussed in Section 6.2.3.4.

6.2.3.1. Disposition and Baseline Demographics

Subject disposition information for patients in the VEKTIS study is presented in Table 7. A total of 169 patients were randomized in this study (57 patients in the QID, 55 patients in the BID, and 57 patients in placebo). Of which, 26 patients (15%) discontinued from the study early (9 in Placebo, 6 in the QID, and 11 in the BID) and the discontinuation rate in the QID group (11%) was relatively lower compared to in the BID (20%) and placebo (16%) groups. Five patients (9%) in each of the BID and placebo groups discontinued the study due to lack of efficacy compared to only one subject in the QID group (about 2%).

A total of 66 patients (39%) in the VEKTIS study received at least one rescue medication during the 4-month efficacy evaluation period (31 in placebo, 18 in the QID, and 17 in the BID). That is, more than half of the patients in the placebo group (54%) and about a third of the patients in each of the Verkazia groups had received at least one rescue medication during the 4-month efficacy evaluation period.

Of the 66 patients who received rescue, 50 patients completed the study and 16 patients discontinued early from the study after rescue therapy; 10 of the 16 patients (4 in placebo, 1 in the QID, and 5 in the BID) discontinued due to lack of efficacy after receiving rescue and the other 6 discontinued due to other reasons.

Table 7. Subject Disposition in the VEKTIS Study

Subject Disposition	Placebo	QID[1]	BID[2]	Total
Randomized	57	57	55	169
Full analysis set	58	56	54	168
Per protocol set	55	52	52	159
Safety set	58	57	54	169
Received at least 1 rescue medication	31 (54.4)	18 (31.6)	17 (30.9)	66 (39.1)
1	14	6	11	31
2	5	6	2	13
≥ 3	12	6	4	22
Completers	48 (84.2)	51 (89.5)	44 (80.0)	143 (84.6)
Without rescue	24	36	33	93
With rescue	25	14	11	50
Discontinued	9 (15.8)	6 (10.5)	11 (20.0)	26 (15.4)
Without rescue	3	2	4	9
With rescue	6	4	6	16
Primary reason				
Lack of efficacy	5 (8.8)	1 (1.8)	5 (9.1)	11 (6.5)
Without rescue	1	0	0	1
With rescue	4	1	5	10
Adverse event	2 (3.5)	2 (3.5)	0	4 (2.4)
Lost to follow-up	0	0	1 (1.8)	1 (0.1)
Patient decision no related to AE	2 (3.5)	2 (3.5)	3 (5.5)	7 (4.1)
Investigator decision	0	1 (1.8)	1 (1.8)	2 (1.2)
Other	0	0	1 (1.8)	1 (0.1)

Source: Review team analysis based on ADSL.xpt dataset located at \\CDSESUB1\evsprod\NDA214965\0001\m5\datasets\nvg09b113\analysis\adam\datasets\
Percentages are based on randomized patients.
Note: (i) Subject (b) (6) randomized to 1 mg/mL QID group actually received placebo during the study and this subject was included in the placebo group in the full and safety analysis set, (ii) Subject (b) (6) randomized and actually received 1 mg/mL BID also received 1 mg/mL QID during Month 4. This subject was analyzed with 1 mg/mL QID group in the safety analysis set and in the 1 mg/mL BID group in the full analysis set, and (iii) Subject (b) (6) was excluded from the full analysis set because the subject did not comply with inclusion criterion 6.
[1] high dose of Verkazia - Verkazia 1.0 mg/mL QID
[2] low dose of Verkazia -Verkazia 1.0 mg/mL BID
Abbreviations: AE, adverse event; BID, twice daily; QID, four times daily

Patient demographic information is presented in Table 8 for patients in the VEKTIS and NOVATIVE studies.

As shown, most patients in the VEKTIS study were male (76%) and Caucasian (71%). The average age of patients was about 9 years of age (range: 4 to 17 years) where most of the patients were 4 to 11 years of age (76%). Slightly more than 50% of the patients in the VEKTIS study had seasonal VKC and most patents had used prior VKC treatment. More than 90% of patients in the BID and placebo groups had baseline CFS score of 4 and less than 10% had a score of 5 whereas 75% of patients in the QID group had baseline CFS score of 4 and about 25% had a score of 5. Overall, the demographic and baseline characteristics in the VEKTIS study were well balanced between the treatment groups. See Section 6.2.3.4 for discussion regarding the supporting NOVATIVE study.

Table 8. Baseline Demographic and Clinical Characteristics in the VEKTIS and NOVATIVE Studies (Full Analysis Set)

	NOVATIVE			VEKTIS		
Demographic	**Placebo (N=40)**	**1 mg/mL QID[1] (N=39)**	**0.5 mg/mL QID[2] (N=39)**	**Placebo (N=58)**	**1 mg/mL QID[1] (N=56)**	**1 mg/mL BID[2] (N=54)**
Age (years)						
Mean (SD)	8.5 (2.4)	9.4 (3.7)	8.5 (2.9)	8.9 (3.2)	9.1 (3.3)	9.6 (3.4)
Median	8.0	9.0	8.0	8.0	9.0	9.0
Range	4-21	4-21	4-15	4-17	4-17	4-17
Age group (n, %)						
4-11 years	33 (82.5)	29 (74.4)	33 (84.6)	46 (79.3)	43 (76.8)	38 (70.4)
11-<18 years	7 (17.5)	9 (23.1)	6 (15.4)	12 (20.7)	13 (23.2)	16 (29.6)
Sex (n, %)						
Male	29 (72.5)	33 (84.6)	34 (87.2)	46 (79.3)	44 (78.6)	42 (77.8)
Female	11 (27.5)	6 (15.4)	5 (12.8)	12 (20.7)	12 (21.4)	12 (22.2)
Race (n, %)						
Caucasian				41 (70.7)	40 (71.4)	38 (70.4)
Black		Data not collected		2 (3.4)	3 (5.4)	5 (9.3)
Asian				13 (22.4)	11 (19.6)	11 (20.4)
Other				2 (3.4)	2 (3.6)	0
Time since VKC diagnosis						
Mean (SD)	3.6 (2.2)	4.3 (2.8)	3.4 (1.9)	3.1 (2.6)	3.5 (2.5)	3.6 (2.8)
Median	3.2	4.2	3.3	2.2	3.0	2.9
Range	0.3-10.6	0-9.7	0.4-7.3	0.3-11.5	0-12.1	0-11.4
Form of VKC (n, %)						
Limbal	-	-	-	7 (12.1)	8 (14.3)	2 (3.7)
Tarsal	16 (40.0)	8 (20.5)	7 (17.9)	13 (22.4)	15 (26.8)	13 (24.1)
Limbal and tarsal	24 (60.0)	31 (79.5)	32 (82.1)	38 (65.5)	33 (58.9)	39 (72.2)
Use of prior VKC treatment (n, %)						
Yes	36 (90.0)	37 (94.9)	39 (100.0)	45 (77.6)	42 (75.0)	46 (85.2)
No	4 (10.0)	2 (5.1)	-	13 (22.4)	14 (25.0)	8 (14.8)
Corneal staining (CFS) (n; %)						
Grade 4	9 (22.5)	11 (28.2)	11 (28.2)	54 (93.1)	42 (75.0)	49 (90.7)
Grade 5	6 (15.0)	3 (7.7)	5 (12.8)	4 (6.9)	14 (25.0)	5 (9.3)
Symptom (itching score)[3]						
Mean (SD)	2.8 (0.58)	2.6 (0.59)	2.6 (0.75)	78.4 (16.3)	78.0 (18.2)	80.2 (14.8)
Median	3	3	3	80	80	80
Range	0-3	1-3	0-3	26-100	10-100	37-100
Region						
EU[4]	15	15	15	35	33	32
ROW[5]	25	24	24	23	23	22

Source: Based on review team analysis and Table 7 of Applicant's Summary of Clinical Efficacy (Module 2.7.3).
[1] High Dose of Verkazia - Verkazia 1.0 mg/mL QID in both studies
[2] Low dose of Verkazia -Verkazia 1.0 mg/mL BID in VEKTIS and Verkazia 0.5 mg/mL QID in NOVATIVE
[3] Measured in a 0 to 3 scale: 0 (absent – no symptom), 1 (mild), 2 (moderate), and 3 (severe symptom) in NOVATIVE study and in a 0 (no symptom) – 100 (maximal symptom) visual analogue scale in the VEKTIS study
[4] Includes France (N=26), Italy (N=10), and Spain (N=9) in the NOVATIVE study and Croatia (N=2), France (N=17), Germany (N=1), Greece (N=5), Hungary (N=12), Italy (N=19), Portugal (N=7), and Spain (N=37) in the VEKTIS study.
[5] Includes Israel (N=51), Morocco (N=29), and Turkey (N=2) in the NOVATIVE study and India (N=34), Israel (N=22), and the United States of America (N=12) in the VEKTIS study
Abbreviations: BID, twice daily; CFS, corneal fluorescein staining; EU, European Union; HD, high dose; LD, lose dose; N, number of patients in treatment group; n, number of patients with given characteristic; QID, four times daily; ROW, rest of the world; SD, standard deviation; VKC, vernal keratoconjunctivitis

6.2.3.2. Primary and Key Secondary Efficacy Results

Table 9 and Table 10 summarize the main efficacy analysis results for the clinical sign of CFS score and for the subjective symptom of itching through the 4-month efficacy evaluation period in the VEKTIS study.

Table 9. Efficacy Results of the Mean Change (SD) in CFS Score From Baseline at Each Visit (Full Analysis Set)

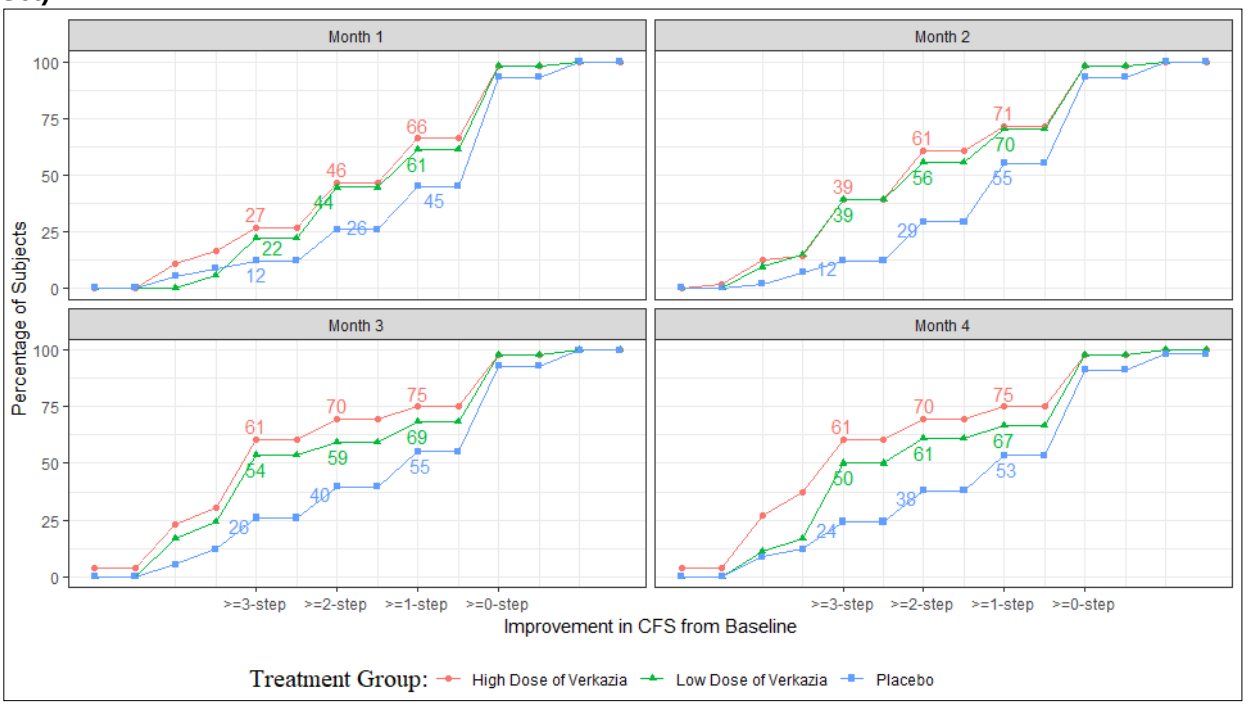
				Treatment Comparison[1]			
				QID[2] vs. Placebo		BID[3] vs. Placebo	
Visit	Placebo (N = 58)	QID[2] (N = 56)	BID[3] (N = 54)	Difference (95% CI)	p-value[4]	Difference (95% CI)	p-value[4]
Baseline	4.1 (0.26)	4.3 (0.44)	4.1 (0.29)	--	--	--	--
Month 1	-0.8 (1.31)	-1.4 (1.42)	-1.3 (1.28)	-0.7 (-1.2, -0.2)	0.0219	-0.5 (-1.0, 0.0)	0.0506
Month 2	-0.9 (1.24)	-1.8 (1.47)	-1.8 (1.46)	-0.9 (-1.4, -0.4)	0.0012	-0.9 (-1.4, -0.4)	0.0012
Month 3	-1.2 (1.48)	-2.3 (1.64)	-2.0 (1.62)	-1.1 (-1.7, -0.5)	0.0007	-0.9 (-1.5, -0.3)	0.0044
Month 4	-1.2 (1.50)	-2.3 (1.68)	-1.9 (1.56)	-1.1 (-1.7, -0.5)	0.0005	-0.7 (-1.3, -0.1)	0.0146

Source: Reviewer team analysis based on ADEFF.xpt dataset located at \\CDSESUB1\evsprod\NDA214965\0001\m5\datasets\nvg09b113\analysis\adam\datasets
Note: For patients who received rescue therapy during the study, all post-rescue data were imputed by the last available data observed prior to rescue initiation
[1] Based on ANCOVA model including baseline CFS score and the proportion of time potentially spent in taking study medication during the VKC season as covariate.
[2] High Dose of Verkazia - Verkazia 1.0 mg/mL QID.
[3] Low dose of Verkazia -Verkazia 1.0 mg/mL BID
[4] Adjusted for multiplicity using Hochberg's multiple comparison procedure.
Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; CFS, corneal fluorescein staining; CI, confidence interval; HD, high dose; LD, low dose; QID, four times daily; SD, standard deviation

As shown in Table 9, the average baseline CFS score across the treatment groups is well balanced, approximately 4 units. However, patients in the two doses of Verkazia (QID and BID) demonstrated a statistically superior improvement in the CFS score from baseline at each month through the 4-month efficacy evaluation period compared to patients in the placebo group. For example, the improvement in CFS score from baseline at each month through the 4-month period was higher, by 0.7 to 1.1 units in the QID group and by 0.5 to 0.9 units in the BID group, than in the placebo group. The Verkazia QID clearly provided a numerically better improvement in the CFS score at each month than Verkazia BID.

Additionally, through Month 4, more patients who received either of the two doses of Verkazia displayed greater improvement in CFS from baseline than patients in the placebo group. Figure 3 below shows the rate of improvement in CFS at each month. For example, at Month 4, about 70% (or 61%) and 61% (or 50%) of patients in the QID and BID groups, respectively, showed at least 2-step (or 3-step) improvement in CFS score from baseline compared to 38% (or 24%) of patients in the Placebo group.

Figure 3. Cumulative Distribution of the Change in CFS From Baseline at Each Visit (Full Analysis Set)



Source: Review team analysis based on ADEFF.xpt dataset
Note: For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last available data observed prior to rescue initiation.
Abbreviations: CFS, corneal fluorescein staining

Similarly, as shown in Table 10, Verkazia-treated eyes also displayed a statistically significant improvement in the clinical symptom of itching at each month through the 4-month efficacy evaluation period compared to placebo-treated eyes. For example, the improvement in the itching score from baseline at each month through the 4-month period was higher by 16 to 19 units in the QID group and by 6 to 14 units in the BID group than in the placebo group. The Verkazia QID clearly displayed a numerically better improvement in itching score at each month than the Verkazia BID.

Table 10. Efficacy Results of the Mean Change in Itching Score (SD) From Baseline at Each Visit (Full Analysis Set)

				Treatment Comparison[1]			
				QID[2] vs. Placebo		BID[3] vs. Placebo	
Visit	Placebo (N = 58)	QID[2] (N = 56)	BID[3] (N = 54)	Difference (95% CI)	p-value[4]	Difference (95% CI)	p-value[4]
Baseline	78.4 (16.26)	78.0 (18.16)	80.1 (14.81)	--	--	--	--
Month 1	-18.3 (21.16)	-33.8 (32.08)	-24.4 (29.60)	-15.7 (-25.8, -5.6)	0.0052	-6.1 (-16.5, 4.2)	0.2436
Month 2	-18.6 (23.03)	-36.0 (35.52)	-29.1 (27.57)	-17.7 (-28.3, -7.1)	0.0023	-10.7 (-21.5, 0.2)	0.0537
Month 3	-21.6 (25.11)	-39.8 (34.85)	-35.4 (31.99)	-18.4 (-29.7, -7.1)	0.0031	-14.2 (-25.7, -2.6)	0.0163
Month 4	-25.4 (26.63)	-44.1 (38.13)	-35.8 (34.89)	-18.9 (-31.1, -6.7)	0.0053	-10.5 (-23.0, 2.0)	0.1000

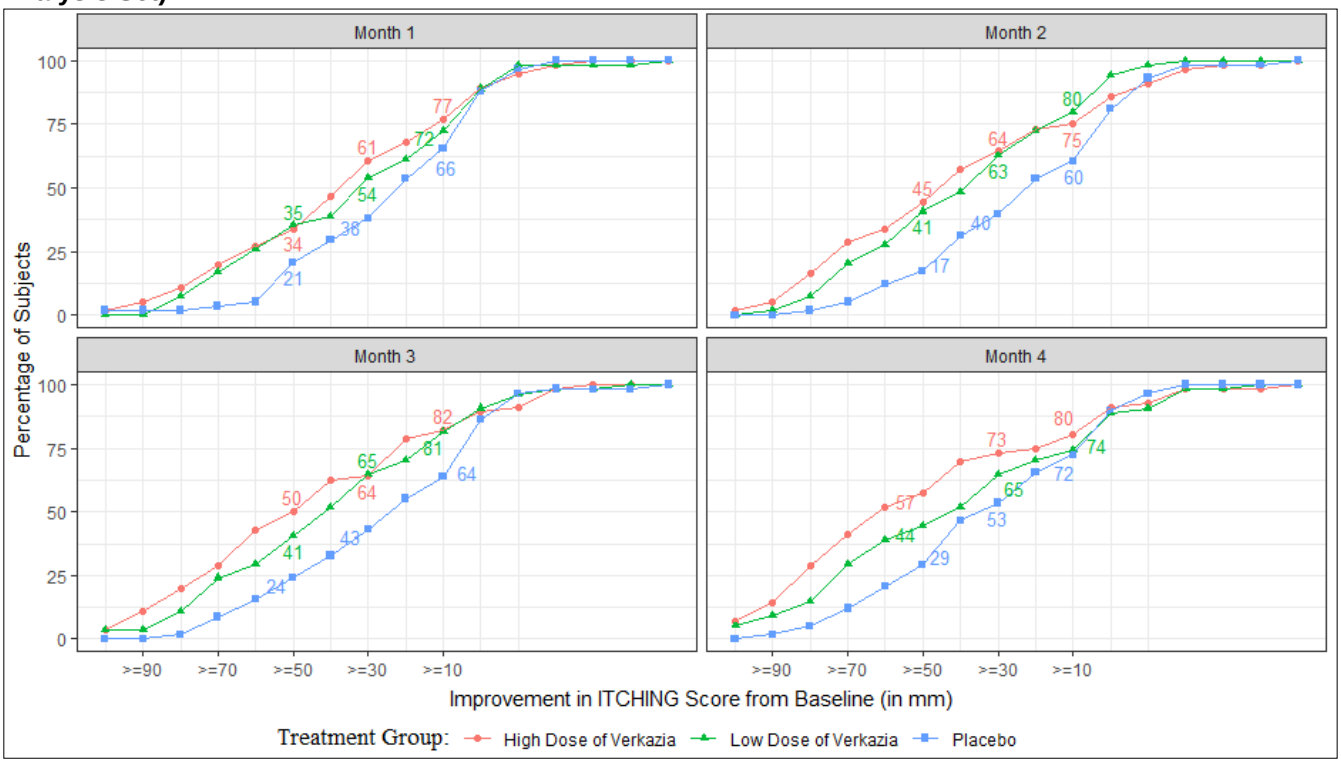
Source: Review team analysis based on ADQS.xpt dataset located at \\CDSESUB1\evsprod\NDA214965\0001\m5\datasets\nvg09b113\analysis\adam\datasets
Note: For patients who received rescue therapy during the study, all Post-Rescue data after the initial rescue therapy were imputed with baseline data.
[1] Based on ANCOVA model including baseline itching score and the proportion of time potentially spent in taking study medication during the VKC season as covariate.
[2] High Dose of Verkazia - Verkazia 1.0 mg/mL QID.
[3] Low dose of Verkazia -Verkazia 1.0 mg/mL BID
[4] Adjusted for multiplicity using Hochberg's multiple comparison procedure.
Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; CI, confidence interval; HD, high dose, LD, low dose; QID, four times daily; SD, standard deviation

Additionally, through Month 4, more patients in the two doses of Verkazia displayed improvement in itching score from baseline compared to patients in the placebo group. For example, as shown in Figure 4 below, at Month 4, about 73% and 65% of patients in QID and BID groups, respectively, demonstrated ≥ 30 mm improvement in itching score from baseline compared to 53% of patients in the placebo group.

In the efficacy analyses results presented in Table 9 and Table 10 and in Figure 3 and Figure 4, all post-baseline data after initiation of the first rescue medication were imputed by the last available data observed prior to rescue. To assess the robustness of imputing Post-Rescue data by the last available pre-rescue data, several sensitivity analyses were performed: (i) imputing all Post-Rescue data by baseline data, (ii) including all data regardless of rescue use in the analysis, and (iii) imputing all Post-Rescue data using control-based multiple imputation for patients who received rescue. As shown in Table 44 and Table 45, all the sensitivity analysis results consistently displayed the efficacy benefit of each dose of Verkazia compared to placebo in improving both the CFS and itching scores through the 4-month efficacy evaluation period.

Additionally, as shown in Figure 19 and Figure 20, patients in both doses of Verkazia maintained the improvement in CFS and itching score through Month 12 (including the 8-month safety follow-up period), however in the absence of a concurrent control, it is not possible to tell whether this differs from the natural history. Analyses for related signs of VKC, such as, hyperemia, conjunctival discharge, papillae and limbal infiltrates (see Table 46) and for additional symptoms of VKC, such as photophobia, tearing, and mucous discharge (see Table 12), showed the treatment benefit of Verkazia compared to placebo in improving the additional signs and symptoms of VKC.

Figure 4. Cumulative Distribution of the Change in Itching Score From Baseline at Each Visit (Full Analysis Set)



Source: Review team analysis based on ADQS.xpt dataset.

6.2.3.3. Secondary Efficacy Results

Responder Analysis

The Applicant defined the proportion of patients with a mean CFS score of the last 3 months of treatment ≤ 50% of baseline who did not withdraw from the study, did not experience an ulceration, and did not use rescue medication in the last 3 months of the 4-month treatment period as secondary endpoint. However, due to the arbitrary nature of the mean CFS cutoff ≤50% of baseline, the Agency considers the stringent responder analysis defined as the proportion of patients with corneal clearing at Month 4 or EW who had not experienced a corneal ulceration and had not used rescue medication in the last 3 months of treatment as a clinically meaningful endpoint. See Table 48 for the results of the Applicant-defined secondary endpoint.

Table 11 below shows the summary of corneal clearing at Month 4/EW (CFS score = 0), occurrence of at least one corneal ulceration during the 4-month treatment period, and at least one rescue received during the last three visits of the 4-month treatment period.

As shown, a total of 21 patients had corneal clearing at Month 4/EW (5 in placebo group, 12 in the QID group, 4 in the BID group), eight patients had at least one corneal ulceration (2 in placebo group, 4 in the QID group, 2 in the BID group), and 54 patients received at least one rescue medication in the last three visits (27 in placebo group, 18 in the QID group, and 9 in the BID group). Across the three components, a total of 21 patients had corneal clearing at Month 4/EW, had not experienced a corneal ulceration during the study, and had not used rescue

medication in the last 3 months of the 4-month treatment (5 in placebo group, 11 in the QID group, and 5 in the BID group). Although not statistically significantly different, 11% more patients in Verkazia QID had corneal clearing at Month 4/EW without experiencing a corneal ulceration or using rescue medication during the study compared to patients in the placebo group.

Table 11. Responder Analysis (Full Analysis Set)

		Placebo (N = 58)	QID[1] (N = 56)	BID[2] (N = 54)	Total (N = 168)
Corneal clearing at Month 4/EW	Yes **(A)**	5	12	4	21
	No	53	44	50	147
Any corneal ulceration	Yes	2	4	2	8
	No **(B)**	56	52	52	160
Any rescue at the last three visits	Yes	27	18	9	54
	No **(C)**	31	38	45	114
(A) and (B) and (C)	n (%)	5 (8.6)	11 (19.6)	5 (9.3)	21 (12.5)
	95% CI	(3.0, 1.9)	(10.0, 32.0)	(3.0, 20.0)	
	Difference (95% CI)	--	0.11 (-0.02, 0.24)	0.01 (-0.10, 0.11)	

Source: Review team analysis based on ADEFF.xpt dataset.
[1] High dose of Verkazia - Verkazia 1.0 mg/mL QID.
[2] Low dose of Verkazia -Verkazia 1.0 mg/mL BID
Abbreviations: BID, twice daily; CI, confidence interval; EW, early withdrawal; HD, high dose, LD, low dose; N, number of patients; n, number of patients with specified conditions; QID, four times daily.

Other Symptom Variables

The symptom variables of the change in photophobia, tearing, and mucous discharge from baseline at each visit through Month 4 were analyzed as additional secondary symptom endpoints in the VEKTIS study. These variables were analyzed similarly to the symptom variable of itching.

Table 12 summarizes the efficacy results for these symptom variables. As shown, Verkazia-treated patients demonstrated a larger improvement in these symptom variables from baseline at each visit compared to placebo-treated patients. For example, through the 4-month efficacy evaluation period, the QID group improved the symptoms of photophobia, tearing, and mucous discharge by more than 15 mm, 10 mm, and 17 mm, respectively, compared to placebo. Similarly, the BID group improved by more than 6 mm, 5 mm, and 7 mm, respectively, compared to placebo. Clearly, patients in the QID group displayed numerically better improvement than patients in the BID group.

Table 12. Efficacy Results of Additional Symptom Variables at Each Visit (Full Analysis Set)

				Treatment Comparison[1]			
				QID[2] vs. Placebo		BID[3] vs. Placebo	
Visit	Placebo (N = 58)	QID[2] (N = 56)	BID[3] (N = 54)	Difference (95% CI)	p-value[4]	Difference (95% CI)	p-value[4]
Photophobia (mm)							
Baseline	76.5	78.5	69.9		--		--
	(15.78)	(17.64)	(24.21)				
Month 1	-12.2	-28.0	-16.4	-15.2	0.0039	-6.5	0.1907
	(22.41)	(30.12)	(26.01)	(-24.7, -5.6)		(-16.4, 3.3)	
Month 2	-10.9	-35.2	-23.2	-23.7	0.0001	-14.6	0.0123
	(24.43)	(34.62)	(31.81)	(-34.8, -12.6)		(-26.0, -3.2)	
Month 3	-16.3	-36.6	-26.9	-19.7	0.0031	-13.0	0.0400
	(27.99)	(39.36)	(32.18)	(-31.8, -7.6)		(-25.4, -0.6)	
Month 4	-19.0	-41.0	-25.2	-21.4	0.0014	-8.6	0.1774
	(27.67)	(37.84)	(34.71)	(-33.6, -9.2)		(-21.1, 3.9)	
Tearing (mm)							
Baseline	65.4	72.0	72.6		--		--
	(21.65)	(19.61)	(14.24)				
Month 1	-14.5	-28.6	-23.4	-9.8	0.1473	-5.3	0.3452
	(24.71)	(38.78)	(28.51)	(-20.5, 0.9)		(-16.2, 5.7)	
Month 2	-15.5	-33.5	-28.9	-13.7	0.0308	-9.7	0.0918
	(24.81)	(37.64)	(31.95)	(-24.7, -2.7)		(-21.0, 1.6)	
Month 3	-19.1	-34.4	-31.9	-11.0	0.1336	-9.1	0.1364
	(25.81)	(38.10)	(35.15)	(-22.8, 0.8)		(-21.1, 2.9)	
Month 4	-19.4	-39.8	-33.3	-16.1	0.0174	-10.2	0.0991
	(27.79)	(38.85)	(35.73)	(-28.0, -4.1)		(-22.4, 1.9)	
Mucous Discharge (mm)							
Baseline	70.4	74.2	67.7		--		--
	(17.85)	(22.06)	(21.56)				
Month 1	-14.3	-32.8	-19.4	-16.8	0.0053	-6.9	0.2216
	(28.70)	(32.12)	(30.96)	(-27.7, -5.9)		(-18.1, 4.2)	
Month 2	-18.1	-37.3	-24.4	-17.6	0.0058	-8.2	0.1715
	(29.34)	(35.23)	(31.24)	(-29.1, -6.1)		(-20.0, 3.6)	
Month 3	-22.2	-41.8	-29.1	-17.9	0.0085	-8.7	0.1706
	(31.13)	(35.79)	(35.95)	(-30.1, -5.7)		(-21.1, 3.8)	
Month 4	-23.3	-43.0	-28.1	-18.1	0.0115	-6.7	0.3112
	(33.32)	(35.79)	(37.94)	(-30.8, -5.3)		(-19.7, 6.3)	

Source: Reviewer analysis based on ADQS.xpt dataset.
Note: For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last Pre-Rescue observed data.
[1] Based on ANCOVA model adjusting for baseline CFS score and the proportion of time potentially spent in taking study medication during the VKC season as covariate
[2] High Dose of Verkazia - Verkazia 1.0 mg/mL QID.
[3] Low dose of Verkazia -Verkazia 1.0 mg/mL BID
[4] Adjusted for multiplicity using Hochberg's multiple comparison procedure.
Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; CFS, corneal fluorescein staining; CI, confidence interval; HD, high dose; LD, low dose; QID, four times daily

6.2.3.4. Supporting Efficacy Results

NOVATIVE Study

In the NOVATIVE study, a total of 118 patients with VKC were enrolled and received Verkazia 0.5 mg/mL (N=39), Verkazia 1 mg/mL (N=39), or placebo (N=40) each administered one drop QID. Of note, the Verkazia QID in the VEKTIS study and 1 mg/mL in the NOVATIVE study were the same doses. See Section 6.2.1 for additional detail regarding the trial design.

Of the 118 patients enrolled in the NOVATIVE study, seven patients (6%) discontinued from the study early (4 in placebo and 3 in 0.5 mg/mL). Three patients in the placebo group discontinued due to worsening of the disease after 2 weeks of treatment and one subject discontinued due to adverse event. In the 1 mg/mL group, one subject discontinued due to ocular intolerance and two patients discontinued due to patient decision (withdrawal of consent).

Most patients in the study were male (81%). The average age of patients was about 9 years of age (range: 4 to 21 years) where most of the patients were 4 to 11 years of age (81%). About 76% of patients in the study had perennial VKC and most patients (>90%) had used prior VKC treatment. About 38% of patients in this study had baseline CFS score of 4 or 5. Overall, the demographic and baseline characteristics in the study were well balanced between the treatment groups. See Table 8 for additional summary of demographic and baseline disease characteristics in the NOVATIVE study.

As in the VEKTIS study, efficacy of Verkazia in the NOVATIVE study was assessed using the CFS score for sign and itching for symptom. Unlike in the VEKTIS study where symptom was assessed using visual analogue scale (0 to 100), symptom in the NOVATIVE study was assessed in a 0 to 3 scale: 0 (absent, no symptom), 1 (mild), 2 (moderate), and 3 (severe symptom). Patients in the NOVATIVE study had scheduled visits at Days 1 (baseline), 7, 14, and 28 during the first 1-month treatment period and at Months 2 and 4 during the safety follow-up period. In the clinical database, efficacy data for the CFS score were not provided at Day 14 and Month 2.

Table 13 and Table 14 below summarize the efficacy results for the CFS score. As shown, at Month 1 of the efficacy evaluation period, patients in the 0.5 mg/mL and 1 mg/mL groups displayed about one more unit improvement in the CFS score from baseline compared to patients in the placebo group. At Month 4, patients in the Verkazia 1 mg/mL group improved by about 2 units and patients in 0.5 mg/mL group improved by 2.4 units. After switching to the Verkazia group at Month 1, patients in the placebo group improved by about 2 units from baseline and by about 1.2 to 1.4 units from Month 1 at Month 4.

Table 13. Efficacy Results of the Mean Change in CFS Score from Baseline at Each Visit (NOVATIVE) (Full Analysis Set)

	Placebo (N = 40)[1]			
	Switched to 0.5mg/mL[2] (N = 20)	Switched to 1mg/mL[3] (N = 20)	0.5mg/mL[2] (N = 39)	1mg/mL[3] (N = 39)
Baseline (Day 0)	3.2 (1.15)		3.2 (1.15)	3.0 (1.08)
Day 7	-0.7 (1.14)		-0.8 (0.99)	-0.8 (1.06)
Month 1	-0.7 (1.70)		-1.8 (1.58)	-1.6 (1.50)
Difference[4] (95% CI)		--	-1.1 (-1.8, -0.4)	-0.9 (-1.6, -0.2)
p-value		--	0.0042	0.0092
Month 4[5]	-1.2 (1.50)	-1.4 (1.76)		
Month 4[6]	-1.9 (1.71)	-2.0 (1.65)	-2.4 (1.46)	-2.0 (1.32)

Source: Review team analysis based on ADEFF.xpt dataset located at \\CDSESUB1\evsprod\NDA214965\0014\m5\datasets\nvg05l101\analysis\adam\datasets
Note: Patients with missing Month 1 and Month 4 data were imputed using the last observation carried forward approach. Efficacy data for CFS score at Day 14 and Month 2 were not provided in the clinical database.
[1] Patients in the placebo group received placebo through Month 1 and switched to the two doses of Verkazia afterwards.
[2] Low dose of Verkazia -Verkazia 0.5 mg/mL QID
[3] High dose of Verkazia - Verkazia 1.0 mg/mL QID
[4] Based on ANCOVA model adjusting for baseline CFS score as covariate; p-value adjusted for multiplicity using Hochberg's multiple comparison procedure.
[5] Using Month 1 as baseline – last observed value prior to switching to LD or HD;
[6] Using Day 0 value as baseline
Abbreviations: ANCOVA, analysis of covariance; CFS, corneal fluorescein staining; CI, confidence interval; HD, high dose; LD, low dose; QID, four times daily

When the same analysis was performed in patients with baseline CFS score of 4 or 5, Verkazia-treated patients improved by more than 1.5 to 1.8 units at Month 1 compared to placebo (Table 14).

Table 14. Efficacy Results of the Mean Change in CFS Score from Baseline at Each Visit in Patients With Severe VKC at Baseline (Baseline CFS = 4 or 5) (NOVATIVE) (Full Analysis Set)

	Placebo (N = 15)[1]			
	Switched to 0.5mg/mL[2] (N = 6)	Switched to 1mg/mL[3] (N = 9)	0.5mg/mL[2] (N = 16)	1mg/mL[3] (N = 14)
Baseline (Day 0)	4.3 (0.52)		4.3 (0.48)	4.2 (0.43)
Day 7	-0.7 (1.21)		-0.9 (0.89)	-1.1 (1.41)
Month 1	-0.5 (0.55)		-2.2 (1.80)	-1.9 (1.83)
Difference[4] (95% CI)		--	-1.8 (-2.9, -0.6)	-1.5 (-2.7, -0.4)
p-value		--	0.0060	0.0127
Month 4[5]	-1.8 (2.04)	-1.3 (1.73)		
Month 4[6]	-2.3 (1.97)	-1.8 (1.92)	-2.8 (1.98)	-2.1 (1.83)

Source: Review team analysis based on ADEFF.xpt dataset located at \\CDSESUB1\evsprod\NDA214965\0014\m5\datasets\nvg05l101\analysis\adam\datasets
Note: Patients with missing Month 1 and Month 4 data were imputed using the last observation carried forward approach. Efficacy data for CFS score at Day 14 and Month 2 were not provided in the clinical database.
[1] Patients in the placebo group received placebo through Month 1 and switched to the two doses of Verkazia afterwards.
[2] Low dose of Verkazia -Verkazia 0.5 mg/mL QID
[3] High dose of Verkazia - Verkazia 1.0 mg/mL QID
[4] Based on ANCOVA model adjusting for baseline CFS score as covariate; p-value adjusted for multiplicity using Hochberg's multiple comparison procedure.
[5] Using Month 1 as baseline – last observed value prior to switching to LD or HD;
[6] Using Day 0 value as baseline
Abbreviations: ANCOVA, analysis of covariance; CFS, corneal fluorescein staining; CI, confidence interval; HD, high dose; N, number of patients; LD, low dose; QID, four times daily

Similarly, Table 15 below shows the efficacy results for the subjective symptom variables of itching, photophobia, tearing, and mucous discharge through the 4-month period in the NOVATIVE study.

As shown, at the Month 1 efficacy evaluation period, except for the symptom of tearing, there was no statistically significant difference between Verkazia-treated and placebo-treated patients in the other symptom variables. However, Verkazia-treated patients displayed a numerically slight improvement than placebo-treated patients in these symptom variables. For the symptom of tearing, the Verkazia-treated groups displayed an improvement by more than 0.5 to 0.8 unit compared to placebo.

