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APPLICATION NUMBER:

214028Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

NDA Number	214028
Link to EDR	EDR Link
Applicant	AbbVie Inc.
Drug, Dosage Form and Strength	Pilocarpine HCl 1.25% ophthalmic solution
Submission Type	Standard; 505(b)(2)
Submission Date	02/22/2021
PUDFA Goal Date	11/05/2021
Proposed Indication	Treatment of presbyopia in adults
Dosing Regimen & Instructions	One drop in each eye once daily
Associated IND	122483
OCP Division	Division of Immune and Inflammation Pharmacology
OND Division	Division of Ophthalmology
OCP Review Team	Qianni Wu, Pharm.D. Clinical Pharmacology Reviewer, DIIP Suneet Shukla, PhD. Clinical Pharmacology Reviewer, DIIP
OCP Final Signatory	Suneet Shukla, PhD.

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Summary and Review

The Applicant, AbbVie Inc., has submitted NDA 214028 for Pilocarpine HCl 1.25% ophthalmic solution administered as topical ophthalmic product to treat presbyopia in adults. The proposed dosing regimen is one drop (pilocarpine HCl 1.25%) in each eye once daily.

Pilocarpine is a muscarinic receptor agonist that mimics the actions of parasympathetic neurotransmitter, acetylcholine, on smooth muscles to stimulate muscarinic receptors to contract the iris sphincter muscle to constrict the pupil to enhance the depth of focus and improve visual acuity. It also contracts the ciliary muscle to facilitate accommodation.

The clinical development program included two Phase 3 studies (Study 1883-301-013/GEMINI 1 and 1883-302-013 / GEMINI 2) in adult patients with presbyopia. In support of the 505(b)(2) application, the Applicant also relied on the FDA's previous findings of systemic safety and clinical pharmacology information for the listed drugs (LDs) - NDA 020237 (Salagen, Concordia Pharmaceuticals Inc.) and NDA 200890 (Isopto Carpine, Alcon Laboratories Inc.), an oral and an ophthalmic drug product of pilocarpine, respectively. The Applicant provided a cross-study comparison of systemic exposure between the proposed drug product and the LDs. The focus of the clinical pharmacology review for this NDA was to assess the systemic PK exposure of the proposed drug product based on the phase 3 study 1883-301-013 (GEMINI 1) and compare with listed products.

Study 1883-301-013 Method and Results:

Study 1883-301-013/GEMINI 1 was a multicenter, double-masked, randomized, parallel-group, vehicle-controlled study in patients with presbyopia. The study participants received either Pilocarpine HCl 1.25% or vehicle placebo one drop in each eye once daily for 30 days. Blood samples for quantification of pilocarpine were collected from 22 subjects who received the investigational drug product. Serial blood samples were collected for PK analysis on Day 1 at pre-dose and on Day 30 or early exit at 0, 0.25, 0.5, 1, 3, 6, 8 and 10 hours post-dose. In this PK substudy, out of 22 subjects, plasma concentration data from 3 subjects was not excluded for descriptive PK statistical analysis. Table 1 summarized the subjects that were excluded from PK parameter and/or descriptive statistics calculations .

Table 1. Subjects That Were Excluded From Applicant's PK Analysis

Subjects	Exclusion	Reason
(b) (6)	Exclude from both PK parameters calculation ($AUC_{0\text{-}t,ss}$, C_{max}, T_{max}, C_{trough}, λ_z and $T_{1/2}$) and descriptive statistical analysis	Only one PK sample collected at pre-dose on Day 1
(b) (6)	Exclude from PK parameters calculation ($AUC_{0\text{-}t,ss}$, λ_z and $T_{1/2}$) and descriptive statistical analysis	Insufficient post-dose samples (only collected at 0, 0.25, 0.5 and 1 hour post-dose on Day 30)

(b) (6)	Exclude from both PK parameters ($AUC_{0-t,ss}$, C_{max}, T_{max}, λ_z and $T_{1/2}$) and descriptive statistical analysis	Insufficient post-dose samples (only collected at 0 and 0.24 hour post-dose on Day 30)
(b) (6)	One sample collected at 1 hour post-dose were excluded from calculating $AUC_{0-t,ss}$. Subject was included in descriptive analysis.	Concentration at 1 hour post-dose was below LLOQ (25 pg/mL)

Source: Reviewer's summary based on CSR-1883-301-013.

It was noted that three subjects (b) (6) had measurable pilocarpine concentrations collected before dosing on day 1. Two of the measurements were 26.2 pg/mL for subject (b) (6) and 73.6 pg/mL for subject (b) (6) which were close to LLOQ of 25 pg/mL. One subject (b) (6) had pre-dose concentration of 2270 pg/mL. The sources of these measurements were not identified. All three subject had plasma concentrations collected at 0 hour on Day 30 were all below LLOQ, which suggested that the pre-dose concentrations on Day 1 had minimal impact on the assessment of steady state PK exposures on Day 30. Thus, it is acceptable for Applicant to include these three subjects in the PK analysis.

