CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 214028
Supplement #:	NA
Drug Name:	VUITY (pilocarpine hydrochloride) ophthalmic solution, 1.25%
Indication(s):	Treatment of near vision impairment associated with presbyopia
Applicant:	AbbVie Inc.
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Review Priority:	Standard
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Keywords: Chi-squared test, sequential gatekeeping testing

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1 EXECUTIVE SUMMARY

This document provides statistical review of the New Drug Application (NDA 214028) submitted by AbbVie Inc. (Applicant) to seek approval of VUITY for the treatment of near vision impairment associated with presbyopia in adults. VUITY is a sterile topical ophthalmic solution containing 12.5 mg/mL pilocarpine hydrochloride ("Pilo HCl") 1.25% for once-daily ocular administration.

The Applicant conducted two pivotal Phase 3 studies (1883-301-013 and 1883-302-013) in the United States. These studies are hereafter referred to as Study 301 and Study 302, respectively. The objective of Studies 301 and 302 is to evaluate the efficacy and safety of Pilo HCl 1.25% versus vehicle in the treatment of presbyopia.

Studies 301 and 302 are multi-center, double-masked, parallel-group, vehicle-controlled, Phase 3 studies in participants with presbyopia. In Study 301, a total of 323 subjects were randomized in a 1:1 ratio to Pilo HCl 1.25% (N = 163) or vehicle (N = 160). In Study 302, a total of 427 were randomized in a 1:1 ratio to Pilo HCl 1.25% (N = 212) or vehicle (N = 215).

Efficacy endpoints included mesopic, high-contrast, binocular distance-corrected near visual acuity (DCNVA), photopic, high-contrast distance-corrected intermediate visual acuity (DCIVA) and two patient-reported outcome (PRO) assessments: near vision presbyopia task-based questionnaire (NVPTQ) performance/satisfaction scores and presbyopia impact and coping questionnaire (PICQ) coping/impact scores.

The primary efficacy endpoint of the two studies is the proportion of the participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA without losing more than 1 line (5 letters) of mesopic, high-contrast, binocular corrected distance visual acuity (CDVA) with the same refraction, at Day 30, Hour 3. Table 1 summarizes the primary analysis results.

Table 1: Primary analysis results for the primary efficacy endpoint

	Study 301		**Study 302**	
	Pilo HCl 1.25%	**Vehicle**	**Pilo HCl 1.25%**	**Vehicle**
	N = 163	**N = 160**	**N = 212**	**N = 215**
Responder Rate, n/N (%)	50/163 (30.7%)	13/160 (8.1%)	51/196[1] (26.0%)	22/203[1] (10.8%)
Difference (Pilo HCl 1.25% - Vehicle)	22.5%		15.2%	
95% CI for Difference [2]	(14.3%, 30.8%)		(7.7%, 22.7%)	
P-value [3]	< 0.0001		< 0.0001	

[1] All subjects (28 subjects) from site 51 of Study 302 were excluded from efficacy analyses because DCNVA measurements were not conducted correctly at the site at the screening and baseline visits.
[2] The 95% CIs (confidence intervals) were estimated using the normal approximation and pooled variance.
[3] P-values were computed using Chi-squared tests.
Source: Reviewer's analysis for Studies 301 and 302.

In both studies, the responder rate was significantly higher in the Pilo HCl 1.25% group compared to that in the vehicle group: 30.7% vs. 8.1% in Study 301 and 26.0% vs. 10.8% in Study 302. The difference (Pilo HCl 1.25% – Vehicle) in the responder rates was 22.5% [95% CI: (14.3%, 30.8%)] in Study 301 and 15.2% [95% CI: (7.7%, 22.7%)] in Study 302.
For each study, the secondary efficacy endpoints (one key and 11 other secondary efficacy endpoints) were tested with a graph-based sequential gatekeeping testing strategy to control the Type I error rate. The nominal 95% confidence interval without adjustment for the testing procedure, and adjusted p-value are reported.

In terms of the key secondary efficacy endpoint (proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 6), Study 301 demonstrated statistically significantly greater improvement in the Pilo HCl 1.25% group compared with the vehicle group (9.7% difference in responder rates [95% CI: (2.3%, 17.0%) and p-value is 0.0114]), but Study 302 provided no strong evidence supporting greater improvement in the Pilo HCl 1.25% group (6.5% difference in responder rates [95% CI: (-0.1%, 13.1%) and the adjusted p-value is 0.0548]).

Results of the other efficacy analyses supported the primary analyses, with statistically significant results in favor of Pilo HCl 1.25% for the following other secondary endpoints: the proportions of participants achieving 20/40 or better for photopic, high-contrast, binocular DCNVA at Day 30, Hours 1 and 3, change from baseline analyses for mesopic, high-contrast DCNVA letters at Day 30, Hours 0.5 and 0.25, change from baseline analyses for photopic, high-contrast DCIVA letters at Day 30, Hour 3, change from baseline analyses for mesopic NVPTQ performance/satisfaction scores at Day 30, Hour 3, and change from baseline analyses for mesopic PICQ coping/impact scores at Day 30, Hour 3.

Results for the proportion of participants gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA at Day 30, Hours 8 and 10 did not show a statistically significantly difference between the Pilo HCl 1.25 group and the vehicle group.

In summary, the reviewer concludes that this application provides adequate statistical evidence of efficacy with respect to the primary efficacy endpoint and the majority of the secondary efficacy endpoints to support an approval of Pilo HCl 1.25% for the treatment of presbyopia.

2 INTRODUCTION

This section provides an overview of the application, a summary of the clinical studies, and information on data sources for the review of NDA 214028.

2.1 Overview

AbbVie Inc. ("Applicant") seeks approval of VUITY for the treatment of presbyopia in adults. VUITY is a sterile topical ophthalmic solution containing 12.5 mg/mL pilocarpine hydrochloride ("Pilo HCl") 1.25% for once-daily ocular administration.

Presbyopia is a condition in which the eye exhibits a diminished ability to focus on near objects with increasing age. Symptoms include eyestrain, difficulty seeing in dim light, and problems focusing on small objects and/or fine prints.

Current treatment options for the correction of presbyopia are nonsurgical (spectacles or contact lenses) and surgical (PRK or LASIK) methods. Per the Applicant, there remains a need for a noninvasive, reversible, pharmacological treatment for presbyopia since these options can follow its own safety risks and associated complications.

Pilo HCl 1.25% contracts the iris sphincter muscle, constricting the pupil to enhance the depth of focus and improve near and intermediate visual acuity. Pilo HCl 1.25% also contracts the ciliary muscle, facilitating accommodation. Other pilocarpine ophthalmic solutions (e.g. Isopto Carpine) were approved for the treatment of glaucoma, a condition in which increased pressure in the eye can lead to gradual loss of vision. Currently, the use of pilocarpine ophthalmic solution is limited due to the commonly reported side effects of temporal and periorbital headache, and visual disturbances.

2.1.1 Class and Indication

Pilocarpine hydrochloride is in a class of medications called cholinergic muscarinic agonist which activates muscarinic receptors located at smooth muscles. The indication with Pilo HCl 1.25% that the Applicant seeks is to treat presbyopia in adults.

2.1.2 History of Drug Development

The Applicant filed the initial Investigational New Drug (IND) application on June 30, 2014 for Phase 2 Study 199201-007. Two follow-on Phase 2 studies (199201-009 and 199201-010) were conducted to explore and confirm the findings from Study 199201-007. Based on the findings in the Phase 2 Studies, the Applicant submitted two Phase 3 Studies (1883-301-013 and 1993-302-013). All protocols and statistical analysis plans (SAPs) under this IND were reviewed by the statistical reviewer, Dr. Solomon Chefo, DB IV (See the DARRTS entries on November 20, 2018, December 5, 2019, and August 7, 2020).

2.1.3 Specific Studies Reviewed

The Applicant conducted the following six clinical studies:

- Study 1883-301-013 (Phase 3)
- Study 1883-302-013 (Phase 3)
- Study 199201-007 (Phase 2)
- Study 199201-009 (Phase 2)
- Study 199201-010 (Phase 2)
- Study 1883-101-013 (Phase 1)

This statistical review focuses on two Phase 3 pivotal studies (1883-301-013 and 1883-302-013). A summary of these studies is outlined in the following Table 2.