Table 15. Efficacy Results of the Mean Change in Symptom Scores From Baseline at Each Visit (NOVATIVE) (Full Analysis Set)

	Placebo (N = 40)[1]				Placebo (N = 40)[1]			
	Switched to 0.5mg/mL[2] (N =20)	Switched to 1mg/mL[3] (N = 20)	0.5mg/mL[2] (N =39)	1mg/mL[3] (N =39)	Switched to 0.5mg/mL[2] (N = 20)	Switched to 1mg/mL[3] (N = 20)	0.5mg/mL[2] (N = 39)	1mg/mL[3] (N = 39)
Visit	**Itching**				**Photophobia**			
Baseline	2.8 (0.58)		2.6 (0.59)	2.6 (0.75)	2.5 (0.82)		2.6 (0.72)	2.5 (0.76)
Day 7	-1.0 (0.86)		-0.9 (0.95)	-1.3 (1.16)	-0.5 (0.96)		-0.5 (0.97)	-0.7 (0.92)
Day 14	-1.4 (1.03)		-1.4 (1.16)	-1.4 (1.12)	-0.6 (1.20)		-0.8 (0.96)	-0.9 (1.07)
Month 1	-1.6 (1.01)		-1.6 (0.96)	-1.5 (1.27)	-0.9 (1.28)		-1.1 (1.04)	-1.2 (0.98)
Difference[4] (95% CI)	--		-0.2 (-0.6, 0.2)	-0.07 (-0.5, 0.4)	--		-0.1 (-0.6, 0.3)	-0.3 (-0.7, 0.2)
p-value			0.4084	0.7575			0.5905	0.2173
Month 2[5]	-0.4 (0.94)	-0.3 (0.91)	-1.9 (0.98)	-1.6 (1.25)	-0.5 (0.89)	-0.4 (0.82)	-1.3 (1.13)	-1.6 (1.21)
Month 4[5]	-0.5 (0.89)	-0.5 (1.10)	-2.2 (0.82)	-2.0 (1.27)	-0.8 (1.07)	-0.8 (1.07)	-1.9 (1.05)	-1.8 (1.25)
Month 2[6]	-2.1 (1.09)	-1.7 (1.17)	-1.9 (0.98)	-1.6 (1.25)	-1.4 (1.43)	-1.3 (1.30)	-1.3 (1.13)	-1.6 (1.21)
Month 4[6]	-2.2 (1.09)	-2.0 (1.19)	-2.2 (0.82)	-2.0 (1.27)	-1.7 (1.34)	-1.7 (1.23)	-1.9 (1.05)	-1.8 (1.25)
	Tearing				**Mucus Discharge**			
Baseline	2.0 (0.86)		1.9 (0.89)	1.9 (0.90)	2.2 (0.66)		1.9 (0.85)	1.9 (0.97)
Day 7	-0.4 (0.93)		-0.7 (0.90)	-0.8 (1.10)	-0.6 (0.98)		-0.5 (0.68)	-0.7 (0.88)
Day 14	-0.7 (1.04)		-1.0 (1.11)	-0.8 (1.39)	-0.8 (0.91)		-0.9 (0.89)	-1.2 (0.88)
Month 1	-0.6 (1.06)		-1.3 (1.19)	-1.0 (1.33)	-0.9 (0.97)		-1.0 (0.96)	-1.0 (0.93)
Difference[4] (95% CI)	--		-0.8 (-1.2, -0.3)	-0.5 (-0.9, -0.02)	--		-0.2 (-0.6, 0.1)	-0.2 (-0.6, 0.2)
p-value			0.0005	0.0395			0.2090	0.2698)
Month 2[5]	-0.5 (0.89)	-0.7 (0.80)	-1.4 (1.12)	-1.3 (1.16)	-0.2 (0.75)	-0.5 (0.76)	-1.3 (0.94)	-1.1 (1.21)
Month 4[5]	-0.7 (0.88)	-0.8 (0.91)	-1.6 (1.05)	-1.5 (1.37)	-0.5 (0.83)	-0.6 (0.69)	-1.4 (1.11)	-1.4 (0.88)
Month 2[6]	-1.2 (1.06)	-1.2 (1.09)	-1.4 (1.12)	-1.3 (1.16)	-1.2 (1.27)	-1.3 (0.92)	-1.3 (0.94)	-1.1 (1.21)
Month 4[6]	-1.4 (0.99)	-1.2 (1.11)	-1.6 (1.05)	-1.5 (1.37)	-1.5 (1.24)	-1.4 (1.10)	-1.4 (1.11)	-1.4 (0.88)

Source: Review team analysis based on ADEFF.xpt dataset located at \\CDSESUB1\evsprod\NDA214965\0014\m5\datasets\nvg05l101\analysis\adam\datasets
Note: Patients with missing data were imputed using the last observation carried forward approach
[1] Patients in the placebo group received placebo through Month 1 and switched to the two doses of Verkazia afterwards.
[2] Low dose of Verkazia -Verkazia 0.5 mg/mL QID
[3] High dose of Verkazia - Verkazia 1.0 mg/mL QID
[4] Based on ANCOVA model adjusting for baseline CFS score as covariate; p-value adjusted for multiplicity using Hochberg's multiple comparison procedure.
[5] Using Month 1 as baseline (last observed value prior to switching to LD or HD);
[6] Using Day 0 value as baseline.
Abbreviations: ANCOVA, analysis of covariance; CFS, corneal fluorescein staining; CI, confidence interval; HD, high dose; LD, low dose; N, number of patients; QID, four times daily

Subgroup Analyses (VEKTIS Study)

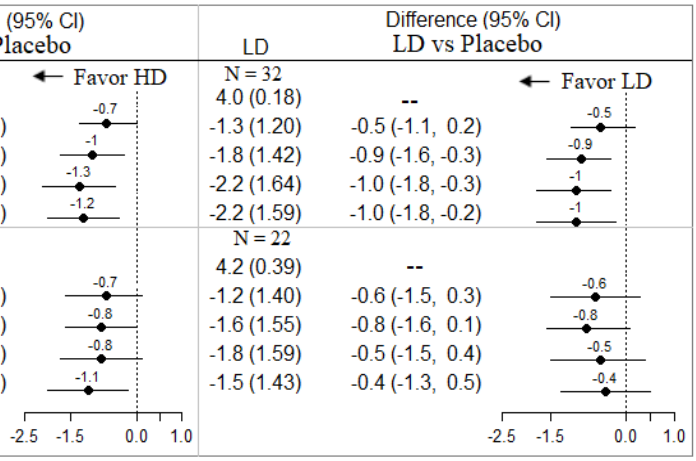
In the VEKTIS study, the key efficacy variables of the change in CFS score and itching score from baseline at each visit were analyzed by the subgroups of region (European Union versus the rest of the world), age group (4 to 11 versus 12 to 18 years), sex (female versus male), and race (Caucasian versus others).

Figure 5 to Figure 8 and Figure 9 to Figure 12 below show the efficacy summaries for the CFS and itching scores, respectively, for each of the subgroups.

As shown, through Month 4, Verkazia-treated patients consistently displayed greater improvement in the CFS and itching scores than placebo-treated patients regardless of the subgroup levels. Within each of the subgroup levels, patients treated with the Verkazia QID showed numerically greater improvement than patients treated with the Verkazia BID.

Figure 5. Efficacy Results of the Mean Change in CFS Score from Baseline at Each Visit by Region (Full Analysis Set)

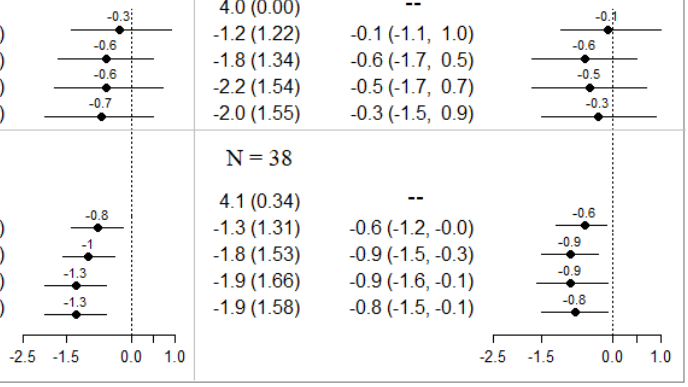
Visit	Placebo	HD	Difference (95% CI) HD vs Placebo	LD	Difference (95% CI) LD vs Placebo
EU	N = 35	N = 33	← Favor HD	N = 32	Favor LD →
Baseline	4.1 (0.28)	4.3 (0.48)	--	4.0 (0.18)	--
Month 1	-0.8 (1.31)	-1.5 (1.44)	-0.7 (-1.3, 0.0)	-1.3 (1.20)	-0.5 (-1.1, 0.2)
Month 2	-0.9 (1.24)	-1.8 (1.53)	-1.0 (-1.7, -0.3)	-1.8 (1.42)	-0.9 (-1.6, -0.3)
Month 3	-1.1 (1.44)	-2.4 (1.70)	-1.3 (-2.1, -0.5)	-2.2 (1.64)	-1.0 (-1.8, -0.3)
Month 4	-1.1 (1.59)	-2.4 (1.72)	-1.2 (-2.0, -0.4)	-2.2 (1.59)	-1.0 (-1.8, -0.2)
ROW	N = 23	N = 23		N = 22	
Baseline	4.0 (0.21)	4.1 (0.34)	--	4.2 (0.39)	--
Month 1	-0.8 (1.34)	-1.6 (1.49)	-0.7 (-1.6, 0.1)	-1.2 (1.40)	-0.6 (-1.5, 0.3)
Month 2	-1.0 (1.26)	-1.8 (1.43)	-0.8 (-1.6, 0.0)	-1.6 (1.55)	-0.8 (-1.6, 0.1)
Month 3	-1.5 (1.58)	-2.3 (1.55)	-0.8 (-1.7, 0.1)	-1.8 (1.59)	-0.5 (-1.5, 0.4)
Month 4	-1.3 (1.43)	-2.4 (1.61)	-1.1 (-2.0, -0.2)	-1.5 (1.43)	-0.4 (-1.3, 0.5)



Source: Review team analysis based on ADEFF.xpt dataset.
Low dose of Verkazia -Verkazia 1.0 mg/mL BID
High dose of Verkazia - Verkazia 1.0 mg/mL QID
Abbreviations: BID, twice daily; CFS, corneal fluorescein staining; CI, confidence interval; EU, European Union; HD, QID dose; LD, BID dose; N, number of patients: QID, four times daily; ROW, rest of the world

Figure 6.Efficacy Results of the Mean Change in CFS Score from Baseline at Each Visit by Age Group (Full Analysis Set)

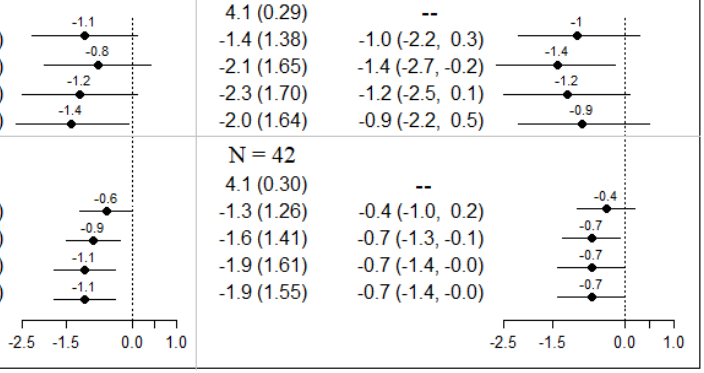
Visit	Placebo	HD	Difference (95% CI) vs Placebo	LD	Difference (95% CI) vs Placebo
Adolecent (12-18 years)	N = 12	N = 13	← Favor HD	N = 16	← Favor LD
Baseline	4.2 (0.39)	4.2 (0.44)	--	4.0 (0.00)	--
Month 1	-1.1 (1.56)	-1.3 (1.17)	-0.3 (-1.4, 0.9)	-1.2 (1.22)	-0.1 (-1.1, 1.0)
Month 2	-1.1 (1.24)	-1.6 (1.32)	-0.6 (-1.7, 0.5)	-1.8 (1.34)	-0.6 (-1.7, 0.5)
Month 3	-1.7 (1.44)	-2.2 (1.41)	-0.6 (-1.8, 0.7)	-2.2 (1.54)	-0.5 (-1.7, 0.7)
Month 4	-1.7 (1.44)	-2.3 (1.48)	-0.7 (-2.0, 0.5)	-2.0 (1.55)	-0.3 (-1.5, 0.9)
Children (4-11 years)	N = 46	N = 43		N = 38	
Baseline	4.0 (0.21)	4.3 (0.44)	--	4.1 (0.34)	--
Month 1	-0.8 (1.25)	-1.6 (1.53)	-0.8 (-1.4, -0.2)	-1.3 (1.31)	-0.6 (-1.2, -0.0)
Month 2	-0.9 (1.25)	-1.9 (1.53)	-1.0 (-1.6, -0.4)	-1.8 (1.53)	-0.9 (-1.5, -0.3)
Month 3	-1.1 (1.50)	-2.4 (1.70)	-1.3 (-2.0, -0.6)	-1.9 (1.66)	-0.9 (-1.6, -0.1)
Month 4	-1.1 (1.53)	-2.4 (1.73)	-1.3 (-2.0, -0.6)	-1.9 (1.58)	-0.8 (-1.5, -0.1)



Source: Review team analysis based on ADEFF.xpt dataset.
Low dose of Verkazia -Verkazia 1.0 mg/mL BID
High dose of Verkazia - Verkazia 1.0 mg/mL QID
Abbreviations: BID, twice daily; CFS, corneal fluorescein staining; CI, confidence interval; HD, QID dose; LD, BID dose; N, number of patients; QID, four times daily

Figure 7. Efficacy Results of the Mean Change in CFS Score from Baseline at Each Visit by Gender (Full Analysis Set)

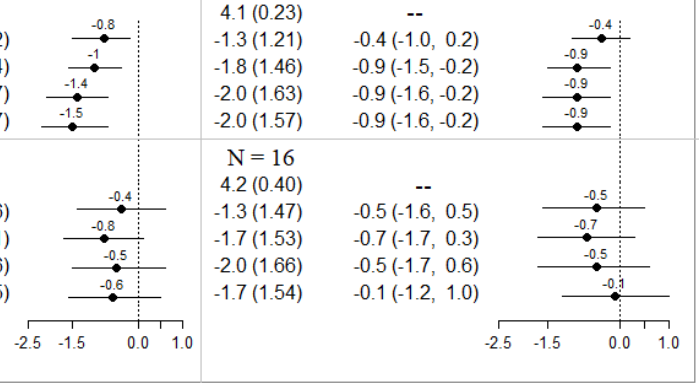
Visit	Placebo	HD	Difference (95% CI) vs Placebo	LD	Difference (95% CI) vs Placebo
Female	N = 12	N = 12	← Favor HD	N = 12	← Favor LD
Baseline	4.3 (0.45)	4.3 (0.49)	--	4.1 (0.29)	--
Month 1	-0.7 (1.39)	-1.8 (1.53)	-1.1 (-2.3, 0.1)	-1.4 (1.38)	-1.0 (-2.2, 0.3)
Month 2	-1.0 (1.32)	-1.8 (1.42)	-0.8 (-2.0, 0.4)	-2.1 (1.65)	-1.4 (-2.7, -0.2)
Month 3	-1.3 (1.60)	-2.5 (1.47)	-1.2 (-2.5, 0.1)	-2.3 (1.70)	-1.2 (-2.5, 0.1)
Month 4	-1.4 (1.61)	-2.8 (1.59)	-1.4 (-2.7, -0.1)	-2.0 (1.64)	-0.9 (-2.2, 0.5)
Male	N = 46	N = 44		N = 42	
Baseline	4.0 (0.15)	4.2 (0.42)	--	4.1 (0.30)	--
Month 1	-0.9 (1.30)	-1.4 (1.43)	-0.6 (-1.2, -0.0)	-1.3 (1.26)	-0.4 (-1.0, 0.2)
Month 2	-0.9 (1.23)	-1.9 (1.51)	-0.9 (-1.5, -0.3)	-1.6 (1.41)	-0.7 (-1.3, -0.1)
Month 3	-1.2 (1.48)	-2.3 (1.68)	-1.1 (-1.8, -0.4)	-1.9 (1.61)	-0.7 (-1.4, -0.0)
Month 4	-1.2 (1.51)	-2.3 (1.69)	-1.1 (-1.8, -0.4)	-1.9 (1.55)	-0.7 (-1.4, -0.0)



Source: Review team analysis based on ADEFF.xpt dataset.
Low dose of Verkazia -Verkazia 1.0 mg/mL BID
High dose of Verkazia - Verkazia 1.0 mg/mL QID
Abbreviations: BID, twice daily; CFS, corneal fluorescein staining; CI, confidence interval; HD, QID dose; LD, BID dose; N, number of patients; QID, four times daily

Figure 8. Efficacy Results of the Mean Change in CFS Score from Baseline at Each Visit by Race (Full Analysis Set)

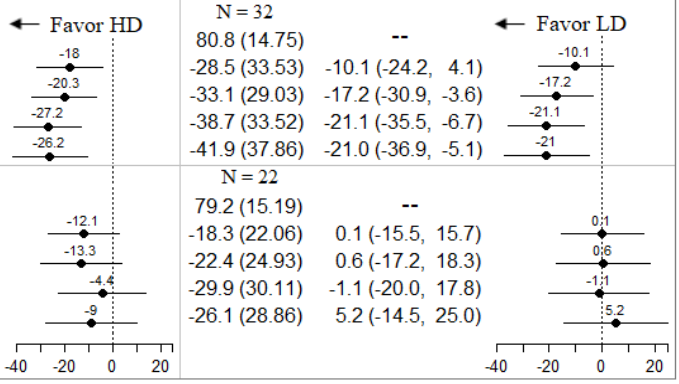
Visit	Placebo	HD	Difference (95% CI) vs Placebo	LD	Difference (95% CI) vs Placebo
Caucasian	N = 41	N = 40	← Favor HD	N = 38	Favor LD →
Baseline	4.1 (0.30)	4.3 (0.46)	--	4.1 (0.23)	--
Month 1	-0.8 (1.35)	-1.6 (1.46)	-0.8 (-1.5, -0.2)	-1.3 (1.21)	-0.4 (-1.0, 0.2)
Month 2	-0.9 (1.31)	-1.8 (1.51)	-1.0 (-1.6, -0.4)	-1.8 (1.46)	-0.9 (-1.5, -0.2)
Month 3	-1.1 (1.50)	-2.4 (1.67)	-1.4 (-2.1, -0.7)	-2.0 (1.63)	-0.9 (-1.6, -0.2)
Month 4	-1.0 (1.52)	-2.4 (1.69)	-1.5 (-2.2, -0.7)	-2.0 (1.57)	-0.9 (-1.6, -0.2)
Others	N = 17	N = 16		N = 16	
Baseline	4.0 (0.00)	4.1 (0.34)	--	4.2 (0.40)	--
Month 1	-0.8 (1.24)	-1.3 (1.45)	-0.4 (-1.4, 0.6)	-1.3 (1.47)	-0.5 (-1.6, 0.5)
Month 2	-1.1 (1.09)	-1.9 (1.44)	-0.8 (-1.7, 0.1)	-1.7 (1.53)	-0.7 (-1.7, 0.3)
Month 3	-1.6 (1.45)	-2.2 (1.56)	-0.5 (-1.5, 0.6)	-2.0 (1.66)	-0.5 (-1.7, 0.6)
Month 4	-1.7 (1.45)	-2.3 (1.64)	-0.6 (-1.6, 0.5)	-1.7 (1.54)	-0.1 (-1.2, 1.0)



Source: Review team analysis based on ADEFF.xpt dataset.
Low dose of Verkazia -Verkazia 1.0 mg/mL BID
High dose of Verkazia - Verkazia 1.0 mg/mL QID
Abbreviations: BID, twice daily; CFS, corneal fluorescein staining; CI, confidence interval; HD, QID dose; LD, BID dose; N, number of patients; QID, four times daily

Figure 9. Efficacy Results of the Mean Change in Itching Score from Baseline at Each Visit by Region (Full Analysis Set)

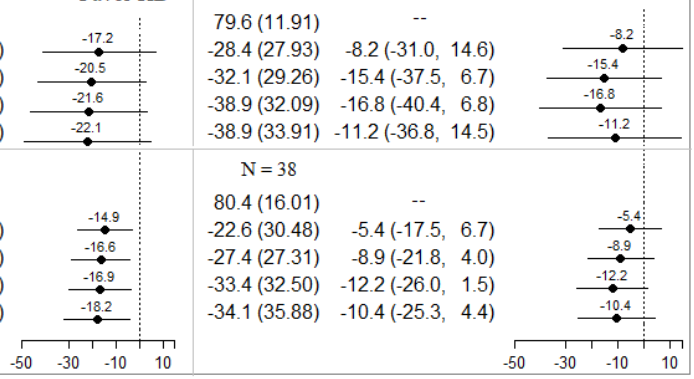
Visit	Placebo	HD	Difference (95% CI) HD vs Placebo	LD	Difference (95% CI) LD vs Placebo
EU	N = 35	N = 33	← Favor HD	N = 32	Favor LD →
Baseline	77.2 (18.32)	74.5 (21.00)	--	80.8 (14.75)	--
Month 1	-16.5 (21.01)	-33.6 (33.84)	-18.0 (-32.0, -4.0)	-28.5 (33.53)	-10.1 (-24.2, 4.1)
Month 2	-13.9 (19.16)	-33.4 (36.62)	-20.3 (-33.8, -6.8)	-33.1 (29.03)	-17.2 (-30.9, -3.6)
Month 3	-15.5 (20.70)	-41.9 (35.42)	-27.2 (-41.5, -13.0)	-38.7 (33.52)	-21.1 (-35.5, -6.7)
Month 4	-18.9 (23.79)	-44.3 (38.23)	-26.2 (-41.9, -10.5)	-41.9 (37.86)	-21.0 (-36.9, -5.1)
ROW	N = 23	N = 23		N = 22	
Baseline	80.2 (12.68)	83.1 (11.73)	--	79.2 (15.19)	--
Month 1	-21.2 (21.54)	-34.0 (30.17)	-12.1 (-27.0, 2.7)	-18.3 (22.06)	0.1 (-15.5, 15.7)
Month 2	-25.7 (26.88)	-39.7 (34.39)	-13.3 (-30.3, 3.7)	-22.4 (24.93)	0.6 (-17.2, 18.3)
Month 3	-31.5 (29.28)	-36.7 (34.61)	-4.4 (-22.6, 13.8)	-29.9 (30.11)	-1.1 (-20.0, 17.8)
Month 4	-34.1 (29.49)	-43.8 (38.89)	-9.0 (-28.1, 10.1)	-26.1 (28.86)	5.2 (-14.5, 25.0)



Source: Review team analysis based on ADQS.xpt dataset.
Low dose of Verkazia -Verkazia 1.0 mg/mL BID
High dose of Verkazia - Verkazia 1.0 mg/mL QID
Abbreviations: BID, twice daily; CI, confidence interval; EU, European Union; HD, QID dose; LD, BID dose; N, number of patients; QID, four times daily; ROW, rest of the world

Figure 10. Efficacy Results of the Mean Change in Itching Score from Baseline at Each Visit by Age Group (Full Analysis Set)

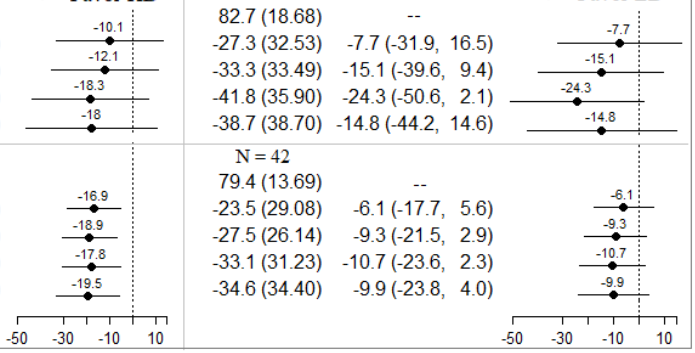
Visit	Placebo	HD	Difference (95% CI) vs Placebo	LD	Difference (95% CI) vs Placebo
Adolecent (12-18 years)	N = 12	N = 13	← Favor HD	N = 16	← Favor LD
Baseline	72.3 (19.91)	74.0 (24.75)	--	79.6 (11.91)	--
Month 1	-18.8 (20.15)	-35.8 (35.67)	-17.2 (-41.0, 6.7)	-28.4 (27.93)	-8.2 (-31.0, 14.6)
Month 2	-15.2 (18.26)	-35.5 (31.67)	-20.5 (-43.5, 2.6)	-32.1 (29.26)	-15.4 (-37.5, 6.7)
Month 3	-20.7 (18.06)	-42.2 (34.11)	-21.6 (-46.3, 3.1)	-38.9 (32.09)	-16.8 (-40.4, 6.8)
Month 4	-26.3 (21.30)	-48.3 (39.65)	-22.1 (-48.9, 4.7)	-38.9 (33.91)	-11.2 (-36.8, 14.5)
Children (4-11 years)	N = 46	N = 43		N = 38	
Baseline	80.0 (15.02)	79.3 (15.82)	--	80.4 (16.01)	--
Month 1	-18.2 (21.63)	-33.2 (31.37)	-14.9 (-26.5, -3.4)	-22.6 (30.48)	-5.4 (-17.5, 6.7)
Month 2	-19.5 (24.26)	-36.1 (36.98)	-16.6 (-29.0, -4.3)	-27.4 (27.31)	-8.9 (-21.8, 4.0)
Month 3	-22.2 (27.22)	-39.0 (35.46)	-16.9 (-30.0, -3.7)	-33.4 (32.50)	-12.2 (-26.0, 1.5)
Month 4	-24.6 (28.51)	-42.8 (38.07)	-18.2 (-32.4, -4.0)	-34.1 (35.88)	-10.4 (-25.3, 4.4)



Source: Review team analysis based on ADQS.xpt dataset.
Low dose of Verkazia -Verkazia 1.0 mg/mL BID
High dose of Verkazia - Verkazia 1.0 mg/mL QID
Abbreviations: BID, twice daily; CI, confidence interval; HD, QID dose; LD, BID dose; N, number of patients; QID, four times daily

Figure 11. Efficacy Results of the Mean Change in Itching Score from Baseline at Each Visit by Gender (Full Analysis Set)

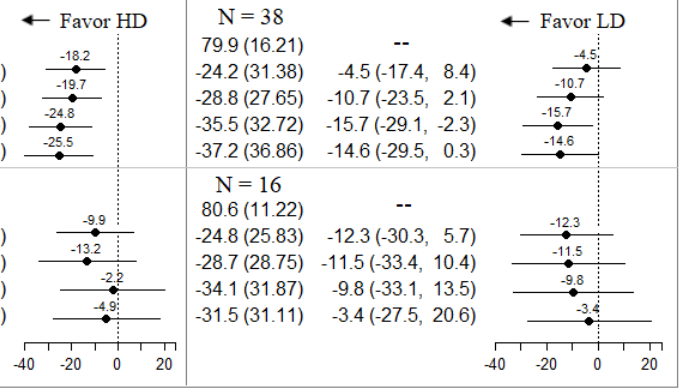
Visit	Placebo	HD	Difference (95% CI) vs Placebo	LD	Difference (95% CI) vs Placebo
Female	N = 12	N = 12	← Favor HD	N = 12	← Favor LD
Baseline	82.1 (15.10)	81.3 (11.01)	--	82.7 (18.68)	--
Month 1	-26.4 (21.99)	-36.3 (28.40)	-10.1 (-33.2, 13.0)	-27.3 (32.53)	-7.7 (-31.9, 16.5)
Month 2	-25.0 (23.30)	-36.9 (27.67)	-12.1 (-35.5, 11.2)	-33.3 (33.49)	-15.1 (-39.6, 9.4)
Month 3	-24.3 (23.04)	-42.4 (35.42)	-18.3 (-43.7, 7.1)	-41.8 (35.90)	-24.3 (-50.6, 2.1)
Month 4	-30.7 (28.22)	-48.5 (38.04)	-18.0 (-46.6, 10.5)	-38.7 (38.70)	-14.8 (-44.2, 14.6)
Male	N = 46	N = 44		N = 42	
Baseline	77.4 (16.57)	77.2 (19.67)	--	79.4 (13.69)	--
Month 1	-16.2 (20.66)	-33.1 (33.30)	-16.9 (-28.3, -5.5)	-23.5 (29.08)	-6.1 (-17.7, 5.6)
Month 2	-16.9 (22.97)	-35.7 (37.68)	-18.9 (-30.8, -6.9)	-27.5 (26.14)	-9.3 (-21.5, 2.9)
Month 3	-21.2 (26.26)	-39.0 (35.09)	-17.8 (-30.5, -5.1)	-33.1 (31.23)	-10.7 (-23.6, 2.3)
Month 4	-23.5 (26.80)	-42.9 (38.53)	-19.5 (-33.1, -5.8)	-34.6 (34.40)	-9.9 (-23.8, 4.0)



Source: Review team analysis based on ADQS.xpt dataset.
Low dose of Verkazia -Verkazia 1.0 mg/mL BID
High dose of Verkazia - Verkazia 1.0 mg/mL QID
Abbreviations: BID, twice daily; CI, confidence interval; HD, QID dose; LD, BID dose; N, number of patients; QID, four times daily

Figure 12. Efficacy Results of the Mean Change in Itching Score From Baseline at Each Visit by Race (Full Analysis Set)

Visit	Placebo	HD	Difference (95% CI) vs Placebo	LD	Difference (95% CI) vs Placebo
Caucasian	N = 41	N = 40	← Favor HD	N = 38	← Favor LD
Baseline	80.0 (17.87)	78.1 (20.63)	--	79.9 (16.21)	--
Month 1	-19.7 (23.15)	-37.2 (33.62)	-18.2 (-31.0, -5.4)	-24.2 (31.38)	-4.5 (-17.4, 8.4)
Month 2	-18.1 (22.74)	-37.1 (35.93)	-19.7 (-32.3, -7.0)	-28.8 (27.65)	-10.7 (-23.5, 2.1)
Month 3	-19.8 (24.56)	-43.9 (33.78)	-24.8 (-38.0, -11.5)	-35.5 (32.72)	-15.7 (-29.1, -2.3)
Month 4	-22.6 (26.47)	-47.4 (37.61)	-25.5 (-40.1, -10.8)	-37.2 (36.86)	-14.6 (-29.5, 0.3)
Others	N = 17	N = 16		N = 16	
Baseline	74.5 (10.97)	77.8 (10.09)	--	80.6 (11.22)	--
Month 1	-15.1 (15.48)	-25.3 (27.06)	-9.9 (-26.5, 6.7)	-24.8 (25.83)	-12.3 (-30.3, 5.7)
Month 2	-19.8 (24.50)	-33.3 (35.54)	-13.2 (-34.0, 7.7)	-28.7 (28.75)	-11.5 (-33.4, 10.4)
Month 3	-26.9 (27.64)	-29.4 (36.48)	-2.2 (-24.5, 20.1)	-34.1 (31.87)	-9.8 (-33.1, 13.5)
Month 4	-30.6 (28.27)	-35.9 (39.47)	-4.9 (-28.0, 18.2)	-31.5 (31.11)	-3.4 (-27.5, 20.6)



Source: Review team analysis based on ADQS.xpt dataset.
Low dose of Verkazia -Verkazia 1.0 mg/mL BID
High dose of Verkazia - Verkazia 1.0 mg/mL QID
Abbreviations: BID, twice daily; CI, confidence interval; HD, QID dose; LD, BID dose; N, number of patients; QID, four times daily

Similar analyses were performed by latitude and longitude groups, and by randomization order. As shown in Table 49 and Table 50, the analysis results by these subgroup variables also provided supporting evidence for the treatment benefit of Verkazia compared to placebo in improving the CFS score and for the itching score for symptom.

Conclusion Regarding Effectiveness

In summary, based on the efficacy data from the adequate and well controlled trial of VEKTIS study and the supporting trial of NOVATIVE study, we conclude that substantial evidence of effectiveness is established for Verkazia for the treatment of VKC.

In both studies, Verkazia 1.0 mg/mL QID demonstrated superior improvement in the CFS score from baseline through the 4-month evaluation period compared to placebo. The improvement achieved through Month 4 was maintained through the 8-month safety follow-up period (Figure 19 and Figure 20), but in the absence of a concurrent control, it cannot be determined if this is due to the drug product. Additionally, Verkazia-treated patients in the VEKTIS study showed greater improvement in the symptoms of itching, photophobia, tearing, and mucous discharge through the 4-month efficacy evaluation period compared to placebo-treated patients.

The NOVATIVE study provided supporting evidence for the clinical benefit of Verkazia 1 mg/mL QID in improving the CFS score as well as in the symptoms of itching, photophobia, tearing, and mucous discharge scores.

See Section 6.3 for the key review issue relevant to the evaluation of benefit and how it was resolved.

6.3. Review Issues Relevant to the Evaluation of Benefit

6.3.1. Primary Endpoint Definition

Issue
In the VEKTIS study, the Applicant's primary efficacy endpoint for the sign of VKC was penalty-adjusted change in CFS score from each month (Month 1 to Month 4) to baseline averaged over the four-month visits. The Agency disagrees with the penalty adjustment and taking the average of the efficacy data over the four-month visits.

Background/Assessment
The primary efficacy endpoint in the VEKTIS study was *penalty-adjusted change in CFS score from each month to baseline averaged over the four-month visits.* Penalty adjustment was made for receipt of rescue therapy and/or occurrence of corneal ulceration during the 4-month efficacy evaluation period. A penalty of -1 per course (with a maximum of 2 courses between 2 scheduled visits) for rescue medication and -1 for occurrence of corneal ulceration was assigned in the Applicant's primary analysis.

The Agency disagrees with the penalty assignment to the CFS score because the applied penalties for either rescue medication or the occurrence of an ulceration were not proportionate to the score. The effect of rescue medication and the timing may have affected the score significantly more or less than the penalty assigned. Additionally, the Agency disagrees with taking the average of the efficacy data over the four-month visits in the primary endpoint because taking the average masks the onset of action and the duration of effect of the product.

Conclusion
During the Type B meeting held on December 18, 2018, the Agency requested that nonpenalized CFS score without averaging over several months be performed. In the NDA, the Applicant submitted the penalized results averaged over 4 months as primary and the nonpenalized efficacy results without averaging as supporting. However, the Agency considers the nonpenalized scores without averaging over 4 months as the primary analysis.

6.3.2. Handling Post-Rescue Data

Issue
In the Applicant's analysis, all data collected regardless of rescue therapy use were included in the analyses of the nonpenalized score for CFS and itching score. The Agency does not agree with the Applicant's rescue data handling approach in the primary analysis.

Background/Assessment
The Applicant performed the analyses of the nonpenalized CFS score and itching score using the following two approaches:

- Including all the data in the analysis regardless of rescue therapy use (a *treatment policy estimand strategy*) and
- Excluding Post-Rescue data and imputing with baseline data.

The Agency disagrees with these analysis approaches as primary because (a) rescue is not part of the intended treatment regimen for the treatment of VKC and including all the data regardless of rescue confounds the actual treatment effect and (b) the assumption that patients' CFS scores return to their baseline level in the absence of rescue is not valid for the disease condition.

Conclusion
The Agency's preferred Post-Rescue data handling approach is to censor and impute all Post-Rescue data by the last available value observed prior to the initiation of rescue (*while on treatment estimand strategy*). The Applicant submitted these analyses on April 9, 2021, in a response to the Agency's information request dated March 30, 2021.

To assess the robustness of this analysis approach, the Agency performed several additional supporting analyses:

- Imputing all Post-Rescue data by baseline data,
- Including all the data in the analysis regardless of rescue therapy use, and
- Imputing all Post-Rescue data using control-based multiple imputation for patients who received rescue.

All the supporting analysis results consistently displayed the efficacy benefit of each dose of Verkazia compared to placebo in improving both the CFS and itching scores through the 4-month efficacy evaluation period (Table 44 and Table 45).

6.3.3. Handling Missing Data for Patients Discontinued Due to Lack of Efficacy

Issue
For patients who discontinued the VEKTIS study due to lack-of-efficacy, the Applicant imputed all post-discontinuation visit data using the worst value observed prior to discontinuation. The Applicant's data handling approach is considered not meaningful from a clinical perspective.

Background/Assessment
In the VEKTIS study, a total of 11 patients (5 in placebo, 1 in the HD, and 5 in the LD) discontinued the study due to lack-of-efficacy (see Table 7). For these patients, the Applicant imputed the post-discontinuation data using the worst observed data prior to discontinuation. The Agency considers this missing data handling approach not clinically meaningful because patients in the placebo group that could be partially improved but drop out due to symptoms of the condition, are interpreted as adverse events.

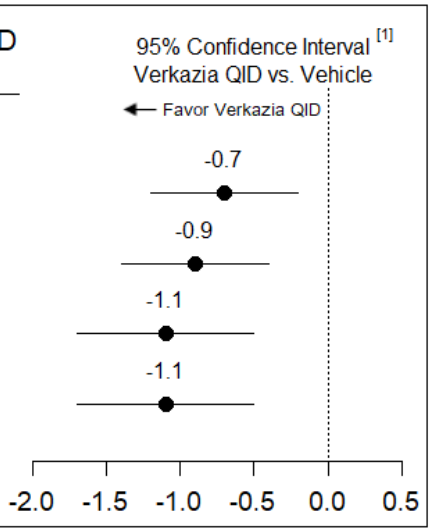
Conclusion
To address this issue, the Agency requested that the last visit data observed prior to discontinuation due to lack of efficacy be imputed for all post-discontinuation visits in the primary efficacy analyses. The Applicant submitted these analyses on April 9, 2021, in a response to the Agency's information request dated March 30, 2021.

Table 16 and Table 17 below show the efficacy results of the mean change in the CFS and

itching score at each visit through Month 4 which addressed the key review issues highlighted in Sections 6.3.1, 6.3.2, and 6.3.3. The Agency recommends that these results from the VEKTIS study be presented in Section 14 of the prescribing information.

Table 16. Efficacy Results of the Mean Change in CFS Score from Baseline at Each Visit (Full Analysis Set)

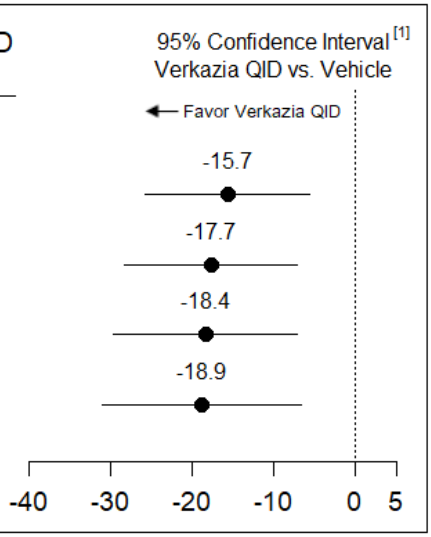
Visit	Vehicle (N = 58)	Verkazia QID (N = 56)	Verkazia BID (N = 54)
Baseline	4.1 (0.3)	4.3 (0.4)	4.1 (0.3)
Month 1	-0.8 (1.3)	-1.4 (1.4)	-1.3 (1.3)
Month 2	-0.9 (1.2)	-1.8 (1.5)	-1.8 (1.5)
Month 3	-1.2 (1.5)	-2.3 (1.6)	-2.0 (1.6)
Month 4	-1.2 (1.5)	-2.3 (1.7)	-1.9 (1.6)



Source: Review team analysis based on ADEFF.xpt dataset.
[1] Treatment differences (numbers in the middle of the horizontal lines) and 95% confidence intervals (horizontal lines) are based on ANCOVA model including baseline CFS score and the proportion of time potentially spent in taking study medication during the VKC season as covariate. For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last available data observed prior to rescue initiation. Approximately a third of patients in the Verkazia groups and 54% of subjects in the placebo group received rescue (topical steroids, dexamethasone 0.1%).
Note 1: CFS score was measured at each visit using a 5-point scale (0=no stain, and 5 = more stain).
Note 2: The Full Analysis Set included all randomized patients who received at least one drop of study medication.
Abbreviations: ANCOVA, analysis of covariance; CFS, corneal fluorescein staining; CI, confidence interval; N, number of patients; VKC, vernal keratoconjunctivitis

Table 17. Efficacy Results of the Mean Change in Itching Score from Baseline at Each Visit (Full Analysis Set)

Visit	Vehicle (N = 58)	Verkazia QID (N = 56)	Verkazia BID (N = 54)
Baseline	78.4 (16.3)	78.0 (18.2)	80.1 (14.8)
Month 1	-18.3 (21.2)	-33.8 (32.1)	-24.4 (29.6)
Month 2	-18.6 (23.0)	-36.0 (35.5)	-29.1 (27.6)
Month 3	-21.6 (25.1)	-39.8 (34.9)	-35.4 (32.0)
Month 4	-25.4 (26.6)	-44.1 (38.1)	-35.8 (34.9)



Source: Review team analysis based on ADQS.xpt dataset.
[1] Treatment differences (numbers in the middle of the horizontal lines) and 95% confidence intervals (horizontal lines) are based on ANCOVA model including baseline itching score and the proportion of time potentially spent in taking study medication during the VKC season as covariate. For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last available data observed prior to rescue initiation.
Note 1: Itching score at each visit was measured using Visual Analogue Scale (0:no itch to 100: maximal itch).
Note 2: The Full Analysis Set included all randomized patients who received at least one drop of study medication.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; N, number of patients; VKC, vernal keratoconjunctivitis

7. Risk and Risk Management

No significant safety issues have been identified by nonclinical data or have been identified during the clinical development of Verkazia.

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Not applicable.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Not applicable.

7.3. Potential Safety Concerns Identified Through Post-market Experience

Verkazia received a marketing authorization in the European Union on 6 July 2018 and is now approved in all European Union countries and additionally in Canada, Iceland, Liechtenstein, Norway, Switzerland, and the United Kingdom. Verkazia is currently marketed in Canada, Denmark, Austria, and the United Kingdom.

Since launch to 19 March 2020, a total of (b) (4) monthly doses of Verkazia have been sold. The total patient years of exposure can be estimated as (b) (4) patient years, calculated by dividing the total sales of monthly doses by the number of months in one year (b) (4) Santen also distributes Ikervis, indicated for the treatment of severe keratitis in adults with dry eye disease. Ikervis and Verkazia are identical in their formulation. In Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, and Myanmar, the indications for Ikervis also include the treatment of severe VKC in children from 4 years of age to adolescents. The cumulative patient exposure (up to 19 March 2020) from post-marketing experience with Ikervis, based on a cumulative total of (b) (4) monthly doses, is estimated as (b) (4) patient years.

During the compassionate use program for Ikervis in France (b) (4) monthly units were distributed, for a further (b) (4) patient years of exposure. In addition to Ikervis and Verkazia, Santen has a third cyclosporine-containing product registered as an orphan drug in Japan under the tradename Papilock. Papilock is indicated for the treatment of VKC when insufficient

efficacy is observed with other anti-allergic medications. The cumulative sales (up to 19 March 2020) of Papilock are (b) (4) monthly units, for (b) (4) estimated patient years of exposure.

For ophthalmic CsA (all products combined), 879 adverse drug reactions have been reported from post- marketing sources (solicited and spontaneous reports) from launch to 19 March 2020. Most spontaneously reported adverse drug reactions (519/855) were coded to the Standard Occupational Classification Eye disorders; eye irritation (113 case reports), eye pain (110 case reports), ocular hyperemia (57 case reports) and lacrimation increased (52 case reports) being the most frequent events.

The 10th Periodic Safety Update Report (PSUR; covering the period from 20 September 2019 to 19 March 2020) including post-marketing safety data for Verkazia, Ikervis, and Papilock is provided in Module 5.3.6. No new signals or any new information which has an impact on the benefit-risk balance of Ikervis or Verkazia have been identified during the reporting period.

From the December 17, 2020, submission, the following list is a summary of PSUR #11:

- No new significant safety and/or efficacy information related to the ophthalmic use of CsA has been identified during the reporting period of March 20, 2020 to September 19, 2020.
- The benefit-risk balance of Verkazia remains unchanged and the routine pharmacovigilance activities are assessed as appropriate for the evaluation of the efficacy and safety of Verkazia.
- There are no proposals for additional risk minimization activities to be incorporated into the safety profile of Verkazia provided in the original NDA.
- There are no ongoing studies with Verkazia.

