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APPLICATION NUMBER:

217836Orig1s000

CLINICAL PHARMACOLOGY
REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	217836
Link to EDR	Link
Submission Date	12/22/2022
Submission Type	Standard; 505(b)(1)
Brand Name	Qlosi
Generic Name	Pilocarpine HCl
Dosage Form and Strength	Pilocarpine HCl 0.4% ophthalmic solution
Route of Administration	Ocular drop
Proposed Indication	Treatment of presbyopia in adults
Dosing Regimen & Instruction	Instill one drop of Qlosi in each eye. This can be repeated a second time after 2-3 h for an effect up to 8 h. Qlosi can be administered on a daily basis, or as needed, up to twice each day.
Applicant	Orasis Pharmaceuticals, Ltd.
OCP Division	Division of Immune and Inflammation Pharmacology (DIIP)
OND Division	Division of Ophthalmology (DO)
OCP Review Team	Sneha Dhapare, PhD. Clinical Pharmacology Reviewer, DIIP Ping Ji, PhD. Clinical Pharmacology Team Lead, DIIP

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1. EXECUTIVE SUMMARY

The Applicant (Orasis) submitted 505(b)(1) new drug application (NDA) 217836 for CSF-1, pilocarpine hydrochloride 0.4%, Ophthalmic Solution for the treatment of presbyopia. Proposed dosing is 1 drop in each eye, which can be repeated 2 to 3 h after the first dose, for an effect up to 8 h. CSF-1 can be administered once a day or as needed, up to twice a day.

The clinical program of CSF-1 includes the following studies: 1) One Phase 1 clinical pharmacology study in healthy volunteers by Orasis (Study 21-100-0004), 2) Phase 2b study (Study 18-150-0006), 3) two Phase 3 studies (Study 20-150-0002 and Study 20-150-0002) and 4) ongoing safety study (Study 21-150-0005). In addition to these data generated by Orasis, the application also references data from Salagen[®] NDA 20237 (pilocarpine HCl oral tablets 5 mg and 7.5 mg), to support its application for CSF-1, relying on nonclinical, clinical pharmacokinetic (Studies 647.83.P90-05 and 647.83.P89-04) studies and long-term clinical safety data supporting the NDA.

The focus of the clinical pharmacology review for this NDA was to assess the systemic PK exposure of CSF-1.

1.1 Recommendations

The Clinical Pharmacology review team has reviewed NDA 217836 and finds the application acceptable from the clinical pharmacology perspective.

Table 1. Summary of Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness comes from two Phase 3 studies (Study 21-150-0002 (NEAR-1) and Study 21-150-0003 (NEAR-2)) of 15 days duration that assessed as the percentage of responders, i.e., subjects with a ≥ 3 -line (15-letter) improvement from baseline in BDCVA at 40 cm and no loss ≥ 5 letters in BDCVA at 4 m (ETDRS chart) in the study eye. Efficacy data from the Phase 2b study, Study 18-150-0006, provides supportive evidence.
General dosing instructions	Proposed dosing is 1 drop in each eye, which can be repeated 2 to 3 h after the first dose, for an effect up to 8 h.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment in any patient subgroups is necessary as it is a local acting drug with limited systemic absorption.
Labeling	Refer to Section 2.4
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal clinical studies as well as the PK study.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

PK of pilocarpine hydrochloride ophthalmic solution 0.4% was evaluated in healthy subjects (Study 21-100-0004). This study was open-label, 8-day multiple dose study in 15 healthy volunteers (HVs). Subjects were given CSF-1 ophthalmic solution in each eye twice a day (2 h apart) for 8 days.

Absorption

Following administration of two drops of CSF-1 ophthalmic solution in each eye daily (separated by 2 h) in healthy subjects for 8 days, plasma pilocarpine maximal concentration of 766 (353.97) pg/mL was achieved at 2.25 h on Day 1, and 897 (287.24) pg/mL at 2.20 h on Day 8. The area under the concentration curve at time curve (AUC) were 2407 (1014.93) and 2991 (888.62) hr•pg/mL on Day 1 and Day 8, respectively. The accumulation ratio was 1.35 and 1.24 for C_{max} and AUC, respectively.

Distribution

Pilocarpine does not bind to human or rat plasma proteins over a concentration range of 5 to 25,000 ng/mL.