Table 2: Summary of studies reviewed

Study ID	**Study 1883-301-013**	**Study 1883-302-013**
Phase/Design	Phase 3, multicenter, double masked, randomized, parallel-grouped, and vehicle- controlled design	
Duration	30 days; Once daily, bilaterally	
Treatment/ Sample Size	• Pilo HCl 1.25%/163 • Vehicle/159	• Pilo HCl 1.25%/212 • Vehicle/215
Study Population	Adult male and female between 40 and 55 years of age with objective and subjective evidence of presbyopia	

Source: Reviewer's summary based on the clinical study reports.

2.2 Data Sources

The data sources for this review include protocols, statistical analysis plans (SAPs), clinical study reports (CSRs), and the datasets for the respective studies.

The protocols, SAPs and CSRs can be found at the following locations:

- \\CDSESUB1\evsprod\NDA214028\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\presbyopia\5351-stud-rep-contr\1883-301-013
- \\CDSESUB1\evsprod\NDA214028\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\presbyopia\5351-stud-rep-contr\1883-302-013.

The datasets were submitted in the formats of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) in electronic submission. The datasets can be located at

- \\CDSESUB1\evsprod\NDA214028\0001\m5\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No major issues were identified regarding the quality and integrity of the submitted SDTM and ADaM datasets under NDA 214028. The data quality control/assurance procedures are properly documented in the CSRs. The Applicant's primary efficacy results are reproducible using the ADaM datasets.

3.2 Evaluation of Efficacy

This section evaluates the efficacy results of Studies 301 and 302.

3.2.1 Study Design and Endpoints

Study design

Studies 301 and 302 have applied an identical design except, in Study 301, the steady-state systemic pharmacokinetics of Pilo HCl 1.25% were evaluated in a subset of approximately 10% (22 subjects) of all enrolled subjects. Both studies are multi-center, double-masked, parallel-group, vehicle-controlled, Phase 3 studies in participants with presbyopia. Randomization was performed as follows:

- In Study 301, a total of 37 sites in the United States enrolled 323 subjects. They were randomized in a 1:1 ratio to Pilo HCl 1.25% (163 subjects) or vehicle (160 subjects),
- In Study 302, a total of 40 sites in the United States enrolled 427 subjects. They were randomized in a 1:1 ratio to Pilo HCl 1.25% (212 subjects) or vehicle (215 subjects).

The randomization was stratified by:

- Age (≤ 50 years and > 50 years),
- Baseline binocular DCNVA (20/40 to 20/60 inclusive and worse than 20/60),
- Iris color (brown and non-brown).

Each study consists of the following visits:

- Screening (Day -30 to Day -1),
- Visit 1 (Day 1: Randomization),
- Visit 2 (Day 3),
- Visit 3 (Day 7 ± 2),
- Visit 4 (Day 14 ± 2),
- Visit 5 (Day 30 ± 3: the primary efficacy endpoint is assessed at Day 30, Hour 3).

The study medications used in this study were Pilo HCl 1.25% or its vehicle, dosed at 1 drop in each eye once daily. The study medication was to be instilled bilaterally by designated site

personnel at Hour 0 (8 am ± 1 hour) of Visit 1 to Visit 5. Between visits, participants were instructed to instill one drop of the dispensed study intervention in the morning once daily into both eyes.

Efficacy endpoints

Efficacy measurements included DCNVA (mesopic and photopic, high-contrast, binocular), DCIVA (photopic, high-contrast, binocular), health outcomes (NVPTQ performance/satisfaction scores and PICQ coping/impact scores). Table 3 summarizes the efficacy endpoints in the two pivotal studies.

Table 3: Efficacy endpoints in Studies 301 and 302

Primary	**Proportion of the participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA without losing more than 1 line (5 letters) of mesopic, high-contrast, binocular corrected distance visual acuity (CDVA) with the same refraction, at Day 30, Hour 3**
Key Secondary	Proportion of the participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 6
Additional Secondary	(S1) Proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 8 (S2) Change from baseline in mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.5 (S3) Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 1 (S4) Change from baseline in photopic, high contrast, binocular DCIVA letters at Day 30, Hour 3 (S5) Change from baseline in Mesopic NVPTQ Performance score at Day 30, Hour 3 (S6) Proportion of participants gaining 3 lines or more in mesopic, high contrast, binocular, DCNVA at Day 30, Hour 10 (S7) Change from baseline in mesopic, high contrast, binocular DCNVA letters at Day 30, Hour 0.25 (S8) Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCVNA at Day 30, Hour 3 (S9) Change from baseline in Mesopic NVPTQ Satisfaction score at Day 30, Hour 3 (S10) Change from baseline in PICQ Coping score at Day 30, Hour 3 (S11) Change from baseline in PICQ Impact score at Day 30, Hour 3

Reviewer's notes on the primary efficacy endpoint

For both Study 301and Study 302, the original primary efficacy endpoint was the proportion of participants gaining 3 lines or more in mesopic, high-contrast, binocular distance-corrected near visual acuity (DCNVA) at Day 30, Hour 3. However, on July 21, 2020 Type C meeting, FDA requested that the primary efficacy endpoint be modified to a multiple component endpoint: the proportion of participants gaining 3 lines or more in mesopic, high-contrast, binocular DCNVA without losing more than 1 line (5 letters) of mesopic, high-contrast, binocular corrected distance visual acuity (CDVA) with the same refraction, at Day 30, Hour 3. Following this request, the primary efficacy endpoint for both studies was revised to the multiple component endpoint.

3.2.2 Statistical Methodologies

In this section we primarily focus on describing statistical methodologies for analyzing the primary and key secondary efficacy endpoints. Statistical methodologies for analyzing additional secondary efficacy endpoints are also briefly described.

Analysis populations

The protocols and SAPs defined two analysis populations as follows:

1. The intent-to-treat (ITT) population consists of all randomized participants. The analysis using the ITT population was based on the study intervention assigned.

2. The safety population consists of all participants who received at least one administration of study intervention. The analysis using the safety population was based on the actual study intervention received.

Analysis of primary and key secondary efficacy endpoints

Recall that the primary and key secondary efficacy endpoints are as follows:

- **Primary: proportion of the participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA without losing more than 1 line (5 letters) of mesopic, high-contrast, binocular corrected distance visual acuity (CDVA) with the same refraction, at Day 30, Hour 3**
- Key secondary: proportion of the participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 6.

The main analytical methods for these two endpoints are a Chi-square test and 95% confidence interval (CI) for the difference in the proportions. The 95% CIs are based on unadjusted analyses using the two-sample tests for the difference in proportions (the normal approximation of the pooled variance without continuity correction). Sensitivity analyses using 95% CI based on the Wilson-Newcombe method were also performed for these two endpoints.

Reviewer's notes:

The Newcombe method first obtains a 95% CI for a single proportion in each arm using Wilson (1927) method. Then, the Newcombe method combines the two individual 95% CIs by a pre-specified rule to obtain a 95% CI for the difference in the proportions. As this method has been shown to work well even for small proportions, the reviewer found this method reasonable for this study data. See the theoretical and numerical results in Newcombe (1998) and Brown et al. (2002) for more details.

Analysis of other secondary efficacy endpoints

Other secondary endpoints S1, S3, S6 and S8 are related to proportion of participants gaining 3 lines or more or achieving 20/40 better. These secondary endpoints were analyzed with the same method as the primary efficacy endpoint.

Secondary endpoints S2 and S7 are the change from baseline in mesopic, high contrast, binocular DCNVA letters. These secondary endpoints were analyzed using mixed model repeated measure (MMRM): the MMRM model includes treatment, visit, treatment by visit interaction, age group, baseline binocular DCNVA severity, iris color, emmetropes/non-emmetropes, baseline DCNVA value and baseline DCNVA value by visit interaction as fixed effects. An unstructured covariance matrix is used to model the within-subject error.