7.4. FDA Approach to the Safety Review

The clinical safety review focused on the safety database from VEKTIS (NVG09B113) and NOVATIVE (NVG05L101). The NOVATIVE Study used two different formulations, containing either (b) (4) or cetalkonium chloride as an excipient. The VEKTIS Study was performed with the cetalkonium chloride formulation only. This review focuses on the patients exposed to Verkazia HD (0.1% dosed QID) and placebo in both studies.

7.5. Adequacy of Clinical Safety Database

The mean exposure to Verkazia 0.1% dosed QID regimen was 37.2 weeks in the VEKTIS Study and 14.4 weeks in the NOVATIVE Study. Approximately 70% of patients were dosed with Verkazia 0.1% dosed QID for ≥33 to <53 weeks.

The safety population is representative of the population that Verkazia is intended to treat. The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

Table 18. Duration of Exposure, Safety Population, VEKTIS and NOVATIVE Studies

	VEKTIS			NOVATIVE		
Variable	0.1% QID N=79 n (%)	0.1% BID N=80 n (%)	Placebo N=58 n (%)	0.1% QID N=56 n (%)	0.05% QID N=58 n (%)	Placebo N=40 n (%)
Duration of treatment (weeks)						
Mean (SD)	37.2 (15.4)	31.9 (16.5)	15.2 (3.7)	14.4 (4.7)	14.7 (3.0)	3.9 (0.8)
Median (min, max)	47.1 (0.0, 52.7)	32.4 (0.0, 55.6)	16.1 (0.1, 19.3)	16.1 (1, 19.6)	15.9 (4.1, 18.1)	4.1 (0.6, 4.6)
Patients treated, by duration, n (%)						
<5 weeks	5 (6.3)	3 (3.8)	1 (1.7)	5 (8.9)	0	15 (37.5)
≥5 to <15 weeks	6 (7.6)	13 (16.2)	7 (12.1)	14 (25.0)	20 (34.5)	25 (62.5)
≥15 to <33 weeks	11 (13.9)	18 (22.5)	50 (86.2)	37 (66.1)	36 (62.1)	0
≥33 to <53 weeks	56 (70.9)	44 (55)	0	0	0	0
≥53 weeks	1 (1.3)	1 (1.2)	0	0	0	0

Source: adex.xpt; Software: Python
Abbreviations: N, number of patients in treatment arm; n, number of patients with given treatment duration; SD, standard deviation

***Reviewer's comment*:**

The overall exposure to the proposed Verkazia 0.1% dosed QID, proposed for marketing, was adequate (Table 18).

Table 19. Baseline Demographic and Clinical Characteristics, Safety Population, VEKTIS and NOVATIVE Studies

	VEKTIS			NOVATIVE		
Characteristic	0.1% QID N=79	0.1% BID N=80	Placebo N=58	0.1% QID N=56	0.05% QID N=58	Placebo N=40
Sex, n (%)						
Female	16 (20.3)	20 (25.0)	12 (20.7)	9 (16.1)	13 (22.4)	11 (27.5)
Male	63 (79.7)	60 (75.0)	46 (79.3)	47 (83.9)	45 (77.6)	29 (72.5)
Age, years						
Mean (SD)	8.9 (3.3)	9.5 (3.3)	8.9 (3.2)	9.0 (3.4)	8.6 (2.8)	8.5 (2.4)
Median (min, max)	8.0 (4.0, 17.0)	9.0 (4.0, 17.0)	8.0 (4.0, 17.0)	8.0 (4.0, 21.0)	8.0 (4.0, 15.0)	8.0 (4.0, 12.0)
Age group						
Children (4-11 years)	61 (77.2)	58 (72.5)	46 (79.3)	44 (78.6)	48 (82.8)	33 (82.5)
Adolescent (12-18 years)	18 (22.8)	22 (27.5)	12 (20.7)	11 (19.6)	10 (17.2)	7 (17.5)
Missing	0	0	0	1 (1.8)	0	0
Ethnicity, n (%)						
Missing	79 (100.0)	80 (100.0)	58 (100.0)	56 (100.0)	58 (100.0)	40 (100.0)
Race, n (%)						
Asian	17 (21.5)	17 (21.2)	13 (22.4)	0	0	0
Black	4 (5.1)	6 (7.5)	2 (3.4)	0	0	0
Caucasian	56 (70.9)	55 (68.8)	41 (70.7)	0	0	0
Other	2 (2.5)	2 (2.5)	2 (3.4)	0	0	0
Missing	0	0	0	56 (100.0)	58 (100.0)	40 (100.0)

Source: Module 2.7.3 Summary of Clinical Efficacy
Abbreviations: N, number of patients in treatment arm; n, number of patients with given treatment duration; SD, standard deviation

Reviewer's comment:
The majority of the patients enrolled in VEKTIS and NOVATIVE were male with a mean age of 9 years, which is representative of the vernal keratoconjunctivitis patient population.

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, VEKTIS (NVG09B113) and NOVATIVE (NVG05L101)

7.6.1.1. Treatment-Emergent Adverse Event Summary

Table 20. Overview of Adverse Events, Safety Population, VEKTIS and NOVATIVE Studies

	VEKTIS			NOVATIVE		
Event Category	**0.1% QID N=79 n (%)**	**0.1% BID N=80 n (%)**	**Placebo N=58 n (%)**	**0.1% QID N=56 n (%)**	**0.05% QID N=58 n (%)**	**Placebo N=40 n (%)**
Any AE	42 (53.2)	33 (41.2)	23 (39.7)	19 (33.9)	28 (48.3)	14 (35.0)
Moderate or severe AEs	19 (24.1)	9 (11.2)	14 (24.1)	10 (17.9)	12 (20.7)	9 (22.5)
Any SAE	3 (3.8)	1 (1.2)	0	0	1 (1.7)	0
SAE with fatal outcome	0	0	0	0	0	0
AE leading to discontinuation of study drug	4 (5.1)	0	4 (6.9)	3 (5.4)	4 (6.9)	6 (15.0)
AE leading to interruption of study drug	3 (3.8)	1 (1.2)	4 (6.9)	0	0	0

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

Reviewer's comment:

The overall adverse event rates in each study and each treatment group were similar. The percentage of adverse events which led to discontinuation was 5% in the Verkazia 1 mg/mL dose groups and 0 to 15% in the other treatment groups (Table 20).

Table 21. Adverse Events, Safety Population, VEKTIS and NOVATIVE Studies

	VEKTIS			NOVATIVE		
Preferred Term	**0.1% QID N=79 n (%)**	**0.1% BID N=80 n (%)**	**Placebo N=58 n (%)**	**0.1% QID N=56 n (%)**	**0.05% QID N=58 n (%)**	**Placebo N=40 n (%)**
Any AE	42 (53.2)	33 (41.2)	23 (39.7)	19 (33.9)	28 (48.3)	14 (35.0)
Instillation site pain	8 (10.1)	5 (6.2)	2 (3.4)	7 (12.5)	6 (10.3)	2 (5.0)
Ulcerative keratitis	4 (5.1)	4 (5.0)	3 (5.2)	0	1 (1.7)	3 (7.5)
Headache	4 (5.1)	1 (1.2)	1 (1.7)	1 (1.8)	0	0
Ocular hyperemia	4 (5.1)	0	1 (1.7)	2 (3.6)	2 (3.4)	1 (2.5)
Cough	4 (5.1)	0	0	0	0	1 (2.5)
Influenza	4 (5.1)	0	0	0	0	0
Nasopharyngitis	3 (3.8)	5 (6.2)	1 (1.7)	0	0	0
Instillation site pruritus	3 (3.8)	4 (5.0)	2 (3.4)	5 (8.9)	8 (13.8)	1 (2.5)
Eye pruritus	3 (3.8)	1 (1.2)	0	0	0	0

	VEKTIS			NOVATIVE		
Preferred Term	**0.1% QID N=79 n (%)**	**0.1% BID N=80 n (%)**	**Placebo N=58 n (%)**	**0.1% QID N=56 n (%)**	**0.05% QID N=58 n (%)**	**Placebo N=40 n (%)**
Ocular discomfort	3 (3.8)	0	0	0	1 (1.7)	0
Pharyngitis	2 (2.5)	2 (2.5)	0	0	0	0
Tonsillitis	2 (2.5)	2 (2.5)	0	0	0	0
Eye pain	2 (2.5)	1 (1.2)	0	0	0	0
Corneal leukoma	2 (2.5)	0	1 (1.7)	0	0	0
Foreign body sensation in eyes	2 (2.5)	0	0	0	0	0
Upper respiratory tract infection	2 (2.5)	0	0	0	0	0
Instillation site erythema	1 (1.3)	2 (2.5)	2 (3.4)	0	0	0
Pyrexia	1 (1.3)	2 (2.5)	2 (3.4)	0	0	0
Visual acuity reduced	0	0	1 (1.7)	3 (5.4)	3 (5.2)	1 (2.5)
Allergic keratitis	0	0	0	2 (3.6)	2 (3.4)	3 (7.5)
Drug intolerance	0	0	0	1 (1.8)	6 (10.3)	0
Pooled Terms						
Eye pain[1]	10 (12.6)	6 (7.5)	2 (3.4)	7 (12.5)	6 (10.3)	2 (5.0)
Nasopharyngitis[2]	5 (6.3)	7 (12.1)	1 (1.7)	0	0	0
Eye pruritus[3]	6 (7.6)	5 (6.3)	2 (3.4)	5 (8.9)	8 (13.8)	1 (2.5)
Ocular discomfort[4]	5 (6.3)	0	0	0	1 (1.7)	0

Source: adae.xpt; Software: Python
Included AEs that occurred in at least two patients
[1] includes instillation site pain and eye pain
[2] includes Nasopharyngitis and Pharyngitis
[3] includes Instillation site pruritus and eye pruritus
[4] includes ocular discomfort and foreign body sensation in eye
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Reviewer's comment:
The adverse events which occurred more frequently in the Verkazia, 1 mg/mL QID groups than in the placebo groups, and occurred in more than one patient, are corneal leukoma, cough, drug intolerance, eye pain, eye pruritus, foreign body sensation, headache, influenza, instillation site pain, instillation site pruritus, nasopharyngitis, ocular discomfort, ocular hyperemia, pharyngitis, tonsillitis, upper respiratory tract infection, visual acuity reduced. Some of these adverse events were consistent with the underlying disease process in vernal keratoconjunctivitis. In Table 21, similar preferred terms were pooled creating new pooled eye pain, eye pruritus, nasopharyngitis and ocular discomfort terms. Pooling of these terms did not demonstrate a significant change in the relative frequency of these events.

It is recommended that adverse event labeling include the following ophthalmic terms: eye pain (instillation site pain and eye pain), eye pruritus (instillation site pruritus and eye pruritus), ocular discomfort (ocular discomfort and foreign body sensation), ocular hyperemia, and visual acuity reduced.

7.6.1.2. Deaths

No patients died during the VEKTIS or NOVATIVE studies.

7.6.1.3. Serious Adverse Events

Five patients reportedly experienced serious adverse events during the VEKTIS or NOVATIVE studies.

Table 22. Serious Adverse Events, Safety Population, VEKTIS and NOVATIVE Studies

	VEKTIS			NOVATIVE		
Preferred Term	**0.1% QID N=79 n (%)**	**0.1% BID N=80 n (%)**	**Placebo N=58 n (%)**	**0.1% QID N=56 n (%)**	**0.05% QID N=58 n (%)**	**Placebo N=40 n (%)**
Any SAE	3 (3.8)	1 (1.2)	0	0	1 (1.7)	0
Phimosis	1 (1.3)	0	0	0	0	0
Tibia fracture	1 (1.3)	0	0	0	0	0
Ulcerative keratitis	1 (1.3)	0	0	0	0	0
Head injury	0	1 (1.2)	0	0	0	0
Asthma	0	0	0	0	1 (1.7)	0

Source: adae.xpt; Software: Python
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event

Reviewer's comment:
One subject experienced a serious adverse event of ulcerative keratitis in the Verkazia QID group in the VEKTIS study (Table 22). This serious adverse event may have been attributable to worsening of VKC.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events

Table 23. Adverse Events Leading to Discontinuation, Safety Population, VEKTIS and NOVATIVE Studies

	VEKTIS			NOVATIVE		
Preferred Term	**0.1% QID N=79 n (%)**	**0.1% BID N=80 n (%)**	**Placebo N=58 n (%)**	**0.1% QID N=56 n (%)**	**0.05% QID N=58 n (%)**	**Placebo N=40 n (%)**
Any AE leading to discontinuation	4 (5.1)	0	4 (6.9)	3 (5.4)	4 (6.9)	6 (15.0)
Ulcerative keratitis	2 (2.5)	0	2 (3.4)	0	1 (1.7)	3 (7.5)
Eye pain	2 (2.5)	0	0	0	0	0
Eye irritation	1 (1.3)	0	0	0	0	0
Visual acuity reduced	0	0	1 (1.7)	0	2 (3.4)	0
Throat tightness	0	0	1 (1.7)	0	0	0
Allergic keratitis	0	0	0	1 (1.8)	1 (1.7)	2 (5.0)
Instillation site lacrimation	0	0	0	1 (1.8)	0	0
Instillation site pruritus	0	0	0	1 (1.8)	0	0
Asthma	0	0	0	0	1 (1.7)	0
Drug intolerance	0	0	0	0	1 (1.7)	0
Urticaria	0	0	0	0	0	1 (2.5)

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

Reviewer's comment:
The most frequently reported adverse event which led to discontinuation, ulcerative keratitis, represents progression of the underlying condition or drug ineffectiveness (Table 23). The other ophthalmic adverse events which led to discontinuation represent signs and symptoms of the underlying condition and those associated with topical instillation of cyclosporine formulations.

The systemic adverse events which led to discontinuation – throat tightness, asthma, and urticaria – are associated with atopy which is common in this patient population.

7.6.1.5. Treatment-Emergent Adverse Events

Table 24 Adverse Events Assessed by Investigator as Treatment-Related, Safety Population, VEKTIS and NOVATIVE Studies

	VEKTIS			NOVATIVE		
Preferred Term	**0.1% QID N=79 n (%)**	**0.1% BID N=80 n (%)**	**Placebo N=58 n (%)**	**0.1% QID N=56 n (%)**	**0.05% QID N=58 n (%)**	**Placebo N=40 n (%)**
Any treatment-related AE	14 (17.7)	9 (11.2)	9 (15.5)	17 (30.4)	21 (36.2)	8 (20.0)
Instillation site pain	8 (10.1)	5 (6.2)	2 (3.4)	7 (12.5)	6 (10.3)	2 (5.0)
Instillation site pruritus	2 (2.5)	3 (3.8)	2 (3.4)	5 (8.9)	8 (13.8)	1 (2.5)
Eye pain	2 (2.5)	0	0	0	0	0
Eye irritation	1 (1.3)	1 (1.2)	0	0	0	0
Corneal leukoma	1 (1.3)	0	1 (1.7)	0	0	0
Ocular hyperemia	1 (1.3)	0	0	2 (3.6)	2 (3.4)	1 (2.5)
Blepharospasm	1 (1.3)	0	0	0	0	0
Eyelid erosion	1 (1.3)	0	0	0	0	0
Headache	1 (1.3)	0	0	0	0	0
Rhinorrhea	1 (1.3)	0	0	0	0	0
Instillation site erythema	0	2 (2.5)	2 (3.4)	0	0	0
Instillation site lacrimation	0	1 (1.2)	0	1 (1.8)	0	0
Application site swelling	0	1 (1.2)	0	0	0	0
Eye pruritus	0	1 (1.2)	0	0	0	0
Instillation site foreign body sensation	0	1 (1.2)	0	0	0	0
Visual acuity reduced	0	0	1 (1.7)	3 (5.4)	1 (1.7)	1 (2.5)
Application site discharge	0	0	1 (1.7)	0	0	0
Cataract subcapsular	0	0	1 (1.7)	0	0	0
Eyelid oedema	0	0	1 (1.7)	0	0	0
Intraocular pressure increased	0	0	1 (1.7)	0	0	0
Rash	0	0	1 (1.7)	0	0	0
Throat tightness	0	0	1 (1.7)	0	0	0
Drug intolerance	0	0	0	1 (1.8)	6 (10.3)	0
Allergic keratitis	0	0	0	1 (1.8)	1 (1.7)	1 (2.5)
Ulcerative keratitis	0	0	0	0	1 (1.7)	2 (5.0)
Keratitis	0	0	0	0	1 (1.7)	0
Pain	0	0	0	0	1 (1.7)	0
Urticaria	0	0	0	0	0	1 (2.5)

Source: adae.xpt; Software: Python
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

7.6.1.6. Laboratory Findings

Laboratory studies were not conducted in the submitted studies.

7.6.1.7. Summary Safety Findings

Routine pharmacovigilance activities appear appropriate for the evaluation of the efficacy and safety of the product. There are no proposals for additional risk minimization activities to be incorporated into the pharmacovigilance plan. No changes are proposed to the reference safety information based on this PSUR.

The most common adverse reactions reported in the 10th PSUR were “eye irritation,” “eye pain,” “ocular hyperemia,” and “lacrimation increased.” “Eye irritation,” “eye pain,” and “ocular hyperemia” were among the most frequently reported adverse events reported in the NOVATIVE and VEKTIS studies. “Lacrimation increased” was reported in ≤1% of patients in the NOVATIVE and VEKTIS studies and is not included in the proposed labeling. No new or significant safety concerns were identified through post-market experience**.**

7.7. Key Review Issues Relevant to Evaluation of Risk

Not applicable.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Not applicable.

8.2. Drug Interactions

Drug interaction studies were not performed during the clinical development for Verkazia.

8.3. Plans for Pediatric Drug Development

The submitted studies enrolled pediatric patients aged 4 through 18 years of age which is representative of the vernal keratoconjunctivitis population.

8.4. Pregnancy and Lactation

Verkazia has not been tested in pregnant or lactating women.

Table 25 Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	Derived from listed drugs: **Oral administration of cyclosporine oral solution to pregnant rats or rabbits was teratogenic at maternally toxic doses of 30 mg/kg/day in rats and 100 mg/kg/day in rabbits, as indicated by increased pre- and post-natal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body weight) were approximately 320 and 2150 times higher than the daily maximum recommended human ophthalmic dose (MRHOD) of 0.015 mg/kg/day, respectively.** No adverse embryofetal effects were observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively (approximately 185 and 645 times higher than the MRHOD, respectively). Derived from Ryffel article An oral dose of 45 mg/kg/day cyclosporine (approximately 485 times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in mothers or offspring were observed at oral doses of up to 15 mg/kg/day (160 times greater than MRHOD).
8.2 Lactation	Derived from listed drugs: Administration of oral cyclosporine to rats during lactation did not produce adverse effects in offspring at clinically relevant doses
8.3 Females and Males of Reproductive Potential	Derived from Ryffel article No impairment of fertility has been reported in animals receiving intravenous cyclosporine
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Derived from Ryffel article Oral administration of cyclosporine to rats for 12 weeks (male) and 2 weeks (female) prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day (160 times higher than MRHOD).

Source: (Ryffel et al. 1983)
Abbreviations: MRHOD, maximum recommended human ophthalmic dose

9. Product Quality

The Office of Pharmaceutical Quality (OPQ) Review team has assessed NDA 214965 with respect to Chemistry, Manufacturing, and Controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such,

the Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

Verkazia™ is a sterile, unpreserved, (b) (4) topical ophthalmic emulsion containing cyclosporine United States Pharmacopeia 1 mg/mL (0.1% weight per weight) and is packaged in single-dose low-density polyethylene vials. The shelf life of 36 months is granted when stored at 20°C to 25°C (68°F to 77°F). The OPQ review team requested that the comment, "We acknowledge your plan to include an additional manufacturer for cetalkonium chloride with the proposed reporting category of CBE-30. However, we remind you that the additional manufacturer should be registered with the FDA and in Good Manufacturing Practice standing" be included in the action letter, but since the requirement to be registered with the FDA and in current good manufacturing practice is already required in the regulations, a separate notation will not be added to the action letter.

Table 26 Composition of Verkazia Ophthalmic Emulsion

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		%w/w[a]	mg/mL
Cyclosporine (USP)	Drug substance	0.10	1.0
Triglycerides, medium-chain (USP)	(b) (4)	(b) (4)	(b) (4)
Tyloxapol (USP)			
Cetalkonium chloride (In-house)			
Glycerol (USP)			
Poloxamer 188 (USP)			
Sodium Hydroxide (USP)	pH adjuster		
Water for Injection (USP)	(b) (4)		
Total			

[a]Density of the emulsion is (b) (4) g/mL. Source: Module 3.2.P.1. Description and Composition of the Drug Product

Table 27 Drug Product Specifications

Characteristics	Acceptance Criteria	Method (Compendia or Excelvision #)
Appearance	(b) (4	(b) (4)
Identification of Cyclosporine[b] HPLC HPLC/UV		
pH		USP <791>
Osmolality (mOsmol/kg)		USP <785>
Zeta Potential (mV)		(b) (4)
Mean Droplets Size (nm)		
Content Uniformity[b]		
Degradation Products (%)		
Sterility		
Cyclosporine Assay % of Label Claim		
	(b) (4)	

Source: Module 3.2.P.5. Control of Drug Product

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice/Inspections/Financial Disclosure

VEKTIS (NVG09B113) study is a pivotal study conducted from 2013 through 2016 by Santen SAS. This study is a global clinical study including 4 sites in the United States. Santen confirmed that none of the financial interests or arrangements described in 21 Code of Federal Regulations Section 54.4(a)(3) exists.

Clinical study NOVATIVE (Protocol NVG05L101) is a supportive, dose ranging study conducted from 2006 through 2007 by Novagali, which was the company's former name before Santen acquired it. The clinical sites of the NOVATIVE study were all located outside of the United States. Despite Santen's diligent efforts to obtain from the participating Investigators the United States financial disclosure form duly filled in and signed by them, Santen was unable to obtain these forms from the Investigators. Refer also to Section 24.

11. Advisory Committee Summary

No Advisory Committee Meeting was held for this application.

III. Appendices

12. Summary of Regulatory History

Novagali Pharma, SA Inc. submitted investigational new drug (IND) 70502 for cyclosporine A (CsA) (NOVA22007) for the treatment of (b) (4) vernal keratoconjunctivitis (VKC) to the Food and Drug Administration on December 27, 2006.

- February 24, 2006: Pre-IND meeting to discuss the development of the NOVATIVE study.
- May 4, 2007: Verkazia was granted an Orphan Drug Designation in the United States for the treatment of VKC.
- October 11, 2011: Santen Ltd. acquired Novagali Pharma including IND 70502.
- January 14, 2008: End of Phase 2 meeting to discuss development of the Phase 3 trial, VEKTIS.
- December 18, 2018: Pre–new drug application (NDA) meeting to discuss the acceptability of VEKTIS and NOVATIVE for an NDA filing.
- April 30, 2020: Pre-NDA meeting to discuss the reanalysis of VEKTIS as additional information to the clinical data package to support the submission and the NDA filing.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

13.1.1. Study N09F1205: Ocular Pharmacokinetic Study Following a Single Topical Administration in Pigmented Rabbits

This study reported the comparative ocular distribution between Restasis® and NOVA22007. After a single (b) (4) µL unilateral instillation of NOVA22007 formulation (0.025%, 0.05%, and 0.1%) and Restasis 0.05% in pigmented rabbit eyes, CsA appeared rapidly in cornea and conjunctiva. CsA absorption in blood was undetectable.

13.1.2. Study N09F0306: Ocular Pharmacokinetic Study Following Multiple Topical Administrations in Pigmented Rabbits

This study reported the comparative ocular distribution between Restasis and NOVA22007. No accumulation of CsA in conjunctiva was observed after 10 days of repeat administration of NOVA22007 (0.05% four times daily [QID], 0.05% twice daily [BID], and 0.1% QID) and

Restasis 0.05% BID. Corneal concentrations were significantly higher than conjunctival ones for all groups. NOVA22007 0.05% BID doubled both the corneal minimum plasma concentration and the concentration at 0.33 hours post-dose of Restasis 0.05% BID. No systemic absorption of CsA was detected after multiple administrations of these products.

13.2. Individual Reviews of Studies Submitted to the NDA

13.2.1. Study Tp118: Cyclosporin A Ocular Pharmacokinetic Study After a Single Application in Eye in the Rabbit

This good laboratory practice (GLP)-compliant study assessed the ocular distribution of CsA to the cornea and bulbar and palpebral conjunctiva after a single ocular application of three different formulations in the rabbit.

Formulations tested include:

- NOVA22007 (0.1%; cetalkonium chloride [CKC]-containing to-be-marketed formulation; Z06EM147Batch#Z06EM106)
- NOVA22007 (b) (4) (b) (4) -containing Generation 2 formulation)
- Cyclosporine A (b) (4) ((b) (4)

The animals from each group received a single bilateral dose ((b) (4) µL) of the test article by topical ocular instillation.

Animals were sacrificed at different time points (0.5, 1, 2, 4, 8, 12, and 24 hours) and cornea and bulbar and palpebral conjunctivae were removed from both eyes.

Results

No changes in appearance and behavior or body weight were reported.

The area under the concentration-time curve from 0 to 24 hours was evaluated in cornea and conjunctiva for each dose group and are reported in the following table:

Table 28. Pharmacokinetics in Cornea and Conjunctiva

	Numerical field name	Units	GROUP 1 NOVA22007 Ref. Z06EM106	GROUP 3 NOVA22007 Ref. Z06EM147	GROUP 4 NOVA22007 Reference Ref. Z06SOL146
Cornea	T_{max}	h	0-0.5	1-2	0.5-1
	$AUC_{0.-24h}$	ng/g x h	18357	15866	59930
Conjunctiva	T_{max}	h	0-0.5	0.5-1	0.5-1
	$AUC_{0.-24h}$	ng/g x h	8836	8563	20167

Source: Applicant study report
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; h, hour; T_{max}, time to maximum concentration

Distribution of CsA to the cornea and conjunctiva was similar; no significant difference between the CKC and (b) (4) formulations was reported (Table 28).

13.2.2. Study N09F34413: Ocular Pharmacokinetic Study of Cyclosporin A Formulations Following a Single Instillation in Pigmented Rabbits

This non-GLP study characterized CsA distribution to the conjunctiva and cornea in pigmented rabbits following administration of three different formulations:

- NOVA22007-CKC (Z06EM106 0.1%); to-be-marketed Verkazia® formulation; Batch#2A44
- CsA in (b) (4) (Z06SOL229 (b) (4); BatchZ06D491.
- CsA in (b) (4) (Z06SOL235 (b) (4); Batch#Z06D499

The animals from each group received a single bilateral dose ((b) (4) µL) of the test article by topical ocular instillation.

CsA was quantified in cornea and conjunctivae at distinct timepoints until 24 hours after instillation.

Analysis focused on the comparative exposure of the CKC and CsA (b) (4) formulations.

Table 29. Pharmacokinetic Parameters (ng/g of Tissue)

	Cornea		Conjunctiva	
	CKC emulsion (Z06EM106)	**CsA (b) (4) (b) (4)**	**CKC emulsion (Z06EM106)**	**CsA (b) (4) (b) (4)**
C_{max} (ng/g)	695	229	239	488
t_{max} (h)	1	0.5	1	0.5
$t_{1/2}$ (h)	13.5	7.8	NA	3.1
$AUC_{0.5\text{-}24\ h}$	7377	1374	1484	382

Note: C_{max}= the highest mean value measured (ng/g of structure), t_{max}= time-point when the highest mean value is measured (hours), $t_{1/2}$ (hour) = ((ln(2)) / (-a) and a = (ln (concentration)-b) / time, $AUC_{0.5\text{-}24h}$= area under the curve in ng/g or ml of structure X hours, NA: not applicable, the data of kinetic still indicate an increasing phase or all values = 0 or not enough time-point to calculate the $t_{1/2}$

Source: Applicant study report

Abbreviations: $AUC_{0.5\text{-}24h}$, area under the concentration-time curve from 0.5 to 24 hours; C_{max}, maximum plasma concentration; CsA, cyclosporine A; h, hour; $t_{1/2}$, time to half maximal concentration; t_{max}, time to maximum concentration

The exposure in cornea and conjunctiva, as determined by the area under the concentration-time curve, was 5.4 times and 3.9 times higher with CKC formulation, respectively, than with (b) (4) (b) (4) formulation (Table 29).

13.2.3. Study N09F0407: Ocular Autoradiographic and Pharmacokinetic Comparative Study in Pigmented Rabbits Following Multiple Daily Instillation of ^{3}H-CsA Ophthalmic Emulsions

This GLP study quantitatively and qualitatively compared the distribution of ^{3}H-labelled CsA of both 3H-CsA NOVA22007 (b) (4) containing formulations (b) (4)% and (b) (4)%CsA), and ^{3}H-Restasis (0.05% CsA) following multiple bilateral administrations (up to four times daily) for 7 days in pigmented male rabbits.

Reviewer's comment:
The to-be-marketed clinical formulation of Verkazia was not studied. Similarity in ocular distribution to the cornea and conjunctiva of the CKC to-be-marketed clinical formulation and the (b) (4) formulation were demonstrated in other studies (see above). Results of this study can be subjectively extrapolated based on this finding.

At Day 7, three animals of each treatment group were sacrificed one hour after the last dosing, while the other three were sacrificed 24 hours after the last administration. Whole blood, cerebrospinal fluid, brain, liver, right kidney, spleen, heart, olfactory nerve and the left cornea, conjunctiva, aqueous humor, iris/ciliary body, lens, vitreous, choroid/retina, sclera, optic nerve, lacrimal glands, orbital fat and nasolacrimal duct were sampled, weighed and used for liquid scintillation counting.

For semiquantitative qualitative autoradiography of the cornea and conjunctiva, right eyes were sampled, processed and six microsections per eye were mounted on slides for further autoradiographic analysis.

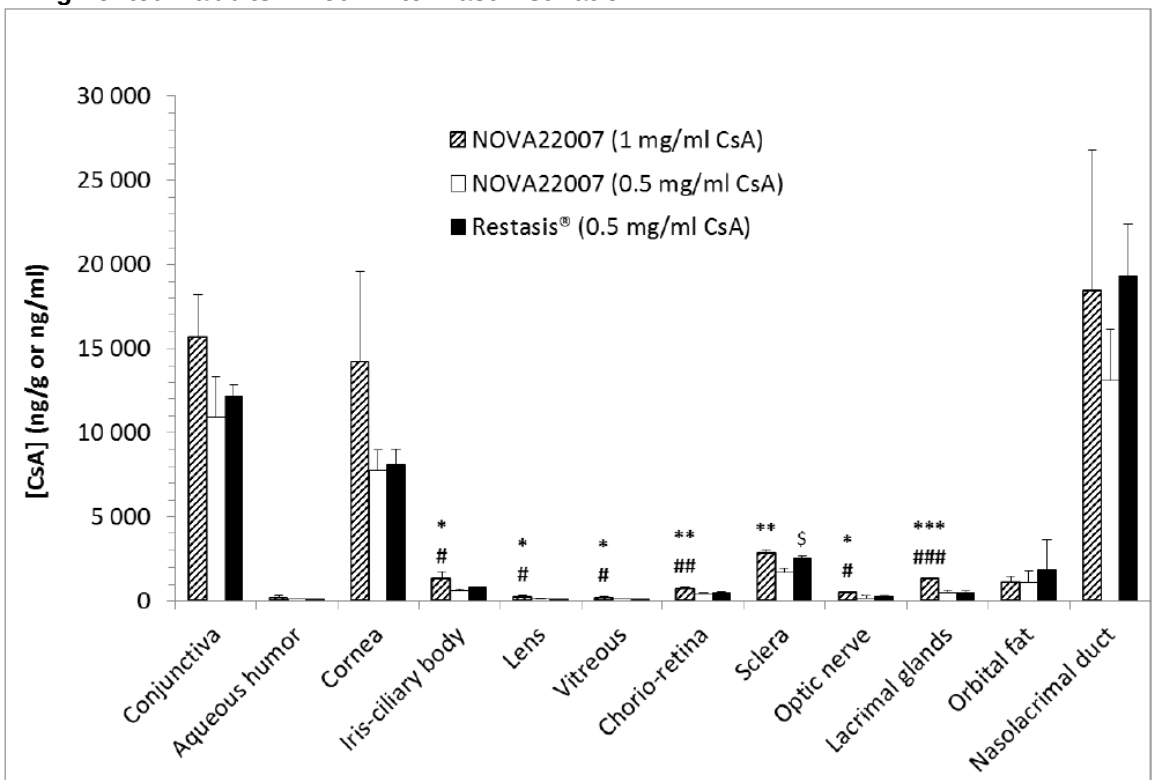
Results showed localization of radioactivity derived from ^{3}H-CsA almost exclusively in cornea and conjunctiva, with no to limited passage into inner ocular tissues (Table 29) and Figure 13). Exposure in the nasolacrimal duct was significant through 24 hours after the final instillation (Figure 14).

Table 29. Cornea and Conjunctiva ^{3}H-CsA Concentrations Determined via Semiquantitative Autoradiography

	NOVA22007				Restasis	
	1 mg/mL		0.5 mg/mL		0.5 mg/mL	
Time	Cornea	Conj.	Cornea	Conj.	Cornea	Conj.
1 hour	1.2 ± 0.5	2.5 ± 0.8	1.6 ± 0.5	2.9 ± 0.8	1.3 ± 0.5	2.4 ± 0.6
24 hours	0.9 ± 0.4	2.1 ± 0.7	1.1 ± 0.4	2.5 ± 1.1	1.1 ± 0.4	2.3 ± 0.6

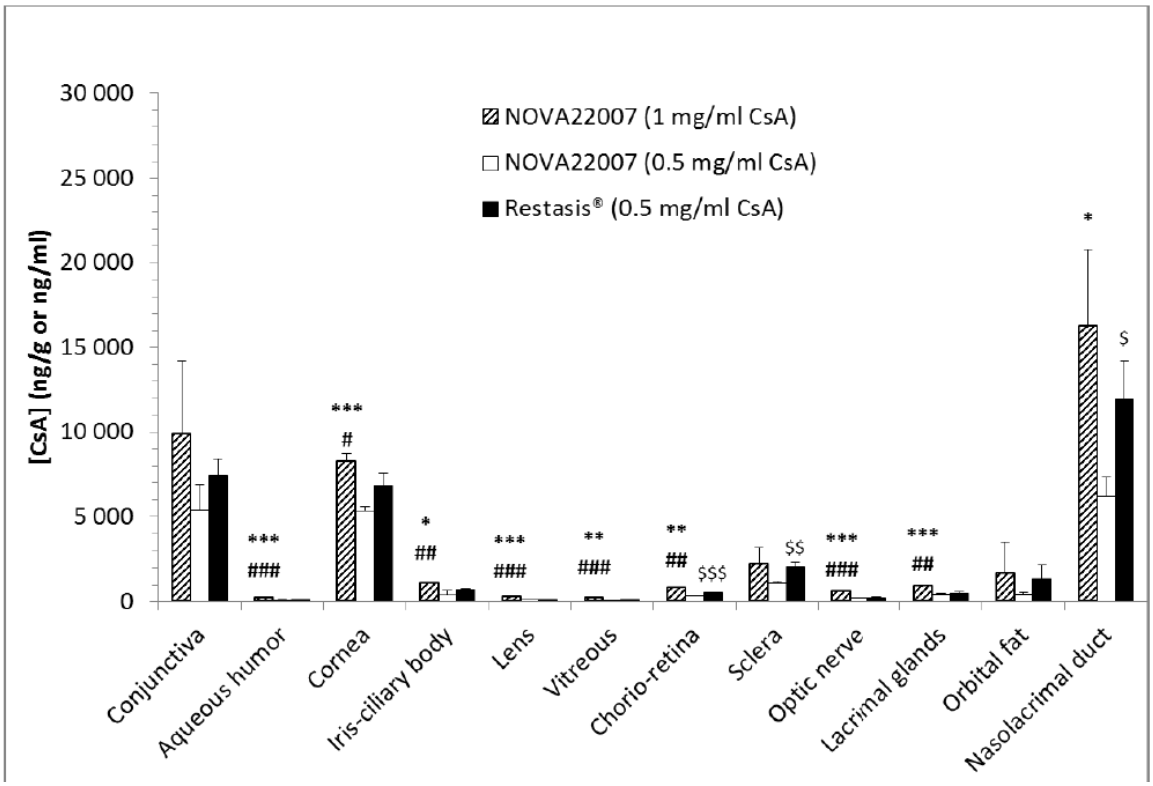
Values expressed as nCi/g of brain. Conj. = conjunctiva.
Source: Applicant study report
Abbreviations: CsA, cyclosporine A

Figure 13. Ocular ^{3}H-CsA Concentrations After 4 Times Daily (QID) Bilateral Instillations for 7 Days in Pigmented Rabbits 1 Hour After Last Instillation



Source: Applicant study report
Abbreviations: CsA, cyclosporine A; QID, four times daily

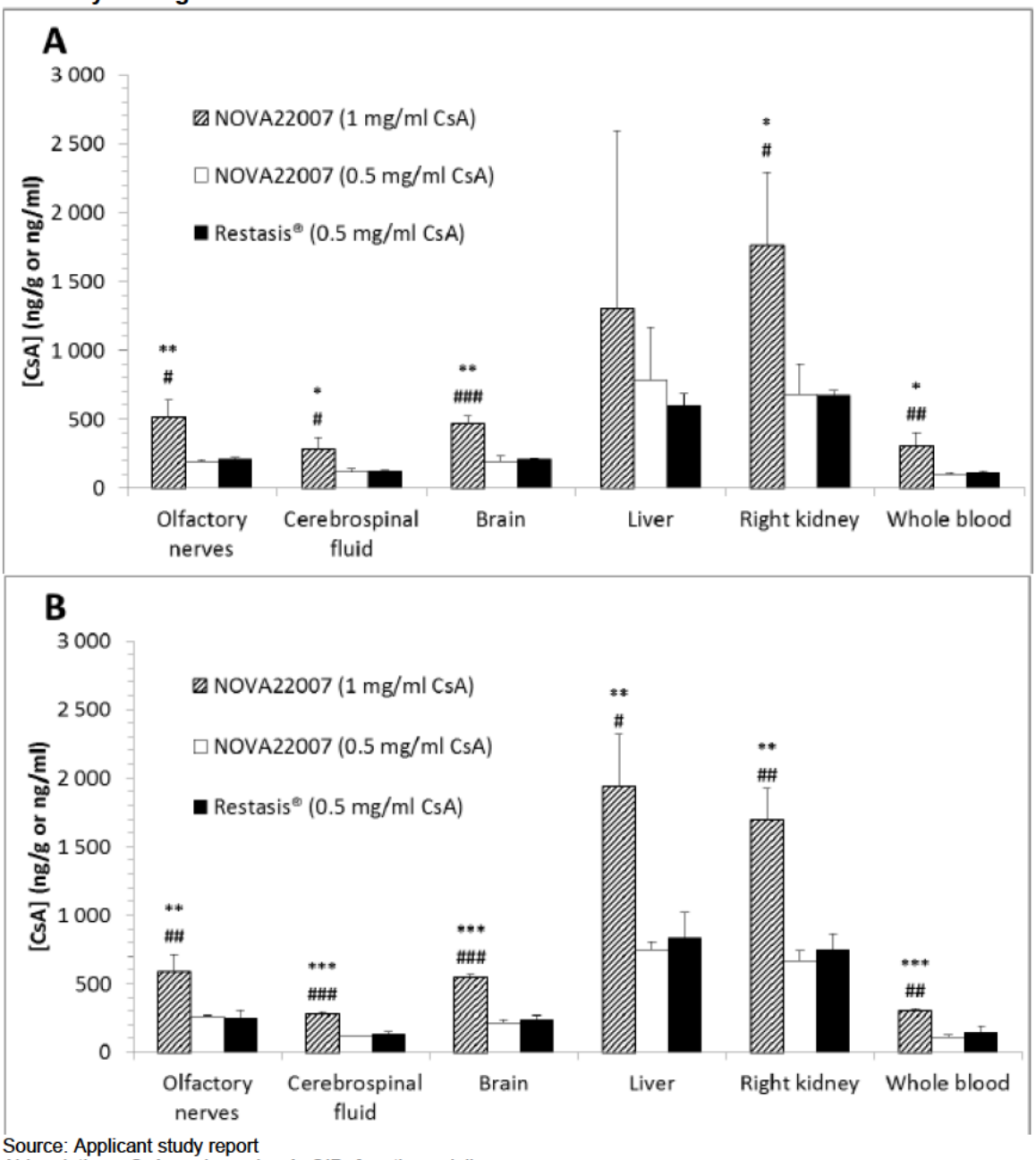
Figure 14. Ocular ^{3}H-CsA Concentrations After 4 Times Daily (QID) Bilateral Instillations for 7 Days in Pigmented Rabbits 24 Hours After Last Instillation



Source: Applicant study report
Abbreviations: CsA, cyclosporine A; QID, four times daily

Significant amounts of radioactivity were found in all analyzed systemic organs at both time points. Since no CsA systemic passage was detected after single and multiple dosing, the detected radioactivity originated most probably from radioactive metabolites. This is supported by the higher count levels found in the major elimination organs, liver and kidney. As for the ocular tissues, the organ distribution profiles of NOVA22007 (0.5 mg/mL and 1 mg/mL) and Restasis were not significantly different, and the level of radioactivity found in the tissues correlated with the total administered CsA dose (Figure 15). In conclusion, NOVA22007 and Restasis have a similar ocular distribution profile. Both emulsions concentrate CsA onto the ocular surface, with very low passage into inner eye tissues. Although low amounts of radioactivity were found in systemic organs, they are attributed to the presence of radiolabeled CsA metabolites.