The descriptive PK statistics on Day 30 were summarized by the Applicant as shown Table 2. The $AUC_{0-t,ss}$ was measured from time 0 to the last measurable concentrations at steady state (i.e., up to 10 hours post-dose). Pilocarpine HCl 1.25% ophthalmic solution was rapidly absorbed into the system with a median $T_{max,ss}$ of 0.3 hour and a range between 0.2 and 0.5 hour. The arithmetic mean (SD) $C_{max,ss}$ and $AUC_{0-10hr,ss}$ were 2.0 (1.0) ng/mL and 4.1 (2.2) ng*hr/mL, respectively. The mean terminal half-life was 1.7 hours. While most subjects had $C_{trough,ss}$ values below LLOQ (< 25 pg/mL), total 5 subjects had C_{trough} detected at pre-dose on Day 30 and all plasma concentrations were < 88 pg/mL with a mean of 11.2 pg/mL.

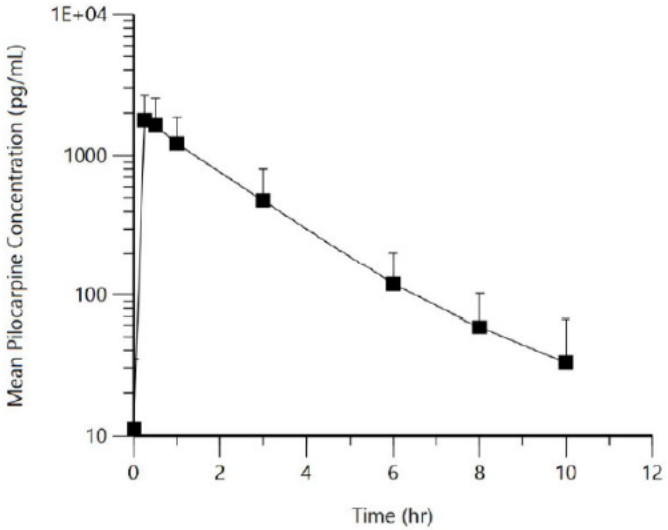
Table 2. Arithmetic Mean (SD) Plasma Pilocarpine Pharmacokinetics Parameters Following Once-daily Topical Ocular Administration of Pilocarpine HCl 1.25 % in Each Eye in Patients with Presbyopia on Day 30

PK Parameter	Mean (SD)	Number of Participants (N)
$AUC_{0-t,ss}$ (pg•hr/mL)	4140 (2160)	19
$C_{max,ss}$ (pg/mL)	1950 (977)	20
$T_{max,ss}$ (hr) median (range)	0.334 (0.200 – 0.533)	20
$C_{trough,ss}$ (pg/mL)	11.2 (23.1)	21
$C_{max,ss}/C_{trough,ss}$	41.1 (26.4)	5
λ_z (hr^{-1})	0.432 (0.113)	19
$T_{1/2}$ (hr)	1.74 (0.576)	19

Source: CSR 1883-301-013, Table 11-4

The mean plasma concentration-time profile for pilocarpine following once daily dosing of the proposed drug product is provided in Figure 1.

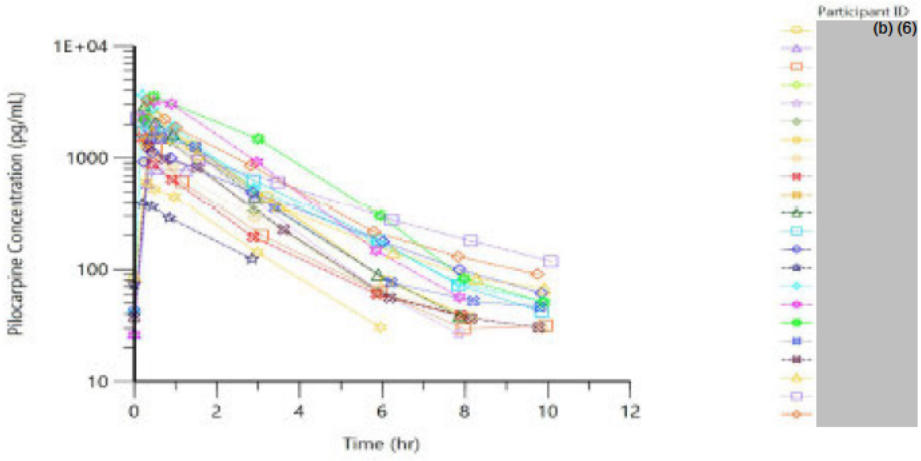
Figure 1. Mean (SD) Plasma Concentration-Time Profile of Pilocarpine Following Once-daily Topical Ocular Administration of Pilocarpine HCl 1.25% For Participants with Presbyopia on Day 30



Source: CSR 1883-301-013, Figure 11-10

In Applicant's analysis of mean concentration-time profile (Figure 1), peak concentrations (C_{max}) were observed immediately after pre-dose concentration, which suggests that the real C_{max} may not have been captured. The reviewer evaluated the individual plasma concentration profile on Day 30 for all subjects who had PK samples collected, as shown in Figure 2.