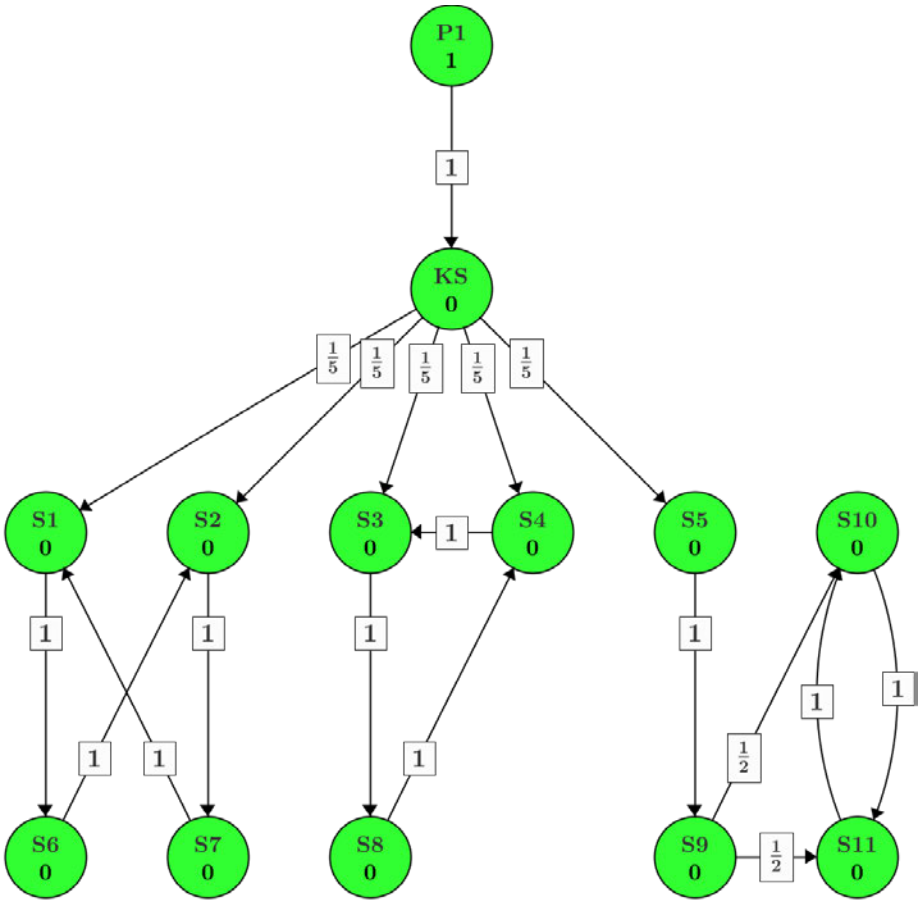
Change from baseline in photopic, high contrast, binocular DCIVA letters (S4) was analyzed similarly as S2 or S7.

Other secondary endpoints S5, S9, S10 and S11 are the change from baseline in the mesopic NVPTQ Performance score, Mesopic NVPTQ Satisfaction score, PICQ Coping score, and PICQ Impact score. These secondary endpoints were analyzed using an analysis of covariance (ANCOVA) model: the ANCOVA model includes treatment, age group, baseline binocular DCNVA severity, iris color and emmetropes/non-emmetropes and baseline domain score as fixed effects.

Type I error control (plan for multiplicity adjustment)

In Study 301, the Applicant used a graph-based sequential gatekeeping testing strategy to control the overall Type I error rate at 5% as described in Figure 1. In this testing strategy, testing for the primary (P1) and key secondary (KS) efficacy endpoints should be met first (p-values < 0.05) in order to test all the other secondary efficacy endpoints (S1 – S11). This approach was previously discussed and considered acceptable by the former statistical reviewer (See the statistical IND review and evaluation for Type B (Pre-NDA) meeting dated on November 1, 2019).

Figure 1: Graphical testing procedure in Study 301



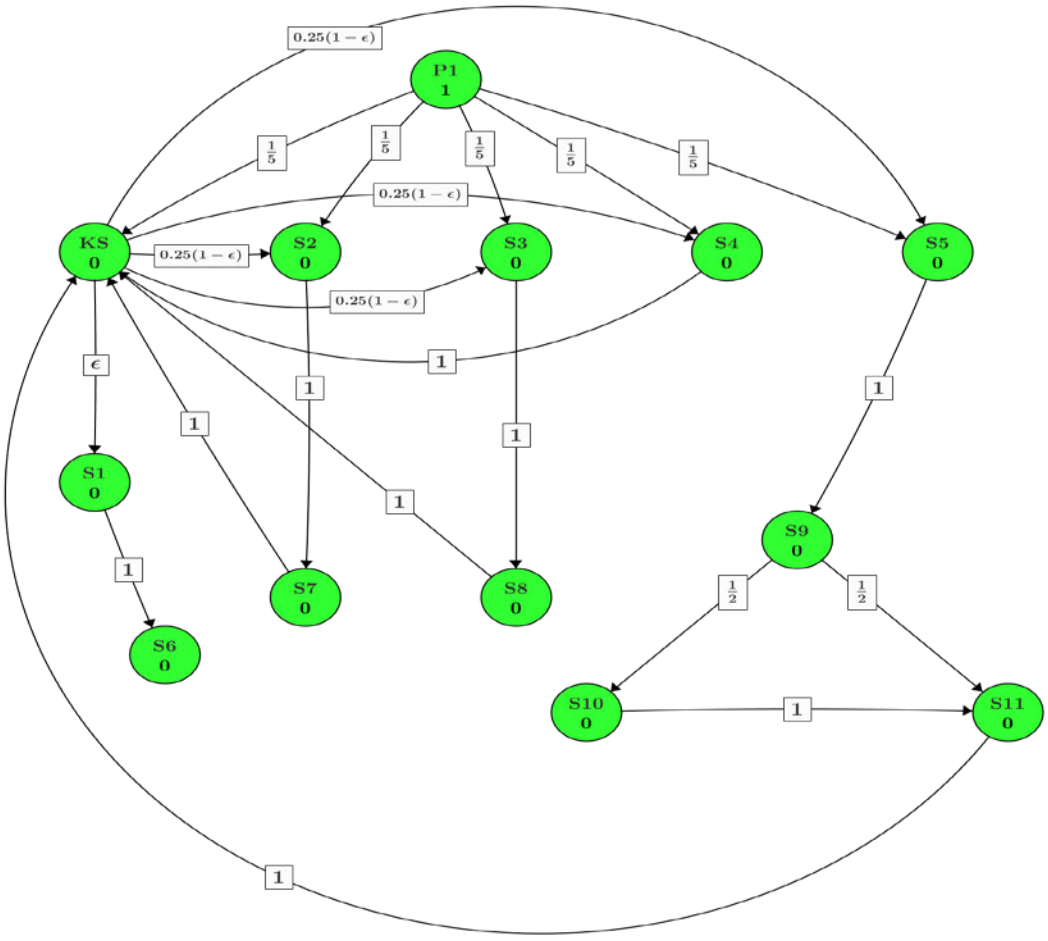
Source: Figure 5-1 of the Applicant's SAP of Study 301. Figure was produced by the reviewer using R package "gMCP".

In Study 302, the Applicant used a revised graph-based sequential gatekeeping testing strategy to control the overall Type I error rate at 5% as described in Figure 2. In the revised testing strategy, all other secondary endpoints could be tested only after testing in the primary efficacy endpoint (P1) were met. This revised strategy was considered acceptable by the former statistical reviewer (See the statistical IND review and evaluation for Type C meeting dated on June 4, 2020).

Reviewer's notes:

1. The reviewer used the algorithm provided in Bretz et al. (2011) to calculate adjusted p-values.
2. Per the submitted SAS code, the Applicant defined ϵ used in Figure 2 below is 10^{-8}.

Figure 2: Graphical testing procedure in Study 302



Source: Figure 5-1 of SAP for Study 302. Figure was produced by the reviewer using R package "gMCP".

Handling of missing values

For the primary and key secondary analyses, a subject with missing data was considered as non-responders. For the other secondary efficacy endpoints, no imputations were performed (i.e. only observed data were used).

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Subject disposition and primary reasons for study discontinuation are summarized in Table 4. In Study 301, two subjects in the Pilo HCl 1.25% and seven in the vehicle group did not complete the study. In Study 302, five subjects in the Pilo HCl 1.25% and six in the vehicle group did not complete the study.