Figure 15. Systemic Organs ^{3}H-CsA Concentrations After 4 Times Daily (QID) Bilateral Instillations for 7 Days in Pigmented Rabbits



Source: Applicant study report
Abbreviations: CsA, cyclosporine A; QID, four times daily

13.2.4. Study N09F04216: Cyclosporine A Formulation Pilot Ocular Pharmacokinetics Study Comparing an [redacted] Cyclosporine [redacted] to Ikervis Following Multiple Daily Instillations in Pigmented Rabbits

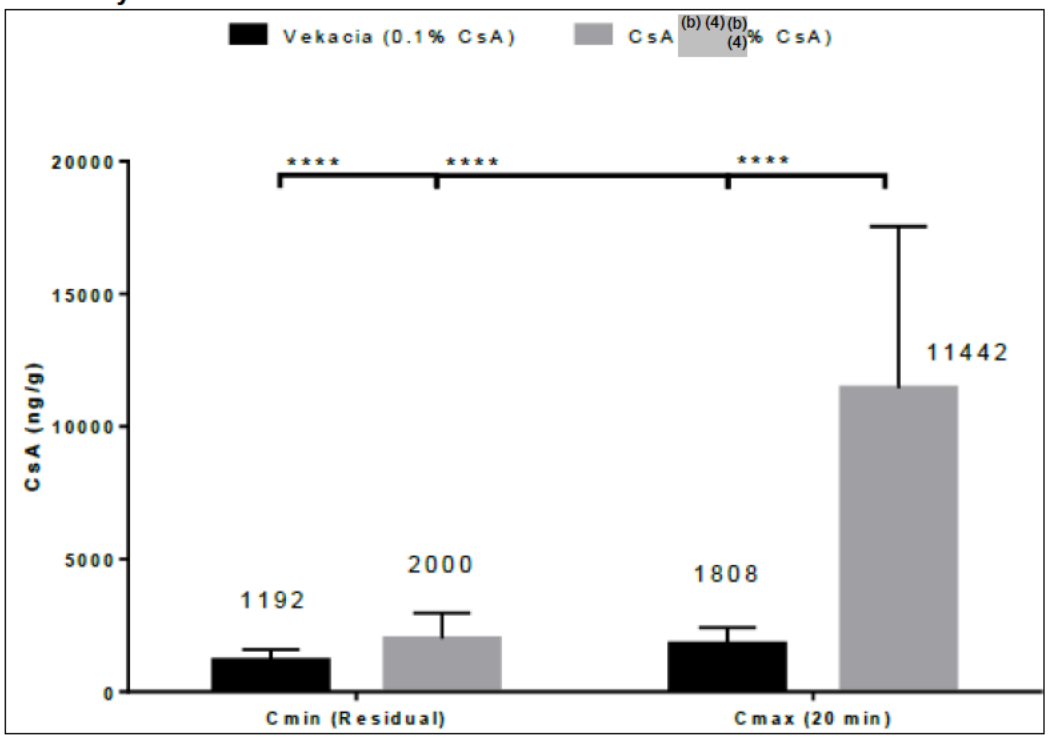
This study compared the to-be-marketed Verkazia 0.1% CsA with [redacted] weight per weight CKC and an [redacted] CsA [redacted] (compounded hospital preparations) in ocular penetration of CsA in ocular tissues and blood after QID instillations for 10 days in right eyes of pigmented rabbits.

Conjunctivae (bulbar and palpebral), cornea and whole blood were measured at 2-time points the maximum plasma concentration (20 minutes) and the minimum plasma concentration (12 hours) after QID instillation for 10 days in 5 rabbits/sex/group.

CsA concentrations after 10 days of administration in the cornea and conjunctiva following Verkazia was lower compared to the [redacted]% CsA [redacted] that mimicked the compounded hospital preparation.

The maximum plasma concentration in the cornea and conjunctiva following instillation of Verkazia 0.1% CsA are: 1,808 ± 610 ng/g and 1279 ± 549 ng/g, respectively (Figure 16). The maximum plasma concentration in the cornea and conjunctiva following the use of [redacted]% CsA [redacted] (compounded hospital preparations) are: 11442 ± 6100 ng/g and 28146 ± 17752 ng/g, respectively (Figure 16).

Figure 16. CsA Concentration in the Cornea at Steady State Following Repeated QID Instillations for 10 Days



Source: Applicant study report
Abbreviations: C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CsA, cyclosporine A; QID, four times daily

13.2.5. Study To146: Ocular Irritation Study After Repeated Applications in the Rabbit

Table 30. Study To146 Information

Parameter	Details
Study no.:	To146
Study report location:	\\CDSESUB1\evsprod\nda214965\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\to146\to146-pre-clinical-study-report.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/8/2008
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	NOVA22007-CKC 0.05%CsA: Batch R541 NOVA22007-CKC 0.1%CsA: Batch R697

Source: Applicant study report
Abbreviations: GLP, good laboratory practices; no, number; QA, quality assurance

Table 31. Study To146 Methods

Parameter	Details
Doses:	Group 1: Vehicle Group 2: 0.05% Group 3: 0.1%
Frequency of dosing:	6 times daily
Route of administration:	Right eye only; Topical ocular instillation
Dose volume:	(b) (4) mL/drop
Formulation/vehicle:	To-be-marketed formulation (CKC containing formulation)
Species/strain:	Rabbit; New Zealand White
Number/sex/group:	4/sex/group
Age:	Not specified
Weight:	2.00-2.34 kg
Deviation from study protocol:	None

Source: Applicant study report
Abbreviations: CKC, cetalkonium chloride

Observations and Results

Mortality

All animals survived until scheduled sacrifice.

Clinical Signs

No changes in clinical signs attributed to the test article.

Body Weights

No changes in body weight attributed to the test article.

Food Consumption

No changes in food consumption attributed to the test article.

Ophthalmoscopy (Dilated; Slit Lamp Biomicroscopy and Indirect Ophthalmoscopy)

Conjunctival irritation

- Described as slight/transient (score 1)
- 0.05% CsA-CKC formulation
  - 100/448 observations (about 22%)
- 0.1% CsA-CKC formulation
  - 111/448 observations (about 25%)
- Also noted transiently on the conjunctiva of eyes receiving 0.9% sodium chloride or untreated eyes, but in smaller proportion (up to 4%)

Gross Pathology

No macroscopic findings attributed to the test article.

Histopathology

Adequate Battery: Eyes only; further details not found (i.e., number of sections examined per eye)

Peer Review: No

Histological Findings

- Chronic conjunctivitis on the bulbar conjunctiva
- Slight focal unilateral
- Untreated eyes
  - 1 eye
- NOVA22007-CKC 0.05% CsA
  - 4 eyes
- NOVA22007-CKC 0.1% CsA
  - 1 eye

Applicant states the finding may be attributable to the treatment since some slight signs of conjunctivae irritation were observed during the experiment.

Toxicokinetics

Systemic exposure to cyclosporine was not detected.

Dosing Solution Analysis

Dosing solutions remained within acceptance criteria for the duration of the treatment phase of the study

13.2.6. Study 20070348TL: NOVA22007-CKC 0.05% and NOVA22007-CKC 0.1%: Study for Evaluation of Local Tolerance After Repeated Daily Instillation in the Eye for 28 Days in the Rabbit

Table 32. Study 20070348TL Information

Parameter	Details
Study no.:	20070348TL
Study report location:	\\CDSESUB1\evsprod\nda214965\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\20070348tl\20070348tl-pre-clinical-study-report.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	9-4-2007
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	Z06EM117: Batch # Z06D201; 97.7% purity Z06EM115: Batch# Z06D202; 98% purity

Source: Applicant study report
Abbreviations: GLP, good laboratory practices; no, number; QA, quality assurance

Key Study Findings

The no observed adverse effect level of the study was considered the high dose of the to-be-marketed CKC formulation 0.1% 6 times daily for 28 days

Table 33. Study 20070348TL Methods

Parameter	Details
Doses:	Group 1: Vehicle Group 2: Saline Group 3: NOVA2207-CKC 0.05% Group 4: NOVA2207-CKC 0.1%
Frequency of dosing:	Four times daily (QID)
Route of administration:	Left eye only; topical ophthalmic instillation
Dose volume:	(b) (4) mL / drop
Formulation/vehicle:	To-be-marketed formulation (CKC containing formulation)
Species/strain:	Rabbit; New Zealand White
Number/sex/group:	4/sex/group
Age:	2-4 months
Weight:	2-2.5 kg
Deviation from study protocol:	None.

Source: Applicant study report
Abbreviations: CKC, cetalkonium chloride; QID, four times daily

Observations and Results

Mortality

All animals survived until scheduled sacrifice.

Clinical Signs

No changes in clinical signs attributed to the test article.

Body Weight

No changes in body weight attributed to the test article.

Food Consumption

No changes in food consumption attributed to the test article.

Ophthalmoscopy (Dilated; Slit Lamp Biomicroscopy and Indirect Ophthalmoscopy)

Vehicle

- One female dosed with the vehicle had a slight redness on day (D) 14.

NOVA22007- CKC 0.05%

- One female had lacrimation on D7 and D14.
- One female had redness on D15.

NOVA22007-CKC 0.1 %

- One female had slight corneal opacity, slight chemosis and slight redness on D2. This female had slight redness and/or lacrimation from D3 to D7 (except D6) and then lacrimation on D14 and redness on D15.

Gross Pathology

No macroscopic findings attributed to the test article.

Histopathology

Adequate Battery: Eyes only (no other details given; i.e., number of slides examined per eye)

Peer Review: No.

Histological Findings

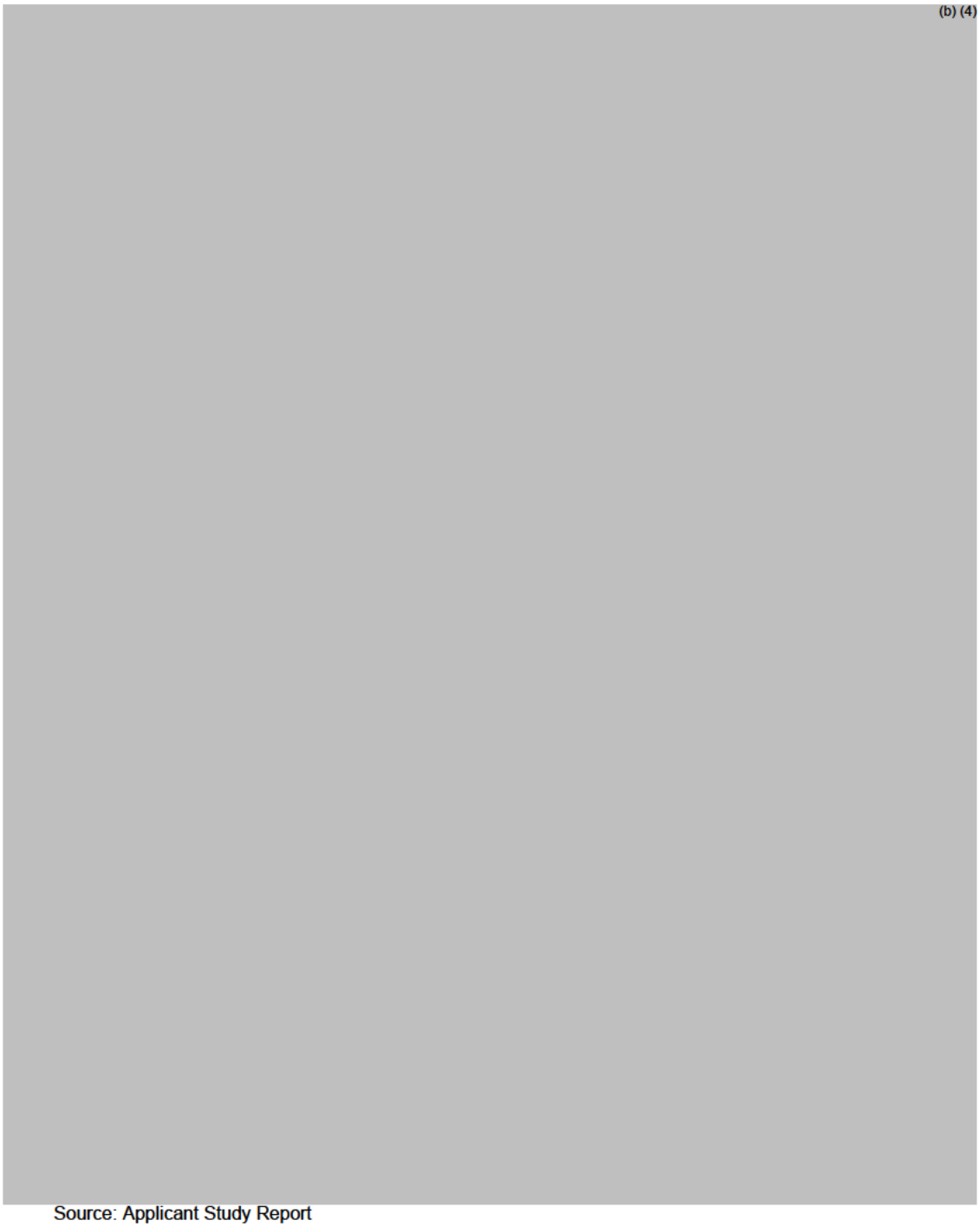
Limbal subacute keratitis.

- No differences in incidence found between untreated eyes, vehicle and CsA-CKC treated rabbits.
- Considered by Applicant as commonplace in laboratory rabbits (historical data not included by Applicant).

Toxicokinetics

Toxicokinetics were not summarized in the report. Individual data shows sporadic detection of exposure with no results exceeding 0.3 ng/mL (Figure 17).

Cyclosporin A concentrations in Study 20070348TL samples



Source: Applicant Study Report
Abbreviations: CKC, cetalkonium chloride; CsA, cyclosporine A; F, female; ILQ, instrument limit of quantification; M, male

Dosing Solution Analysis

Dosing solutions remained within acceptance criteria for the duration of the treatment phase of the study.

13.2.7. Study 451424: 26-Week Ocular Toxicity Study in Rabbits

Table 34. Study 451424 Information

Parameter	Details
Study no.:	451424
Study report location:	\\CDSESUB1\evsprod\nda214965\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\451424\451424-pre-clinical-study-report.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7-29-1994
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	Week 1-12: DE-076 (0.1%): Lot CIC930820-4; 101.5% DE-076 (0.5%): Lot CIC930820-5; 101.5% DE-076 (1.0%): Lot CIC930820-6; 102.6% Week 13-26: DE-076 (0.1%): Lot CIC931116-4; 102.4% DE-076 (0.5%): Lot CIC93116-5; 101.5% DE-076 (1.0%): Lot CIC931116-6; 101.2%

Source: Applicant study report
Abbreviations: GLP, good laboratory practices; no, number; QA, quality assurance

Table 35. Study 451424 Methods

Parameter	Details
Doses:	Group 1: Vehicle for 0.1% DE-076 (left eye) / physiological saline (right eye) Group 2: Vehicle for 1.0% DE-076 Group 3: 0.1% DE-076 Group 4: 0.5% DE-076 Group 5: 1.0% DE-076
Frequency of dosing:	1 drop TID
Route of administration:	Left eye only; topical ocular instillation.
Dose volume:	Not specified; assumed as (b) (4) mL/drop
Formulation/vehicle:	DE-076 (Papilock Mini formulation; see above)
Species/strain:	Rabbit / New Zealand White
Number/sex/group:	3/sex/group
Age:	3 months
Weight:	2.5-3 kg
Deviation from study protocol:	No deviations reported.

Source: Applicant study report
Abbreviations: DE-076, Papilock mini formulation; TID, three times daily

Observations and Results

Mortality

All animals survived until scheduled sacrifice.

Clinical Signs

No changes in clinical signs attributed to the test article.

Body Weights

No changes in body weight attributed to the test article.

Food Consumption

No changes in food consumption attributed to the test article.

Ophthalmoscopy (slit lamp / dilated indirect ophthalmoscopy)

Watery discharge and conjunctival redness/swelling were apparent in the left eye of some animals in all groups (including the controls), however the duration of these effects was greatest in the rabbits receiving 0.5% or 1.0% DE-076 (Papilock miniformulation).

Gross Pathology

Yellow staining around the eyes with mild reddening of the conjunctiva was recorded in one of six and two of six animals from Groups 2 and 5, respectively. These findings are consistent with those seen in the ophthalmoscopic assessments (see above).

Histopathology

Adequate Battery: Eye and adnexa only (eyelids including nictitating membrane, palpebral conjunctiva, cornea, bulbar conjunctiva, iris, ciliary body, lens, sclera, choroid, retina, optic nerve, Harderian glands, lacrimal glands, nasal mucosa, ocular muscles). Details regarding sectioning of the eye or number of sections examined were not found in the report. Corneas of some animals (2/group) were fixed and prepared for scanning electron microscopic analysis.

Peer Review: No.

Histological Findings

No microscopic findings attributed to the test article including analysis of the corneal endothelium by electron microscopy.

Toxicokinetics

Systemic exposure to cyclosporine was not detected. The lower limit of detection of the assay was 23.5 ng/mL

Dosing Solution Analysis

Dosing solutions remained within acceptance criteria for the duration of the treatment phase of the study.

13.2.8. Study N09F0805: Evaluation of Corneal Sensitivity Following Repeated Instillation in Albino Rabbits

New Zealand white rabbits (n=3/group) were administered with five instillations within 20 minutes in the right eye.

Treatment groups:

- NOVA22007 (0.1% CsA)
- NOVA23016 (vehicle of NOVA22007)
- 0.9% sodium chloride
- Novesine (0.4% oxybuprocaine hydrochloride).

Corneal sensitivity of both eyes was tested using an esthesiometer and evaluated before treatment and 10, 20, 30, 45, 60 and 120 min after the last instillation.

NOVA22007 and its vehicle NOVA23016 did not induce a decrease of the corneal sensitivity of the treated eyes in New Zealand White albino rabbits.

13.2.9. Study 29412TSS: Evaluation of Skin Sensitization Potential in Mice Using the Local Lymph Node Assay

This study evaluated the potential of the vehicle of Verkazia® (to-be-marketed CKC-containing vehicle) to induce delayed contact hypersensitivity using the murine Local Lymph Node Assay (LLNA).

- Female CBA/J mice (4 per group) received repeated (3 days) local applications of the vehicle of NOVA22007 1 mg/mL on the ears. The test product was either applied without dilution, or after dilution in water at 1:2 or 1:4.
- No lymphoproliferation (tritiated thymidine incorporation) was observed with the test products, whereas significant lymphoproliferation was observed in the positive control group (Table 36).

Table 36. Study 29412TSS: Evaluation of Skin Sensitization Potential

Treatment	Dilution factor (% (b) (4)	Cutaneous reaction	Irritant potential	Stimulation index (SI)
Vehicle of NOVA22007 1 mg/mL	(b) (4)	No	No	0.82
		No	No	1.46
		No	No	1.05
α-hexylcinnamaldehyde (HCA)		ND	ND	19.91
Negative control	Purified water	ND	ND	1.00

Source: Applicant study report
Note: SI is dpm of treated group/dpm of negative control group
Abbreviations: dpm, disintegrations per minute; HCA, hexylcinnamaldehyde; ND, not determined; SI, stimulation index

13.2.10. Study 20080145TRP: Nonradioactive Local Lymph Node Assay Test Method in Mouse Using In Vivo 5-Bromo-2-Deoxyiridine Incorporation

This GLP-compliant study evaluated the potential of the to-be-marketed CKC formulation of NOVA22007 1 mg/mL to induce delayed contact hypersensitivity using the murine LLNA.

Female CBA/j mice (4 per group) received repeated (3 days) local application of NOVA22007 1 mg/mL on the ears.

Local irritation was assessed by measuring ear thickness.

No treatment-related adverse clinical signs, cutaneous reactions or increased ear thickness were observed.

No lymphoproliferation was observed in animals treated with the test product (NOVA22007 1 mg/mL and vehicle), while significant lymphoproliferation was observed in the positive control group.

13.2.11. Study 41506TSS: Assessment of Phototoxic and Photoallergic Potential With the Murine Local Lymph Node Assay (UV-LLNA by Dermal Route)

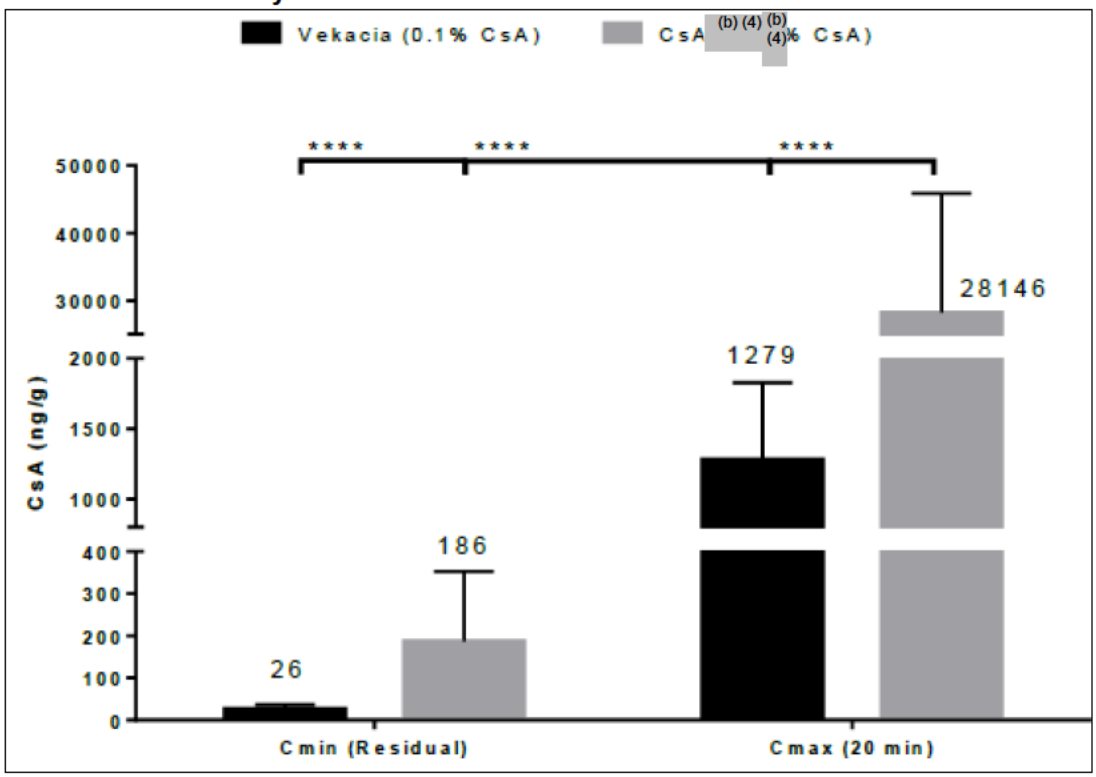
This study evaluated the phototoxic and photosensitizing (photoallergic) potential of NOVA22007 and its vehicle after dermal application to female BALB/c mice (6 per group) using the murine LLNA.

The mice were treated for 2 consecutive days by applying a variable volume of the preparation on the external surface of both ears of each mouse. Within 20 to 30 minutes following treatment, 5 of them were exposed to a UVA/Visible light dose of at least 10 J/cm^2.

No phototoxic (photo-irritant) effect of NOVA22007 was evident.

No photosensitizing (photoallergic) effect of NOVA22007 was evident.

Figure 18. CsA Concentration in the Conjunctiva at Steady State Following Repeated QID Instillations for 10 Days



Source: Applicant Study Report
Abbreviations: C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CsA, cyclosporine A; QID, four times daily

13.2.12. Fertility Study (Ryffel et al. 1983)

Methods

Male Wistar rats (15 per group) were treated orally for 12 weeks with CsA in 2% gelatin at doses of 1.5, 5, or 15 mg/kg/day. Female Wistar rats (30 per group) were treated 2 weeks prior to mating until weaning of their offspring. Controls received 2% gelatin only. Examination of the adult rats included:

- Clinical observation and mortality
- Body weight gain
- Copulation rate
- Pregnancy rate
- Precoital interval
- Gestation length

Necropsy of the male rats was performed at the end of the drug administration period, whereas half of the females from each group were euthanized and examined before delivery and the remainder at weaning. Examinations included embryonic development, physical and functional development, survival and fertility of the offspring. The surviving offspring were sacrificed at the end of the study and necropsied.

Results

In male filial generation (F) 0 rats (sires), CsA inhibited body weight gain (up to 9%), induced nephrotoxicity (polyuria and mild chronic nephritis), and divergent incisor teeth due to atrophic gingivitis.

In female F0 rats (dams) no adverse effect was found except for dystocia in two dams of the high dose group (45 mg/kg/day).

Copulation, pregnancy rates and pregnancy lengths were not significantly affected by CsA administration (Table 37).

CsA had no significant effects on implantation, embryonic survival, litter size, body weights, or malformations.

In single cases, where mother animals were allowed to litter and raise their offspring, a relatively high pre-/perinatal mortality was observed at the 15 mg/kg dose level; the difference to the control value was not, however, statistically significant.

Fertility of randomly selected F1 animals and the development of their offspring (F2 generation) were normal.

Table 37. Ryffel et al. 1983 Fertility Study
Results, F_0 females[a]

Dose (mg/kg)	No. of females						Copulation rate (%)		Pregnancy rate (%)	
	Total		Died		Paired					
Controls	15	15	0	0	15	15	100	100	93	73
1.5	15	15	0	0	15	15	100	87	87	85
5	15	15	0	0	15	15	100	93	87	86
15	15	15	0	0	15	15	100	100	80	67

Dose (mg/kg)	Weight gain (%)						Precoital interval (days)		Pregnancy length (days)	
	Before pairing		During pregnancy		During lactation					
Controls	9	8	40	43	–	4	4.3	3.5	–	22.1
1.5	10	8	43	44	–	6	4.2	3.5	–	22.2
5	9	9	44	41	–	9	3.6	4.1	–	22.2
15	11	9	41	42	–	9	5.5	3.0	–	22.2

[a] Left columns: prenatal part/right columns: postnatal part

Source: Ryffel et al. 1983
Abbreviations: F, filial generation; No, number

13.2.13. Pre/Perinatal Development (Ryffel et al. 1983)

Methods

Inseminated female Wistar rats (24 per group) were given CsA orally at doses of 5, 15, and 45 mg/kg/day from Day 15 precoital until Day 21 postpartum. Adults were observed for toxic signs and sacrificed at the end of the treatment period. The peri- and postnatal survival, the physical and functional development as well as the fertility and general reproductive performance of the offspring were analyzed.

Results

Doses up to and including 15 mg/kg/day were well tolerated.

45 mg/kg/day (Table 38)

- Weight gain in dams was reduced 12% at the high dose compared to control animals.
- An increase of pre-/perinatal mortality (19.1%) as well as early postnatal mortality (70.2%) of the offspring compared to controls was observed at the high dose.
- Body weight development of the offspring was markedly inhibited (-18%) compared to controls.
- The incidence of morphological and functional alterations in the offspring of treated animals was not changed compared to the controls.
- The fertility of randomly selected F1 pups and the development of their offspring (F2 generation) were not significantly affected.

Table 38. Ryffel et al. 1983 Pre/Perinatal Development

Results of F_0 females

Dose (mg/kg)	No. of females		weight gain (%) during treatment		Pregnancy rate (%)	Pregnancy length (days)
	Inseminated	Died	Pregnancy[a]	Lactation		
Controls	24	0	16	10	92	22.3
5	24	0	15	13	96	22.1
15	24	0	15	14	92	22.3
45	24	0	4	18	96	22.1

Litter Data

Dose (mg/kg)	Implantations	Litter size (day 0 pp)	Pre- and perinatal loss (%)	Postnatal loss (%)	Body weight day 21 pp (g)[b]	Abnormal pups (4)	Behavior affected pups (%)
Controls	10.5	9.8	7.7	0.9	47.6	4.0	29.2
5	10.8	9.9	8.2	4.9	48.3	1.1	35.8
15	11.0	10.3	7.3	0.0	51.3	0.5	35.4
45	9.2	7.0	26.8*	71.6*	29.5*	0.0	–

Results of F_1 fertility study

Dose (mg/kg)	Copulation rate (%)	Pregnancy rate (%)	Pre- and perinatal loss (%)	Postnatal loss (%)	Abnormal F_2 pups (%)
Controls	100	95	4.0	0.6	0.4
5	100	81	5.2	1.5	1.6
15	95	80	5.1	1.8	0.0
45	100	100	6.0	0.0	0.0

* $p < 0.05$
[a] Days 15–20 p.c.
[b] Combined results of males and females

Source: Ryffel et al., 1983
Abbreviations: F, filial generation; No, number; pp, postpartum

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

The systemic exposures following administration of the to-be-marketed product have been characterized in the VEKTIS study. The relevant information from this study is discussed in the Clinical Pharmacology Section 5 of the Integrated Review.

15. Trial Design: Additional Information and Assessment

15.1. NOVATIVE (Study NVG05L101): A Phase 2/3, Multicenter, Double-Masked, Randomized, Parallel Group, Dose Ranging, Controlled Trial of Efficacy and Tolerance of NOVA22007 (Cyclosporine A (CSA) 0.05% and 0.1% Ophthalmic Cationic Emulsion) Versus Vehicle in Patients with Vernal Keratoconjunctivitis

Objectives

Primary Objective

- To assess the efficacy of NOVA22007 0.05% and 0.1%, a CsA cationic emulsion administered QID, versus vehicle in patients with VKC after a 4-week treatment period.

Secondary Objectives

- To compare the safety and ocular tolerance (objective and subjective) of NOVA22007 0.05% and 0.1%, a CsA cationic emulsion administered QID, versus vehicle in patients with VKC after a 4-week treatment period.
- To assess the long-term safety and ocular tolerance (objective and subjective) of NOVA22007 0.05% and 0.1%, administered QID or BID, in patients with VKC after three additional months of treatment.
- To assess long term efficacy of NOVA22007 0.05% and 0.1%, administered QID or BID, or as a maintenance dosing of BID for 3 to 4 months.
- To assess the decrease in frequency of artificial tears use.

Trial Design

This was a Phase 3/3, multicenter, double-masked, randomized, parallel group, double ranging, controlled trial divided in two treatment periods:

Period I

A 4-week multicenter, double-masked, randomized, three parallel-group, vehicle-controlled, treatment period.

Patients were randomized to one of the three treatment groups: QID treatment with NOVA22007 0.05%, 0.1%, or vehicle eye drops. Patients could have been prematurely withdrawn from the trial in case of worsening disease after 2 weeks of treatment. In case of ocular intolerance at 2 weeks of treatment, Investigators were allowed to decrease dosing schedule to BID.

114 patients were planned to be included and 118 patients were included; all 118 patients were included in both the safety analysis and full analysis sets and 99 patients were included in the per protocol set.

Period II

A 3-month, multicenter, double-masked, two parallel-group, treatment period.

Following completion of the first period of the trial, all patients were to be administered NOVA22007 (i.e., CsA 0.05% or 0.1%) as QID or BID instillations in both eyes for an additional 3-month period.

Depending upon the ocular tolerance of the investigational medicinal product as assessed by the Investigator at the end of Period I, patients were to continue the treatment either with NOVA22007 (0.05% or 0.1%) administered QID, or with NOVA22007 administered BID for an additional 3 months.

The schedule of NOVA22007 could have been decreased to BID at any time during the open-label treatment period, depending on the ocular tolerance of NOVA22007.

Patients were allowed to use commercially available unpreserved artificial tears as needed up to the 4th month of the trial. Patients were instructed not to use concomitant artificial tears within 30 minutes before or after use of the investigational medicinal product.

A total of 111 patients entered Period II of the trial; all patients were treated and included in the safety analysis and in the full analysis sets.

Study Investigators

Table 39. NOVATIVE Study Investigators

Principal / Coordinating Investigator	Site Address
Prof. David Ben Ezra	Hadassah University Hospital Department of Ophthalmology Jerusalem, Israel
Dr. Ronit Yagev	Soroka University Medical Centre Beer Sheva, Israel
Prof. Abraham Spierer	Pediatric Unit, Goldschleger Eye Institute Sheba Medical Centre Tel-Hashomer and Tel-Aviv University Ramat Efal, Israel
Dr. Judith Raz	Meir Hospital Sapir Medical Centre Kfar Saba Sackler Faculty of Medicine Tel Aviv University, Israel
Dr. Yilmaz Ozyazgan	Istanbul University Cerrahpasa Faculty of Medicine Department of Ophthalmology Cerrahpasa Tip Fakultesi Dekanlik

Principal / Coordinating Investigator	Site Address
	Binasi Cerrahpasa Istanbul, Turkey
Dr. Ilknur Tugal Tutkun	Istanbul Faculty of Medicine Department of Ophthalmology Istanbul Tip Fakultesi Dekanlik Binasi CAPA 34390 Istanbul, Turkey
Prof. Stefano Bonini	Dipartimento di Oftalmologi Universita' di Roma Campus BioMedico Via Cassia Antica 35 Roma, Italia
Dr. Andrea Leonardi	Dipartimento di Neuroscienze Unita' di Oftalmologia Via Giustiniani, 2 35128 Padova, Italia
Professor Jorge Alio y Sanz	VISSUM Instituto Oftalmologico de Alicante C/Cabanal, 1 03016 Alicante Espana
Dr. Jose Manuel Benitez del Castillo	Unidad de Superficie e Inflamacion Ocular Department of Ophthalmology Hospital Clinico de San Carlos Martin Lagos s/n 28040 Madrid, Espana
Dr. Miguel Angel Teus Guezala	VISSUM Hospital Oftalmologico de Madrid C/Santa Hortensia, 58 28002 Madrid, Espana
Prof. Christophe Baudouin	Hopital des XV – XX Service d'Ophthalmologie 28 rue de Charenton 75012 Paris France
Dr. Catherine Creuzot-Garcher	Hopital General, CHU de Dijon Service d'Ophthalmologie 3 rue Faubourg Raines 21033 Dijon France
Prof. Thanh Hoang-Xuan	Group Hospitalier Bichat-Claude Bernard Service d'Ophthalmologie 46 rue Henri Huchard 75018 Paris France
Dr. Pierre-Jean Pisella	Hopital Bretonneau – CHRU Service d'Ophthalmologie 2 boulevard Tonnelle 37000 Tours France

Principal / Coordinating Investigator	Site Address
Dr. Amina Berraho Hammani	Hopital des Specialites Service d'Ophthalmologie B CHU IBN SINA 10000 – Rabat Maroc
Dr. Khalid Zaghloul	Hopital 20-aout 1953 Ophtalmologie Pediatrique 56, Av. Hassan Souktani Casablanca, Maroc

Diagnosis and Main Criteria for Inclusion

Criteria at the Screening Visit

- Informed Consent form signed. If the patient was a minor, the parent(s) (or legal representative) who was/were able and willing, had to provide a written informed consent and the child as well if he/she was old enough to understand and sign and date the written informed consent;
- Male or female at least 4 years of age;
- Able and willing to follow instructions and attend the required trial visits or had a parent/legal representative who was able and willing to follow the trial visits;
- Patient presenting with active VKC (acute or chronic) needing treatment.

Criteria at the Inclusion Visit

- At least the two following signs, in at least one eye*:
  - Presence of giant papillae with a diameter ≥1 mm on the upper tarsal conjunctiva; AND
  - Superficial keratitis;
- At least two of the following ocular symptoms with a score >2 in at least one eye*: burning/stinging, tearing, itching, pain, sticky eyelids, foreign body sensation, mucus discharge, and photophobia;
- Hyperemia score equal to or greater than 2.

* The same eye had to fulfill both of these criteria.

Test Product

Periods I and II

NOVA22007 0.05% or 0.1%: ophthalmic cationic emulsion in single use vials containing 0.05% or 0.1% CsA.

Duration of Treatment

112±7 days, i.e., 105 to 119 days.

Dose and Mode of Administration

One drop in each eye, QID (morning, noon, afternoon and evening) from Day 0 to Day 112±7 days.

The Investigator was allowed to decrease the schedule of NOVA22007 to BID at any time starting on Day 14 (Week 2) of treatment and depending on the ocular tolerance of NOVA22007 instilled QID.

Batch Numbers

- NOVA22007 0.1%: Z06E35, Expiry date: February 16, 2007
- NOVA22007 0.05%: Z06E34, Expiry date: February 16, 2007 (last patient, last visit was (b) (6), but the patient received last dose before the expiry date).

Reference Therapy

Period I

NOVA22007 0% (vehicle): ophthalmic cationic emulsion in single use vials containing 0% CsA.

Period II

None.

Dose and Mode of Administration

One drop in each eye, QID (morning, noon, afternoon and evening) from Day 0 to Day 28±3 days.

Batch Numbers

- Z01E32: Expiry date: February 16, 2007.

Original Protocol Defined Criteria for Evaluation

Efficacy

Primary Efficacy Criterion

- Overall rating of subjective symptoms at Week 4 (Month 1): treatment success.

Reviewer's Comments:
Agency disagree with the original protocol defined criteria for evaluation. The submitted application included analyses of both the original and Agency defined endpoint.

Original Protocol Defined Statistical Methods

The primary efficacy endpoint was the overall rating of subjective symptoms assessed at the Day 28 visit. The primary analysis was interindividual comparison of NOVA22007 0.05% versus vehicle and NOVA22007 0.1% versus vehicle.

All tests were two-sided with level of significance set at 5%. No adjustment for center effect or for multiplicity was used.

For the primary analysis, the comparison of NOVA22007 0.05% and NOVA22007 0.1% groups versus vehicle for Period I was performed by means of Mantel Haenszel Chi-square test from the frequency procedure (FREQ) within SAS®. As it was likely to have some cells with expected

counts less than 5, which could invalidate the test, the p-value was computed using the Exact option. In addition, due to the sensitivity of the test to coding of rows and columns, the rank scores option were used.

Reviewer's Comments:
Agency disagree with the original protocol defined criteria for evaluation. The submitted application included analyses of both the original and Agency defined endpoint.

15.2. VEKTIS (Study NVG09B113): A Multicenter, Randomized, Double-Masked, 3 Parallel Arms, Placebo-Controlled Study to Assess the Efficacy and Safety of NOVA22007 1 mg/mL (Ciclosporine/Cyclosporine) Eye Drops, Emulsion Administered in Pediatric Patients With Active Severe Vernal Keratoconjunctivitis With Severe Keratitis

Objectives

Primary

The primary objective of the study was to compare the efficacy of two different dosing regimens of NOVA22007 versus placebo (vehicle of the formulation) on both the evolution of severe keratitis and the need for rescue medication.

Secondary

- To assess the safety and tolerability including ocular tolerance of two dosing regimens of NOVA22007 versus placebo.
- To assess the efficacy of two dosing regimens of NOVA22007 versus placebo on other signs and symptoms of VKC not covered in the primary objective.

Methodology

A multicenter, randomized, double-masked, 3 parallel arms, placebo-controlled, 4-month Phase 3 study with an 8-month safety follow-up period to evaluate the efficacy and safety of two dosing regimens of NOVA22007 1 mg/mL CsA eye drops, emulsion administered QID in pediatric patients with active severe VKC.

Duration of Study

The study duration per patient was 12 months divided into 2 parts: a 4-month efficacy evaluation treatment period and an 8-month safety follow-up period.