Elimination

The estimated t_{1/2} of pilocarpine for Days 1 and 8 were 3.18 (0.90) and 3.96 (1.22) h, respectively.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The proposed dosing regimen is one drop of Pilocarpine HCl 0.4% ophthalmic solution in each eye. This can be repeated a second time after 2-3 h for an effect up to 8 h. Pilocarpine HCl 0.4% ophthalmic solution can be administered daily, or as needed, up to twice each day.

2.2.2 Therapeutic Individualization

Therapeutic individualization is not applicable for Pilocarpine HCl 0.4% ophthalmic solution because it is administered locally as topical eye drop with low systemic exposure.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The proposed labeling is overall reasonable. We have the following recommendations:

- (1) Add standard deviations (SD) for all reported C_{max} and AUC values.
- (2) Specify number of days of dosing for C_{max} and AUC

The recommended changes for the proposed labeling are in red:

12.3 Pharmacokinetics

Systemic absorption of pilocarpine was evaluated in 12 healthy subjects following Qlosi administration (2 doses daily **in each eye**, 2 hours apart, for 8 days). The overall median T_{max} in plasma after Day 8 dosing was 2.20 hr (b) (4) and the mean (SD) overall plasma (b) (4) C_{max} and AUC 0-t **after Day 8 dosing** were 897.2 (287.2) pg/mL and 2699 (741.4) hr*pg/mL, respectively. The mean T_{1/2} after Day 8 dosing was 3.96 hr.

3. Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

In IND 131464, the sponsor submitted a pre-IND meeting request on to gain feedback on their proposed development plan for pilocarpine (0.2%) (b) (4) ophthalmic solution (b) (4) for the treatment of presbyopia by 505b2 pathway. (b) (4)

Table 2 provides a summary of key clinical pharmacology-related communication with the applicant.

Table 2. Summary of key clinical pharmacology-related communication with the Applicant

Submission date	Meeting/Discussion topics	Clinical Pharmacology comments
07/06/2016	(b) (4)	
11/07/2019	The clinical PK study required to characterizing systemic PK of ocular pilocarpine	An estimation of the systemic PK exposure of pilocarpine is needed to establish a scientific bridge to the reference product
05/05/2020	Initial pediatric study plan	Full Waiver
03/18/2021	Pediatric Study Plan - Initial Agreement	
08/25/2021	Proposed plan for 505(b)(1) by obtaining right of reference to SALAGEN	
09/15/2021	PK study protocol (study 21-100-0004)	- Extend PK sampling up to 12 h - Modify the washout period description for the prohibited prescription and non-

		prescription medications to “14 days or 5 half-lives of the drug, whichever is longer”.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Table 3. General Pharmacology and Pharmacokinetics

Characteristics	Drug Information
Pharmacologic Activity	
Established pharmacologic class (EPC)	Cholinergic Muscarinic Receptor Agonist
Mechanism of Action	Pilocarpine muscarinic receptor agonist which constricts the pupil (an action termed miosis). Pupil constriction improves the resolution of the retinal image by preventing diverging light rays hitting the periphery of the cornea and lens, from reaching the retina. Miosis further increases the optical depth of field of the eye and leads to better visual acuity of near objects.
General Information	
Bioanalysis	A validated LC-MS/MS analytical method for the determination of pilocarpine in human plasma (See Appendix 4.5)
Bridge Between to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal clinical studies (NEAR 1 and NEAR 2) as well as dedicated PK study 21-100-0004.
QT prolongation	Cardiovascular function was assessed in an in vitro human ether-a-go-go (hERG) assay. Pilocarpine HCl at 30 µM did not have an impact on hERG cells. This concentration is well above the plasma concentrations detected in the clinical PK study. Thus, the risk of QT prolongation with ocular administration of CSF-1 appears low.
Absorption	
SALAGEN (USPI)	“In a multiple-dose pharmacokinetic study in male volunteers following 2 days of 5 or 10 mg of oral pilocarpine hydrochloride tablets given at 8 a.m., noontime, and 6 p.m., T _{max} values were 1.25 h and 0.85 h. C _{max} values were 15 ng/mL and 41 ng/mL. The AUC trapezoidal values were 33 ng·h/mL and 108 ng·h/mL, respectively, for the 5 and 10 mg doses following the last 6-hour dose.”
QLOSI	Following 8-day administration of two drops of QLOSI ophthalmic solution, 2 h apart, daily in each eye, the median T _{max} at Day 8 was 2.2 h with a range from 0.25 to 2.50 h. The mean (SD) C _{max} and AUC _{0-t} on Day 8 were 897 (287.2) pg/mL and 2699 (741.4) pg·hr/mL, respectively.
Distribution	