Table 4: Subject disposition, n (%)

	Study 301		**Study 302**	
	Pilo HCl 1.25%	Vehicle	Pilo HCl 1.25%	Vehicle
Subjects randomized (ITT population)	163	160	212	215
Subjects treated (Safety population)	163	159[1]	212	215
Subjects completed study				
Yes	161	153	207	209
No	2 (1.2%)	7 (4.4%)	5 (2.4%)	6 (2.8%)
- Adverse event	2	2	3	1
- Withdrawal by subject	0	2	1	2
- Lost to follow-up	0	1	1	2
- Physician decision	0	2	0	0
- Other	0	0	0	1[2]

[1] One participant was excluded from the vehicle group due to not being treated with study intervention.
[2] Scheduling issues.
Source: Table 10-1 of CSRs for Studies 301 and 302.

Demographic characteristics are summarized in Table 5. In general, the demographic characteristics were balanced between the Pilo HCl 1.25% group and the vehicle group. In terms of age and ethnicity, no notable imbalance was observed between the Pilo HCl 1.25% group and the vehicle group. The proportion of female was lower in the Pilo HCl 1.25% group compared to that in the vehicle group: 69.3% vs. 76.3% in Study 301 and 65.1% vs. 75.3% in Study 302. However, these imbalances are not considered to be remarkable.

Table 5: Demographic characteristics

	Study 301			Study 302		
	All	**Pilo HCl 1.25%**	**Vehicle**	**All**	**Pilo HCl 1.25%**	**Vehicle**
Randomized Population	N = 323	N = 163	N = 160	N = 427	N = 212	N = 215
Age (years)						
Mean (SD)	49.6 (3.5)	49.5 (3.8)	49.7 (3.2)	49.8 (3.6)	49.6 (3.7)	49.9 (3.5)
Median	50	50	50	50	50	50
Min - Max	40 - 55	40 – 55	41 – 55	40 - 55	40 - 55	40 – 55
Age Group, n (%)						
<= 50	185 (57.3)	92 (56.4)	93 (58.1)	231 (54.1)	115 (54 2)	116 (54.0)
> 50	138 (42.7)	71 (43.6)	67 (41.9)	196 (45.9)	97 (45.8)	99 (46.0)
Gender, n (%)						
Female	235 (72.8)	113 (69.3)	122 (76.3)	300 (70.3)	138 (65.1)	162 (75.3)
Male	88 (27.2)	50 (30.7)	38 (23.8)	127 (29.7)	74 (34.9)	53 (24.7)
Race, n (%)						
White	292 (90.4)	148 (90.8)	144 (90.0)	347 (81.3)	171 (80.7)	176 (81.9)
Black or African American	25 (7.7)	13 (8.0)	12 (7.5)	64 (15.0)	35 (16.5)	29 (13.5)
Asian	3 (0.9)	2 (1.2)	1 (0.6)	13 (3.0)	5 (2.4)	8 (3.7)
American Indian or Alaska Native	2 (0.6)	0 (0.0)	2 (1.3)	3 (0.7)	1 (0.5)	2 (0.9)
Multiple	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)						
Not Hispanic or Latino	266 (82.4)	132 (81.0)	134 (83.8)	349 (81.7)	175 (82 5)	174 (80.9)
Hispanic or Latino	57 (17.6)	31 (19.0)	26 (16.3)	78 (18.3)	37 (17.5)	41 (19.1)

Source: Table 10-4 of the CSRs for Studies 301 and 302.

Baseline and disease characteristics are summarized in Table 6. In general, the two groups were comparable.

Table 6: Baseline and disease characteristics

	Study 301			Study 302		
	All	**Pilo HCl 1.25%**	**Vehicle**	**All**	**Pilo HCl 1.25%**	**Vehicle**
Randomized Population	N = 323	N = 163	N = 160	N = 427	N = 212	N = 215
Mesopic, High-contrast, Binocular DCNVA, n (%)						
20/40 to 20/60	128 (39.6)	66 (40.5)	62 (38.8)	208 (48.7)	103 (48.6)	105 (48.8)
Worse than 20/60	195 (60.4)	97 (59.5)	98 (61.3)	219 (51.3)	109 (51.4)	110 (51.2)
Iris Color, n (%)						
Brown	155 (48.0)	78 (47.9)	77 (48.1)	211 (49.4)	107 (50 5)	104 (48.4)
Non-Brown	168 (52.0)	85 (52.1)	83 (51.9)	216 (50.6)	105 (49 5)	111 (51.6)
Emmetrope, n (%)						
Emmetrope	248 (76.8)	125 (76.7)	123 (76.9)	322 (75.4)	161 (75 9)	161 (74.9)
Non-emmetrope	75 (23.2)	38 (23.3)	37 (23.1)	105 (24.6)	51 (24.1)	54 (25.1)

Source: Table 10-5 of the CSRs for Studies 301 and 302.

3.2.4 Results and Conclusions

This section provides efficacy results of the primary, key secondary and other secondary efficacy endpoints in both studies.

3.2.4.1 Primary Efficacy Endpoint

Table 7 presents the primary analysis results of the primary efficacy endpoint: proportion of the participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA without losing more than 1 line (5 letters) of mesopic, high-contrast, binocular corrected distance visual acuity (CDVA) with the same refraction, at Day 30, Hour 3.

Table 7: Primary analysis results for the primary efficacy endpoint

	Study 301		Study 302	
	Pilo HCl 1.25% N = 163	**Vehicle N = 160**	**Pilo HCl 1.25% N = 212**	**Vehicle N = 215**
Responder Rate, n/N (%)	50/163 (30.7%)	13/160 (8.1%)	51/196[1] (26.0%)	22/203[1] (10.8%)
Difference (Pilo HCl 1.25% - Vehicle)	22.5%		15.2%	
95% CI for Difference [2]	(14.3%, 30.8%)		(7.7%, 22.7%)	
95% CI for Difference [3]	(14.1%, 30.7%)		(7.6%, 22.7%)	
P-value [4]	< 0.0001		< 0.0001	

[1] All subjects (28 subjects) from site 51 were excluded from efficacy analyses because DCNVA measurements were not conducted correctly at the site at the screening and baseline visits.
[2] The 95% CIs were estimated using the normal approximation and pooled variance.
[3] The 95% CIs were estimated using the Wilson-Newcombe method.
[4] P-values were computed using Chi-squared tests.
Source: Reviewer's analysis for Studies 301 and 302.

In the two studies, the Pilo HCl 1.25% group showed higher responder rate compared to the vehicle group: 30.7% vs. 8.1% in Study 301 and 26.0% vs. 10.8% in Study 302. The treatment difference (Pilo HCl 1.25% - Vehicle) in the responder rates was statistically significant: 22.5% [95% CI: (14.3%, 30.8%)] and 15.2% [95% CI: (7.7%, 22.7%)] in Study 301 and Study 302, respectively. The 95% CIs for the difference using the Wilson-Newcombe method were also reported: (14.1%, 30.7%) in Study 301 and (7.6%, 22.7%) in Study 302. The p-values from the Chi-squared test were < 0.0001 in both studies.

Sensitivity analysis

In Study 302, the Applicant excluded all subjects (28 subjects: 16 subjects of the Pilo HCl 1.25% group and 12 subjects of the vehicle group) from site 51 from the efficacy analyses because DCNVA at screening and baseline was incorrectly measured with near correction instead of distance correction, so the baseline values of the DCNVA were not obtained for all participants from this site. To evaluate the effect of this issue on the efficacy results, the reviewer conducted a sensitivity analysis by including the subjects in the site 51. Subjects with no DCNVA baseline value were considered as non-responder (3-line gain failure) as planned in the SAPs.

Table 8 shows the results of this sensitivity analysis. The responder rates of subjects with site 51, and without site 51 were similar between the primary analysis and the sensitivity analysis: 26.0% vs. 24.1% in the Pilo HCl 1.25% group and 10.8% vs. 10.2% in the vehicle group. The estimated difference (Pilo HCl 1.25% - Vehicle) in the responder rates was slightly higher in the primary analysis compared to that in the sensitivity analysis: 15.2% vs. 13.8%. However, the p-values from the Chi-squared test were < 0.0001 and 0.00015. Thus, it does not appear that this issue has a significant impact on the primary efficacy conclusions.

Reviewer's notes:
Regarding missing data, very few subjects in both studies had missing data: 9 subjects (2.8%) in Study 301 and 11 subjects (2.6%) in Study 302. Sensitivity analysis with the case that a subject with missing data was regarded as failure for the Pilo HCl 1.25% group and as success for the Vehicle group was also conducted. The result for this worst-case analysis was still highly significant. Therefore, the efficacy for the primary endpoint was robust against missing data handling.