Schedule of Assessments

		Randomized, double-masked study treatment Period				Safety Follow-up Period				Unscheduled Visit
Study procedures	**Baseline** Day 0	**Month 1** Week 4 ± 3 days	**Month 2** Week 8 ± 3 days	**Month 3** Week 12 ± 3 days	**Month 4** Week 16 ± 3 days/ Early discontinuation[5]	**Month 6** Week 24 ± 14 days	**Month 8** Week 32 ± 14 days	**Month 10** Week 40 ± 14 days	**Month 12** Week 48 ± 14 days/ Early discontinuation[7]	
Informed consent	X									
Demographic information	X									
Ocular and systemic medical history	X									
Previous and Concomitant ocular and systemic medications (incl. concomitant artificial tear usage)	X	X	X	X	X	X	X	X	X	X
QUICK questionnaire	X	X[2]	X[2]	X[2]	X[2]				X	X
VAS	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X
Local Global tolerance of IMP		X	X	X	X[6]	X	X	X	X	X
Best corrected distance visual acuity (BCDVA in LogMAR)	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X
Corneal fluorescein staining (Modified Oxford Scale)	X	X	X	X	X	X	X	X	X	X
Investigator global evaluation					X				X	
Intraocular Pressure (IOP)	X	X	X	X	X	X	X	X	X	X
Vital Signs	X				X		X		X	X
Blood sampling for CsA	X		X		X				X	
Blood sampling for safety analysis	X[3]		X		X[3]				X[3]	
Urine pregnancy test (women of childbearing potential only)	X[4]				X				X	X
Inclusion/exclusion criteria	X									
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X
Dispense study medication	X[1]	X	X	X	X[6]	X[6]	X[6]	X[6]		
Collection of used study medication		X	X	X	X	X[6]	X[6]	X[6]	X[6]	X

1 Only patients fulfilling eligibility criteria were randomized and received the study medication.
2 VAS and Quick questionnaires were performed at the beginning of the visit before medical history and any study assessment.
3 Blood was analyzed in the sites for measurements of creatinine and transaminase serum levels (ALT, AST). A sample of 4 mL whole blood was collected.
4 Urine serum pregnancy test (women of child bearing potential only) could be repeated at each visit as per request of Institutional Review Boards/Independent ECs or as required by local regulations.
5 The Month 4 assessments were also performed in case of premature treatment discontinuation after Baseline visit and before Month 4.
6 Only patients who needed to continue active therapy.
7 The Month 12 assessment were also performed in case of discontinuation during the 8-month safety period if the discontinuation occured after the Month 4 visit and before the Month 12 visit.

Source: NDA 214965, Module 5.3.5.1, Study Report NVG09B113, Page 46-47
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCDVA; best corrected distance visual acuity; CsA, cyclosporine A; EC, ethics committee; IMP, investigational medicinal product; IOP, intraocular pressure; LogMAR, logarithm of the minimum angle of resolution; VAS, visual analogue scale

Study Investigators

Table 40. VEKTIS Study Investigators

Site Number	Principal / Coordinating Investigator	Site Address	Number of Randomized Patients
1201	Prof. Dominique Bremond-Gignac	CHU d'Amiens – Centre St. Victor Ophthalmology Service 354 bd de Beauville Somme, 80054 France Hopital Necker – Enfants Malades Ophthalmology Service 149 rue de Sevres Paris, 75015 France	7
1202	Dr. Serge Doan	Ophthalmology Groupe Hospitalier Bichat-Claude Bernard 46 rue Henri Huchard Paris cedex 8, 75877 France	4
1204	Dr. Catherine Creuzot-Garcher	CHU de Dijon – Bocage Central Ophthalmology Service 14 rue Gaffarel – BP 77908 Dijon Cedex, 21079 France	1
1205	Prof. Frederic Chiambaretta	Ophthalmology CHU Clermont-Ferrand – Hopital Montpied 58 rue Montalembert Clermont-Frerrand cedex 1, 63003 France	1
1206	Dr. Stephane Fauquier	Centre d'Ophtalmologie Paradis Monticelli 433 rue Paradis Marseille, 13008 France	1
1208	Dr. Bertrand Vabres	Ophthalmology CHU de Nantes – Hopital Hotel Dieu 1 Place Alexis Ricordeau Nantes cedex 1, 44093 France	1
1209	Dr. Philippe Gohier	Ophthalmology CHU Angers 4 rue Larrey Angers cedex 9, 49933 France	1
1210	Dr. Pierre-Jean P. Pisella	Ophthalmology CHU Bretonneau 2 Boulevard Tonnelle Tours cedex 9, 37044 France	1
1303	Dr. Katrin Lorenz	Augenklinik und Poliklinik der Universitätsmedizin Mainz Klinisches Studienzentrum Johannes Gutenberg- Universität Langenbeckstr. 1 Mainz, D-55131 Germany	1
1401	Dr. Zoltan Sohajda	Kenézy Kórház, Szemészeti Osztály Bartók Béla út 2-26. Debrecen, 4032 Hungary	3
1402	Prof. Dr. Janos Nemeth	Semmelweis Egyetem, Szemészeti Klinika Mária u. 39. Budapest, H-1085 Hungary	8
1404	Prof. Dr. Andrea Facsko	University of Szeged, Dept. of Ophthalmology Korányi fasor 10-11. Szeged, H-6720 Hungary	1
1503	Dr. Racapalle Reddi Sudhir	Ophthalmology Vision Research Foundation, Sankara Nethralaya 18 College Road Nungambakkam, Tamil Nadu Chennai, 600006 India	5

Site Number	Principal / Coordinating Investigator	Site Address	Number of Randomized Patients
1506	Dr. Vupputuri Venkata Lakshmi; Narasimha Rao	Regional Institute of Ophthalmology Resaveripalem Vishakapatnam, 530002 India	12
1510	Dr. Srikant Sahu Dr. Sujata Das	L V Prasad Eye Institute, Patia, Bhubhaneshwar - 751024 Odisha India	5
1513	Dr. Sheela Kerkar	KEM Hospital Acharya Donde marg Parel Mumbai, 400012 India	1
1514	Dr. Ritu Arora	Guru Nanak Eye Centre Maulana Azad Medical College Maharana Ranjit Singh Marg New Delhi, 110002 India	4
1515	Dr. Siddharth Agarwal	King George's Medical University Department of Ophthalmology Chowk Lucknow, 226003 India	7
1601	Dr. Reut Parness-Yossifon	Kaplan Medical Center Pasternak Street POB-1, Rehovot, 76100 Israel	3
1603	Dr. Eliya Levinger Gad Dotan	Ophthalmology Tel Aviv Sourasky Medical Center 6 Weisman street, Tel Aviv, 64239 Israel	2
1604	Dr. Nitza Cohen-Goldenberg	Ophthalmology Rabin Medical Center Jabotinsky n 39, Petach Tikva, 49100 Israel	5
1605	Dr. Ronit Yagev	Ophthalmology Soroka University Medical Center Beer-Sheva P.O.Box 151, Beer-Sheva, 84101 Israel	4
1606	Dr. Irene Anteby	Ophthalmology Hadassah Medical Center POB 12000, Jerusalem, 91120 Israel	8
1701	Prof. Emilio Campos	U.O.Oftalmologia Universitaria S.Orsola Malpighi Via Palagi, 9, Bologna, 40138 Italy	3
1702	Dr. Neri Pucci	Ophthalmology "A.Meyer" Children`s Hospital Viale Pieraccini 24, Florence, 50132 Italy	1
1703	Prof. Andrea Leonardi	Ophthalmology University Hospital Padova Via giustiniani 2, Padova, 35128 Italy	7
1709	Prof. Marco Nardi	Ophthalmology A.O.U.P. P.O. di Cisanello U.O. Oculistica Universitaria Via Paradisa 2, Pisa, 56124 Italy	1
1710	Prof. Pasquale Aragona	A.O.U.Policlinico"G.Martino"di Messina U.O.C. Specialità Chirurgiche Oftalmologia Via Consolare Valeria, 1 Messina, 98125 Italy	4
1711	Dr. Pia Allegri	Allergology and Immunology of the Eye Ospedale di Lavagna S.C. Pediatria Centro di Riferimento per le Congiuntiviti Allergiche Via Don Bobbo, 25, Lavagna (GE) Liguria, 16033 Italy	3

Site Number	Principal / Coordinating Investigator	Site Address	Number of Randomized Patients
1803	Dr. Alcina Maria Pinho Toscano	Hospital de S. José Rua Jose António Serrano Lisboa, 1150-199 Portugal	1
1804	Dr. Jose Pedro Silva	Ophthalmology Hospital dos Lusíadas R. Abílio Mendes, Alto dos Moinhos Lisboa, 1500-458 Portugal	0
1805	Dr. Rosario Varandas	Ophthalmology Centro Hospitalar de Vila Nova de Gaia Rua Conceição Fernandes Rua quinta das Chãs nº 180 casa 17, Vila Nova de Gaia, 4400556 Portugal	5
1806	Dr. Maria Jorge Raposo	Instituto de Oftalmologia Dr. Gama Pinto Travessa Larga, n.º 2 Lisboa, 1169-019 Portugal	1
1901	Dr. Jose Belda	Hospital De Torrevieja Carretera CV-95 SN Torrevieja Alicante, 03186 Spain	4
1902	Dr. Javier Mendicute	Hospital Universitario Donostia Ophthalmology Service Paseo Dr. Beguiristáin, 115 San Sebastián, 20014 Spain	2
1903	Dr. Ramon Calvo	Hospital General Universitario de Valencia Ophthalmology Department Av.Tres Cruces nº2 Valencia, 46014 Spain	4
1904	Dr. Cristina Peris Martinez	Fundacion Oftalmologica del Mediterraneo Bifurcación Pío Baroja-general Aviles, S/N Valencia, 46015 Spain	6
1905	Dr. Jesus Montero	Cartuja Vision C/ Imagen nº9, Planta 5 Sevilla, 41003 Spain	9
1907	Dr. Jorge Luis Alio	Ophthalmology Vissum Corporation (Alicante) Cabañal Nº1, Alicante, 03016 Spain	3
1908	Dr. Marta Galdos Iztueta	Hospital de Cruces Ophthalmology Service Plaza de Cruces nº12 Barakaldo (Vizcaya), 48903 Spain	4
1909	Dr. Teresa Colas	Hospital del Tajo Ophthalmology Service Avda. de las Amazonas Central s/n Aranjuez-Madrid, 28300 Spain	1
1911	Dr. Jose Saavedra Pazos	Centro de Ojos de La Coruña Fernandez Latorre 120 bajo A Coruña, 15006 Spain	1
1913	Dr. Felix Armada Maresca	Hospital Universitario La Paz Ophthalmology department Paseo de la Castellana, 261 Madrid, 28046 Spain	2
1915	Dr. Belen Gutierrez	Hospital Infantil Universitario Niño Jesus Ophthalmology Service Avda. Menendez Pelayo, 65 Madrid, 28009 Spain	2
2101	Dr. Joseph Martel	Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, California 95670 United States	4

Site Number	Principal / Coordinating Investigator	Site Address	Number of Randomized Patients
2103	Dr. Sherif El-Harazi	Ophthalmology Lugene Eye Institute 801 S. Chevy Chase Dr., Suite 103 Glendale, California 91205 United States	4
2106	Dr. Robert Lingua	Ophthalmology UC Irvine 118 Med Surge I Irvine, CA 92697 United States	1
2110	Dr. Kara Cavuoto	Ophthalmology Bascom Palmer Eye Institute 900 NW 17th Street Miami, Florida 33136 United States	3
2301	Dr. Ivana Mravicic	Paediatric Ophthalmology Unit Eye Clinic Svjetlost Heinzelova 39 Zagreb, 10000 Croatia	2
2401	Asso. Prof Evangelia Tsironi	University Ophthalmology Clinic University General Hospital of Larissa Mezourlo Larissa, 41110 Greece	1
2402	Assoc. Prof. Nikolaos Ziakas	A' University Ophthalmology Clinic University General Hospital of Thessaloniki 'AHEPA' St. Kyriakidi 1 Thessaloniki, 54636 Greece	3
2405	Asso. Prof Ioannis Asproudis	Ophthalmology University General Hospital of Ioannina Stavros Niarchos Avenue Ioannina, 45500 Greece	1

Number of Patients

Planned

At least 168 children or adolescents.

At least 50% of the study participants were planned to be enrolled in Europe.

Analyzed

169 patients were randomized, including 101 patients in Europe (Table 41).

Table 41. VEKTIS Randomized Patients

	High dose regimen	Low dose regimen	Placebo	Total
Safety Set	57	54	58	169
Full Analysis Set	56	54	58	168
Per Protocol Set	52	52	55	159
	High dose regimen in Period 2		Low dose regimen in Period 2	
	Total		Total	
Follow-Up Total Set	72		70	

Source: Module 5.3.5.1: Clinical Study Report VEKTIS NVG09B113, page 3.

Diagnosis and Main Criteria for Inclusion:

Male and female patients from 4 to less than 18 years of age with active severe VKC with severe keratitis (grade 4 or 5 on the modified Oxford scale).

Inclusion Criteria

1. Documented informed consent form signed by the patient or legal guardian and assent of the child, as appropriate, in accordance with local regulation and legal requirements. Assent was required (as children per local regulation and for those who, in the Investigator's judgment, were able to comprehend.
2. Male or female patients from 4 to less than 18 years of age.
3. Females of childbearing potential had to have a negative pregnancy test plus a medically acceptable, highly effective method of birth control (such as hormonal implants, injectable or oral contraceptives together with condoms, some intrauterine devices, sexual abstinence or vasectomized partner) throughout the conduct of the study and up to 2 weeks after the study end.
4. History of at least 1 recurrence of VKC in the past year prior to enrollment.
5. Patients not receiving any treatment for established and active VKC; or patients already receiving treatment for their VKC, provided that treatment was stopped according to the washout period specified in the exclusion criteria.
6. Active severe VKC consistent with grade 3 or 4 of Bonini scale (Bonini 2007) with severe keratitis (grade 4 or 5 on the modified Oxford scale).
7. Mean score of four subjective symptoms (photophobia, tearing, itching and mucous discharge) ≥60 mm using a 100 mm visual analogue scale (where "0" means no symptom and "100" means the worst that had been ever experienced).
8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
9. Patient enrolment had to occur early during the site VKC season in order to allow the 4-month treatment period during the site VKC season.

Exclusion Criteria

Ocular Conditions/Diseases

10. Any relevant ocular anomaly other than VKC interfering with the ocular surface including trauma, post radiation keratitis, severe blepharitis, rosacea, corneal ulcer, etc.
11. Abnormal lid anatomy, abnormalities of the nasolacrimal drainage system or blinking function in either eye.
12. Active herpes keratitis or history of ocular herpes.
13. History of ocular varicella zoster or vaccinia virus infection.
14. Active ocular infection (viral, bacterial, fungal, protozoal).
15. Any ocular diseases other than VKC requiring topical ocular treatment during the course of the study.
16. Contact lens wear during the study.

Ocular Treatments

17. Topical and/or systemic use of corticosteroids within one week prior to enrolment.

18. Topical CsA (e.g., Restasis), tacrolimus or sirolimus within 90 days prior to enrolment.
19. Scraping of the vernal plaque within 1 month prior to the Baseline visit.
20. Ocular surgery within 6 months prior to the Baseline visit (excluding surgical treatment of the vernal plaque).

Systemic Conditions/Diseases or Treatments

21. Disease not stabilized within 30 days before the Baseline Visit (e.g., diabetes with glycemia out of range, thyroid malfunction, uncontrolled autoimmune disease, current systemic infections) or judged by the Investigator to be incompatible with the study.
22. Presence or history of severe systemic allergy.
23. Any intake of systemic immunosuppressant drugs within 90 days before the Baseline Visit.
24. Known hypersensitivity to one of the components of the study or procedural medications (e.g., fluorescein, etc.).
25. History of malignancy in the last 5 years.
26. Pregnancy or lactation at the Baseline Visit.

Compliance/Administrative

27. History of drug addiction or alcohol abuse.
28. Presence or history of any systemic or ocular disorder, condition or disease that could possibly interfere with the conduct of the required study procedures or the interpretation of study results.
29. Patient not covered by a health insurance if required by the national legislation.
30. Participation in a clinical study with an investigational substance within the past 30 days.
31. Participation in another clinical study at the same time as the present study.

Investigational Product

Dose, Mode of Administration, and Batch Number(s)

Four-Month Efficacy Evaluation Treatment Period

Patients were randomized in one of the three groups:

- 1 drop of CsA (NOVA22007) 1 mg/mL QID as monotherapy (morning, noon, afternoon and evening).
- 1 drop of CsA (NOVA22007) 1 mg/mL BID and 1 drop of placebo BID (active study treatment morning and evening and placebo noon and afternoon) as monotherapy.
- 1 drop of placebo QID as monotherapy.

Eight-Month Safety Follow-Up Period

Treatment with active study medication may have been continued during the 8-month follow-up safety period for those patients enrolled early in the study for which the VKC allergy season was ongoing at the end of the 4-month efficacy evaluation treatment period.

During the 8-month follow-up safety period patients enrolled at the beginning of the VKC season and randomized to either arm of active study treatment for the 4-month efficacy evaluation

treatment period may have continued with the same active study treatment regimen until the end of the VKC allergy season.

Patients enrolled at the beginning of the VKC season and randomized to the placebo group may have been switched in a masked fashion to an active study treatment arm in a 1:1 ratio until the end of the VKC allergy season based on the Investigator's judgment.

All patients enrolled late in the VKC season discontinued study treatment (active and placebo) at the end of the VKC allergy season upon the completion of their 4-month efficacy evaluation period.

The target population for this study was expected to include patients with perennial VKC that persists throughout the year. Therefore, should a patient have experienced a recurrence of active VKC or a worsening in VKC symptoms following the discontinuation of study treatment outside of the VKC allergy season during the remaining months of their 8-month safety follow-up period, the patient was allowed to resume, in a masked fashion, active study treatment with NOVA22007 based on the Investigator judgment. Subsequently, active study treatment was discontinued at the discretion of the Investigator once a quiescent VKC state (grade 0 on the Bonini grading scale) was reached.

Batch Numbers

X528 NOVA22007 B60 (b) (4); Reference: A0021882X0; Expiry date: Oct 2014

2A44 NOVA22007 Z06EM106; Reference: A0025392X0; Expiry date: Jun 2016

Reference Therapy

Dose, Mode of Administration, and Batch Number(s)

Placebo: vehicle of NOVA22007

1 drop of placebo QID (morning, noon, afternoon, evening) in each eye during the 4-month randomized, double masked study treatment period

Batch Numbers

X632 Placebo NOVA22007 B60 (b) (4); Reference: A0021872X0; Expiry date: Sep 2014

2A43 Placebo NOVA22007 Z06EM106; Reference: A0025382X0; Expiry date: Jun 2016

Rescue Therapy

Dexamethasone 0.1% eye drops provided by the Applicant, 1 drop QID for 5 days and a maximum of 2 courses of rescue between 2 scheduled visits during the 4-month treatment period and a maximum of 4 courses of rescue between 2 scheduled visits during the follow-up period were allowed. The need for rescue medication was assessed by the Investigator during a visit and rescue medication was given if the patient satisfied the following conditions:

- Keratitis worsening of at least one grade on the modified Oxford scale or maintained during 2 months at the entry level and/or
- Symptom worsening of at least 1 centimeter on at least 1 of the 4 symptoms along with the worsening of the mean of the 4 symptoms or maintenance at the entry level.

The need for a second consecutive course of rescue therapy could be allowed by the Investigator after a phone call.

Patients receiving rescue medication had their intraocular pressure assessed at each study visit and were carefully monitored because of the risks of glaucoma as well as the occurrence of AEs with an increased risk of infections.

Unpreserved artificial tears were only allowed for patients who were unable to reach their study doctor to evaluate the need for rescue therapy.

Original Protocol Defined Criteria for Evaluation

Primary Efficacy Endpoint

Composite efficacy score at 4 months, defined as the mean of the 4 efficacy scores taken at each monthly visit.

Efficacy was assessed every month during the 4-month treatment period and compared with Baseline using a composite criterion based on:

- Keratitis assessed by the modified Oxford scale.
- Need for rescue medication.
- Occurrence of corneal ulceration.

The efficacy score was calculated as followed:

- Patient's score at month X= CFS (Baseline) – CFS (Month X) + penalty (ies).
- Penalty for rescue medication: -1 (per course, with a maximum of 2 courses between 2 scheduled visits).
- Penalty for corneal ulceration: -1 (per occurrence).

Reviewer's Comments:
Agency disagree with the original protocol defined criteria for evaluation. The submitted application included analyses of both the original and Agency defined endpoint.

Original Protocol Defined Statistical Methods

Sample Size Calculation

According to the results of the previous study (NOVATIVE) performed in patients with VKC, we noted that: results at Month 1 (the duration of the double-masked period) showed an improvement in modified Oxford scale of 1.5 grade more in the active group than in the placebo. In the proposed 4-month study, it seemed reasonable to expect a slightly lower difference but maintained over the 4-month efficacy evaluation treatment period (1.25 grade of difference in the mean of the 4 assessments between active groups and placebo).

Based on this assumption and a standard deviation of 2 that was observed in the previous study, and setting the two-sided alpha risk at 2.5% to take into account a multiplicity adjustment for the two tested dose regimens, a sample size of 50 patients per group was required to have 80% chance (power) to achieve a significant difference between the most efficacious dose and placebo.

A provision of 12% was arbitrarily added to the sample size (56 patients per group) for the decrease of power linked to an early end of VKC season in some regions and possibly early withdrawals.

Analyses

Descriptive statistics are presented per treatment group. Mean, standard deviation, minimum, median, maximum and number of observations were used for quantitative variables, and frequencies and percentages for categorical variables.

Primary Analysis of the Primary Efficacy Endpoint

Test of superiority of each dosing regimen of NOVA22007 compared to placebo was done using a linear model (analysis of covariance) with 2 covariates: the treatment and the proportion of time spent in being exposed to the randomized treatment within the VKC season.

Evidence of efficacy is provided if the treatment effect was significant between at least one treatment group versus placebo.

Time course of keratitis (modified Oxford scale)

The change from Baseline in the modified Oxford scale value was fitted by a general linear mixed model for repeated measurements.

Responder analysis

A patient was a responder if:

- The mean CFS score of the last 3 months of treatment was equal or smaller than 50% of the Baseline.
- He did not withdraw from the study for a reason possibly due to treatment.
- He did not experience an ulceration, and
- He did not use rescue medication in the last 3 months of treatment.

The rate of responders was compared with a logistic regression using the treatment and the proportion of time spent under treatment during the VKC season as covariates.

Use of rescue medication

The frequency distribution of the number of courses of rescue medication for each group is provided and each dose was compared to placebo through a nonparametric Savage test.

Reviewer's Comments:
Agency disagree with the original protocol defined criteria for evaluation. The submitted application included analyses of both the original and Agency defined endpoint.

16. Pharmacokinetics: Additional Information and Assessment

Table 42. Detection of Circulating CsA During 2-Month and 4-Month Early Termination

Visit	Score	0.1% QID Regimen (N=57)	0.1% BID Regimen (N=54)	Placebo (N=58)
Baseline	N	55	53	58
	ND[a]	50 (90.9%)	47 (88.7%)	50 (86.2%)
	<LLOQ[b]	0	2 (3.8%)	0
	QUANTIFIABLE	0	0	0
	>ULOQ[c]	0	0	0
	NR[d]	5 (9.1%)	4 (7.5%)	8 (13.8%)
Month 2	n	51	45	51
	ND[a]	18 (35.3%)	23 (51.1%)	48 (94.1%)
	<LLOQ[b]	15 (29.4%)	12 (26.7%)	0
	QUANTIFIABLE	12 (23.5%)	6 (13.3%)	0
	>ULOQ[c]	0	0	0
	NR[d]	6 (11.8%)	4 (8.9%)	3 (5.9%)
Month 4/ Early Termination	n	50	47	51
	ND[a]	20 (40.0%)	34 (72.3%)	47 (92.2%)
	<LLOQ[b]	13 (26.0%)	7 (14.9%)	1 (2.0%)
	QUANTIFIABLE	14 (28.0%)	5 (10.6%)	0
	>ULOQ[c]	0	0	0
	NR[d]	3 (6.0%)	1 (2.1%)	3 (5.9%)

Source: NDA 214965, Module 2.7.2, Pages 8-9
[a] Samples where analytes are not detected, or values calculated as inferior to the limit of detection (0.0500 ng/mL) will be reported as ND
[b] Analyte concentrations below the lower limit of quantification (0.100 ng/mL or 0.25 ng/mL) will be reported as <LLOQ
[c] Analyte concentrations above the upper limit of quantification (0.500 ng/mL) will be reported as >ULOQ
[d] Samples where analyte concentrations could not be reported are reported as NR
Abbreviations: LLOQ, lower limit of quantification; N, number of patients; n, number of patients at the indicated time; NR, not reported; ULOQ, upper limit of quantification

Table 43. Detection of Circulating CsA During 4-Month and 8-Month Follow-Up Period

Visit	Score	High dose regimen in Period 2			Low dose regimen in Period 2		
		High dose regimen (N=50)	Placebo (N=22)	Total (N=72)	Low dose regimen (N=44)	Placebo (N=26)	Total (N=70)
Month 4	n	47	20	67	42	26	68
	ND[a]	18 (38.3%)	20 (100%)	38 (56.7%)	28 (66.7%)	24 (92.3%)	52 (76.5%)
	<LLOQ[b]	12 (25.5%)	0	12 (17.9%)	8 (19.0%)	0	8 (11.8%)
	QUANTIFIABLE	14 (29.8%)	0	14 (20.9%)	5 (11.9%)	0	5 (7.4%)
	>ULOQ[c]	0	0	0	0	0	0
	NR[d]	3 (6.4%)	0	3 (4.5%)	1 (2.4%)	2 (7.7%)	3 (4.4%)
Month 12/ Early Termination	n	49	19	68	37	24	61
	ND[a]	28 (57.1%)	10 (52.6%)	38 (55.9%)	30 (81.1%)	17 (70.8%)	47 (77.0%)
	<LLOQ[b]	7 (14.3%)	3 (15.8%)	10 (14.7%)	3 (8.1%)	3 (12.5%)	6 (9.8%)
	QUANTIFIABLE	10 (20.4%)	2 (10.5%)	12 (17.6%)	2 (5.4%)	3 (12.5%)	5 (8.2%)
	>ULOQ[c]	0	0	0	0	0	0
	NR[d]	4 (8.2%)	4 (21.1%)	8 (11.8%)	2 (5.4%)	1 (4.2%)	3 (4.9%)

[a] Samples where analytes are not detected or values calculated as inferior to the Limit of Detection (0.0500 ng/mL) will be reported as ND for Not Detected
[b] Analyte concentrations below the lower quantification limit (0.100 ng/mL or 0.25 ng/mL) will be reported as <LLOQ.
[c] Analyte concentrations above the upper quantification limit (5.00 ng/mL) will be reported as >ULOQ
[d] Samples where analyte concentrations could not be reported are reported as NR for Not Reported.

Source: NDA 214965, Module 2.7.2, Page 9
Abbreviations: LLOQ, lower limit of quantification; N, number of patients; n, number of patients at the indicated time; NR, not reported; ULOQ, upper limit of quantification

17. Efficacy: Additional Information and Assessment

Table 44. Sensitivity Analyses: Efficacy Results of the Mean Change in CFS Score From Baseline at Each Visit (VEKTIS Study)

	Placebo	QID	BID	Difference (95% CI)[1]	
Visit	N = 58	N = 56	N = 54	QID vs. Placebo	BID vs. Placebo
Post-Rescue data imputed by baseline data					
Baseline	4.1 (0.26)	4.3 (0.44)	4.1 (0.29)	--	--
Month 1	-0.8 (1.31)	-1.5 (1.45)	-1.3 (1.28)	-0.7 (-1.2, -0.2)	-0.5 (-1.1, -0.0)
Month 2	-1.0 (1.16)	-1.8 (1.48)	-1.7 (1.44)	-0.9 (-1.4, -0.4)	-0.8 (-1.4, -0.3)
Month 3	-1.1 (1.46)	-2.2 (1.69)	-1.9 (1.62)	-1.1 (-1.7, -0.5)	-0.8 (-1.4, -0.2)
Month 4	-1.1 (1.48)	-2.2 (1.75)	-1.8 (1.55)	-1.0 (-1.6, -0.4)	-0.7 (-1.3, -0.1)
Post-Rescue data used in the analysis					
Baseline	4.1 (0.26)	4.3 (0.44)	4.1 (0.29)	--	--
Month 1	-1.3 (1.39)	-1.6 (1.48)	-1.7 (1.27)	-0.4 (-0.9, 0.2)	-0.4 (-1.0, 0.1)
Month 2	-1.6 (1.21)	-2.1 (1.44)	-2.3 (1.31)	-0.5 (-1.0, 0.0)	-0.8 (-1.3, -0.3)
Month 3	-2.1 (1.37)	-2.7 (1.54)	-2.5 (1.41)	-0.6 (-1.2, -0.1)	-0.5 (-1.1, -0.0)
Month 4	-2.2 (1.36)	-2.8 (1.53)	-2.5 (1.35)	-0.6 (-1.1, -0.1)	-0.4 (-0.9, 0.2)
Post-Rescue data imputed by placebo-based multiple imputation					
Baseline	4.1 (0.26)	4.3 (0.44)	4.1 (0.29)	--	--
Month 1	-1.1 (1.43)	-1.6 (1.45)	-1.5 (1.31)	-0.5 (-1.0, 0.1)	-0.5 (-1.1, 0.1)
Month 2	-1.6 (1.10)	-2.0 (1.39)	-2.1 (1.24)	-0.4 (-0.9, 0.1)	-0.6 (-1.2, -0.0)
Month 3	-2.2 (1.25)	-2.8 (1.34)	-2.6 (1.30)	-0.6 (-1.1, -0.0)	-0.4 (-1.0, 0.2)
Month 4	-2.3 (1.35)	-2.9 (1.38)	-2.5 (1.30)	-0.6 (-1.2, -0.0)	-0.3 (-0.9, 0.3)

Source: Review team analysis based on ADEFF.xpt dataset
[1] Based on ANCOVA model including baseline CFS score and the proportion of time potentially spent in taking study medication during the VKC season as covariate.
Abbreviations: ANCOVA, analysis of covariance; CFS, corneal fluorescein staining; CI, confidence interval; HD, 0.1% QID; BID, 0.1% BID; VKC, vernal keratoconjunctivitis

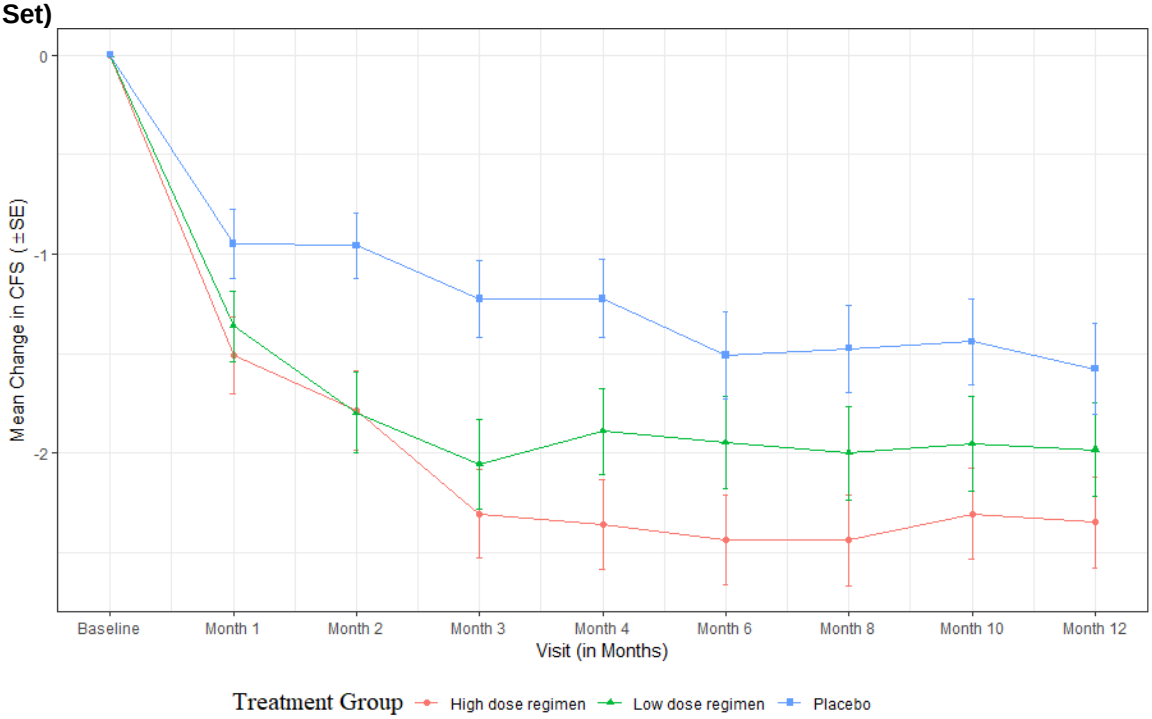
Table 45. Sensitivity Analyses: Efficacy Results of the Mean Change in Itching Score From Baseline at Each Visit (VEKTIS Study)

	Placebo	QID	BID	Difference (95% CI)[1]	
Visit	N = 58	N = 56	N = 54	QID vs. Placebo	BID vs. Placebo
Post-Rescue data imputed by baseline data					
Baseline	78.4 (16.26)	78.0 (18.16)	80.1 (14.81)	--	--
Month 1	-18.3 (21.16)	-33.8 (32.10)	-24.4 (29.60)	-15.6 (-25.8, -5.5)	-6.2 (-16.6, 4.1)
Month 2	-15.2 (22.45)	-34.7 (35.83)	-28.2 (28.09)	-19.7 (-30.4, -9.1)	-13.3 (-24.2, -2.4)
Month 3	-17.2 (25.08)	-35.9 (35.10)	-33.2 (32.69)	-18.9 (-30.4, -7.4)	-16.3 (-28.0, -4.5)
Month 4	-20.3 (27.19)	-39.4 (39.05)	-33.3 (35.79)	-19.4 (-32.0, -6.7)	-13.2 (-26.1, -0.4)
Post-Rescue data used in the analysis					
Baseline	78.4 (16.26)	78.0 (18.16)	80.1 (14.81)	--	--
Month 1	-24.4 (24.32)	-37.0 (32.00)	-33.1 (30.90)	-12.9 (-23.5, -2.2)	-9.3 (-20.2, 1.6)
Month 2	-22.7 (27.31)	-40.7 (35.97)	-39.6 (28.38)	-18.3 (-29.3, -7.3)	-17.5 (-28.7, -6.3)
Month 3	-25.2 (28.47)	-46.0 (34.31)	-40.7 (31.87)	-21.1 (-32.3, -9.8)	-16.1 (-27.6, -4.6)
Month 4	-32.9 (28.76)	-51.7 (37.54)	-41.9 (36.05)	-19.1 (-31.4, -6.9)	-9.6 (-22.1, 2.9)

Visit	Placebo N = 58	QID N = 56	BID N = 54	Difference (95% CI)[1] QID vs. Placebo	Difference (95% CI)[1] BID vs. Placebo
Post-Rescue data imputed by placebo-based multiple imputation					
Baseline	78.4 (16.26)	78.0 (18.16)	80.1 (14.81)	--	--
Month 1	-22.9 (21.97)	-35.1 (31.57)	-27.9 (29.22)	-12.3 (-23.0, -1.6)	-5.4 (-16.2, 5.5)
Month 2	-25.1 (25.86)	-38.1 (35.33)	-33.4 (27.52)	-13.2 (-25.2, -1.1)	-8.7 (-21.2, 3.8)
Month 3	-31.8 (27.75)	-43.1 (34.53)	-41.5 (30.72)	-11.5 (-24.4, 1.3)	-10.1 (-23.4, 3.3)
Month 4	-39.9 (26.77)	-50.1 (35.67)	-44.3 (33.15)	-10.4 (-23.6, 2.8)	-4.7 (-18.1, 8.7)

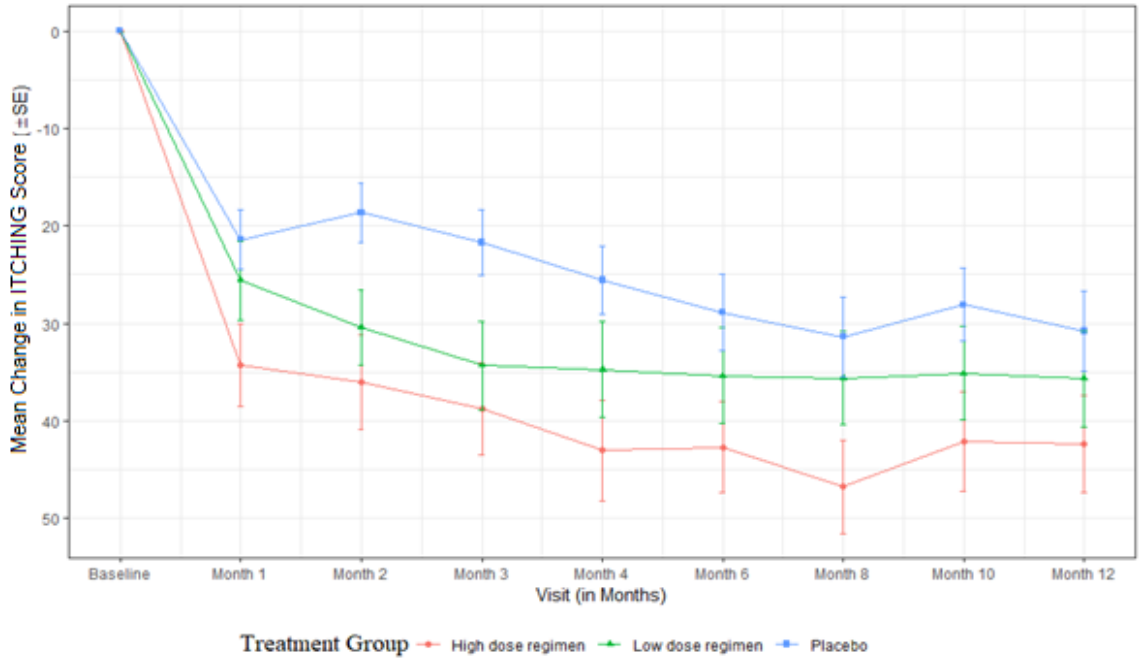
Source: Review team analysis based on ADQS.xpt dataset
[1] Based on ANCOVA model including baseline itching score and the proportion of time potentially spent in taking study medication during the VKC season as covariate.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; QID, 0.1% QID; BID, 0.1% BID; VKC, vernal keratoconjunctivitis

Figure 19. Mean Change in CFS Score Over Time Through Month 12 (VEKTIS Study) (Full Analysis Set)



Source: Review team analysis based on ADEFF.xpt dataset.
Abbreviations: CFS, corneal fluorescein stain; SE, standard error

Figure 20. Mean Change in Itching Score Over Time Through Month 12 (VEKTIS Study) (Full Analysis Set)



Source: Review team analysis based on ADQS.xpt dataset.
Note: For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last available data observed prior to rescue initiation.
Abbreviations: SE, standard error

Table 46. Efficacy Results for Additional Sign of VKC Variables at Each Visit (VEKTIS Study) (Full Analysis Set)

				Treatment Comparison[1]			
				QID vs. Placebo		BID vs. Placebo	
Visit	Placebo (N = 58)	QID (N = 56)	BID (N = 54)	Difference (95% CI)	p-value[2]	Difference (95% CI)	p-value[2]
Conjunctival discharge							
Baseline	1.7 (0.74)	1.6 (0.89)	1.7 (0.83)	--	--	--	--
Month 1	-0.4 (0.73)	-0.7 (0.98)	-0.7 (0.80)	-0.3 (-0.6, 0.0)	0.0560	-0.2 (-0.5, 0.0)	0.0963
Month 2	-0.5 (0.88)	-0.8 (1.11)	-0.8 (0.88)	-0.4 (-0.7, -0.1)	0.0152	-0.3 (-0.6, 0.0)	0.0745
Month 3	-0.6 (0.95)	-0.9 (1.23)	-0.9 (1.00)	-0.3 (-0.7, 0.0)	0.0535	-0.3 (-0.7, 0.0)	0.0764
Month 4	-0.7 (1.00)	-0.9 (1.22)	-0.9 (0.96)	-0.3 (-0.6, 0.0)	0.0829	-0.3 (-0.6, 0.1)	0.1402
Conjunctival erythema/hyperemia							
Baseline	2.2 (0.73)	2.3 (0.76)	2.2 (0.64)	--	--	--	--
Month 1	-0.4 (0.83)	-0.9 (1.09)	-0.6 (0.71)	-0.4 (-0.7, -0.1)	0.0067	-0.3 (-0.6, 0.0)	0.0681
Month 2	-0.4 (0.85)	-1.1 (1.13)	-0.9 (0.92)	-0.6 (-0.9, -0.3)	0.0002	-0.5 (-0.9, -0.2)	0.0019
Month 3	-0.5 (0.92)	-1.2 (1.13)	-0.9 (0.95)	-0.7 (-1.0, -0.4)	0.0001	-0.5 (-0.8, -0.2)	0.0050
Month 4	-0.5 (1.05)	-1.3 (1.18)	-0.9 (1.04)	-0.7 (-1.1, -0.3)	0.0002	-0.5 (-0.8, -0.1)	0.0208
Limbal infiltrates							
Baseline	2.1 (1.37)	2.1 (1.34)	1.9 (1.27)	--	--	--	--
Month 1	-0.3 (0.96)	-0.8 (1.26)	-0.3 (0.88)	-0.5 (-0.8, -0.1)	0.0089	-0.1 (-0.5, 0.2)	0.5594
Month 2	-0.4 (1.12)	-0.8 (1.29)	-0.5 (1.06)	-0.4 (-0.8, -0.1)	0.0238	-0.2 (-0.6, 0.2)	0.2159
Month 3	-0.5 (1.34)	-0.9 (1.39)	-0.6 (1.07)	-0.4 (-0.8, -0.0)	0.0351	-0.2 (-0.6, 0.2)	0.3123
Month 4	-0.6 (1.33)	-1.0 (1.46)	-0.7 (1.20)	-0.5 (-0.9, -0.0)	0.0331	-0.2 (-0.6, 0.2)	0.3169