SALAGEN (USPI)	“Pilocarpine does not bind to human or rat plasma proteins over a concentration range of 5 to 25,000 ng/mL”
QLOSI	Not studied
Elimination	
SALAGEN (USPI)	“Metabolism/Excretion: Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma. Pilocarpine and its minimally active or inactive degradation products, including pilocarpic acid, are excreted in the urine. The mean elimination half-life was 0.76 h for the 5 mg dose and 1.35 h for the 10 mg dose.”
QLOSI	The elimination half-life (t1/2) of pilocarpine HCl was approximately 3 to 4 h.
Intrinsic Factors and Specific Populations	
SALAGEN (USPI)	“Pharmacokinetics in elderly male volunteers (n = 11) were comparable to those in younger men. In five healthy elderly female volunteers, the mean C_{max} and AUC were approximately twice that of elderly males and young normal male volunteers. In patients with mild to moderate hepatic impairment (n=12), administration of a single 5 mg dose resulted in a 30% decrease in total plasma clearance and a doubling of exposure (as measured by AUC). Peak plasma levels were also increased by about 30% and half-life was increased to 2.1 hrs. There were no significant differences in the pharmacokinetics of oral pilocarpine in volunteer subjects (n=8) with renal insufficiency (mean creatinine clearances 25.4 mL/min; range 9.8 – 40.8 mL/min) compared to the pharmacokinetics previously observed in normal volunteers.”
QLOSI	N/A

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Pilocarpine HCl 0.4% ophthalmic solution is a topical eye drop for the treatment of presbyopia. The site of action is the eye. Therefore, the systemic exposure is not expected to influence treatment effect and thus does not provide pivotal or supportive evidence for the effectiveness of pilocarpine HCl 0.4% ophthalmic solution.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of one drop of pilocarpine HCl 0.4% ophthalmic solution in each eye that can be repeated a second time after 2-3 h for an effect up to 8 h is appropriate. This proposed dosing regimen was assessed in the two pivotal clinical studies, NEAR-1 and NEAR-2 for efficacy and safety of pilocarpine HCl 0.4% ophthalmic solution. Refer to the clinical/statistical review for detailed efficacy and safety information of pilocarpine HCl 0.4% ophthalmic solution.

Following 2 drops 2 hours apart of pilocarpine HCl 0.4% ophthalmic solution in healthy subjects, C_{max} was 0.766 ng/ml and AUC_{0-t} was 2.380 hr*ng/mL, which was much lower than that after approved dose of the listed drug, SALAGEN (5 mg oral tablet; C_{max}= 14.61 ng/mL; AUC=33.04 hr*ng/mL), supporting systemic safety of pilocarpine HCl 0.4% ophthalmic solution.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Not applicable. Pilocarpine HCl 0.4% ophthalmic solution is locally administered as topical eye drop with low systemic exposure.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No applicable. The proposed product is locally administered as topical eye drop with low systemic exposure.

*3.3.5 Was there PK bridging between **to-be-marketed** product and clinical trial product?*

The final-to-be-marketed formulation was used in the PK study 21-100-0004 and the Phase 3 studies (NEAR-1 and NEAR-2).

4. Appendices

4.1 Study 21-100-0004

Pharmacokinetics of CSF-1

PK of CSF-1 was assessed in an open-label, 8-day multiple dose study in 15 healthy volunteers (HVs). Subjects were assigned to CSF-1 ophthalmic solution for twice a day (2 hours apart) for 8 days. All subjects with adequate PK data, such that PK parameters could be derived, were evaluated. Of the 15 subjects enrolled in this trial, 15 subjects (100%) were included in the PK population. No subjects discontinued, and all 15 subjects completed the study.

Study Schema:



All PK analyses were based on the PK population. The mean (standard deviation [SD]) plasma pilocarpine concentrations over time following CSF-1 dosing on Days 1 and 8 are shown Figure 1.