Table 8: Sensitivity analysis for the primary efficacy endpoint in Study 302

	Excluding the site 51 (Primary Analysis)		**Including the site 51** (Sensitivity Analysis)	
	Pilo HCl 1.25%	**Vehicle**	**Pilo HCl 1.25%**	**Vehicle**
Number of Subjects	N = 196	N = 203	N = 212	N = 215
Responder, n (%)				
No responder, n (%)	145 (74.0)	181 (89.2)	161 (75.9)	193 (89.8)
Responder, n (%)	**51 (26.0)**	**22 (10.8)**	**51 (24.1)**	**22 (10.2)**
Treatment Comparison				
Difference (95% CI) [1]	**15.2% (7.7%, 22.7%)**		**13.8% (6.8%, 20.9%)**	
Difference (95% CI) [2]	15.2% (7.6%, 22.7%)		13.8% (6.7%, 20.9%)	
P-value [3]	< 0.0001		0.00015	

[1] The 95% CIs were estimated using the normal approximation and pooled variance.
[2] The 95% CIs were estimated using the Wilson-Newcombe method.
[3] P-values were computed using Chi-squared tests
Source: Reviewer's analysis

3.2.4.2 Key Secondary Efficacy Endpoint

Table 9 presents the results of the key secondary efficacy endpoint: proportion of the participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 6. In both studies, the Pilo HCl 1.25% group showed higher responder rate compared to the vehicle group: 18.4% vs. 8.8% in Study 301 and 16.3% vs. 9.9% in Study 302. In Study 301, the treatment difference (Pilo HCl 1.25% - Vehicle) in the responder rates was statistically significant: 9.7% [95% CI: (2.3%, 17.0%)]. However, in Study 302, the treatment difference (Pilo HCl 1.25% - Vehicle) in the responder rates was not statistically significant: 6.5% [95% CI: (-0.l%, 13.1%)] and p-value was 0.0548.

Table 9: Analysis results for the key secondary efficacy endpoint

	Study 301		Study 302	
	Pilo HCl 1.25% N = 163	**Vehicle N = 160**	**Pilo HCl 1.25% N = 212**	**Vehicle N = 215**
Responder Rate, n/N (%)	30/163 (18.4%)	14/160 (8.8%)	32/196[1] (16.3%)	20/203[1] (9.9%)
Difference (Pilo HCl 1.25% - Vehicle)	9.7%		6.5%	
95% CI for Difference [2]	(2.3%, 17.0%)		(-0.1%, 13.1%)	
P-value [3]	0.0114		0.0548	
Adjusted P-value [4]	0.0114		0.0548	

[1] All subjects (28 subjects) from site 51 were excluded from efficacy analyses because DCNVA measurements were not conducted correctly at the site at the screening and baseline visits.
[2] The 95% CIs were estimated using the normal approximation and pooled variance.
[3] P-values were computed using Chi-squared tests.
[4] Adjusted p-values were calculated using the algorithm provided in Bretz et al. (2011).
Source: Reviewer's analysis for Studies 301 and 302.

3.2.4.3 Other Secondary Efficacy Endpoints

The significances of the other secondary endpoints depend on the pre-specified decision rule in each study (For more details, see Figures 1 and 2 in Section 3.2.2)

Proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA

Table 10 presents proportions of subjects gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 8 and at Day 30, Hour 10. The differences (Pilo HCl 1.25% - Vehicle) of the responder rate were not statistically significant for both Studies 301 and 302.

Table 10: Proportions of subjects gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA

	Study 301		Study 302	
	Pilo HCl 1.25%	**Vehicle**	**Pilo HCl 1.25%**	**Vehicle**
	N = 163	**N = 160**	**N = 212**	**N = 215**
At Day 30, Hour 8 (S1)				
Responder Rate [1], n/N (%)	17/161 (10.6%)	13/153 (8.5%)	28/193 (14.5%)	17/197 (8.6%)
Difference (Pilo HCl 1.25% - Vehicle)	2.1%		5.9%	
95% CI for Difference [2]	(-4.4%, 8.5%)		(-0.5%, 12.2%)	
P-value [3]	0.5344		0.0693	
Adjusted P-value [4]	1.0000		0.0693	
At Day 30, Hour 10 (S6)				
Responder Rate [1], n/N (%)	12/152 (7.5%)	13/152 (8.6%)	24/191 (12.6%)	17/195 (8.7%)
Difference (Pilo HCl 1.25% - Vehicle)	-1.1		3.8	
95% CI for Difference [2]	(-7.1%, 5.0%)		(-2.3%, 10.0%)	
P-value [3]	0.7321		0.2200	
Adjusted P-value [4]	1.0000		0.2200	

[1] Responder rates are based on observed data only.
[2] The 95% CIs were estimated using the normal approximation and pooled variance.
[3] P-values were computed using Chi-squared tests.
[4] Adjusted p-values were calculated using the algorithm provided in Bretz et al. (2011).
Source: Reviewer's analysis for Studies 301 and 302.

Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA

Table 11 presents proportions of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA at Day 30, Hour 1 and Day 30, Hour 3. The responder rate differences between groups (Pilo HCl 1.25% - Vehicle) were statistically significant in favor of the Pilo HCl 1.25%. At Day 30 Hour 1, the treatment differences were 18.7% [95% CI: (10.6%, 26.7%)] and 9.9% [95% CI: (3.5%, 16.3%)] in Study 301 and Study 302, respectively. At Day 30 Hour 3, the treatment differences were 12.6% [95% CI: (3.5%, 21.6%)] and 12.4% [95% CI: (5.2%, 19.5%)] in Study 301 and Study 302, respectively.

Table 11: Proportion of participants achieving 20/40 or better in photopic, high contrast, binocular, DCNVA

	Study 301		Study 302	
	Pilo HCl 1.25% **N = 163**	**Vehicle** **N = 160**	**Pilo HCl 1.25%** **N = 212**	**Vehicle** **N = 215**
At **Day 30, Hour 1 (S3)**				
Responder Rate [1], n/N (%)	149/161 (92.5%)	113/153 (73.9%)	179/193 (92.7%)	164/198 (82.8%)
Difference (Pilo HCl 1.25% - Vehicle)	18.7%		9.9%	
95% CI for Difference [2]	(10.6%, 26.7%)		(3.5%, 16.3%)	
P-value [3]	< 0.0001		0.0028	
Adjusted P-value [4]	0.0114		0.0140	
At Day 30, Hour 3 (S8)				
Responder Rate [1], n/N (%)	136/161 (84.5%)	110/153 (71.9%)	174/193 (90.2%)	154/198 (77.8%)
Difference (Pilo HCl 1.25% - Vehicle)	12.6%		12.4%	
95% CI for Difference [2]	(3.5%, 21.6%)		(5.2%, 19.5%)	
P-value [3]	0.0068		0.0009	
Adjusted P-value [4]	0.0170		0.0140	

[1] Responder rates are based on observed data only.
[2] The 95% CIs were estimated using the normal approximation and pooled variance.
[3] P-values were computed using Chi-squared tests.
[4] Adjusted p-values were calculated using the algorithm provided in Bretz et al. (2011).
Source: Reviewer's analysis for Studies 301 and 302.

Change from baseline in mesopic, high contrast, binocular DCNVA letters

Table 12 presents the analysis results for the changes from baseline in mesopic, high contrast, binocular DCNVA letters at Day 30 Hour 0.5 and Day 30 Hour 0.25. The table shows the treatment differences (Pilo HCl 1.25% - Vehicle) and the corresponding 95% CIs including p-values based on MMRM model. At Day 30 Hour 0.5, the treatment differences were 5.1 [95% CI: (3.7, 6.5)] and 4.1 [95% CI: (2.9, 5.2)] in Study 301 and Study 302, respectively. At Day 30 Hour 0.25, the treatment differences were 2.6 [95% CI: (1.3, 3.9)] and 2.6 [95% CI: (1.5, 3.7)] in Study 301 and Study 302, respectively. In both studies, the Pilo HCl 1.25% group showed higher changes from baseline in the mesopic DCNVA letters at Day 30, Hour 0.5 and Day 30, Hour 0.25 than the vehicle group.