				Treatment Comparison[1]			
				QID vs. Placebo		BID vs. Placebo	
Visit	Placebo (N = 58)	QID (N = 56)	BID (N = 54)	Difference (95% CI)	p-value[2]	Difference (95% CI)	p-value[2]
Papillae							
Baseline	2.8 (1.01)	2.9 (1.09)	2.9 (0.94)	--	--	--	--
Month 1	-0.4 (0.80)	-0.6 (1.01)	-0.5 (0.79)	-0.1 (-0.4, 0.2)	0.4552	-0.0 (-0.4, 0.3)	0.7656
Month 2	-0.4 (0.94)	-0.8 (1.35)	-0.7 (0.98)	-0.4 (-0.8, -0.1)	0.0252	-0.3 (-0.7, 0.0)	0.0732
Month 3	-0.5 (1.06)	-1.0 (1.43)	-0.9 (1.11)	-0.5 (-0.9, -0.1)	0.0110	-0.4 (-0.8, 0.1)	0.0555
Month 4	-0.5 (1.10)	-1.0 (1.46)	-0.9 (1.16)	-0.5 (-0.9, -0.1)	0.0211	-0.4 (-0.8, 0.0)	0.0619

Source: Review team analysis based on ADOCEFF.xpt dataset located at \\CDSESUB1\evsprod\NDA214965\0001\m5\datasets\nvg09b113\analysis\adam\datasets
Note: For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last available data observed prior to rescue initiation
[1] Based on ANCOVA model adjusting for baseline score and the proportion of time potentially spent in taking study medication during the VKC season as covariate
[2] Unadjusted p-values.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; QID, 0.1% QID; BID, 0.1% BID; N, number of patients; VKC, vernal keratoconjunctivitis

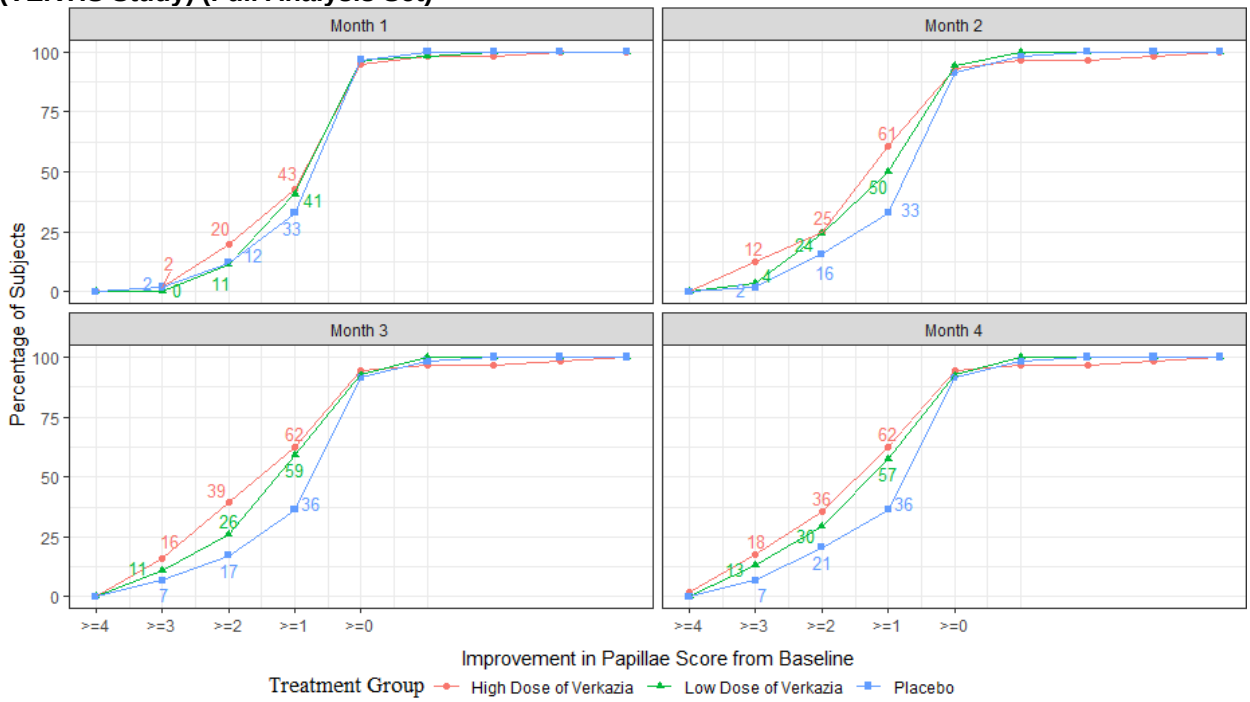
Additional Summary of Papilla Score

Table 47. Distribution of Papillae Score at Baseline and Complete Clearance at Each Monthly Visit (VEKTIS Study)

Distribution of Papillae Score at Baseline by Treatment Group				Complete Clearance in Papillae (Score = 0) at Each Visit by Treatment Group			
Baseline Score	Placebo (N = 58)	QID (N = 56)	BID (N = 54)	Visit	Placebo (N = 58)	QID (N = 56)	BID (N = 54)
0	0	1 (1.8%)	0	Month 1	0	3 (5.4%)	1 (1.9%)
1	5 (8.6%)	5 (8.9%)	4 (6.9%)	Month 2	2 (3.5%)	3 (5.4%)	2 (3.7%)
2	20 (34.5%)	16 (28.6)	14 (24.1%)	Month 3	2 (3.5%)	7 (12.5%)	4 (7.4%)
3	13 (22.4%)	13 (23.2%)	19 (32.8%)	Month 4	2 (3.5%)	7 (12.5%)	5 (9.3%)
4	20 (34.5%)	21 (37.5%)	17 (29.3%)				

Source: Review team analysis based on ADOCEFF.xpt dataset located
Note: Papillae score was measured at each visit in 5-point scale (0 - Absent; 1 - Mild hyperemic scattered papillae; 2 – Moderate diffuse hyperemic swollen papillae; 3 – Severe; 4 – Hyperemic swollen giant papillae covering the superior tarsal plate).
Abbreviations: QID, 0.1% QID; BID, 0.1% BID; N, number of patients

Figure 21. Cumulative Distribution of the Change in Papillae Score From Baseline at Each Visit (VEKTIS Study) (Full Analysis Set)



Source: Review team analysis based on ADOCEFF.xpt dataset.
Note: For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last available data observed prior to rescue initiation.

Table 48. Responder Analysis (VEKTIS Study): Applicant's Preferred Secondary Endpoint

		Placebo (N=58)	QID (N = 56)	BID (N = 54)
Average of last 3 visit CFS score < 50% of baseline?	Yes (A)	20	36	31
	No	38	20	23
Any corneal ulceration during the study?	Yes	2	4	2
	No (B)	56	52	52
Received any rescue at the last three visits?	Yes	27	18	9
	No (C)	31	38	45
Did subject discontinue from the study?	Yes	9	6	10
	No (D)	49	50	44
(A) and (B) and (C) and (D)	n (%)	18 (31.0%)	32 (57.1%)	28 (51.9%)
	95% CI	(19.1%, 42.9%)	(44.2%, 70.1%)	(38.5%, 65.2%)
	Difference	--	26.1%	20.8%
	(95% CI)		(8.5%, 43.7%)	(3.0%, 38.7%)

Source: Review team analysis based on ADEFF.xpt dataset.
Note 1: A patients with a mean CFS score of the last 3 months of treatment ≤ 50% of baseline (A) who did not withdraw from the study (D), did not experience an ulceration (B), and did not use rescue medication in the last 3 months of the 4-month treatment period (C) was considered a responder.
Note 2: For patients who received rescue therapy during the study, all Post-Rescue data were censored and imputed by the last available data observed prior to rescue initiation
Abbreviations: CFS, corneal fluorescein stain; CI, confidence interval; QID, 0.1% QID; BID, 0.1% BID; N, number of patients

Table 49. Efficacy Results of the Mean Change in CFS Score From Baseline at Each Visit by Administrative Split (VEKTIS Study)

	Placebo	QID	BID	Difference (95% CI)	
Visit	(N = 58)	(N = 56)	(N = 54)	QID vs. Placebo	BID vs. Placebo
Latitude Group[1]					
< 39	**n = 28**	**n = 34**	**n = 28**		
Baseline	4.0 (0.19)	4.2 (0.39)	4.1 (0.36)		
Month 1	-0.9 (1.33)	-1.7 (1.46)	-1.4 (1.36)	-0.8 (-1.5, -0.1)	-0.7 (-1.4, 0.1)
Month 2	-1.0 (1.20)	-2.1 (1.44)	-1.8 (1.49)	-1.2 (-1.9, -0.5)	-1.0 (-1.7, -0.2)
Month 3	-1.3 (1.50)	-2.5 (1.53)	-2.0 (1.60)	-1.2 (-2.0, -0.5)	-0.9 (-1.7, -0.1)
Month 4	-1.1 (1.35)	-2.6 (1.56)	-1.7 (1.46)	-1.4 (-2.2, -0.7)	-0.7 (-1.5, 0.1)
>= 39	**n = 30**	**n = 22**	**n = 26**		
Baseline	4.1 (0.31)	4.4 (0.49)	4.0 (0.20)		
Month 1	-0.8 (1.31)	-1.0 (1.29)	-1.2 (1.19)	-0.3 (-1.1, 0.4)	-0.3 (-1.0, 0.4)
Month 2	-0.9 (1.29)	-1.2 (1.33)	-1.7 (1.46)	-0.3 (-1.1, 0.4)	-0.7 (-1.4, -0.0)
Month 3	-1.2 (1.49)	-1.9 (1.75)	-2.0 (1.67)	-0.7 (-1.7, 0.2)	-0.7 (-1.6, 0.1)
Month 4	-1.3 (1.64)	-1.9 (1.80)	-2.1 (1.65)	-0.7 (-1.6, 0.3)	-0.7 (-1.6, 0.2)
Longitude Group[1]					
< 15	**n = 33**	**n = 28**	**n = 28**		
Baseline	4.1 (0.33)	4.4 (0.50)	4.1 (0.26)		
Month 1	-0.8 (1.34)	-1.3 (1.51)	-1.2 (1.24)	-0.5 (-1.2, 0.3)	-0.3 (-1.0, 0.4)
Month 2	-1.0 (1.27)	-1.6 (1.51)	-1.8 (1.54)	-0.7 (-1.5, 0.1)	-0.9 (-1.6, -0.1)
Month 3	-1.2 (1.46)	-2.1 (1.80)	-2.0 (1.75)	-0.9 (-1.8, -0.0)	-0.9 (-1.7, 0.0)
Month 4	-1.3 (1.56)	-2.2 (1.90)	-2.0 (1.70)	-1.0 (-1.9, -0.0)	-0.7 (-1.6, 0.2)
>= 15	**n = 25**	**n = 28**	**n = 26**		
Baseline	4.0 (0.00)	4.1 (0.31)	4.1 (0.33)		
Month 1	-0.8 (1.30)	-1.6 (1.33)	-1.4 (1.32)	-0.9 (-1.6, -0.2)	-0.8 (-1.6, -0.0)
Month 2	-0.9 (1.22)	-1.9 (1.44)	-1.7 (1.40)	-1.1 (-1.9, -0.4)	-1.0 (-1.7, -0.2)
Month 3	-1.3 (1.53)	-2.5 (1.47)	-2.0 (1.50)	-1.3 (-2.1, -0.5)	-0.9 (-1.7, -0.0)
Month 4	-1.2 (1.44)	-2.4 (1.45)	-1.8 (1.41)	-1.4 (-2.2, -0.6)	-0.8 (-1.6, -0.0)
Randomization Order[2]					
1	**n = 31**	**n = 31**	**n = 24**		
Baseline	4.1 (0.30)	4.3 (0.48)	4.0 (0.20)		
Month 1	-0.8 (1.24)	-1.5 (1.54)	-1.2 (1.14)	-0.9 (-1.6, -0.2)	-0.4 (-1.2, 0.3)
Month 2	-0.9 (1.22)	-1.7 (1.54)	-1.9 (1.47)	-0.9 (-1.7, -0.2)	-1.1 (-1.8, -0.3)
Month 3	-1.0 (1.37)	-2.2 (1.70)	-2.1 (1.66)	-1.3 (-2.1, -0.4)	-1.1 (-1.9, -0.2)
Month 4	-1.0 (1.37)	-2.3 (1.77)	-2.1 (1.64)	-1.4 (-2.2, -0.5)	-1.1 (-2.0, -0.2)
2	**n = 27**	**n = 25**	**n = 30**		
Baseline	4.0 (0.19)	4.2 (0.37)	4.1 (0.35)		
Month 1	-0.9 (1.40)	-1.3 (1.27)	-1.4 (1.39)	-0.5 (-1.3, 0.3)	-0.6 (-1.4, 0.1)
Month 2	-1.0 (1.28)	-1.8 (1.40)	-1.6 (1.47)	-0.9 (-1.7, -0.1)	-0.8 (-1.5, -0.0)
Month 3	-1.4 (1.60)	-2.3 (1.60)	-1.9 (1.60)	-1.0 (-1.8, -0.1)	-0.6 (-1.5, 0.2)
Month 4	-1.5 (1.62)	-2.3 (1.59)	-1.7 (1.48)	-0.9 (-1.8, -0.1)	-0.4 (-1.3, 0.4)

Source: Review team analysis based on ADEFF.xpt dataset.
Note: For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last available data observed prior to rescue initiation
[1] Categories are based on median of latitude and longitude.
[2] Categories are based on median of the dates of inclusion of the first patient per site: 1: < 07/14/2013 and 2: >=07/14/2013
Abbreviations: CI, confidence interval; QID, 0.1% QID; BID, 0.1% BID; N, number of patients; n, number of patients with specification

Table 50. Efficacy Results of the Mean Change in Itching Score From Baseline at Each Visit by Administrative Split (VEKTIS Study)

	Placebo	QID	BID	Difference (95% CI)	
Visit	(N = 58)	(N = 56)	(N = 54)	QID vs. Placebo	BID vs. Placebo
Latitude Group					
< 39	**n = 28**	**n = 34**	**n = 28**		
Baseline	80.8 (14.16)	82.6 (13.05)	78.4 (14.03)		
Month 1	-19.9 (21.33)	-43.2 (33.67)	-26.5 (28.21)	-22.5 (-36.8, -8.1)	-11.1 (-26.6, 4.5)
Month 2	-24.1 (26.12)	-46.6 (35.00)	-27.5 (27.91)	-21.6 (-36.6, -6.6)	-7.8 (-24.0, 8.3)
Month 3	-29.1 (28.31)	-46.1 (35.85)	-35.9 (31.60)	-16.1 (-31.9, -0.2)	-11.1 (-28.1, 5.9)
Month 4	-31.3 (28.70)	-51.3 (37.71)	-32.9 (31.28)	-19.2 (-35.5, -2.8)	-6.1 (-23.6, 11.5)
>= 39	**n = 30**	**n = 22**	**n = 26**		
Baseline	76.2 (17.96)	71.0 (22.57)	82.0 (15.65)		
Month 1	-16.9 (21.26)	-19.3 (23.45)	-22.0 (31.42)	-2.6 (-16.5, 11.4)	-2.7 (-16.0, 10.7)
Month 2	-13.3 (18.68)	-19.7 (30.33)	-30.8 (27.64)	-6.6 (-20.2, 7.0)	-15.1 (-28.1, -2.1)
Month 3	-14.6 (19.67)	-30.1 (31.59)	-35.0 (33.03)	-15.7 (-30.8, -0.6)	-17.9 (-32.4, -3.5)
Month 4	-20.0 (23.74)	-33.0 (36.85)	-39.0 (38.78)	-13.1 (-30.9, 4.6)	-16.5 (-33.5, 0.5)
Longitude Group [1]					
< 15	**n = 33**	**n = 28**	**n = 28**		
Baseline	79.2 (16.26)	79.1 (15.78)	80.7 (17.38)		
Month 1	-18.8 (21.94)	-34.6 (34.85)	-28.7 (34.81)	-15.3 (-30.4, -0.3)	-10.0 (-25.1, 5.1)
Month 2	-19.1 (23.84)	-33.5 (39.06)	-32.5 (30.58)	-14.0 (-29.5, 1.5)	-13.6 (-29.2, 2.0)
Month 3	-19.9 (24.02)	-41.9 (35.82)	-36.4 (33.55)	-21.5 (-37.1, -5.9)	-16.5 (-32.2, -0.9)
Month 4	-25.1 (26.77)	-45.6 (40.01)	-39.0 (38.35)	-20.1 (-37.5, -2.7)	-14.1 (-31.5, 3.4)
>= 15	**n = 25**	**n = 28**	**n = 26**		
Baseline	77.3 (16.53)	77.0 (20.50)	79.6 (11.75)		
Month 1	-17.6 (20.51)	-33.0 (29.68)	-19.7 (22.49)	-15.5 (-29.2, -1.8)	-1.9 (-16.2, 12.4)
Month 2	-17.8 (22.39)	-38.5 (32.13)	-25.4 (23.96)	-20.8 (-35.6, -6.1)	-7.5 (-22.8, 7.8)
Month 3	-23.8 (26.82)	-37.7 (34.37)	-34.4 (30.86)	-14.0 (-31.0, 3.0)	-10.5 (-28.1, 7.1)
Month 4	-25.9 (26.99)	-42.6 (36.82)	-32.4 (31.12)	-16.8 (-34.4, 0.9)	-6.3 (-24.5, 11.9)
Randomization Order [2]					
1	**n = 31**	**n = 31**	**n = 24**		
Baseline	80.2 (17.75)	76.8 (20.80)	79.5 (17.02)		
Month 1	-20.8 (21.69)	-36.1 (34.85)	-27.3 (35.40)	-17.2 (-32.2, -2.1)	-6.7 (-22.8, 9.3)
Month 2	-19.5 (23.37)	-37.8 (35.38)	-32.5 (29.23)	-20.1 (-34.4, -5.8)	-13.2 (-28.5, 2.0)
Month 3	-20.8 (24.74)	-44.5 (33.51)	-35.6 (32.30)	-25.6 (-40.3, -10.8)	-15.0 (-30.8, 0.7)
Month 4	-24.4 (24.90)	-49.4 (35.30)	-39.6 (37.49)	-26.8 (-42.5, -11.2)	-15.5 (-32.2, 1.3)
2	**n = 27**	**n = 25**	**n = 30**		
Baseline	76.4 (14.43)	79.6 (14.49)	80.7 (13.05)		
Month 1	-15.5 (20.57)	-31.0 (28.73)	-22.0 (24.39)	-15.1 (-28.7, -1.5)	-7.7 (-21.1, 5.7)
Month 2	-17.3 (23.03)	-33.8 (36.30)	-26.4 (26.34)	-16.1 (-32.1, -0.2)	-10.3 (-25.9, 5.3)
Month 3	-22.5 (25.98)	-34.0 (36.27)	-35.3 (32.29)	-11.1 (-28.5, 6.4)	-14.0 (-31.0, 3.0)
Month 4	-26.6 (28.93)	-37.6 (41.16)	-32.8 (32.98)	-10.6 (-29.7, 8.4)	-7.4 (-25.8, 11.1)

Source: Review team analysis based on ADQS.xpt dataset.
Note: For patients who received rescue therapy during the study, all Post-Rescue data were imputed by the last available data observed prior to rescue initiation
[1] Categories are based on median of latitude and longitude.
[2] Categories are based on median of the dates of inclusion of the first patient per site: 1: < 07/14/2013 and 2: >=07/14/2013
Abbreviations: CI, confidence interval; QID, 0.1% QID; BID, 0.1% BID; N, number of patients; n, number of patients with specification

18. Clinical Safety: Additional Information and Assessment

Not applicable.

19. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable.

20. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

21. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

An Office of Scientific Investigations (OSI) clinical inspection summary was completed on 3/20/21. Two clinical investigators (CIs): Drs. Joseph Martel (Site 2101) and Kara Cavuoto (Site 2110) were inspected for Study VEKTIS (NVG09B113).

Based on the results of these CI inspections, Study VEKTIS (NVG09B113) appears to have been conducted adequately, and the data generated by these sites and submitted by the applicant appear acceptable in support of the respective indication.

22. Labeling Summary of Considerations and Key Additional Information

Following is the Applicant's final agreed-upon labeling (i.e., package insert, instructions for use, carton and container labeling) submitted on June 21, 2021.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

23. Post-marketing Requirements and Commitments

Routine safety monitoring is recommended following the approval of this drug product.

24. Financial Disclosure

Table 51. Covered Clinical Studies: VEKTIS (NVG09B113) and NOVATIVE (NVG05L101)

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 52 (VEKTIS)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason?	Yes ☐	No ☐ (Request explanation from Applicant)

The VEKTIS (NVG09B113) study was a Phase 3, randomized, double-masked, placebo-controlled, multicenter study conducted from 2013 through 2016 by Santen SAS. This study was a global clinical study including 4 sites in the United States. The study design minimized potential bias. Santen confirmed that none of the financial interests or arrangements described in 21 Code of Federal Regulations Section 54.4(a)(3) existed.

Clinical study NOVATIVE (Protocol NVG05L101) is a supportive, dose-ranging study conducted from 2006 through 2007 by Novagali, which was the company's former name before Santen acquired it. The clinical sites of the NOVATIVE study were all located outside of the United States. Despite Santen's diligent efforts to obtain from the participating Investigators the United States financial disclosure form duly filled in and signed by them Santen was unable to obtain these forms from the Investigators.

25. References

Leonardi, A, S Doan, M Amrane, D Ismail, J Montero, J Nemeth, P Aragona, D Bremond-Gignac, and VS Group, 2019, A Randomized, Controlled Trial of Cyclosporine A Cationic Emulsion in Pediatric Vernal Keratoconjunctivitis: The VEKTIS Study, Ophthalmology, 126(5):671-681.

Ryffel, B, P Donatsch, M Madorin, BE Matter, G Ruttimann, H Schon, R Stoll, and J Wilson, 1983, Toxicological evaluation of cyclosporin A, Arch Toxicol, 53(2):107-141.

Wigger, M, E Druckler, J Muscheites, HJ Stolpe, G Kundt, and R Wacke, 2003, Comparison of cyclosporine absorption profiles over a 12-month period in stable pediatric renal transplant recipients, Transplant Proc, 35(4):1300-1303.

26. Review Team

Table 52. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Wendy Streight, PhD
Nonclinical Reviewer	Erin M. Ruhland, PhD
Nonclinical Team Supervisor	Lori E. Kotch, PhD, DABT
Office of Clinical Pharmacology Reviewer	Amit Somani, PhD
Office of Clinical Pharmacology Team Leader	Bhawana Saluja, PhD
Clinical Reviewer	Rhea A. Lloyd, MD
Clinical Team Leader	William Boyd, MD
Statistical Reviewer	Solomon Chefo, PhD
Statistical Team Leader	Guoxing Soon, PhD
Cross-Disciplinary Team Leader	William Boyd, MD
Division Director (pharm/tox)	Mukesh Summan, PhD – on behalf of Lori Kotch
Division Director (Clinical) and Signatory Authority	Wiley Chambers, MD

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 53. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ ATL	Chunchun Zhang, PhD
DP	Milton Sloan, PhD, Chunchun Zhang, PhD
DS	Zhengfu Wang, PhD, Suong Tran, PhD
Microbiology	Sallie Crenshaw, PhD, Erika Pfeiler, PhD
Biopharmaceutics	Joan Zhao, PhD, Poonam Delvadia, PhD
RBPM	Kelly Ballard
OPDP	Carrie Newcomer, PharmD
OSI	Ling Yang, MD, PhD
OSE/DMEPA	Nasim Roosta, PhD
Medical Editors	Erica Boehm, PhD; Katharine Bradley; Megan Young, PhD
Labeling Reviewer	Derek Alberding, PharmD

Abbreviations: ATL, application technical lead; DMEPA, Division of Medication Error Prevention and Analysis; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; RBPM, regulatory business process manager

Table 54 Signature of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Management	Wendy Streight, PhD	OND/ORO/DROSM	Enter sections. ☐ Authored ☒ Contributed ☐ Approved
Regulatory Project Manager	**Signature:** Wendy M. Streight -S Digitally signed by Wendy M. Streight -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300371573, cn=Wendy M. Streight -S Date: 2021.06.22 08:40:41 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Rhea A. Lloyd, MD	OND/OSM/DO	Enter sections. ☒ Authored - IA ☐ Contributed ☐ Approved
Reviewer	**Signature:** Rhea A. Lloyd -S Digitally signed by Rhea A. Lloyd -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rhea A. Lloyd -S, 0.9.2342.19200300.100.1.1=1300227253 Date: 2021.06.22 11:34:04 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	William Boyd, MD	OND/ OSM/DO	Enter sections. ☒ Authored- ES ☒ Contributed – IA ☒ Approved ES, IA
Clinical Lead, CDTL, Deputy Director	**Signature:** William M. Boyd -S Digitally signed by William M. Boyd -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300139743, cn=William M. Boyd -S Date: 2021.06.22 08:34:50 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Erin M. Ruhland, PhD	OND/ORDPURM/DPTRDPURM	Enter sections. ☒ Authored - IA ☐ Contributed ☐ Approved
Reviewer	**Signature:** Erin M. Ruhland -S Digitally signed by Erin M. Ruhland -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300424364, cn=Erin M. Ruhland -S Date: 2021.05.28 16:20:35 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Lori E. Kotch, PhD, DABT	OND/ORDPURM/DPTRDPURM	Enter sections. ☐ Authored ☒ Contributed - IA ☒ Approved
Supervisor	Mukesh Summan, PhD is signing for Lori Kotch, PhD **Signature:** Mukesh Summan -S Digitally signed by Mukesh Summan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mukesh Summan -S, 0.9.2342.19200300.100.1.1=2000337340 Date: 2021.06.22 11:30:45 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Amit Somani, PhD	OTS/OCP/DIIP	Enter sections. ☒ Authored - IA ☐ Contributed ☐ Approved
Reviewer	**Signature:** Amit A. Somani -S Digitally signed by Amit A. Somani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amit A. Somani -S, 0.9.2342.19200300.100.1.1=2002153064 Date: 2021.06.08 09:32:48 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Bhawana Saluja, PhD	OTS/OCP/DIIP	Enter sections. ☐ Authored ☒ Contributed- IA ☒ Approved
Team Leader	**Signature:** Bhawana Saluja -S Digitally signed by Bhawana Saluja -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Bhawana Saluja -S, 0.9.2342.19200300.100.1.1=2000559312 Date: 2021.06.08 10:54:30 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Solomon Chefo, PhD	OB/DBIV	Enter sections. ☒ Authored - IA ☐ Contributed ☐ Approved
Reviewer	**Signature:** Solomon Chefo -S Digitally signed by Solomon Chefo -S Date: 2021.06.22 09:54:49 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Guoxing Soon, PhD	OB/DBIV	Enter sections. ☐ Authored ☒ Contributed IA ☒ Approved
Team Leader	**Signature:** Guoxing Soon -S Digitally signed by Guoxing Soon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Guoxing Soon -S, 0.9.2342.19200300.100.1.1=1300124920 Date: 2021.06.22 08:52:04 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Chunchun Zhang, PhD	OPQ/ONDP/DNDPIII/NDPB6	Enter sections. ☒ Authored ☒ Contributed ☒ Approved
Team Leader	**Signature:** Chunchun Zhang -S Digitally signed by Chunchun Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chunchun Zhang -S, 0.9.2342.19200300.100.1.1=2001178137 Date: 2021.06.04 16:22:12 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

WENDY M STREIGHT
06/23/2021 11:38:26 AM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	214965
Supporting document/s:	SDN001
Applicant's letter date:	8-26-2020
CDER stamp date:	8-26-2020
Product:	Verkazia (Cyclosporine Ophthalmic Emulsion, 0.1%)
Indication:	For the treatment (b) (4) vernal keratoconjunctivitis (b) (4) for children from 4 through 18 years of age
Applicant:	Santen Inc (Emeryville, CA)
Review Division:	DPT- ORPURM/OSM, supporting the Division of Ophthalmology Products (DO)
Reviewer:	Erin Ruhland, PhD
Supervisor:	Lori Kotch, PhD, DABT
Division Director:	Mukesh Summan, PhD, DABT
Project Manager:	Wendy Streight, PhD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214965 are owned by Santen Inc or are data for which Santen Inc has obtained a written right of reference.
Any information or data necessary for approval of NDA 214965 that Santen Inc does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 214965.

Reference ID: 4798171

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Reference ID: 4798171

1 Executive Summary

1.1 Introduction

The Applicant is proposing a novel formulation of cyclosporine A (CsA; 0.1%) for the treatment of (b) (4) vernal keratoconjunctivitis (b) (4) for children from 4 through 18 years of age. The Application is a 505(b)(2) NDA which relies on the listed drugs, Sandimmune and Neoral, for characterization of the systemic toxicity of CsA. All nonclinical elements of the application were submitted with the NDA and it is considered approvable from the nonclinical perspective.

1.2 Brief Discussion of Nonclinical Findings

- The Applicant changed formulations of the drug product throughout development.
- The final to-be-marketed formulation of Verkazia contains a novel excipient, cetalkonium chloride (CKC). No toxicity was associated with the CKC containing vehicle or the drug product in toxicity studies conducted in the rabbit for up to 28-days.
- The Applicant provided a justifiable bridge between the to-be-marketed formulation and other supporting toxicity studies included in the application including a chronic toxicity study of 6-months duration in the rabbit.
- Nonclinical systemic toxicity data was bridged through direct dose comparison to LD/published doses. Large dose multiples exist between the relied upon systemic drug products (oral/intravenous: Neoral and Sandimmune, CS-A) and Applicant's drug product, per dosing information. Systemic exposure to CsA following topical ocular instillation of Verkazia was typically undetectable or negligible in the nonclinical studies.

1.3 Recommendations

1.3.1 Approvability

The NDA application is approvable from the Pharmacology/Toxicology discipline viewpoint.

1.3.3 Labeling

1.3.3.1 Applicant's Proposed Labeling (nonclinical sections only)

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 59865-13-3

Generic Name: Cyclosporine Ophthalmic Emulsion, 0.1%

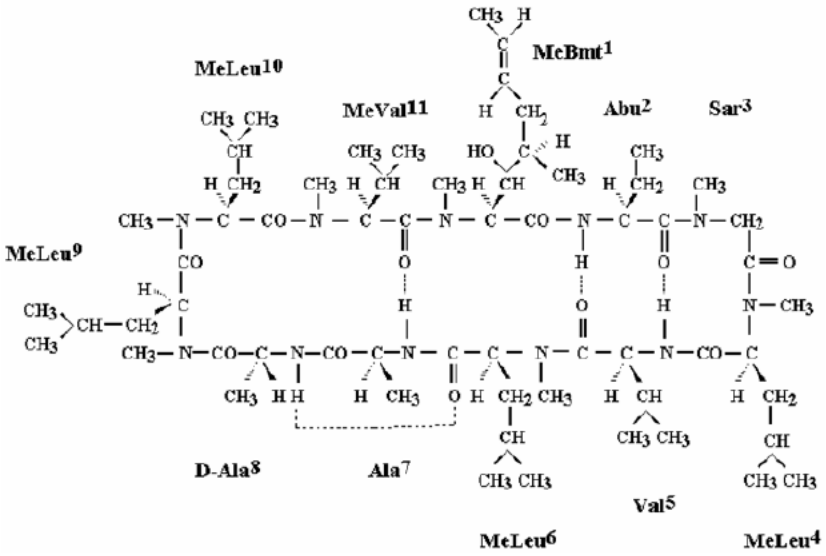
Code Name: Verkazia®; NOVA22007; Ikervis

Chemical Name: Cyclo-[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]

Molecular Formula/Molecular Weight: $C_{62}H_{111}N_{11}O_{12}$ / 1202.6 g/mol

Reference ID: 4798171

Structure:



Pharmacologic Class: Calcineurin inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- DMF (b) (4)
- IND 70,502
- NDA 050573 (Sandimmune®; LD on Form 356h)
- NDA 050715 (Neoral®; LD on Form 356h)

2.3 Drug Formulation

The formulation of the drug product changed throughout development. Initial clinical and nonclinical studies were performed using "2nd generation NOVA22007" formulation (b) (4)

As development progressed, the Applicant (b) (4)

A further change of the 3rd generation formulation resulted in the to-be-marketed formulation. In particular, the (b) (4) component of the formulation was replaced with cetalkonium chloride (CKC). The Applicant summarizes the rationale for this change as:

(b) (4)

(b) (4)

Comparative results between formulations showed that the replacement of (b) (4) with CKC did not significantly impact the CsA pharmacokinetic profile (see Study Tp118 below) and no additional toxicity was reported following 2 separate 28-day toxicology studies in rabbits with the to-be-marketed CKC containing formulation.

2nd generation formulation:

Component	Function	Strength (% w/w)
(b) (4)		

3rd generation formulation:

Component	Function	Strength (% w/w)
[redacted]		(b) (4)

To-be-marketed formulation:

Component	Function	Strength (% w/w)
Cyclosporine	Drug substance	0.1%
Triglycerides, Medium chain		(b) (4)
Tyloxapol		
Cetalkonium chloride		
Glycerol		
Poloxamer 188		

The Applicant performed nonclinical toxicology studies with 4 different formulations of the drug product:

- DE-076: used only in the chronic 26-week toxicology study in rabbits (Study 451424)*
- NOVA22007 1 mg/mL (b) (4) formulation (2nd gen)
- NOVA22007 1 mg/mL (b) (4) formulation (3rd gen)
- NOVA22007 1mg/mL CKC formulation (i.e. the to-be-marketed formulation)

*the composition of DE-076 was requested from the Applicant and the Applicant provided the following:

The Applicant provided scientific justification to bridge chronic ocular toxicity data obtained for the DE-076 formulation to the Verkazia formulations. The Applicant states:

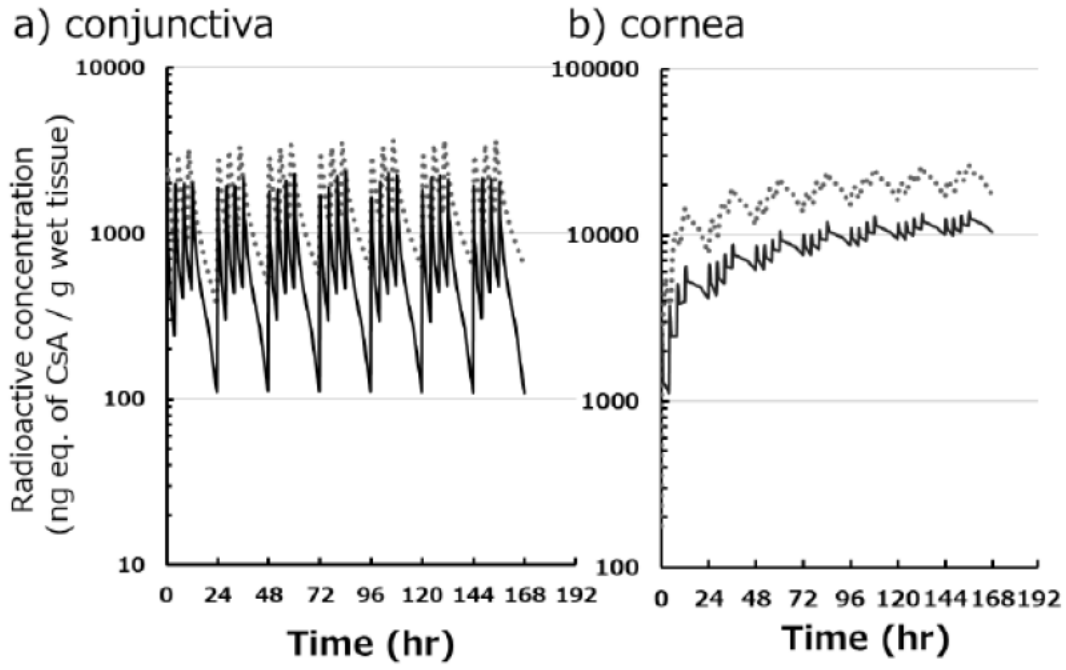
> *Kuwano et al. reported that an ocular pharmacokinetic study using ^{3}H-CsA showed that the distribution of CsA in ocular tissues, such as cornea, bulbar conjunctiva, and lacrimal gland, after topical instillation of DE-076 was superior to that after instillation of an oil-in-water emulsion of the same concentration (Kuwano et al., 2002).*
>
> - *Reviewer's note: The concentration of CsA used in this study was 0.1%.*
>
> *The ocular distribution data with single dose 0.05% DE-076 showed higher penetration and retention to cornea and conjunctiva compared with Verkazia 1.0 mg/mL (DE-076 ocular PK study: 047DN010-047DN020) (Kawazu et al., 2003). Pharmacokinetic simulation was performed to estimate the steady-state using these single dose data of DE-076 and Verkazia by the superposition principle method (Figure 1). Ocular distribution with 0.05% DE-076 was extrapolated to show a higher penetration and retention in cornea and conjunctiva compared with that of 0.1% Verkazia. These ocular PK data bridge the ocular safety study up to 1% (10 mg/mL CsA) of DE-076 (Study 451424) demonstrating CsA-derived ocular safety of Verkazia 1 mg/mL (0.1%) with a suitable enough safety margin (Module 2.4.5 Table 13).*

Ocular tissue concentrations of radioactivity after instillation of ^{3}H-CsA ophthalmic solution to rabbits

	0.05% 3H-CsA (DE-076)[a]		0.1% 3H-CsA emulsion (Verkazia)[b]	
Time (hr)	Conjunctiva*	Cornea**	conjunctiva*	cornea
0.33	--[c]	--	1914.13 ± 1640.72	2691.69 ± 1433.73
0.5	2428.9 ± 1041.6	2646.5 ± 485.5	--	--
0.67	--	--	820.23 ± 192.06	2066.10 ± 544.97
1	--	--	753.13 ± 362.68	1292.12 ± 392.15
2	1411.1 ± 207.1	5557.7 ± 2271.3	417.45 ± 172.33	1247.30 ± 490.52
4	746.5 ± 318.6	3786.9 ± 756.0	233.8 ± 116.03	1112.87 ± 594.99
8	363.9 ± 126.4	5322.1 ± 3087.9	164.19 ± 56.75	1352.15 ± 424.74
12	--	--	53.14 ± 18.56	1527.39 ± 670.26
24	62.9 ± 32.5	1766.1 ± 324.3	8.75 ± 14.56	627.59 ± 135.70
48	--	--	N.D.[d]	466.61 ± 207.84
72	--	--	N.D.	335.97 ± 114.86
96	12.5 ± 14.1	435.9 ± 167.7	--	--
144	2.8 ± 0.9	233.9 ± 53.0	--	--

a Study No. 047DN010, 047DN020
b Study No. N09F1205
c Not determined
d Not detected
Note:
* conjunctiva; bulbar conjunctiva, Study No. 047DN010, 047DN020; bulbar + palpebral conjunctiva, Study No. N09F1205
** The concentrations of radioactivity for the whole cornea tissue were recalculated using the data of corneal epithelium and cornea (without epithelium)(No. 047DN010, 047DN020) (Kawazu et al., 2003).

PK simulation of ^{3}H-CsA concentration following administration of DE-076 or Verkazia in Conjunctiva and Cornea by superposition principle



····· 0.05% ^{3}H-CsA (DE-076) TID, 5hr intervals, study No. 047DN010-047DN020

——— 0.1% ^{3}H-CsA (b) (4) emulsion (Verkazia), QID, 4hr intervals, Study No. N09F1205

Note: conjunctiva; bulbar conjunctiva (047DN010-047DN020) (Kawazu et al., 2003), bulbar conjunctiva and palpebral conjunctiva (Study No. N09F1205)

References:

- Kuwano, M. et al., 2002, "Cyclosporine A formulation affects its ocular distribution in rabbits", *Pharm Res*., 19(1): 108 – 11.
- Kawazu, K., *et al*., 2003, "Concentrations of radioactivity in ocular tissues after the instillation of a single dose of 0.05% ^{3}H-ciclosporin ophthalmic solution in white rabbits"

***Reviewer's note*:** Reviewer agrees with Applicant's justification that, in rabbits, ocular absorption following DE-076 is similar or more than an oil-in-water formulation of the same concentration. Further, the chronic toxicology study using DE-076 to support this application found no significant toxicity associated with DE-076 containing cyclosporine at a concentration which was 10-fold higher (1% cyclosporine) than the to-be-marketed formulation of Verkazia (0.1% cyclosporine); see below for review of GLP Study 451424. This large dose margin provides an additional source of justification for the bridge.

2.4 Comments on Novel Excipients

Cetalkonium chloride (CKC)
CKC is included in FDA's current list of OTC ingredients. CKC is part of at least two OTC products in the US: Sedagel® Teething gel which contains CKC at a concentration of 0.01% (w/w) and Babee® (Pfeiffer), which is used in the treatment of oral lesions. (b) (4) The Applicant qualified the excipient at a concentration of (b) (4) in two 28-day ocular toxicity studies in rabbit using the to-be-marketed formulation (see below).