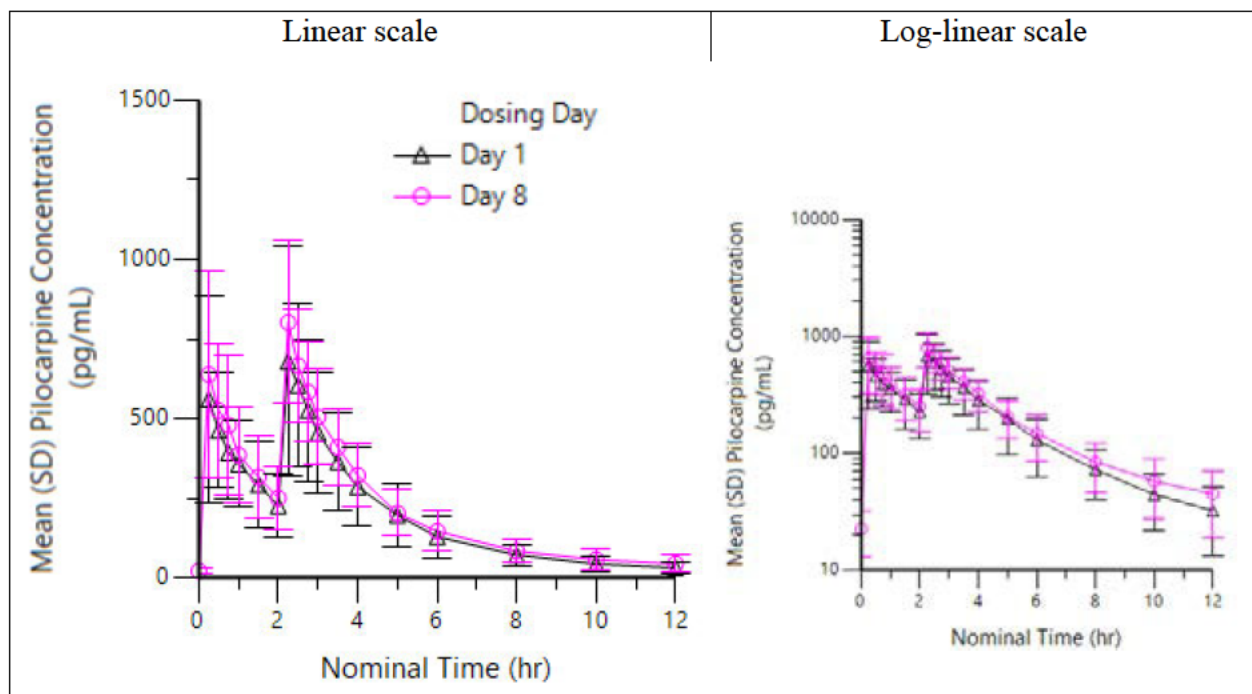


Figure 1. Mean (SD) Plasma Pilocarpine Concentration-Time Profiles for CSF-1 on Day 1 and Day 8

Source: Clinical Study Report: 21-100-0004; Figure 1

Plasma pilocarpine PK parameters for CSF-1 on Days 1 and 8 were calculated by the applicant as presented in Table 4.

Table 4. Plasma Pilocarpine PK Parameters in Study 21-100-0004

Source: 2.7.2 Summary of Clinical Pharmacology Studies and Clinical Study Report: 21-100-0004

Parameter (Unit) Statistic	CSF-1 (N=15) Visit 2 (Day 1)	CSF-1 (N=15) Visit 3 (Day 8)
C_{max} (pg/mL)		
n	15	15
Mean (SD)	766 (353.97)	897 (287.24)
Median	600	841
Min, Max	365, 1489	451, 1423
Geometric Mean	696	855
CV%	46.2	32.0
T_{max} (hr)		
n	15	15
Median	2.25	2.20
Min, Max	0.25, 2.53	0.25, 2.50
Q ₂₅ , Q ₇₅	2.25, 2.25	0.27, 2.25
AUC_{0-t} (hr*pg/mL)		
n	15	15
Mean (SD)	2380 (951.86)	2699 (741.41)
Median	2380	2735
Min, Max	944, 3937	912, 3930
Geometric Mean	2186	2575
CV%	40.0	27.5
AUC_{0-inf} (hr*pg/mL)		
n	13	12
Mean (SD)	2406 (1014.93)	2990 (888.62)
Median	2402	3135
Min, Max	972, 4119	935, 4050
Geometric Mean	2199	2819
CV%	42.2	29.7
T_{1/2} (hr)		
n	13	12
Mean (±SD)	3.18 (0.90)	3.96 (1.22)
Median	2.77	3.83
Min, Max	2.09, 5.53	2.60, 6.54
Geometric Mean	3.08	3.80
CV%	28.3	30.8

AUC_{0-inf} = area under the concentration versus time curve from 0 hour extrapolated to time infinity;
AUC_{0-t} = area under the concentration-time curve from 0 hour to the time of the last quantifiable concentration;
C_{max} = maximum observed plasma concentration; CSR = clinical study report; CV = coefficient of variance;
T_{1/2} = terminal half-life; T_{lag} = time between dosing and the first measurable concentration; T_{max} = time to reach maximum observed plasma concentration.