Table 12: Change from baseline in mesopic, high contrast, binocular DCNVA letters

	Study 301		Study 302	
	Pilo HCl 1.25% N = 163	Vehicle N = 160	Pilo HCl 1.25% N = 212	Vehicle N = 215
Baseline				
N	163	160	196	203
Mean (SD)	29.2 (6.6)	29.1 (6.0)	29.6 (6.4)	29.8 (6.8)
At Day 30, Hour 0.5 (S2)				
N	158	153	193	197
Mean (SD)	38.6 (8.1)	33.5 (7.2)	38.6 (7.9)	34.6 (7.3)
Change from baseline				
LS Mean (SE)[1]	9.3 (0.5)	4.2 (0.6)	8.8 (0.45)	4.7 (0.4)
LS Mean Difference	5.1		4.1	
95% CI	(3.7, 6.5)		(2.9, 5.2)	
P-value [2]	< 0.0001		< 0.0001	
Adjusted P-value [3]	0.0114		< 0.0001	
At Day 30, Hour 0.25 (S7)				
N	158	153	193	196
Mean (SD)	35.5 (8.0)	32.9 (7.0)	36.3 (7.4)	33.8 (7.1)
Change from baseline				
LS Mean (SE) [1]	6.3 (0.5)	3.7 (0.5)	6.5 (0.4)	3.9 (0.4)
LS Mean Difference	2.6		2.6	
95% CI	(1.3, 3.9)		(1.5, 3.7)	
P-value [2]	< 0.0001		< 0.0001	
Adjusted P-value [3]	0.0114		< 0.0001	

[1] MMRM with treatment, visit, visit by treatment interaction, age group, baseline binocular DCNVA severity, iris color, emmetrope/non-emmetrope, baseline and baseline by visit interaction as fixed effects.
[2] P-values were un-adjusted p-values.
[3] Adjusted p-values were calculated using the algorithm provided in Bretz et al. (2011).
Source: Table 14.2-2.3 of CSRs for Study 301 and Study 302. This table was produced by the reviewer.

Change from baseline in photopic, high contrast, binocular DCIVA letters

Table 13 presents the analysis results for the changes from baseline in mesopic, high contrast, binocular DCIVA letters at Day 30, Hour 3. The treatment differences (Pilo HCl 1.25% - Vehicle) were 3.5 [95% CI: (2.4, 4.6)] and 3.4 [95% CI: (2.4, 4.4)] in Study 301 and Study 302, respectively. In both studies, the Pilo HCl 1.25% group showed higher change from baseline in the mesopic DCIVA letters at Day 30, Hour 3 than the vehicle group.

Table 13: Change from baseline in mesopic, high contrast, binocular DCIVA letters

	Study 301		Study 302	
	Pilo HCl 1.25% **N = 163**	**Vehicle** **N = 160**	**Pilo HCl 1.25%** **N = 212**	**Vehicle** **N = 215**
Baseline				
N	163	160	196	203
Mean (SD)	53.4 (7.2)	53.4 (6.9)	54.4 (7.2)	54.1 (7.5)
At Day 30, Hour 3 (S4)				
N	161	153	193	198
Mean (SD)	60.0 (7.1)	56.4 (6.4)	60.8 (7.0)	57.3 (7.2)
Change from baseline				
LS Mean (SE)[1]	6.6 (5.6)	3.1 (5.6)	6.4 (0.4)	2.9 (0.4)
LS Mean Difference	3.5		3.4	
95% CI	(2.4, 4.6)		(2.4, 4.4)	
P-value [2]	< 0.0001		< 0.0001	
Adjusted P-value [3]	0.0114		< 0.0001	

[1] MMRM with treatment, visit, visit by treatment interaction, age group, baseline binocular DCNVA severity, iris color, emmetrope/non-emmetrope, baseline and baseline by visit interaction as fixed effects.
[2] P-values were un-adjusted p-values.
[3] Adjusted p-values were calculated using the algorithm provided in Bretz et al. (2011).
Source: Table 14.2-2.6 of CSRs for Study 301 and Study 302. This table was produced by the reviewer.

Change from baseline in mesopic NVPTQ performance and satisfaction scores

Table 14 presents the analysis results for the change from baseline in mesopic NVPTQ performance and satisfaction scores at Day 30, Hour 3. For NVPTQ performance score, the differences (Pilo HCl 1.25% - Vehicle) were 0.8 [95% CI: (0.6, 1.1)] and 0.8 [95% CI: (0.5, 1.0)] in Study 301 and Study 302, respectively, indicating greater improvement in NVPTQ performance score in the Pilo HCl 1.25% group compared to the vehicle group. For NVPTQ satisfaction score, the differences (Pilo HCl 1.25% - Vehicle) were 0.8 [95% CI: (0.5, 1.1)] and 0.7 [95% CI: (0.5, 1.0)] in Study 301 and Study 302, respectively, indicating greater improvement in NVPTQ satisfaction score in the Pilo HCl 1.25% group compared to the vehicle group.

Table 14: Change from baseline in mesopic NVPTQ performance and satisfaction scores

	Study 301		Study 302	
	Pilo HCl 1.25% N = 163	Vehicle N = 160	Pilo HCl 1.25% N = 212	Vehicle N = 215
NVPTQ Performance Score (S5)				
Baseline				
N	156	154	195	203
Mean (SD)	0.9 (1.0)	0.8 (0.9)	0.7 (0.9)	0.7 (0.9)
Day 30, Hour 3				
N	161	153	193	197
Mean (SD)	2.2 (1.52)	1.3 (1.34)	2.0 (1.5)	1.2 (1.3)
Change from baseline				
LS Mean (SE)[1]	1.4 (0.1)	0.6 (0.1)	1.3 (0.1)	0.5 (0.1)
LS Mean Difference	0.8		0.8	
95% CI	(0.6, 1.1)		(0.5, 1.0)	
P-value [2]	< 0.0001		< 0.0001	
Adjusted P-value [3]	0.0114		< 0.0001	
NVPTQ Satisfaction Score (S9)				
Baseline				
N	156	154	195	203
Mean (SD)	0.6 (0.9)	0.5 (0.8)	0.5 (0.8)	0.5 (0.8)
Day 30, Hour 3				
N	161	153	193	197
Mean (SD)	1.9 (1.4)	1.1 (1.2)	1.8 (1.3)	1.0 (1.1)
Change from baseline				
LS Mean (SE) [1]	1.4 (0.1)	0.6 (0.1)	1.2 (0.1)	0.5 (0.1)
LS Mean Difference	0.8		0.7	
95% CI	(0.5, 1.1)		(0.5, 1.0)	
P-value [2]	< 0.0001		< 0.0001	
Adjusted P-value [3]	0.0114		< 0.0001	

[1] ANCOVA with treatment, age group, baseline binocular DCNVA severity, iris color, emmetrope/non-emmetrope, baseline domain score (covariate) as fixed effects.
[2] P-values were un-adjusted p-values.
[3] Adjusted p-values were calculated using the algorithm provided in Bretz et al. (2011).
Source: Table 14.2-2.8 and Table 14.2-2.9 of CSRs for Study 301 and Study 302. This table was produced by the reviewer.

Change from baseline in mesopic PICQ coping and impact scores

Table 15 presents the analysis results for the change from baseline in PICQ coping and impact scores at Day 30, Hour 3. For PICQ coping score, the differences (Pilo HCl 1.25% - Vehicle) were -0.5 [95% CI: (-0.6, -0.3)] and -0.4 [95% CI: (-0.5, -0.2)] in Study 301 and Study 302, respectively, indicating greater reduction in PICQ coping score in the Pilo HCl 1.25% group compared to the vehicle group. For PICQ impact score, the differences (Pilo HCl 1.25% - Vehicle) were -0.3 [95% CI: (-0.4, -0.1)] and -0.3 [95% CI: (-0.4, -0.2)] in Study 301 and Study

302, respectively, indicating greater reduction in PICQ impact score in the Pilo HCl 1.25% group compared to the vehicle group.