Medium chain triglycerides (MCT)
Medium chain triglycerides (MCTs) are a family of triglycerides, containing predominantly, caprylic (C8) and capric (C10) fatty acids with lesser amounts of caproic (C6) and lauric (C12) fatty acids. MCTs are widely used for parenteral nutrition in individuals requiring supplemental nutrition and are being more widely used in foods, drugs and cosmetics. MCTs are essentially non-toxic in acute toxicity tests conducted in several species of animals. In ocular and dermal irritation testing MCTs exhibit virtually no potential as ocular or dermal irritants, even with prolonged eye or skin exposure (reviewed in Traul *et al*., 2000, "Review of the toxicologic properties of medium-chain triglycerides", *Food and Chem Toxicol*, 38(1): 79 – 98). The Applicant qualified the excipient at a concentration of (b) (4) in two 28-day ocular toxicity studies in rabbit using the to-be-marketed formulation (see below).

2.5 Comments on Impurities/Degradants of Concern

All proposed specifications for impurities and degradants in the drug product are below qualification thresholds recommended in ICHQ3 guidance.

2.6 Proposed Clinical Population and Dosing Regimen

Verkazia is indicated for treatment of (b) (4) vernal keratoconjunctivitis (b) (4) in children from 4 through 18 years of age. The patient is to instill one drop of Verkazia ophthalmic emulsion 4 times daily (morning, noon, afternoon, and evening) to each affected eye (b) (4) (b) (4) (b) (4) Treatment should be discontinued after signs and symptoms are resolved and reinitiated upon their recurrence. Verkazia can be used concomitantly with ophthalmic medications, allowing a (b) (4)-minute interval between products.

Maximum total bilateral 1 mg/mL QID dose per day (assuming (b) (4) mL drop size): (b) (4) mg/eye/day or (b) (4) mg/day total dose. This calculates as (b) (4) mg/kg for a 16 kg child.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacokinetics

- Study N09F1205: Ocular pharmacokinetic study following a single topical administration in pigmented rabbits
- Study N09F0306: Ocular pharmacokinetic study following multiple topical administrations in pigmented rabbits
- Study Tp118: Cyclosporin A Ocular pharmacokinetic study after a single application in eye in the rabbit
- Study N09F34413: Ocular pharmacokinetic study of cyclosporin A formulations following a single instillation in pigmented rabbits
- Study N09F0407: Ocular autoradiographic and pharmacokinetic comparative study in pigmented rabbits following multiple daily instillation of 3H-CsA ophthalmic emulsions
- Study N09F04216: Cyclosporine A formulation pilot ocular pharmacokinetics study comparing an (b) (4) cyclosporine solution to Ikervis following multiple daily instillations in pigmented rabbits

Toxicology

- Study N09F0405: 28-day ocular tolerance study in New Zealand White albino rabbits
- Study N09F1306: Toxicokinetic study following multiple daily topical ocular administrations for 28-days in albino rabbits
- Study 20070348TL: Study for evaluation of local tolerance after repeated daily instillation in the eye for 28 days in the rabbit
- Study To146: Ocular irritation study after repeated application in the rabbit
- Study 451424: 26 Week ocular tolerability study in rabbits
- Study N09F0805: Evaluation of corneal sensitivity following repeated instillations in albino rabbits
- Study 29412TSS: Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA)
- Study 20080145TRP: Non-radioactive local lymph node assay (LLNCA) test method in mouse using in vivo 5-bromo-2-deoxyiridine incorporation
- Study 41506TSS: Assessment of phototoxic and photoallergic potential with the murine local lymph node assay (UV-LLNA by dermal route)
- Ryffel, B., *et al*., 1983, “Toxicological evaluation of cyclosporin A”, *Arch Toxicol*, 53(2): 107 – 141.

3.2 Studies Not Reviewed

- Study N09F0304: Validation of an HPLC-MS method in pigmented rabbit ocular specimens and plasma

Reference ID: 4798171

- Study N09F0305: Validation of an HPLC-MS method in rabbit whole blood using SFSTP and FDA guidelines
- Study 480112: Validation of an HPLC-MS method for the quantification of cyclosporin A in rabbit whole blood
- Study 480119: Development and validation of a quantitative LC-MS/MS assay for cyclosporin A in rabbit cornea and conjunctiva samples
- Study Tm380-06-1817: Assessment of phototoxic and photoallergic potentials after topical applications in the guinea pig
- *Reviewer's note:* (b) (4) *containing formulation used in the study which is not the to-be-marketed formulation therefore the study was not reviewed (summary results indicated no potential for phototoxic and photoallergic reactions).*

3.3 Previous Reviews Referenced

Studies N09F1205, N09F0407, N09F0405 and N09F1306 were previously reviewed (Dr. Conrad Chen dated 2-16-2007; IND 70,502).

4 Pharmacology

4.1 Primary Pharmacology

Drug class: Calcineurin inhibitor
Mechanism of Action:

(*excerpted from Neoral package insert)*
The effectiveness of cyclosporine results from specific and reversible inhibition of immunocompetent lymphocytes in the G0- and G1-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine also inhibits lymphokine production and release including interleukin-2.

*Reviewer's note**:** The exact mechanism through which cyclosporine acts to ameliorate signs and symptoms of keratoconjunctivitis sicca (Dry Eye Syndrome) has not been established. The established pharmacologic class of cyclosporine is calcineurin inhibitor immunosuppressant. The mechanism of this mode of immunosuppression acts mainly on T-lymphocytes. Another potential mechanism of cyclosporin A which has been demonstrated in the literature is to block the opening of the mitochondrial permeability transition pore which is associated with preventing cellular apoptosis. Either of these mechanisms may potentiate the amelioration of dry eye sequelae as T-cells and cellular apoptosis have been implicated in the pathogenesis of dry eye disease [reviewed in: Ames, P., and A. Galor, 2015, "Cyclosporine ophthalmic emulsions for the treatment of dry eye: a review of the clinical evidence", Clin Invest (Lond.), 5(3): 267 – 285.]*

Reference ID: 4798171

4.3 Safety Pharmacology

Systemic exposure, even to the entire intraocular dose at once, is not a significant safety pharmacology concern, given approved LD doses. The Applicant will rely on the systemic safety established for the LD drugs.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study N09F1205: Ocular pharmacokinetic study following a single topical administration in pigmented rabbits

- This study reported the comparative ocular distribution between Restasis® and the 3rd generation (b) (4) containing NOVA22007.
- This study was previously reviewed for the initial IND submission (SDN009; dated 12/27/2006)
    - Author: Conrad Chen, PhD
    - Review dated: 2-16-2007

The following is excerpted from Dr. Chen's review:

Key study findings: After a single (b) (4) µl unilateral instillation of NOVA22007 formulation (0.025%, 0.05%, and 0.1%) and Restasis™ 0.05% in pigmented rabbit eyes, CsA appeared rapidly in cornea and conjunctiva. CsA absorption in blood was undetectable.

Study no.: N09F1205
Volume #, and page #: Vol. 2, Page 537
Conducting laboratory and location: (b) (4)
Date of study initiation: October 17, 2005
GLP compliance: Yes
QA report: yes (x) no ( )
Methods

Doses: NOVA 0.025%, 0.05%, 0.1% and Restasis™ 0.05%
Species/strain: HY R NZ 104 (pigmented) rabbits
Number/sex/group or time point (main study): 3/sex/time point (240 animals)
Route, formulation, volume, and infusion rate: a single instillation ((b) (4) µl) into right eye
Age: Approximately 4 months
Weight: 2.0-2.5 kg
Sampling times: 0.33 h, 0.67 h, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h

Results:
In cornea and conjunctiva, C_{max} and AUC values increased linearly with the dose. C_{max} levels were generally achieved within 0.33 h in both cornea and conjunctiva. In conjunctiva, CsA levels declined more rapidly than in cornea (conjunctiva elimination

Reference ID: 4798171

half-life 3.19-6.68 h vs. 26.21-53.25 h in cornea). It is noted that AUC in cornea for NOVA 22007 0.05% was twice of that for Restasis® 0.05% (26477 vs. 14210). The AUC in conjunctiva for NOVA22007 and Restasis® 0.05% were equal.
CsA blood levels for these products were < LOD (limit of detection) 0.1 ng/mL, showing that systemic absorption is negligible.

Pharmacokinetics parameters for cornea and conjunctiva are presented: .

Table 51. Pharmacokinetics parameters of NOVA22007 and Restasis ®

	NOVA22007 0.025%		NOVA22007 0.05%		NOVA22007 0.1%		Restasis® 0.05%	
	Cornea	*Conjunctiva*	*Cornea*	*Conjunctiva*	*Cornea*	*Conjunctiva*	*Cornea*	*Conjunctiva*
Cmax (ng/g)	574	336	1372	696	2692	1914	748	849
Tmax (h)	0.67	0.33	0.33	0.33	0.33	0.33	0.33	0.33
AUC (0.33h-72 h) (trapezoidal) (ng/g * h)	14476	1427	26477	2781	51373	3668	14210	2375
T1/2 (h)	36.86	3.19	26.21	6.68	53.25	3.98	27.74	6.55

Study N09F0306: Ocular pharmacokinetic study following multiple topical administrations in pigmented rabbits

- This study reported the comparative ocular distribution between Restasis® and the 3rd generation (b) (4) containing NOVA22007.
- This study was previously reviewed for the initial IND submission (SDN009; dated 12/27/2006)
    - Author: Conrad Chen, PhD
    - Review dated: 2-16-2007

The following is excerpted from Dr. Chen's review:

Key study findings: No accumulation of CsA in conjunctiva was observed after 10 days of repeat administration of NOVA22007 (0.05% qd, 0.05% bid, and 0.1% qd) and Restasis™ 0.05% bid. Corneal concentrations were significantly higher than conjunctival ones for all groups. NOVA22007 0.05% bid doubled both C_{min} and $C_{0.33H}$ corneal levels of Restasis™ 0.05% bid. No systemic absorption of CsA was detected after multiple administrations of these products.

Study no.: N09F0306
Volume #, and page #: Vol. 2, page 661
Conducting laboratory and location: (b) (4)
Date of study initiation: April 14, 2006
GLP compliance: Yes
QA report: yes (x) no ( )
Methods

Doses: NOVA22007 0.05% qd, NOVA22007 0.05% bid, NOVA22007 0.1% qd,

and Restasis® 0.05% bid
Species/strain: HY R NZ 104 (pigmented) rabbits
Number/sex/group or time point (main study): 12 males/group (total 48 males, 6 animals/time point)
Route, formulation, volume, and infusion rate: one or two daily instillations of (b) (4) µl during 10 days into the right eye
Age: approximately 4 months
Weight: 2.1-2.9 kg
Sampling times: on the 10th day, 2 time-points were sampled for each group (before and 0.33 h after the last administration); the 2 time-points correspond to residual trough and expected maximal concentrations at steady state, respectively.

Results:
No accumulation of CsA was observed in the conjunctiva at any dosage and schedule as demonstrated by the trough (C_{min}) levels. This is consistent with the short elimination half-life reported above for N09F1205 (single dose ocular PK study). The corneal concentrations were significantly higher than conjunctival ones. NOVA 22007 0.05% qd displayed similar C_{min} and $C_{0.33H}$ corneal levels compared to Restasis® 0.05% bid. NOVA22007 0.05% bid doubled both Cmin and $C_{0.33H}$ corneal levels of that of Restasis® 0.05% bid (1244.10 vs.659.51 and 2209.16 vs. 1071.80). No systemic absorption was detected after multiple administrations of these products (all values < LOD of 0.1 ng/mL).

Table 52. CsA concentration after 10 days multiple ocular instillation of NOVA22007 and Restasis®

TIME-POINT	TISSUE	CORNEA		CONJUNCTIVA	
	TIME-POINT	MEAN	SD	MEAN	SD
Cmin	NOVA22007 0.05% qd	736.41	250.07	5.65	8.76
	NOVA22007 0.05% bid	1,244.10	433.32	31.67	8.85
	NOVA22007 0.1% qd	905.24	341.68	18.21	16.00
	Restasis® bid	659.51	156.49	8.07	8.84
$C_{0.33H}$	NOVA22007 0.05% qd	1,220.33	345.94	539.67	419.03
	NOVA22007 0.05% bid	2,209.16	684.58	397.92	388.98
	NOVA22007 0.1% qd	1,200.06	412.97	843.39	384.35
	Restasis® bid	1,071.80	368.98	212.57	86.02

Study Tp118: Cyclosporin A Ocular pharmacokinetic study after a single application in eye in the rabbit

- This GLP compliant study assessed the ocular distribution of Cyclosporine A to the cornea and bulbar and palpebral conjunctiva in 3 formulations after a single ocular application in the rabbit.
- Formulations tested include:
  - NOVA22007 (0.1%; CKC containing to-be-marketed formulation; Batch#Z06EM106)

  - NOVA22007 (b) (4) %; (b) (4) containing Generation 2 formulation; Batch# Z06EM147)
  - Cyclosporin A (b) (4) (b) (4)
- The animals from each group received a single bilateral dose ((b) (4) µl) of the test article by topical ocular instillation.
- Animals were sacrificed at different time points (0.5h, 1h, 2h, 4h, 8h, 12h and 24h) and cornea and bulbar and palpebral conjunctivae were removed from both eyes.
- Results
  - No changes in appearance and behavior or body weight were reported.
  - $AUC_{(0\text{-}24h)}$ evaluated in cornea and conjunctiva for each dose group were reported in the following table:

	Numerical field name	Units	GROUP 1 NOVA22007 Ref. Z06EM106	GROUP 3 NOVA22007 Ref. Z06EM147	GROUP 4 NOVA22007 Reference Ref. Z06SOL146
Cornea	T_{max} $AUC_{0.-24h}$	h ng/g x h	0-0.5 18357	1-2 15866	0.5-1 59930
Conjunctiva	T_{max} $AUC_{0.-24h}$	h ng/g x h	0-0.5 8836	0.5-1 8563	0.5-1 20167

- Distribution of CsA to the cornea and conjunctiva were similar; no significant difference between the CKC and (b) (4) formulations was reported.

Study N09F34413: Ocular pharmacokinetic study of cyclosporin A formulations following a single instillation in pigmented rabbits

- This non-GLP study characterized CsA distribution to the conjunctiva and cornea in pigmented rabbits of three different formulations:
  - NOVA22007-CKC (Z06EM106 0.1%); to-be-marketed Verkazia® formulation; Batch#2A44
  - (b) (4)
- The animals from each group received a single bilateral dose ((b) (4) µl) of the test article by topical ocular instillation.
- CsA was quantified in cornea and conjunctivae at distinct timepoints until 24 h after instillation.
- Analysis focused on the comparative exposure of the CKC and CsA (b) (4) formulations.

Pharmacokinetic Parameters (ng/g of Tissue)

	Cornea		Conjunctiva	
	CKC emulsion (Z06EM106)	CsA (b) (4) (b) (4)	CKC emulsion (Z06EM106)	CsA (b) (4) (b) (4)
C_{max} (ng/g)	695	229	239	488
t_{max} (h)	1	0.5	1	0.5
$t_{1/2}$ (h)	13.5	7.8	NA	3.1
$AUC_{0.5\text{-}24\ h}$	7377	1374	1484	382

Note: C_{max}= the highest mean value measured (ng/g of structure), t_{max}= time-point when the highest mean value is measured (hours), $t_{1/2}$ (hour) = ((ln(2)) / (-a) and a = (ln (concentration)-b) / time, $AUC_{0.5\text{-}24h}$= area under the curve in ng/g or ml of structure X hours, NA: not applicable, the data of kinetic still indicate an increasing phase or all values = 0 or not enough time-point to calculate the $t_{1/2}$

- The exposure of cornea and conjunctiva, as determined by the AUC, was 5.4 times and 3.9 times higher with CKC formulation, respectively, than with (b) (4) (b) (4) formulation.

Study N09F0407: Ocular autoradiographic and pharmacokinetic comparative study in pigmented rabbits following multiple daily instillation of 3H-CsA ophthalmic emulsions

- This GLP study quantitatively and qualitatively compared the distribution of ^{3}H-labelled CsA of both 3H-CsA NOVA22007 (b) (4) containing formulations (0.05% and 0.1%CsA), and ^{3}H-Restasis® (0.05% CsA) following multiple bilateral administrations (up to four times daily) for 7 days in pigmented male rabbits.
  - *Reviewer's note*: *The to-be-marketed clinical formulation of Verkazia was not studied. Similarity in ocular distribution to the cornea and conjunctiva of the CKC to-be-marketed clinical formulation and the (b) (4) formulation were demonstrated in other studies (see above). Results of this study can be subjectively extrapolated based on this finding.*
- At day seven, three animals of each treatment group were sacrificed one hour after the last dosing, while the other three were sacrificed 24 hours after the last administration. Whole blood, cerebrospinal fluid, brain, liver, right kidney, spleen, heart, olfactory nerve and the left cornea, conjunctiva, aqueous humor, iris/ciliary body, lens, vitreous, choroid/retina, sclera, optic nerve, lacrimal glands, orbital fat and nasolacrimal duct were sampled, weighed and used for liquid scintillation counting.
- For semi-quantitative qualitative autoradiography of the cornea and conjunctiva, right eyes were sampled, processed and six microsections per eye were mounted on slides for further autoradiographic analysis.
- Results showed localization of radioactivity derived from ^{3}H-CsA almost exclusively in cornea and conjunctiva, with no to limited passage into inner ocular

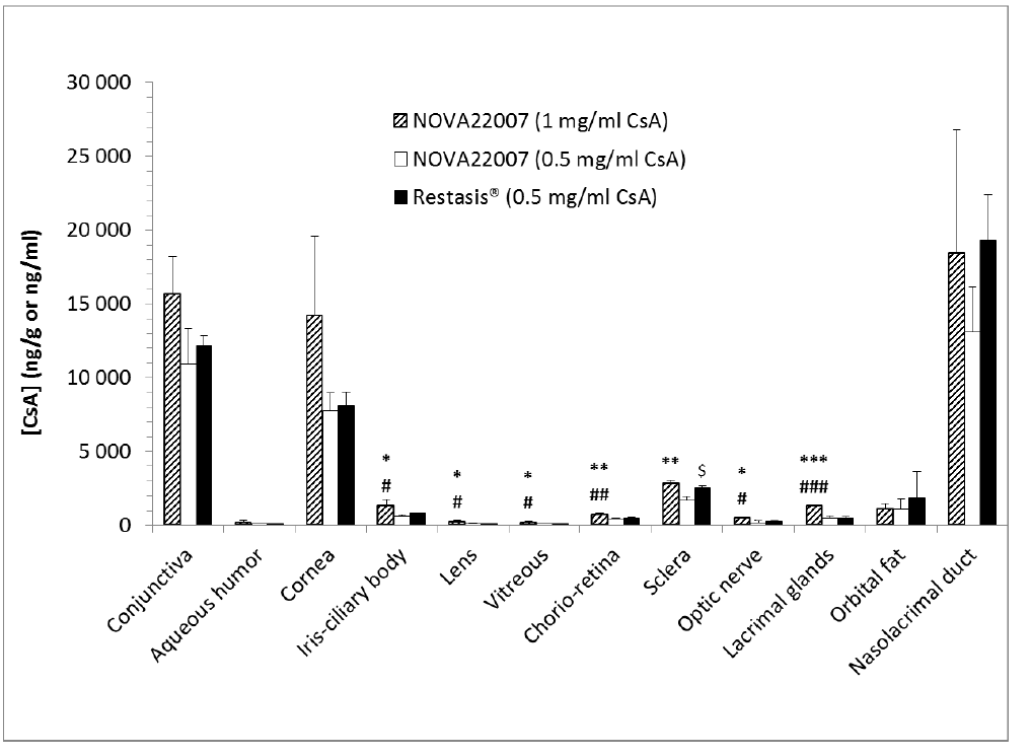
tissues. Exposure in the nasolacrimal duct was significant through 24 hours after the final instillation.

Cornea and Conjunctiva ^{3}H-CsA Concentrations Determined via Semi-Quantitative Autoradiography

	NOVA22007				Restasis	
	1 mg/mL		0.5 mg/mL		0.5 mg/mL	
Time	Cornea	Conj.	Cornea	Conj.	Cornea	Conj.
1 hour	1.2 ± 0.5	2.5 ± 0.8	1.6 ± 0.5	2.9 ± 0.8	1.3 ± 0.5	2.4 ± 0.6
24 hours	0.9 ± 0.4	2.1 ± 0.7	1.1 ± 0.4	2.5 ± 1.1	1.1 ± 0.4	2.3 ± 0.6

Values expressed as nCi/g of brain. Conj. = conjunctiva.

Ocular ^{3}H-CsA Concentrations After Four Times Daily (QID) Bilateral Instillations for Seven Days in Pigmented Rabbits One Hour After the Last Instillation



(cyclosporine) concentrations were determined one hour after the last instillation at day seven. The error ba

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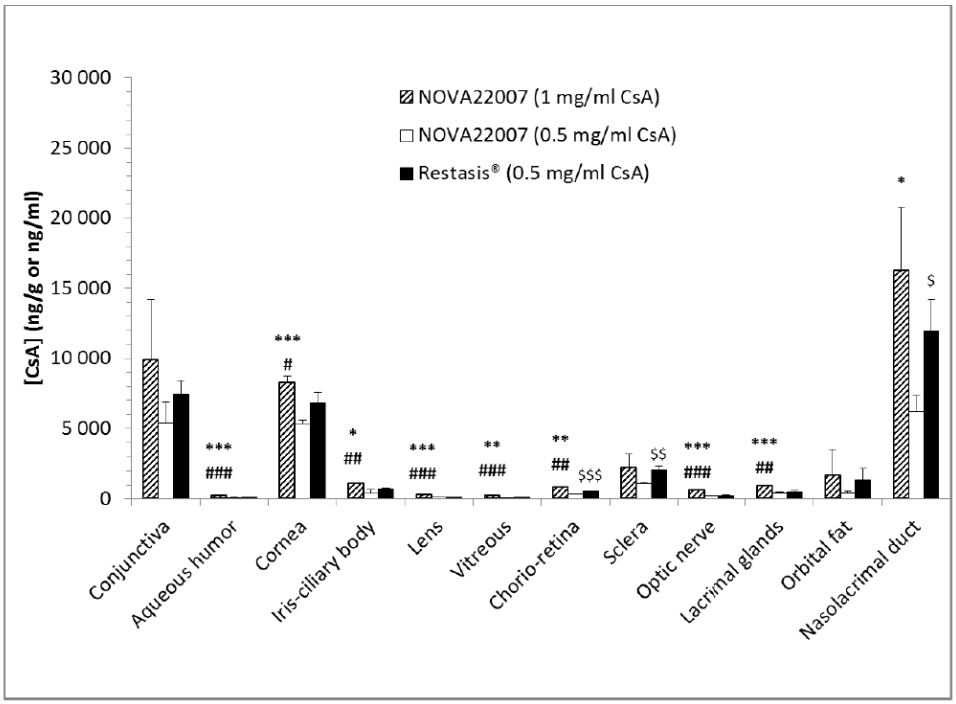
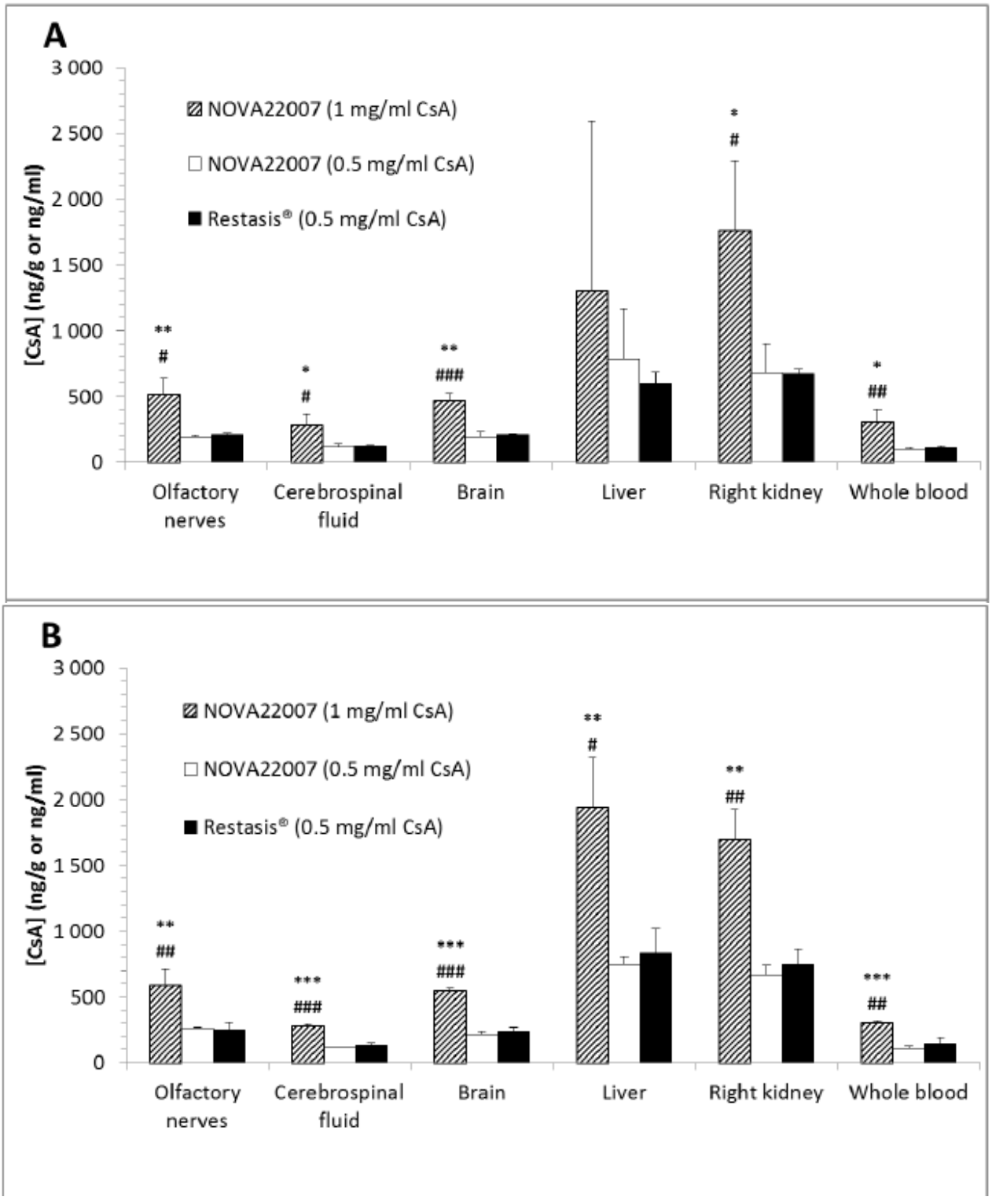
Ocular ^{3}H-CsA Concentrations After Four Times Daily (QID) Bilateral Instillations for Seven Days in Pigmented Rabbits 24 hours After the Last Instillation



- Significant amounts of radioactivity were found in all analyzed systemic organs at both time points. Since no CsA systemic passage was detected after single and multiple dosing, the detected radioactivity originated most probably from radioactive metabolites. This is supported by the higher count levels found in the major elimination organs, liver and kidney. As for the ocular tissues, the organ distribution profiles of NOVA22007 (0.5 mg/mL) and 1 (mg/mL) and Restasis® were not significantly different, and the level of radioactivity found in the tissues correlated with the total administered CsA dose. In conclusion, NOVA22007 and Restasis® have a similar ocular distribution profile. Both emulsions concentrate CsA onto the ocular surface, with very low passage into inner eye tissues. Although low amounts of radioactivity were found in systemic organs, they are attributed to the presence of radiolabeled CsA metabolites.

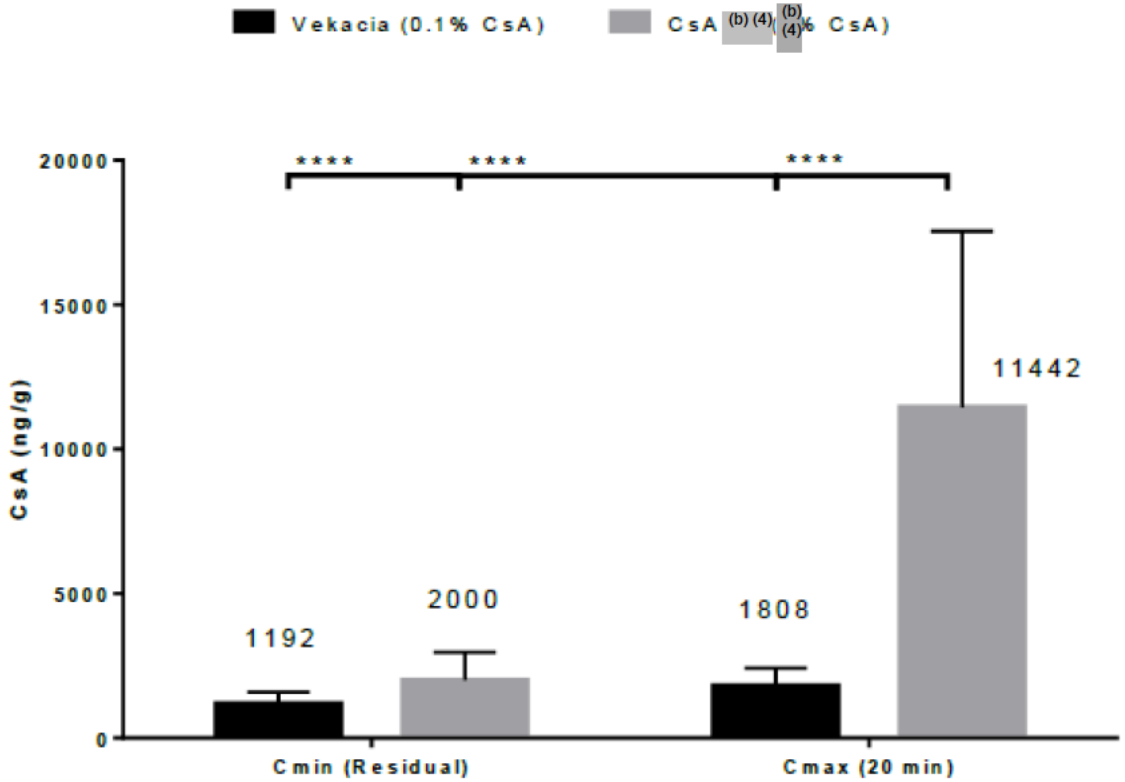
Systemic Organs ^{3}H-CsA Concentrations After Four Times Daily (QID) Bilateral Instillations for Seven Days in Pigmented Rabbits



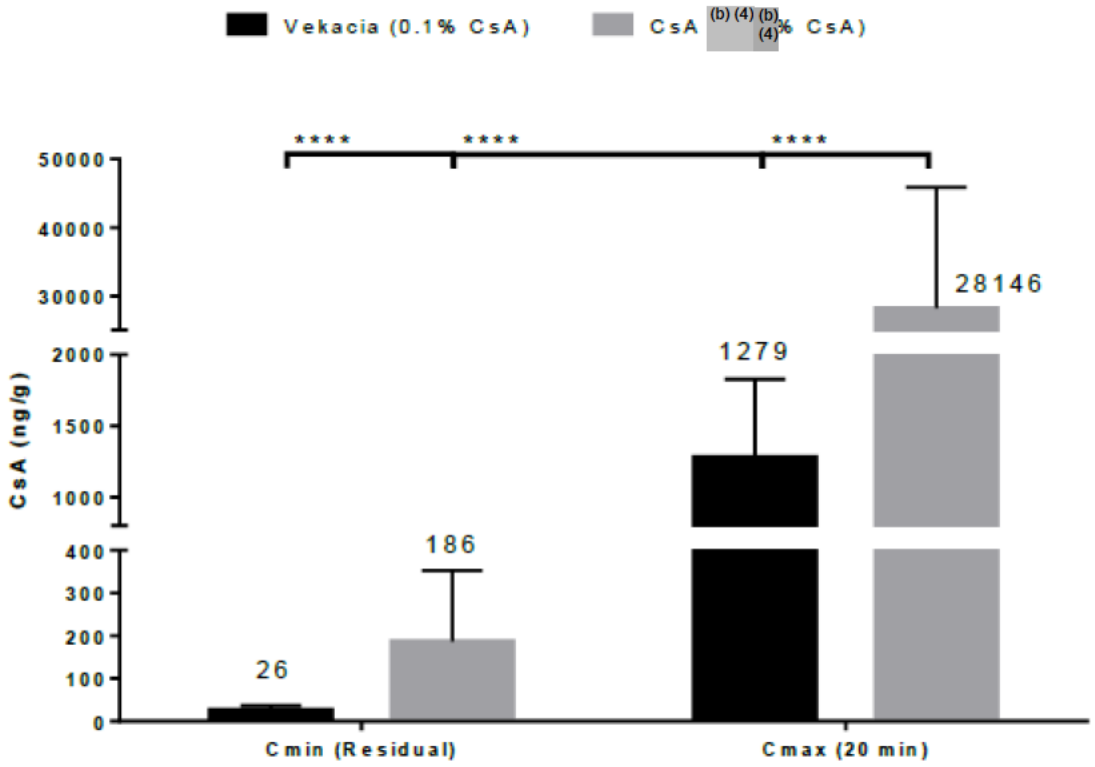
Study N09F04216: Cyclosporine A formulation pilot ocular pharmacokinetics study comparing an (b) (4) cyclosporine solution to Ikervis following multiple daily instillations in pigmented rabbits

- This study compared the to-be-marketed Verkazia 0.1% CsA with (b) (4) w/w CKC and an (b) (4) CsA solution (compounded hospital preparations) in ocular penetration of CsA in ocular tissues and blood QID instillations for 10 days in right eyes of pigmented rabbits.
- Conjunctivae (bulbar and palpebral), cornea and whole blood were measured at 2-time points C_{max} (20 minutes) and C_{min} (12 hours) after QID instillation for 10 days in 5 rabbits/sex/group.
- CsA concentrations after 10 days administration in the cornea and conjunctiva following Verkazia was lower compared to 1% CsA (b) (4) solution mimicking compounded hospital preparation.
- The C_{max} in the cornea and conjunctiva following instillation of Verkazia 0.1% CsA are: 1,808 ± 610 ng/g and 1279 ± 549 ng/g, respectively. The C_{max} in the cornea and conjunctiva following the use of 1% CsA (b) (4) solution (compounded hospital preparations) are: 11442 ± 6100 ng/g and 28146 ± 17752 ng/g, respectively.

CsA concentration in the cornea at steady state following repeated QID instillations for 10 days



CsA concentration in the conjunctiva at steady-state following repeated QID instillations for 10 days



6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Ocular irritation study after repeated applications in the rabbit

Study no.:	To146
Study report location:	\\CDSESUB1\evsprod\nda214965\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\to146\to146-pre-clinical-study-report.pdf
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/8/2008
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	NOVA22007-CKC 0.05%CsA: Batch R541 NOVA22007-CKC 0.1%CsA: Batch R697

Methods

Doses:	Group 1: Vehicle Group 2: 0.05% Group 3: 0.1%
Frequency of dosing:	6 times daily
Route of administration:	Right eye only; Topical ocular instillation
Dose volume:	(b) (4) mL/drop
Formulation/Vehicle:	To-be-marketed formulation (CKC containing formulation)
Species/Strain:	Rabbit ; New Zealand White
Number/Sex/Group:	4/sex/group
Age:	Not specified
Weight:	2.00 – 2.34 kg
Deviation from study protocol:	None

Observations and Results

Mortality

- All animals survived until scheduled sacrifice.

Clinical Signs

- No changes in clinical signs attributed to the test article.

Body Weights

- No changes in body weight attributed to the test article.

Food Consumption

- No changes in food consumption attributed to the test article.

Ophthalmoscopy (Dilated; Slit lamp biomicroscopy and indirect ophthalmoscopy)

- Conjunctival irritation
  - Described as slight/transient (score 1)
  - 0.05% CsA-CKC formulation
    - 100/448 observations (about 22%)
  - 0.1% CsA-CKC formulation
    - 111/448 observations (about 25%)
  - Also noted transiently on the conjunctiva of eyes receiving 0.9% NaCl or untreated eyes, but in smaller proportion (up to 4%)

Gross Pathology

- No macroscopic findings attributed to the test article.

Reference ID: 4798171

Histopathology

Adequate Battery: Eyes only; further details not found (i.e. number of sections examined per eye)

Peer Review: No

Histological Findings

- Chronic conjunctivitis on the bulbar conjunctiva
  - Slight focal unilateral
  - Untreated eyes
    - 1 eye
  - NOVA22007-CKC 0.05% CsA
    - 4 eyes
  - NOVA22007-CKC 0.1% CsA
    - 1 eye
  - Applicant states the finding may be attributable to the treatment since some slight signs of conjunctivae irritation were observed during the experiment.

Toxicokinetics

- Systemic exposure to cyclosporine was not detected.

Dosing Solution Analysis

- Dosing solutions remained within acceptance criteria for the duration of the treatment phase of the study. .

Study title: NOVA22007-CKC 0.05% and NOVA22007-CKC 0.1%: Study for evaluation of local tolerance after repeated daily instillation in the eye for 28 days in the rabbit

Study no.:	20070348TL
Study report location:	\\CDSESUB1\evsprod\nda214965\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\20070348tl\20070348tl-pre-clinical-study-report.pdf
Conducting laboratory and location:	(b) (4) (b) (4)
Date of study initiation:	9-4-2007
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	Z06EM117: Batch # Z06D201; 97.7% purity Z06EM115: Batch# Z06D202; 98% purity

Key Study Findings

Reference ID: 4798171

- The NOAEL of the study was considered the high dose of the to-be-marketed CKC formulation 0.1% 6-times daily for 28-days

Methods

Doses:	Group 1: Vehicle Group 2: Saline Group 3: NOVA2207-CKC 0.05% Group 4: NOVA2207-CKC 0.1%
Frequency of dosing:	Four times daily (QID)
Route of administration:	Left eye only; right eye served as untreated control; topical ophthalmic instillation
Dose volume:	(b) (4) mL / drop
Formulation/Vehicle:	To-be-marketed formulation (CKC containing formulation)
Species/Strain:	Rabbit ; New Zealand White
Number/Sex/Group:	4/sex/group
Age:	2 – 4 months
Weight:	2 – 2.5 kg
Deviation from study protocol:	None.

Observations and Results

Mortality

- All animals survived until scheduled sacrifice.

Clinical Signs

- No changes in clinical signs attributed to the test article.

Body Weights

- No changes in body weight attributed to the test article.

Food Consumption

- No changes in food consumption attributed to the test article.

Ophthalmoscopy (Dilated; Slit lamp biomicroscopy and indirect ophthalmoscopy)

- Vehicle
  - One female dosed with the vehicle had a slight redness on D14.
- NOVA22007- CKC 0.05%
  - One female had lacrimation on D7 and D14.
  - One female had redness on D15.
- NOVA22007-CKC 0.1 %

Reference ID: 4798171

- One female had slight corneal opacity, slight chemosis and slight redness on D2. This female had slight redness and/or lacrimation from D3 to D7 (except D6) and then lacrimation on D 14 and redness on D15.

Gross Pathology

- No macroscopic findings attributed to the test articles.

Histopathology

Adequate Battery: Eyes only (no other details given; i.e. number of slides examined per eye)

Peer Review: No.

Histological Findings:

- Limbal subacute keratitis.
  - No significant differences reported in incidence found between untreated eyes, vehicle and CsA-CKC treated rabbits.
  - Considered commonplace in laboratory rabbits (no historical data referenced), however the finding was present in untreated right eyes as well.