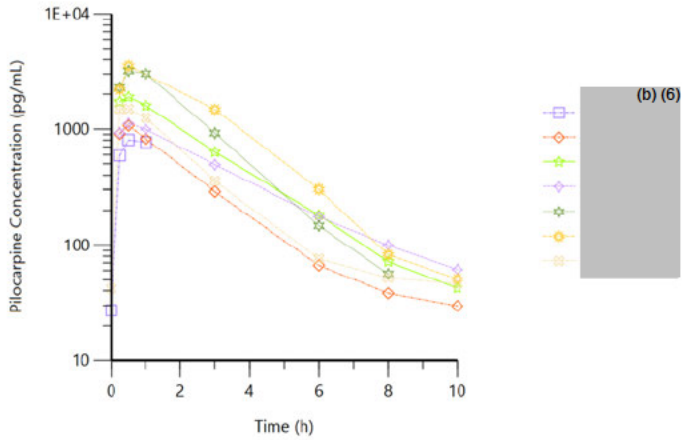
Figure 2. Plasma Concentration-Time Profile of Pilocarpine Following Once Daily Topical Ocular Administration of Pilocarpine HCl 1.25% For Individual Participant on Day 30



Source: Reviewer's analysis using Applicant's dataset ADPC.xpt

Figure 2 revealed a potential issue of not capturing real C_{max} with the PK sampling regimen used in Study 1883-301-013, as the C_{max} for many subjects (13 out of 22) appeared immediately following baseline (pre-dose) concentration. Seven subjects were identified whose concentration-time profile included at least one time point at which lower concentration between the baseline and the peak C_{max} time point were observed. The concentration-time profile of these 7 subjects is shown in Figure 3.

Figure 3. Plasma Concentration-Time Profile of Pilocarpine In Selected 7 Subjects



Source: Reviewer's analysis using Applicant's dataset ADPC.xpt

The reviewer performed a non-compartmental analysis of concentration-time profile data from these 7 subjects and descriptive summary statistics is reported in Table 3.

Table 3. Arithmetic Mean (SD) of Plasma Pilocarpine PK Parameters In the Selected 7 Subjects

PK Parameters	Mean (SD)	Number of Subjects
$C_{max,ss}$ (pg/mL)	1876 (1083)	7
$T_{max,ss}$ (h) median (range)	0.5 (0.25-0.5)	7
$AUC_{0-t,ss}$ (pg*h/mL)	4438 (2537)	7
λ_z (hr^{-1})	0.42 (0.11)	6

Source: Reviewer's analysis using Applicant's dataset ADPC.xpt

Reviewer's comment: The reviewer's summary statistics of C_{max}, T_{max}, and AUC_{0-t} from selected subjects whose plasma concentration time profile included at least one concentration time point before C_{max} was comparable to Applicant's analysis. By comparing reviewer's analysis and

Applicant's results, it is reasonable to believe that T_{max} may be achieved sooner than 0.5 h in some patients, which resulted in a concentration-time profile with a peak immediately after pre-dose concentration. The samples collected at 0.25 h appears adequate to characterize the C_{max} in most patients. Thus, it is acceptable to use the Applicant's C_{max} and AUC_{0-t} for the Label and the cross-study comparison with LDs.

Cross-Study Comparison of System Exposure Between Proposed Product and LDs:

A cross-study comparison between Pilocarpine HCl 1.25% and the two LDs (i.e., Salagen tablet and Isopto Carpine ophthalmic solution) is provided in Table 4. The systemic exposure information for both the LDs were obtained from their approved Package Inserts (PI).