Table 15: Change from baseline in PICQ coping and impact scores

	Study 301		Study 302	
	Pilo HCl 1.25%	**Vehicle**	**Pilo HCl 1.25%**	**Vehicle**
	N = 163	**N = 160**	**N = 212**	**N = 215**
PICQ Coping Score (S10)				
Baseline				
N	161	155	196	203
Mean (SD)	2.6 (0.7)	2.7 (0.7)	2.6 (0.8)	2.6 (0.8)
Day 30, Hour 3				
N	161	152	193	197
Mean (SD)	1.7 (0.9)	2.2 (0.9)	1.7 (0.9)	2.1 (1.0)
Change from baseline				
LS Mean (SE)[1]	-1.0 (0.1)	-0.5 (0.1)	-0.9 (0.1)	-0.5 (0.1)
LS Mean Difference	-0.5		-0.4	
95% CI	(-0.6, -0.3)		(-0.5, -0.2)	
P-value [2]	< 0.0001		< 0.0001	
Adjusted P-value [3]	0.0114		0.0001	
PICQ Impact Score (S11)				
Baseline				
N	161	155	196	203
Mean (SD)	1.6 (0.8)	1.8 (0.8)	1.7 (0.8)	1.7 (0.9)
Day 30, Hour 3				
N	161	152	193	197
Mean (SD)	1.0 (0.8)	1.4 (0.9)	1.0 (0.8)	1.3 (0.9)
Change from baseline				
LS Mean (SE) [1]	-0.7 (0.1)	-0.4 (0.1)	-0.7 (0.1)	-0.4 (0.1)
LS Mean Difference	-0.3		-0.3	
95% CI	(-0.4, -0.1)		(-0.4, -0.2)	
P-value [2]	0.0010		< 0.0001	
Adjusted P-value [3]	0.0114		0.0001	

[1] ANCOVA with treatment, age group, baseline binocular DCNVA severity, iris color, emmetrope/non-emmetrope, baseline domain score (covariate) as fixed effects.
[2] P-values were un-adjusted p-values.
[3] Adjusted p-values were calculated using the algorithm provided in Bretz et al. (2011).
Source: Table 14.2-2.10 and Table 14.2-2.11 of CSRs for Study 301 and Study 302. This table was produced by the reviewer.

3.2.4.4 Efficacy Conclusion

Based on the collective efficacy evidence in the two pivotal studies, the reviewer concludes that the application demonstrated evidence of efficacy of the Pilo HCl 1.25% for the treatment of presbyopia.

3.3 Evaluation of Safety

In this section, high-level summaries of adverse events are provided; see the FDA medical reviews for a comprehensive safety evaluation.

3.3.1 Summary of Adverse Events

Table 16 presents a high-level summary of adverse events (AEs). For both studies, the proportions of subjects with treatment-emergent AEs (TEAEs) were higher in the Pilo HCl 1.25% group compared with that in the vehicle group: 35.0% vs. 23.3% in Study 301 and 34.4% vs. 23.7% in Study 302. The proportions of subjects with treatment-related TEAEs were more than doubled in the Pilo HCl 1.25% group compared with that in the vehicle group: 26.4% vs. 11.9% in Study 301 and 24.5% vs. 11.6% in Study 302. Most of treatment-related TEAEs were ocular, mild in severity and resolved by study exit. No death was reported in both groups. No serious TEAEs were reported in the Pilo HCl 1.25% group. In Study 302, two subjects in the vehicle group experienced serious TEAEs.

Table 16: Summary of adverse events (AEs)

	Study 301		Study 302	
	Pilo HCl 1.25%	**Vehicle**	**Pilo HCl 1.25%**	**Vehicle**
Safety Population	163	159	212	215
Subjects with TEAE[1]	**57 (35.0%)**	**37 (23.3%)**	**73 (34.4%)**	**51 (23.7%)**
Subjects with ocular	41 (25.2%)	21 (13.2%)	53 (25.0%)	33 (15.3%)
Subjects with non-ocular	27 (16.6%)	18 (11.3%)	34 (16.0%)	24 (11.2%)
Subjects with treatment-related TEAE[2]	**43 (26.4%)**	**19 (11.9%)**	**52 (24.5%)**	**25 (11.6%)**
Subjects with ocular	34 (20.9%)	13 (8.2%)	42 (19.8%)	20 (9.3%)
Subjects with non-ocular	14 (8.6%)	6 (3.8%)	19 (9.0%)	5 (2.3%)
Subjects withdrawn due to TEAE	2 (1.2%)	1 (0.6%)	4 (1.9%)	3 (1.4%)
Subjects with TESAE[3]	0 (0%)	0 (0%)	0 (0%)	2 (0.9%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)

[1] TEAE: Treatment-emergent AE; Subjects with ≥ 1 ocular TEAEs in the study eye or ≥ 1 non-ocular TEAEs.
[2] Subjects with ≥ 1 ocular treatment-related TEAEs in the study eye or ≥ 1 non-ocular treatment-related TEAEs.
[3] TESAE: Treatment-emergent serious adverse events
Source: Table 12-1 of CSRs for Study 301 and Study 302.

3.3.2 Safety Conclusion

Based on the overall safety evaluation, Pilo HCl 1.25% appeared to be well tolerated; however, deference is made to the FDA medical reviews for a comprehensive safety evaluation and conclusion.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, the primary efficacy endpoint is analyzed across the subgroups defined by the following factors: age group (≤ 50 and > 50 years), baseline binocular DCNVA (20/40 to 20/60 and worse than 20/60), iris color (brown and non-brown) and emmetrope status (emmetropes and non-emmetropes). For each subgroup, a 95% confidence interval for the difference in the responder rates was obtained mentioned in Section 3.2.2.

Table 17 shows the results for the subgroup analyses by age, baseline binocular DCNVA, iris color and emmetrope status. All subgroups consistently show favorable results for the Pilo HCl 1.25% group. The observed differences in responder rates between two groups range from 16.4% to 30.9% in Study 301 and from 7.4% to 21.9% in Study 302 across the subgroups. In both studies, the 95% confidence intervals for the difference overlap indicating that the difference between the two subgroups is not statistically significant.

The reviewer also conducted the subgroup analyses by gender and race. It should be noted that the race categories of 'Black or African American', 'Asian', 'American Indian or Alaska Native', and 'Multiple' were pooled as 'Other' due to small sample sizes. Table 18 shows the results for the subgroup analyses by gender and race, and favorable results for the Pilo HCl 1.25% group compared with the vehicle group. All subgroups consistently show favorable results for the Pilo HCl 1.25% group.

Reviewer's notes:

- *There seems to be an interaction between age group and studies because the differences of the primary efficacy endpoint between age groups by studies show opposite direction (16.4% < 30.9% vs. 21.9% > 7.4%; p-value from a Chi-squared test of independence was less than 0.0001).*
- *Within each study, there is no strong evidence to suggest that the treatment effect varies by age group. However, as showing above, there is a change to an opposite direction in the magnitude of the treatment effects between the two studies, which is highly statistically significant. This indicates the relative performance of the drug varied by study, which could be due to the differences between the two trials.*

Table 17: Subgroup analysis by age, baseline binocular DCNVA, iris color and emmetrope status for the primary efficacy endpoint

	Study 301		Study 302	
	Pilo HCl 1.25%	**Vehicle**	**Pilo HCl 1.25%**	**Vehicle**
Age				
Age ≤ 50				
Responder Rate	27/92 (29.3%)	12/93 (12.9%)	30/106 (28.3%)	7/109 (6.4%)
Difference [95% CI]	**16.4% [4.9%, 28.0%]**		**21.9% [12.1%, 31.6%]**	
Age > 50				
Responder Rate	23/71 (32.4%)	1/67 (1.5%)	21/90 (23.3%)	15/94 (16.0%)
Difference [95% CI]	**30.9% [19.6%, 42.2%]**		**7.4% [-4.1%, 18.8%]**	
Baseline DCNVA				
Baseline DCNVA: 20/40 to 20/60				
Responder Rate	16/66 (24.2%)	4/62 (6.5%)	21/87 (24.1%)	5/93 (5.4%)
Difference [95% CI]	**17.8% [5.8%, 29.8%]**		**18.8% [8.7%, 28.9%]**	
Baseline DCNVA: worse than 20/60				
Responder Rate	34/97 (35.1%)	9/98 (9.2%)	30/109 (27.5%)	17/110 (15.5%)
Difference [95% CI]	**25.9% [14.8%, 37.0%]**		**12.1% [1.3%, 22.8%]**	
Iris Color				
Brown				
Responder Rate	27/78 (34.6%)	8/77 (10.4%)	32/100 (32.0%)	17/98 (17.3%)
Difference [95% CI]	**24.2% [11.7%, 36.8%]**		**14.7% [2.8%, 26.5%]**	
Non-brown				
Responder Rate	28/85 (27.1%)	5/83 (6.0%)	19/96 (19.8%)	5/105 (4.8%)
Difference [95% CI]	**21.0% [15.7%, 38.1%]**		**15.0% [6.1%, 24.0%]**	
Emmetrope Status				
Emmetropes				
Responder Rate	39/125 (31.2%)	11/123 (8.9%)	39/145 (26.9%)	15/149 (10.1%)
Difference [95% CI]	**22.3% [12.7%, 31.8%]**		**16.8% [9.0%, 25.5%]**	
Non-emmetropes				
Responder Rate	11/38 (28.9%)	2/37 (5.4%)	12/51 (23.5%)	7/54 (13.0%)
Difference [95% CI]	**23.5% [7.4%, 39.7%]**		**10.6% [-4.1%, 25.3%]**	