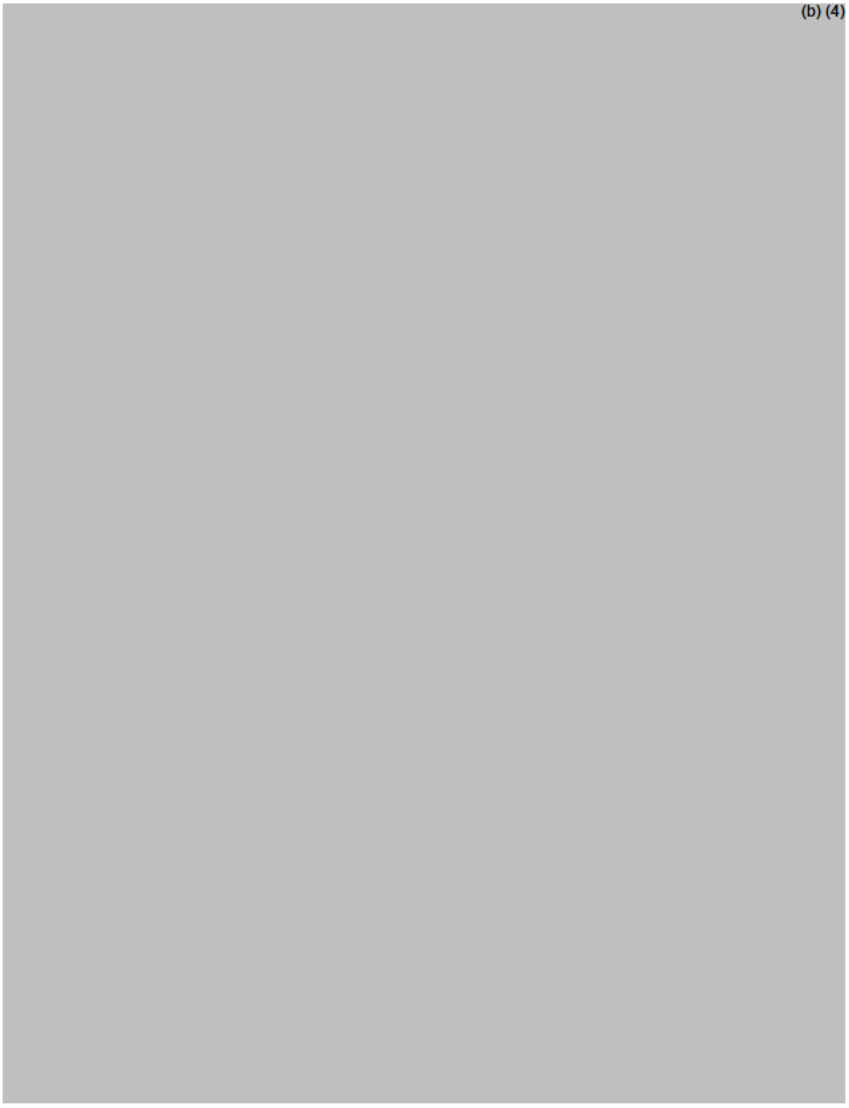
Finding:		Vehicle (n=8)	Saline (n=8)	NOVA2207-CKC 0.05% (n=8)	NOVA2207-CKC 0.1% (n=8)	Untreated eyes from all groups (n=32)
Limbal subacute keratitis	Minimal	3	5	4	3	11
	Mild	2	0	0	1	2
	Moderate	0	0	0	0	1

Toxicokinetics

- Toxicokinetics were not summarized in the report. Individual data shows sporadic detection of exposure with no results exceeding 0.6 ng/mL.

Reference ID: 4798171

Cyclosporin A concentrations in Study 20070348TL samples



Dosing Solution Analysis

- Dosing solutions remained within acceptance criteria for the duration of the treatment phase of the study. .

Study title: 26-week ocular toxicity study in rabbits

Study no.:	451424
Study report location:	\\CDSESUB1\evsprod\nda214965\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\451424\451424-pre-clinical-study-report.pdf
Conducting laboratory and location:	(b) (4) (b) (4)
Date of study initiation:	7-29-1994
GLP compliance:	Yes
QA statement:	Yes; signed
Drug, lot #, and % purity:	Week 1 – 12: DE-076 (0.1%): Lot CIC930820-4; 101.5% DE-076 (0.5%): Lot CIC930820-5; 101.5% DE-076 (1.0%): Lot CIC930820-6; 102.6% Week 13 – 26: DE-076 (0.1%): Lot CIC931116-4; 102.4% DE-076 (0.5%): Lot CIC93116-5; 101.5% DE-076 (1.0%): Lot CIC931116-6; 101.2%

Key Study Findings

Methods

Doses:	Group 1: Vehicle for 0.1% DE-076 (left eye) / physiological saline (right eye) Group 2: Vehicle for 1.0% DE-076 Group 3: 0.1% DE-076 Group 4: 0.5% DE-076 Group 5: 1.0% DE-076
Frequency of dosing:	1 drop TID
Route of administration:	Left eye only; topical ocular instillation.
Dose volume:	Not specified; assumed as (b) (4) mL/drop
Formulation/Vehicle:	DE-076 (Papilock Mini formulation; see above)
Species/Strain:	Rabbit / New Zealand White
Number/Sex/Group:	3/sex/group
Age:	3 months
Weight:	2.5 – 3 kg
Deviation from study protocol:	No deviations reported.

Observations and Results

Mortality

- All animals survived until scheduled sacrifice.

Reference ID: 4798171

Clinical Signs

- No changes in clinical signs attributed to the test article.

Body Weights

- No changes in body weight attributed to the test article.

Food Consumption

- No changes in food consumption attributed to the test article.

Ophthalmoscopy (slit lamp / dilated indirect ophthalmoscopy)

- Watery discharge and conjunctival redness/swelling were apparent in the left eye of some animals in all groups (including the Controls), however the duration of these effects was greatest in the rabbits receiving 0.5% or 1.0% DE-076**.**

Gross Pathology

- Yellow staining around the eyes with mild reddening of the conjunctiva was recorded in 1/6 and 2/6 animals from Groups 2 and 5, respectively. These findings are consistent with those seen in the ophthalmoscopic assessments (see above).

Histopathology

Adequate Battery: Eye and adnexa only (eyelids including nictitating membrane, palpebral conjunctiva, cornea, bulbar conjunctiva, iris, ciliary body, lens, sclera, choroid, retina, optic nerve, Harderian glands, lacrimal glands, nasal mucosa, ocular muscles). Details regarding sectioning of the eye or number of sections examined was not found in the report. Corneas of some animals (2/group) were fixed and prepared for scanning electron microscopic analysis.

Peer Review: No.

Histological Findings: No microscopic findings attributed to the test article including analysis of the corneal endothelium by electron microscopy.

Toxicokinetics

- Systemic exposure to cyclosporine was not detected. The lower limit of detection of the assay was 23.5 ng/mL

Dosing Solution Analysis

Reference ID: 4798171

- Dosing solutions remained within acceptance criteria for the duration of the treatment phase of the study.

Study N09F0805: Evaluation of corneal sensitivity following repeated instillation in albino rabbits

- New Zealand white rabbits (n=3/group) were administered with five instillations within 20-min in right eye.
- Treatments groups:
  - NOVA22007 (0.1% cyclosporin A(
  - NOVA23016 (vehicle of NOVA22007)
  - 0.9% sodium chloride
  - Novesine (0.4% oxybuprocaine hydrochloride).
- Corneal sensitivity of both eyes was tested using an esthesiometer and evaluated before treatment and 10, 20, 30, 45, 60 and 120 min after the last instillation.
- NOVA22007 and its vehicle NOVA23016 did not induce a decrease of the corneal sensibility of the treated eyes in New Zealand White albino rabbits.

Study 29412TSS: Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA)

- This study evaluated the potential of the vehicle of Verkazia® (to-be-marketed CKC containing vehicle) to induce delayed contact hypersensitivity using the murine Local Lymph Node Assay (LLNA).
  - Female CBA/J mice (4 female/group) received repeated (three days) local applications of the vehicle of NOVA22007 1 mg/mL on the ears. The test product was either applied without dilution, or after dilution in water at 1:2 or 1:4.
  - No lymphoproliferation (tritiated thymidine incorporation) was observed with the test products, whereas significant lymphoproliferation was observed in the positive control group.

Treatment	Dilution factor (% (b) (4) (b) (4)	Cutaneous reaction	Irritant potential	Stimulation index (SI)
Vehicle of NOVA22007 1 mg/mL		No	No	0.82
		No	No	1.46
		No	No	1.05
α-hexylcinnamaldehyde (HCA)		ND	ND	19.91
Negative control	Purified water	ND	ND	1.00

SI: dpm of treated group/dpm negative control group; ND: Not determined; dpm: disintegration per minute.

Study 20080145TRP: Non-radioactive local lymph node assay (LLNCA) test method in mouse using in vivo 5-bromo-2-deoxyiridine incorporation

- This GLP-compliant study evaluated the potential of the to-be-marketed CKC formulation of NOVA22007 1 mg/mL to induce delayed contact hypersensitivity using the murine LLNA.
- Female CBA/j mice (4 / group) received repeated (three days) local application of NOVA22007 1 mg/mL on the ears.
- Local irritation was assessed by measuring ear thickness.
- No treatment-related adverse clinical signs, cutaneous reactions or increased ear thickness were observed.
- No lymphoproliferation was observed in animals treated with the test product (NOVA22007 1 mg/mL and vehicle), while significant lymphoproliferation was observed in the positive control group.

Study 41506TSS: Assessment of phototoxic and photoallergic potential with the murine local lymph node assay (UV-LLNA by dermal route)

- This study evaluated the phototoxic and photosensitizing (photoallergic) potential of NOVA22007 (and its vehicle:) after dermal application to female BALB/c mice (6 / group) using the murine LLNA.
- The mice were treated for 2 consecutive days by topical route by applying a variable volume of the preparation on the external surface of both ears of each mouse. Within 20 to 30 minutes following treatment, 5 of them were exposed to a UCA/Vis light dose of at least 10 J/cm2.
- No phototoxic (photo-irritant) effect of the NOVA22007 was evident.
- No photosensitizing (photoallergic) effect of the NOVA22007 was evident.

7 Genetic Toxicology

The Applicant will rely on the listed drugs for support regarding genotoxicity.

The Neoral® and Sandimmune® labels are similar and state the following:

> *Cyclosporine was not mutagenic in appropriate test systems. Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes in vitro gave indication of a positive effect (i.e., induction of SCE), at high concentrations in this system.*

Reference ID: 4798171

8 Carcinogenicity

The Applicant will rely on the listed drugs for support regarding Carcinogenicity. The labeling for each listed drug is similar but differs in some aspects.

Sandimmune® labeling:

> *Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.*

Neoral® Labeling:

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. Doses used in the mouse and rat studies were 0.01 to 0.16 times the clinical maintenance dose (6 mg/kg). The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. Published reports indicate that co-treatment of hairless mice with UV irradiation and cyclosporine or other immunosuppressive agents shorten the time to skin tumor formation compared to UV irradiation alone.

9 Reproductive and Developmental Toxicology

The Applicant will rely on the listed drugs for support regarding Reproductive and Developmental Toxicology. Additionally, the following published citation is necessary for approval to provide the necessary details for PLLR compliance:

- Ryffel, B., *et al*., 1983, “Toxicological evaluation of cyclosporin A”, *Arch Toxicol*, 53(2): 107 – 141.

Bridging the data in this citation was accomplished by dose comparison (large dose multiples over clinical dose; see below and proposed labeling for details).

The labeling for each listed drug is similar but differs in some aspects of language specific to the formulation.

Sandimmune® labeling: *Pregnancy Category C*

Reference ID: 4798171

Animal studies have shown reproductive toxicity in rats and rabbits. Cyclosporine gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally). Sandimmune Oral Solution (cyclosporine oral solution, USP) has been shown to be embryo- and fetotoxic in rats and rabbits when given in doses 2-5 times the human dose. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), Sandimmune Oral Solution (cyclosporine oral solution, USP) was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg/day and rabbits at up to 30 mg/kg/day), Sandimmune Oral Solution (cyclosporine oral solution, USP) proved to be without any embryolethal or teratogenic effects.

There are no adequate and well-controlled studies in pregnant women and therefore, Sandimmune (cyclosporine) should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant transplant recipients who are being treated with immunosuppressants, the risk of premature birth is increased. The following data represent the reported outcomes of 116 pregnancies in women receiving Sandimmune (cyclosporine) during pregnancy, 90% of whom were transplant patients, and most of whom received Sandimmune (cyclosporine) throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of Sandimmune (cyclosporine) on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, preeclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Preterm delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal. More information on cyclosporine use in pregnancy is available from Novartis Pharmaceuticals Corporation.

A limited number of observations in children exposed to cyclosporine in utero are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

The alcohol content of the Sandimmune formulations should also be taken into account in pregnant women. (See WARNINGS, Special Excipients)

Neoral labeling:

Pregnancy Category C

Animal studies have shown reproductive toxicity in rats and rabbits. Cyclosporine gave no evidence of mutagenic or teratogenic effects in the standard test systems with oral application (rats up to 17 mg/kg and rabbits up to 30 mg/kg per day orally.) Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. Cyclosporine has been shown to be embryo- and fetotoxic in rats and rabbits following oral administration at maternally toxic doses. Fetal toxicity was noted in rats at 0.8 and rabbits at 5.4 times the transplant doses in humans of 6.0 mg/kg, where dose corrections are based on body surface area. Cyclosporine was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardation.

There are no adequate and well-controlled studies in pregnant women therefore, Neoral should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant transplant recipients who are being treated with immunosuppressants the risk of premature birth is increased. The following data represent the reported outcomes of 116 pregnancies in women receiving cyclosporine during pregnancy, 90% of whom were transplant patients, and most of whom received cyclosporine throughout the entire gestational period. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, preeclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility, and fetoplacental dysfunction. Pre-term delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. Therefore, the risks and benefits of using Neoral during pregnancy should be carefully weighed.

A limited number of observations in children exposed to cyclosporine in utero are available, up to an age of approximately 7 years. Renal function and blood pressure in these children were normal.

Because of the possible disruption of maternal-fetal interaction, the risk/benefit ratio of using Neoral in psoriasis patients during pregnancy should carefully be weighed with serious consideration for discontinuation of Neoral.

The alcohol content of the Neoral formulations should also be taken into account in pregnant women. (See WARNINGS, Special Excipients).

Reference ID: 4798171

Fertility

The labeling should include the following statement:

> *"Oral administration of cyclosporine to rats for 12 weeks (male) and 2 weeks (female) prior to mating produced no adverse effects on fertility at doses up to 15 mg/kg/day ([redacted] times higher than the maximum recommended human ophthalmic dose)."*

This statement is supported by the following published article:

- Ryffel, B., *et al*., 1983, "Toxicological evaluation of cyclosporin A", *Arch Toxicol*, 53(2): 107 – 141.
  - Methods:
    - Male Wistar rats (n=15/group) were treated orally for 12 weeks with CS-A in 2% gelatin at doses of 1.5, 5, or 15 mg/kg/day. Female Wistar rats (n=30/group) were treated 2 weeks prior to mating until weaning of their offspring. Controls received 2% gelatin only. Examination of the adult rats included:
      - Clinical observation and mortality
      - Body weight gain
      - Copulation rate
      - Pregnancy rate
      - Pre-coital interval
      - Gestation length
    - Necropsy of the male rats was performed at the end of the drug administration period, whereas half of the females from each group were killed and examined before delivery and the remainder at weaning. Examinations included embryonic development, physical and functional development, survival and fertility of the offspring. The surviving offspring were sacrificed at the end of the study and necropsied.
  - Results:
    - In male F0 rats (sires), Cs-A inhibited body weight gain (up to 9%), induced nephrotoxicity (polyuria and mild chronic nephritis), and divergent incisor teeth due to atrophic gingivitis.
    - In female F0 rats (dams) no adverse effect was found except for dystocia in two dams of the high dose group (45 mg/kg/day).
    - Copulation, pregnancy rates and pregnancy lengths were not significantly affected by Cs-A administration.
    - Cs-A had no significant effects on implantation, embryonic survival, litter size, body weights, or malformations.
    - In single cases, where mother animals were allowed to litter and raise their offspring, a relatively high pre-/perinatal mortality was observed at the 15 mg/kg dose level; the difference to the control value was not, however, statistically significant.

Reference ID: 4798171

- Fertility of randomly selected F1 animals and the development of their offspring (F2 generation) were normal.

Results, F_0 females[a]

Dose (mg/kg)	No. of females						Copulation rate (%)		Pregnancy rate (%)	
	Total		Died		Paired					
Controls	15	15	0	0	15	15	100	100	93	73
1.5	15	15	0	0	15	15	100	87	87	85
5	15	15	0	0	15	15	100	93	87	86
15	15	15	0	0	15	15	100	100	80	67

Dose (mg/kg)	Weight gain (%)						Precoital interval (days)		Pregnancy length (days)	
	Before pairing		During pregnancy		During lactation					
Controls	9	8	40	43	–	4	4.3	3.5	–	22.1
1.5	10	8	43	44	–	6	4.2	3.5	–	22.2
5	9	9	44	41	–	9	3.6	4.1	–	22.2
15	11	9	41	42	–	9	5.5	3.0	–	22.2

[a] Left columns: prenatal part/right columns: postnatal part

Reviewer's note: The dose margin calculated by the Applicant in the proposed labeling is incorrect. It appears it was calculated without converting the dose administered to the animal to a human equivalent dose. The correct margin has been calculated (see labeling above and will be sent to the Applicant for consideration).

Peri-/Post-natal Development

The labeling should contain the following statement:

> *"An oral dose of 45 mg/kg/day cyclosporine (approximately (b) (4) times higher than MRHOD) administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. No adverse effects in mothers or offspring were observed at oral doses of up to 15 mg/kg/day ((b) (4) times greater than MRHOD).*

This statement is supported by the following published article:

- Ryffel, B., *et al*., 1983, "Toxicological evaluation of cyclosporin A", *Arch Toxicol*, 53(2): 107 – 141.
  - Methods:
    - Inseminated female Wistar rats (n=24/group) were given CS-A orally at doses of 5, 15, and 45 mg/kg/day from day 15 p.c. until 21 post-partum. Adults were observed for toxic signs and killed at the

end of the treatment period. The peri- and postnatal survival, the physical and functional development as well as the fertility and general reproductive performance of the offspring were analyzed.

- Results:
  - Doses up to 15 mg/kg/day were well tolerated.
  - 45 mg/kg/day
    - Weight gain in dams was reduced (12% lower) at the high dose compared to control animals.
    - An increase of pre-/perinatal mortality (+19.1%) as well as early postnatal mortality (+70.2%) of the offspring compared to controls was observed at high dose.
    - Body weight development of the offspring was markedly inhibited (-18%) compared to controls
    - The incidence of morphological and functional alterations in the offspring of treated animals was not changed compared to the controls.
    - The fertility of randomly selected F1 pups and the development of their offspring (F2 generation) were not significantly not affected.

Reference ID: 4798171

Results of F_0 females

Dose (mg/kg)	No. of females		weight gain (%) during treatment		Pregnancy rate (%)	Pregnancy length (days)
	Inseminated	Died	Pregnancy[a]	Lactation		
Controls	24	0	16	10	92	22.3
5	24	0	15	13	96	22.1
15	24	0	15	14	92	22.3
45	24	0	4	18	96	22.1

Litter Data

Dose (mg/kg)	Implantations	Litter size (day 0 pp)	Pre- and perinatal loss (%)	Postnatal loss (%)	Body weight day 21 pp (g)[b]	Abnormal pups (4)	Behavior affected pups (%)
Controls	10.5	9.8	7.7	0.9	47.6	4.0	29.2
5	10.8	9.9	8.2	4.9	48.3	1.1	35.8
15	11.0	10.3	7.3	0.0	51.3	0.5	35.4
45	9.2	7.0	26.8*	71.6*	29.5*	0.0	–

Results of F_1 fertility study

Dose (mg/kg)	Copulation rate (%)	Pregnancy rate (%)	Pre- and perinatal loss (%)	Postnatal loss (%)	Abnormal F_2 pups (%)
Controls	100	95	4.0	0.6	0.4
5	100	81	5.2	1.5	1.6
15	95	80	5.1	1.8	0.0
45	100	100	6.0	0.0	0.0

* $p < 0.05$
[a] Days 15–20 p.c.
[b] Combined results of males and females

Reviewer's note: The dose margin calculated by the Applicant is incorrect. It appears it was calculated without converting the dose administered to the animal to a human equivalent dose. The correct margin has been calculated (see labeling above and will be sent to the Applicant for consideration).

11 Integrated Summary and Safety Evaluation

Safety margins comparing NOAEL of pivotal nonclinical studies and the maximum proposed clinical dose

Toxicity	Species	Study Duration / NOAEL	Safety Margin Based on direct topical dose comparison to proposed clinical dose ((b) (4) mg/eye/day)*
None	Rabbit	28-days (to-be-marketed CKC formulation): 0.1%; 6-times daily ((b) (4) mg/eye)	(b) (4)-fold
		6-months (bridged from DE-076 formulation): 1% TID ((b) (4) mg/eye)	(b) (4)-fold

Reference ID: 4798171

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIN M RUHLAND
05/19/2021 04:20:43 PM

LORI E KOTCH
05/19/2021 04:44:52 PM

PHARMACOLOGY/TOXICOLOGY REVIEW

IND number: 70,502
Sequence number/date/type of submission: SN000, 12/27/06, Initial IND
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Novagali Pharma S.A.
Reviewer name: Conrad H. Chen, Ph.D.
Division name: Division of Anti-Infective and Ophthalmology Products
Review completion date: January 23, 2007
Drug: NOVA22007, Cyclosporine A (CsA) Topical Ophthalmic Solution
Relevant INDs/NDAs/DMFs: NDA 50-790 (Restasis™, cyclosporine ophthalmic anionic emulsion for keratoconjunctivitis sicca) and NDA 50-715 (Neoral™, cyclosporing oral capsule and oral solution for prophylaxis of organ rejection)
Drug class: Immunosuppressant
Indication: Keratoconjunctivitis (b) (4)
Clinical formulation: The drug product is a Cyclosporine A (CsA) Cationic Emulsion (b) (4) 0.1%.

(b) (4)

The excipients used in NOVA22007 are commonly found in approved drugs. (See review for M005 dated Feb. 10, 2006 for details.)
Route of administration: Eye drop
Proposed clinical protocol:
This is a Phase III, multicenter, randomized, double-masked, controlled, (b) (4)-month trial to evaluate the safety and efficacy of two concentrations of NOVA22007 (CsA (b) (4) 0.1%) ophthalmic cationic emulsion administered (b) (4) daily in comparison with vehicle in patients with dry eye syndrome. (b) (4) A total of up to (b) (4) patients will be enrolled.
Previous clinical experience:
A Phase II study for KCS using 3 different doses of NOVA 22007 (CsA 0.025%, 0.05%, and 0.1%) and vehicle with 2 instillation per day for 3 months was conducted in France. A Phase II/III study of NOVA22007 (CsA 0.05% and 0.1%) in the treatment of vernal keratoconjunctivitis (VKC) for 3 months is currently underway in Europe and other countries.

Pharmacology

Brief summary

CsA is widely used as an oral immunosuppressive drug and has tremendously improved graft survival in all areas of transplantation. It acts by selective inhibition of interleukin-2 release (and other cytokines: IL3, IL4, G-CSF and TNF) during the activation of T-cells and causes suppression of the cell-mediated immune response.
The beneficial effects of topical CsA treatment were first reported in dogs with keratoconjunctivitis sicca. Over the past years, CsA has been evaluated clinically for several potential applications related to local immune disorder in the eye. Restasis™ (NDA 50-790) is marketed for the treatment of KCS. The inactive ingredients in Restasis™ are as follows: Glycerin (b)(4)%, castor oil (b)(4)%, polysorbate 80 (b)(4)%, carbomer (b)(4)%, purified water (b)(4)%, and sodium hydroxide to adjust the pH.

Pharmacokinetics

1. Study title: Ocular pharmacokinetic study following single topical administration in rabbits
Key study findings: After a single (b)(4) µl unilateral instillation of NOVA22007 formulation (0.025%, 0.05%, and 0.1%) and Restasis™ 0.05% in pigmented rabbit eyes, CsA appeared rapidly in cornea and conjunctiva. CsA absorption in blood was undetectable.

Study no.: N09F1205
Volume #, and page #: Vol. 2, Page 537
Conducting laboratory and location: (b)(4)
Date of study initiation: October 17, 2005
GLP compliance: Yes
QA report: yes (x) no ( )
Methods

Doses: NOVA 0.025%, 0.05%, 0.1% and Restasis™ 0.05%
Species/strain: HY R NZ 104 (pigmented) rabbits
Number/sex/group or time point (main study): 3/sex/time point (240 animals)
Route, formulation, volume, and infusion rate: a single instillation ((b)(4) µl) into right eye
Age: Approximately 4 months
Weight: 2.0-2.5 kg
Sampling times: 0.33 h, 0.67 h, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h, 48 h, and 72 h

Results:
In cornea and conjunctiva, Cmax and AUC values increased linearly with the dose. Cmax levels were generally achieved within 0.33 h in both cornea and conjunctiva. In conjunctiva, CsA levels declined more rapidly than in cornea (conjunctiva elimination half life 3.19-6.68 h vs. 26.21-53.25 h in cornea). It is noted that AUC in cornea for

NOVA 22007 0.05% was twice of that for Restasis™ 0.05% (26477 vs. 14210). The AUC in conjunctiva for NOVA22007 and Restasis™ 0.05% were equal.
CsA blood levels for these products were < LOD (limit of detection) 0.1 ng/mL, showing that systemic absorption is negligible.
Pharmacokinetics parameters for cornea and conjunctiva are presented in the following Table 51: (Vol. 2, page 360)

Table 51. Pharmacokinetics parameters of NOVA22007 and Restasis ®

	NOVA22007 0.025%		NOVA22007 0.05%		NOVA22007 0.1%		Restasis ® 0.05%	
	Cornea	*Conjunctiva*	*Cornea*	*Conjunctiva*	*Cornea*	*Conjunctiva*	*Cornea*	*Conjunctiva*
Cmax (ng/g)	574	336	1372	696	2692	1914	748	849
Tmax (h)	0.67	0.33	0.33	0.33	0.33	0.33	0.33	0.33
AUC (0.33h-72 h) (trapezoidal) (ng/g * h)	14476	1427	26477	2781	51373	3668	14210	2375
T1/2 (h)	36.86	3.19	26.21	6.68	53.25	3.98	27.74	6.55

2. Study title: Ocular pharmacokinetic study following multiple topical administrations in pigmented rabbits

Key study findings: No accumulation of CsA in conjunctiva was observed after 10 days of repeat administration of NOVA22007 (0.05% qd, 0.05% bid, and 0.1% qd) and Restasis™ 0.05% bid. Corneal concentrations were significantly higher than conjunctival ones for all groups. NOVA22007 0.05% bid doubled both Cmin and $C_{0.33H}$ corneal levels of Restasis™ 0.05% bid. No systemic absorption of CsA was detected after multiple administrations of these products.

Study no.: N09F0306
Volume #, and page #: Vol. 2, page 661
Conducting laboratory and location: (b) (4)
Date of study initiation: April 14, 2006
GLP compliance: Yes
QA report: yes (x) no ( )
Methods

Doses: NOVA22007 0.05% qd, NOVA22007 0.05% bid, NOVA22007 0.1% qd, and Restasis™ 0.05% bid
Species/strain: HY R NZ 104 (pigmented) rabbits
Number/sex/group or time point (main study): 12 males/group (total 48 males, 6 animals/time point)
Route, formulation, volume, and infusion rate: one or two daily instillations of (b) (4) µl during 10 days into the right eye
Age: approximately 4 months
Weight: 2.1-2.9 kg

Sampling times: on the 10th day, 2 time-points were sampled for each group (before and 0.33 h after the last administration); the 2 time-points correspond to residual trough and expected maximal concentrations at steady state, respectively.

Results:

No accumulation of CsA was observed in the conjunctiva at any dosage and schedule as demonsrated by the trough (Cmin) levels. This is consistent with the short elimination half life reported above for N09F1205 (single dose ocular PK study).

The corneal concentrations were significantly higher than conjunctival ones. NOVA 22007 0.05% qd displayed similar Cmin and $C_{0.33H}$ corneal levels compared to Restasis™ 0.05% bid. NOVA22007 0.05% bid doubled both Cmin and $C_{0.33H}$ corneal levels of that of Restasis™ 0.05% bid (1244.10 vs.659.51 and 2209.16 vs. 1071.80). No systemic absorption was detected after multiple administrations of these products (all values < LOD of 0.1 ng/mL).

Table 52 summarizes obtained cornea and conjunctiva concentrations: (Vol. 2, page 361)

Table 52. CsA concentration after 10 days multiple ocular instillation of NOVA22007 and Restasis®

TIME-POINT	TISSUE	CORNEA		CONJUNCTIVA	
	TIME-POINT	MEAN	SD	MEAN	SD
Cmin	NOVA22007 0.05% qd	736.41	250.07	5.65	8.76
	NOVA22007 0.05% bid	1,244.10	433.32	31.67	8.85
	NOVA22007 0.1% qd	905.24	341.68	18.21	16.00
	Restasis® bid	659.51	156.49	8.07	8.84
$C_{0.33H}$	NOVA22007 0.05% qd	1,220.33	345.94	539.67	419.03
	NOVA22007 0.05% bid	2,209.16	684.58	397.92	388.98
	NOVA22007 0.1% qd	1,200.06	412.97	843.39	384.35
	Restasis® bid	1,071.80	368.98	212.57	86.02

Toxicology and Toxicokinetics

3. Study title: Ocular tolerance—28-day ocular irritation study in rabbits with NOVA22007

Key study findings: In a 28-day study in rabbits, ocular instillation of NOVA22007 (0.025%, 0.05%, 0.1%) (b) (4) µl 4 times daily did not produce any systemic adverse effects. There were no detectable levels of CsA in blood of treated animals. Increased frequency of slight local reactions (mostly redness of conjunctiva) was found in 0.1% group. Redness of conjunctiva was also found in other groups.

Study no.: N09F0405
Volume #, and page #: Vol. 3, page 726
Conducting laboratory and location: (b) (4)
Date of study initiation: January 24, 2005
GLP compliance: Yes
QA report: yes (x) no ( )

Methods

Doses: NOVA22007 (0.025%, 0.05% and 0.1%) and NaCl 0.9% (control)
Species/strain: New Zealand White rabbits
Number/sex/group or time point (main study): 5 or 7/sex/group (total 62 animals)
Route, formulation, volume, and infusion rate: 4 instillations/day (4 h apart) of (b) (4) µl into right eye for 28 days, left eye untreated (control)
Age: approximately 4 months
Weight: 2.0-2.5 kg
Sampling times: animals were sacrificed on Day 29

Observation and Times:

Clinical signs: daily
Body weights: before the test, then weekly
Food consumption: every other day
Ophthalmoscopy: ocular observations using Draize's scale twice daily, ocular examinations using McDonald-Shadduck's scale once weekly, corneal observation after florescein instillation at the end of examinations.
Hematology and Clinical chemistry: blood was collected on baseline from the ear vein, then by cardiac puncture at sacrifice; systemic CsA exposure was evaluated just before the first administration on the last day (through ear vein).
Gross pathology: both eye balls, eye lids, conjunctiva, nictitating membranes, Harderian and lachrymal glands were sampled and fixed in Bouin-Hollande solution for ocular histopathology.
Organs: during the autopsy, the macroscopically visible lesions were sampled and fixed in Bouin-Hollande solution and archived.

Results:

Mortality, appearance and behavior were not affected by the treatments. No treatment-related changes in body weight, food and water consumption, organ weight, hematological and blood chemistry parameters were noted. No remarkable observations at necropsy due to the treatment were found.
Ocular observations with a slit lamp revealed no clear differences between groups and between treated and untreated eyes. Ocular reactions were confined to slight conjunctival redness in all groups, occurring more frequently at the high dose. Ocular histology indicated slight irritation mainly in nictitating membrane and eyelids, due to repeated instillation.
CsA blood concentration was below LLOQ (lower limit of quantification) of 2 ng/mL, except for one female in 0.1% group showing 9.6 ng/mL. This was just a single incidence from a group of 9 females and could be an experimental error simply an outlier. No explanation for this single incidence was provided.

4. Study title: Toxicokinetic study following multiple daily topical administration for 28 days in albino rabbits (for the assessment of (b) (4) effect)

Key study findings: The purpose of the study was to assess the impact of (b) (4) (b) (4) removal from NOVA22007 formulation on systemic CsA absorption and ocular tolerance after instillation in the right eye of rabbits 4 times/day for 28 days. The results showed that the withdrawal (b) (4) had no impact on the systemic exposure to NOVA22007, and the detectable whole blood CsA levels were not significant.

Study no.: N09F1306
Volume #, and page #: Vol. 3, page 1000
Conducting laboratory and location: (b) (4)
Date of study initiation: August 4, 2006
GLP compliance: Yes
QA report: yes (x) no ( )
Methods

Doses:
Formulation Z06EM053, 0.1% CsA cationic emulsion, containing (b) (4) (b) (4)
Formulation Z06EM060, 0.1% CsA cationic emulsion, without (b) (4)
Species/strain: New Zealand White rabbits
Number/sex/group or time point (main study): 5/sex/group (total 20 animals)
Route, formulation, volume, and infusion rate: instilled (b) (4) µl, 4 times/day with a 3 h interval into right eye for 28 day; left eyes untreated (control)
Age: approximately 4 months
Weight: 2.0-2.5 kg
Sampling times: Blood was sampled for CsA levels at Days 14 and 28, 20 minutes before and 30 minutes after the last dose of the day (corresponding to the trough and peak systemic levels at steady state). Animals were sacrificed on Day 28.

Results:
Rabbit whole blood concentration of CsA was determined by HPLC-MS using a validated method (Study N09F0304 & N09F0305 in the IND).
Since most values obtained were < LLOQ, those results which were >LOD (0.1ng/mL) and <LLOQ (2 ng/mL) were calculated using the established standard curve in order to compare the different groups. The calculated results showed that thirty minutes after the last administration of Day 14, CsA whole blood concentrations were 1.56 $\pm$ 0.16 ng/ml and 1.41 $\pm$ 0.41 ng/ml for NOA22007 0.1% CsA with and without (b) (4), respectively. After 28 days of qid administration, the trough and maximal systemic levels were of 1.93 $\pm$ 0.29 and 2.14 + 0.21 ng/ml ((b) (4) (b) (4)) and 1.93 $\pm$ 0.39 and 2.04 $\pm$ 0.39 ng/ml ((b) (4) (b) (4)), respectively.
It is concluded that the withdrawal of (b) (4) had no impact on the systemic exposure to NOVA22007, and the detectable whole blood CsA levels were not significant.

5. Study title: Corneal sensitivity in rabbits

Key study findings: NOVA22007 0.1% and its vehicle, after 5 instillations in rabbit eye, did not induce a decrease of the sensitivity of cornea.

Study no.: N09F0805
Volume #, and page #: Vol. 3, page 1023
Conducting laboratory and location: (b) (4)
Date of study initiation: May 16, 2005
GLP compliance: Yes
QA report: yes (x) no ( )
Methods

Doses: NOVA 0.1%, vehicle, 0.9% NaCl (negative control), and 0.4% oxybuprocaine hydrochloride (positive control)
Species/strain: New Zealand White rabbits
Number/sex/group or time point (main study): 3/group
Route, formulation, volume, and infusion rate: 5 instillations of (b) (4) µl (within 20 minutes) into right eye; left eye untreated (control)
Age: approximately 4 months
Weight: 2.0-2.5 kg
Sampling times: The corneal sensitivity was tested using an esthesiometer of Cochet-Bonnet. Corneal anesthesia was evaluated by the number of stimuli necessary to induce a blinking reflex. This was done just before, and then 10, 20, 30, 45, 60, and 120 minutes after the last instillation.

Results:
No decrease in corneal sensitivity was observed after repeated treatment (5 instillations within 20 minutes) with NOVA2207 0.1%, vehicle, or saline. The instillations of 0.4% oxybuprocaine hydrochloride induced corneal anesthesia for 45 minutes after treatment.

6. Study title: Sensitization potential in mice (local lymph node assay) with the NOVA22007 vehicle

Key study findings: No treatment-related adverse clinical signs, cutaneous reactions or increased ear thickness were observed in this test. No lymphoproliferation was observed with vehicle of NOVA22007, whereas significant lymphoproliferation was observed in the positive control group.

Study no.: 29412TSS
Volume #, and page #: Vol. 3, page 1058
Conducting laboratory and location: (b) (4)
Date of study initiation: February 1, 2005
GLP compliance: Yes
QA report: yes (x) no ( )
Methods

Doses: 0.5%, 1%, and 2% active material, purified water (negative control), and 25% alpha-hexylcinnamaldehyde (HCA, positive control)

Species/strain: CBA/J mouse, nulliparous and non-pregnant females
Number/sex/group or time point (main study): 4 females/group (total 5 groups)
Route, formulation, volume, and infusion rate: During the induction phase, the test materials were applied over the ears (25 µl per ear) for 3 consecutive days
Age: approximately 9 weeks old
Weight: 19.7 $\pm$ 0.8 g
Sampling times: After 2 days of resting following 3 days of induction phase, the proliferation of lymphocytes in the lymph node draining the application site was measured by incorporation of tritiated methyl thymidine (Day 6). The irritant potential of the test item was assessed in parallel by measurement of ear thickness on Days 1, 2, 3, and 6.

Results:
No mortality and no clinical signs were observed. No cutaneous reactions and no increase in ear thickness were observed in the animals of the treated groups. No lymphoproliferation was noted at any tested concentration, while significant lymphoproliferation was observed with HCA at 25%. Under the experimental conditions, the vehicle of NOVA22007 did not induce delayed contact hypersensitivity in the murine local lymph node assay.

Summary and Evaluation
The Oral form of cyclosporine (Neoral™) is marketed for prophylaxis of organ rejection. A cyclosporine ophthalmic anionic emulsion (Restasis™ 0.05%) is marketed for keratoconjunctivitis sicca (KCS). The subject of this IND, NOVA22007, a cyclosporine ophthalmic cationic emulsion ((b) (4) 0.1%), is being developed for keratoconjunctivitis (b) (4).

In the IND, the following pre-clinical studies for NOVA22007 were submitted.

1. Single dose ocular PK study in rabbits
2. Multiple dose ocular PK study in rabbits
3. 28-ocular irritation study in rabbits
4. TK study in rabbits after 28-day ocular administration of a NOVA22007 formulation without (b) (4)
5. Corneal sensitivity in rabbits
6. Sensitization potential in mice (local lymph node assay) with the NOVA22007 vehicle.

In single or multiple (qd or bid for 10 days) ocular instillation studies of NOVA22007 (0.025%, 0.05%, and 0.1%) or Restasis™ (0.05%) in rabbits, CsA appeared rapidly in cornea and conjunctiva. Corneal concentrations were significantly higher than conjunctival ones for all groups. It is notable that the CsA concentration in cornea from NOVA22007 0.05% bid was double of that from Restasis™ 0.05% bid. No systemic absorption was detected after administration of these CsA ophthalmic products (all values <LOD of 0.1 ng/mL).

In a 28-day ocular irritation study in rabbits, ocular instillation of NOVA22007 (0.025%, 0.05%, 0.1%) (b) (4) µl 4 times daily did not produce any systemic adverse effects. There were no detectable levels of CsA in blood of treated animals. The CsA blood concentrations were below LLOQ in this study. Increased frequency of slight local reactions (mostly redness of conjunctiva) was found in 0.1% group. Redness of conjunctiva was also found in other groups.

In a 28-day TK study assessing the effects of (b) (4), the removal of (b) (4) (b) (4) from NOVA22007 formulation had no impact on the systemic exposure of CsA in the rabbits. In a separate study, NOVA22007 0.1% and its vehicle, after 5 instillations in rabbit eye, did not induce a decrease of the corneal sensitivity in rabbits. In another study, the vehicle of NOVA22007 did not induce delayed contact hypersensitivity in the murine local lymph node assay.

The use of marketed Restasis™ for keratoconjunctivitis sicca (KCS) is well established. The formulations of Restasis™ and NOVA22007 are different. However, all excipients for NOVA22007 formulation, except MCT and (b) (4), are used in approved ophthalmic products in the US. MCT (medium chain triglyceride) is used in Europe in ophthalmic formulations. (b) (4) The sponsor has conducted a 28-day ocular irritation study with NOVA22007 in rabbits. There were no systemic or topical ocular adverse effects observed. The CsA blood concentration in the 28-day rabbit ocular study was below LLOQ of 2 ng/mL.

In the comparative single dose and multiple dose ocular PK/TK studies in rabbits, it was found that NOVA22007 (b) (4)% doubled the corneal CsA concentration of that of Restasis™ 0.05%. However, the blood CsA concentrations for both products were below the LLOQ. In the development of Restasis™ 0.05% (NDA 50-790), 6-month ocular (at 0.05%, 0.2%, and 0.4%, 6 times/day) toxicity studies in rabbits and 12-month ocular (0.1%, 0.2%, and 0.4%, 3-6 times/day) toxicity study in dogs were conducted. The maximum level of CsA in the blood was 1.36 ng/mL in rabbits and 1.16 ng/mL in dogs, respectively. No ocular or systemic toxicity was found in these studies.

NOVA22007 is a new formulation of a well established drug product. The sponsor was told during the previous sponsor/FDA meeting that no additional pre-clinical study will be required if no new issue arises.

The proposed clinical study is a multicenter Phase III study in patients with dry eye syndrome by administration of NOVA22007 (0.05% and 0.1%) (b) (4)/daily for (b) (4) months. In the previous Phase II study, NOVA22007 (0.025%, 0.05%, and 0.1%, two instillations/day) was studied in KCS for 3 months. Since the submitted pre-clinical studies for NOVA22007 did not reveal any unexpected adverse effects and the proposed clinical dose is similar to the established clinical dose for ocular CsA, it is felt that the proposed clinical study is safe to proceed.

Conrad H. Chen, Ph.D.
Reviewing Pharmacologist

Concurrence by: Terry Peters, DVM
Pharmacology Team Leader

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/s/

Conrad Chen
2/15/2007 12:37:49 PM
PHARMACOLOGIST
The proposed clinical study is safe to proceed.
This review has been discussed with Dr. A. Nostrandt.

Terry Peters
2/16/2007 02:36:57 PM
PHARMACOLOGIST