Table 4. Cross-Study Comparison of Pilocarpine Pharmacokinetics Following Ocular administration of Pilocarpine HCl 1.25% (study 1883-301-013) and Isopto Carpine 4% and oral administration of 5 mg or 10 mg Salagen

	Study1883-301-013 Pilocarpine HCl 1.25% x 1 drop OU once daily	**Salagen 5 or 10 mg TID (Day 2) [a]**	**Isopto Carpine 4% x 2 drops OU QID (Day 8) [b]**
	Mean ± SD	Mean	Mean ± SD
C_{max} (ng/mL)	1.95±0.977	5 mg: 15 10 mg: 41	3.7±3.2
AUC (ng*h/mL)	4.14±2.16 [c]	5 mg: 33 [d] 10 mg: 108 [d]	7.7±8.4[e]

Source: adapted from Module 2.7.2 Summary of Clinical Pharmacology Table 3-1

a. Salagen PI 2019, NDA 020237
b. Isopto Carpine PI 2020; NDA 200890
c. $AUC_{0-10hr,ss}$
d. $AUC_{0-6hr,ss}$
e. $AUC_{0-6hr,ss}$ (timepoints were measured up to 6 hours post dose on Day 8)

Reviewer's Comment: The systemic exposure (i.e., AUC and C_{max}) following the proposed dose of pilocarpine HCl 1.25% ophthalmic solution from Study 1883-301-013/GEMINI 1 is lower compared to the LDs (Salagen tablet and Isopto Carpine ophthalmic solution) based on a cross-study comparison. The PK samples were collected at steady-state for Salagen® and Isopto Carpine®, respectively. It was noted that the AUC values reported for Salagen and Isopto Carpine were over 6 hours, which is shorter compared to the PK sampling time in Study 1883-301-013. Despite the shorter sampling duration, the reported AUC values for Salagen® and Isopto Carpine® were greater than the AUC for the proposed drug product. Given that the

systemic exposures measured by C_{max} and AUC for the proposed drug product with a once daily dosing regimen is 8-fold lower compared to the oral product (Salagen®) at 5 mg TID regimen and nearly 2-fold lower than that of Isopto Carpine® ophthalmic solution, the cross-study comparison supports the establishment of a scientific bridge with the two LDs from a clinical pharmacology perspective.

There was no information regarding the use in renal/ hepatic impairment patients or drug-drug interactions in the proposed label. This is in line with the approved Prescribing Information (PI) of Isopto Carpine®.

Bioanalytical Method:

Pilocarpine was quantified in plasma using a validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method. The lower and upper quantification limits for plasma pilocarpine were 25 to 5000 pg/mL, respectively. The validation summary for the bioanalytical method used to measure pilocarpine in human plasma is presented in Table 5.

Table 5. Validation Summary of Bioanalytical Method

Validation Report	**Validation of a HPLC Method Using LC-MS/MS Detection for the Determination of Pilocarpine in Human Plasma (Report 188242)**
Matrix (Anticoagulant)	Human plasma (K_2 EDTA)
Injection volume	10 µL
Analytical Method/detection	LC-MS/MS
Internal Standard	Pilocarpine-d_3 HCl (Lot: 3161-043A6)
Validated Range	25 pg/mL to 5,000 pg/mL
Calibration model	Linear Regression
Weighting factor	$1/x^2$
Quantification method	Peak area ratio
Sensitivity	25 pg/mL (lower limit of quantification)
Inter-assay accuracy (%RE)	LLOQ QC: -4%; LQC: -2.27%; MQC: -2%; HQC: 0.375%
Inter-assay precision (%CV)	LLOQ QC: 7.58%; LQC: 4.34%; MQC: 4.26%; HQC: 3.14%
Intra-assay accuracy (%RE)	LLOQ QC: -7.20% to -2.00%; LQC: -3.87% to 0.267%; MQC: 4.00% to 0.500%; HQC: -2.05% to 1.75%
Inter-assay precision (%CV)	LLOQ QC: ≤8.69%; LQC: ≤5.35%; MQC: ≤5.56%; HQC: ≤3.67%
Dilution Linearity	40,000 pg/mL QC diluted 10-fold
Selectivity	No significant matrix effect was observed
Effect of hemolyzed and lipemic plasma	No significant interference from hemolyzed or lipemic plasma
Extraction efficacy	69.3%-70.7%

Freeze-thaw matrix stability	5-cycles at -20°C/ room temperature
Frozen matrix stability	285 days at -20°C 285 days at -70°C
Ambient matrix stability	7 hours at room temperature
Studies	Study 1883-301-013

Source: Module 5.3.1.4 Validation Report 188242.
Abbreviation: CV=coefficient of variation; LC=liquid chromatography; MS/MS= tandem mass spectrometry; RE=relative error; QC= quality control.

Reviewer's comment: Method validation (validation report number: 188242) and sample analysis supporting the relative BA clinical study (analytical report number: 188244) were in-line with the Agency's recommendations outlined in the guidance for industry Bioanalytical Method Validation (May 2018), and all acceptance criteria as specified in the guidance were met.

1.1 Recommendations

The Clinical Pharmacology review team deems that the systemic PK exposure of Pilocarpine HCl 1.25% ophthalmic solution has been well characterized in this NDA. The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 214028 and finds the application acceptable.

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/

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