Source: Reviewer's analysis

Table 18: Subgroup analysis by gender and race for the primary efficacy endpoint

	Study 301		Study 302	
	Pilo HCl 1.25%	**Vehicle**	**Pilo HCl 1.25%**	**Vehicle**
Gender				
Female				
Responder Rate	32/113 (28.3%)	8/122 (6.6%)	30/138 (21.7%)	17/162 (10.5%)
Difference [95% CI]	**21.8% [12.4%, 31.2%]**		**11.2% [2.9%, 19.6%]**	
Male				
Responder Rate	18/50 (36.0%)	5/38 (13.2%)	21/74 (28.4%)	5/53 (9.4%)
Difference [95% CI]	**22.8% [5.7%, 40.0%]**		**18.9% [6.0%, 31.9%]**	
Race				
White				
Responder Rate	48/148 (32.4%)	13/144 (9.0%)	39/171 (22.8%)	17/176 (9.7%)
Difference [95% CI]	**23.4% [14.5%, 32.3%]**		**13.1% [5.5%, 20.8%]**	
Other				
Responder Rate	2/15 (13.3%)	0/16 (0.0%)	12/41 (29.3%)	5/49 (10.2%)
Difference [95% CI]	**13.3% [-3.9%, 30.5%]**		**19.1% [2.8%, 35.4%]**	

Source: Reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The reviewer did not identify any major statistical issues that can impact the overall conclusions.

5.2 Collective Evidence

The Applicant seeks approval of the Pilo HCl 1.25% for the treatment of presbyopia in adults. Efficacy and safety were evaluated in the two pivotal studies, Study 301 and Study 302.

The primary efficacy endpoint is the proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA without losing more than 1 line (5 letters) of mesopic, high-contrast, binocular corrected distance visual acuity (CDVA) with the same refraction, at Day 30, Hour 3. In terms of the primary efficacy endpoint, the two pivotal studies demonstrated that the responder rate was significantly higher in the Pilo HCl 1.25% group compared with that in the vehicle group: 30.7% vs. 8.1% in Study 301 and 26.0% vs. 10.8% in Study 302. The treatment difference (Pilo HCl 1.25% - Vehicle) in the responder rates was statistically significant: 22.5% [95% CI: (14.3%, 30.8%)] and 15.2% [95% CI: (7.7%, 22.7%)] in Study 301 and Study 302, respectively. P-value from a Chi-squared test comparing the responder rates in the two groups was less than 0.0001 for both studies.

In terms of the key secondary efficacy endpoint (proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 6), Study 301

demonstrated statistically significantly greater improvement in the Pilo HCl 1.25% group compared with the vehicle group (9.7% difference in responder rates [95% CI: (2.3%, 17.0%) and p-value is 0.0114]), but Study 302 provided no strong evidence supporting greater improvement in the Pilo HCl 1.25% group (6.5% difference in responder rates [95% CI: (-0.1%, 13.1%) and p-value is 0.0548]).

Analyses for the additional secondary endpoints are described as follows:
The proportions of participants achieving 20/40 or better for photopic, high-contrast, binocular DCNVA at Day 30, Hours 1 and 3 demonstrated statistically significantly greater improvement for the Pilo HCl 1.25% group compared with the vehicle group. At Hour 1, the treatment differences were 18.7% [95% CI: (10.6%, 26.7%)] and 9.9% [95% CI: (3.5%, 16.3%)] in Study 301 and Study 302, respectively. At Hour 3, the treatment differences were 12.6% [95% CI: (3.5%, 21.6%)] and 12.4% [95% CI: (5.2%, 19.5%)] in Study 301 and Study 302, respectively.

Change from baseline analyses for mesopic, high-contrast DCNVA letters at Day 30, Hours 0.5 and 0.25 demonstrated statistically significantly greater improvement for the Pilo HCl 1.25% group compared with the vehicle group. At Hour 0.5, the treatment differences were 5.1 [95% CI: (3.7, 6.5)] and 4.1 [95% CI: (2.9, 5.2)] in Study 301 and Study 302, respectively. At Hour 0.25, the treatment differences were 2.6 [95% CI: (1.3, 3.9)] and 2.6 [95% CI: (1.5, 3.7)] in Study 301 and Study 302, respectively.

Change from baseline analyses for photopic, high-contrast DCIVA letters at Day 30, Hour 3 demonstrated statistically significantly greater improvement for the Pilo HCl 1.25% group compared with the vehicle group. The treatment differences (Pilo HCl 1.25% - Vehicle) were 3.5 [95% CI: (2.4, 4.6)] and 3.4 [95% CI: (2.4, 4.4)] in Study 301 and Study 302, respectively.

Change from baseline analyses for mesopic NVPTQ performance and satisfaction scores at Day 30, Hour 3 demonstrated statistically significantly greater improvement in the Pilo HCl 1.25% group compared with the vehicle group. For NVPTQ performance score, the differences (Pilo HCl 1.25% - Vehicle) were 0.8 [95% CI: (0.6, 1.1)] and 0.8 [95% CI: (0.5, 1.0)] in Study 301 and Study 302. For NVPTQ satisfaction score, the differences (Pilo HCl 1.25% - Vehicle) were 0.8 [95% CI: (0.5, 1.1)] and 0.7 [95% CI: (0.5, 1.0)] in Study 301 and Study 302, respectively.

Change from baseline analyses for mesopic PICQ coping and impact scores at Day 30, Hour 3 demonstrated statistically significantly greater improvement in the Pilo HCl 1.25% group compared with the vehicle group. For PICQ coping score, the differences (Pilo HCl 1.25% - Vehicle) were -0.5 [95% CI: (-0.6, -0.3)] and -0.4 [95% CI: (-0.5, -0.2)] in Study 301 and Study 302, respectively. For PICQ impact score, the differences (Pilo HCl 1.25% - Vehicle) were -0.3 [95% CI: (-0.4, -0.1)] and -0.3 [95% CI: (-0.4, -0.2)] in Study 301 and Study 302, respectively.

In terms of safety, the proportions of subjects with treatment-emergent AEs (TEAEs) were higher in the Pilo HCl 1.25% group compared with that in the vehicle group: 35.0% vs. 23.3% in Study 301 and 34.4% vs. 23.7% in Study 302. No death was reported in both groups. No serious TEAEs were reported in the Pilo HCl 1.25% group. In Study 302, two subjects in the vehicle group experienced serious TEAEs.

5.3 Conclusions and Recommendations

Based on the totality of evidence from Study 301 and Study 302, the reviewer concludes that the application provided adequate evidence of efficacy to support an approval of Pilo HCl 1.25% for the proposed indication.

5.4 Labeling Recommendations

Table 1 in Section 14 of the Applicant's proposed labeling presents the efficacy results of the primary efficacy endpoint including corresponding p-values. Instead of or in addition to p-values, we recommend that the treatment difference and the 95% confidence interval for the difference be included. More importantly, from the statistical reviewer's perspective, these p-values do not provide helpful information to healthcare providers and patients for better understanding of the treatment effect of Pilo HCl 1.25%. Next, the Applicant's Figures 1 and 2 included in their proposed labeling presents the proportion of participants with 3-lines or more mesopic DCNVA at Day 30 over time (from Hour 0 to Hour 10). We also recommend that p-values be removed from the Figures 1 and 2.

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