Following the first and second doses of CSF-1 administered on Days 1 and 8, mean C_{max}1 and C_{max}2 values were achieved at the first time point taken 0.25 hours after each administration. C_{max}2 was higher than C_{max}1 on Day 1 and Day 8. Mean (SD) AUC_{0-t} values on Day 1 and Day 8 were 2380 (951.9) and 2699 (741.4) hr.pg/mL, respectively. Accumulation ratios based on Day 8 versus Day 1 AUC values were also calculated (RAUC_{0-t} and RAUC_{0-inf} were reported to be 1.24 and 1.26, respectively). Accumulation of pilocarpine after repeated CSF-1 dosing for 8 days, approximately 35% for C_{max} and 25% for AUC. The K_{el} could be determined for 13/15 subjects,

and therefore related parameters derived from the Kel ($t_{1/2}$) were calculated for 13/15 subjects; the values for 2 subjects were set to missing.

Study 21-100-0004 consisted of 11 males and 4 females. A gross comparison of C_{max} and AUC between males and females in this study showed no apparent differences. No dedicated studies have been conducted comparing PK parameters in young versus elderly populations. Most of the patient populations involved in the Phase 3 clinical trials of CSF-1 have consisted of subjects between the ages of 45 and 64, consistent with the population enrolled to Study 21-100-0004 and with the intended target presbyopic population.

Reviewer's comments: *Based on Figure 1, the C_{max1} appeared at the first time point studied, 0.25 hours after first dose administration, and C_{max2} appeared soon after second dose, at 2.25 hours. Since C_{max2} was greater than C_{max1}, overall study C_{max} (0.8972 ng/ml) was therefore observed following the second administration of CSF-1 on Day 8 of the study.*

*AUC_{0-t} and AUC_{0-inf} on study Day 8 (2.699 and 2.990 hr*ng/mL, respectively) were marginally higher than on Day 1 (2.380 and 2.406 ng*hr/mL, respectively). The accumulation of pilocarpine after repeated CSF-1 dosing for 8 days was calculated to be approximately 35% for C_{max} and 25% for AUC. The median T_{max} for pilocarpine was around 2.2 h. Systemic exposure of pilocarpine HCl 0.4% ophthalmic solution in patients with presbyopia has not been evaluated.*

4.2 Study 647.83.P90-05 and 647.83.P89-04

Pharmacokinetics of Salagen®

The applicant provided study reports for two studies conducted for SALAGEN (5 mg oral tablet containing pilocarpine HCl).

Study 647.83.P90-05 was a Phase 1 single-center, open-label, randomized, crossover study in healthy male subjects to compare the PK and safety of pilocarpine HCl following a single dose of a 5 mg oral tablet, or 2 drops of a pilocarpine HCl 8% ophthalmic solution administered orally or topically to the eyes. Twenty-four subjects were randomly assigned to receive a treatment sequence which would include a single dose of each of the following treatments: a) pilocarpine HCl ophthalmic solution (8%) administered ocularly (5 mg total dose); b) 5 mg pilocarpine HCl tablet administered orally; or c) two drops of pilocarpine HCl ophthalmic solution (8%) (5 mg total dose). Pharmacokinetic variables including C_{max}, T_{max}, AUC, absorption half-life, elimination half-life, and lag time were analyzed using a non-linear, one compartment, first-order-input, first-order-output, lag time model.

The applicant has noted that the only FDA approved treatment was 5 mg oral tablet (treatment b). However, the PK parameters obtained via ocular administration are also reported in this review as a reference. Plasma pilocarpine concentration vs time data is plotted in Figure 2. Plasma pilocarpine PK parameters for the oral tablet and ocular drop products are presented in Table 5. Although similar dose was administered via oral and ocular route, the systemic exposure (C_{max} and AUC) via ocular route is noted to be significantly lower for ophthalmic solution than for oral

tablet. Pilocarpine HCl administered via ocular instillation exhibited a very fast systemic availability although it had a significantly lower C_{max} and AUC compared to both oral treatment groups. There was a significantly greater lag time and T_{max} in both oral treatments relative to the ocular instillation treatment group which indicated delayed systemic availability. All three treatment groups exhibited similar elimination half-lives.

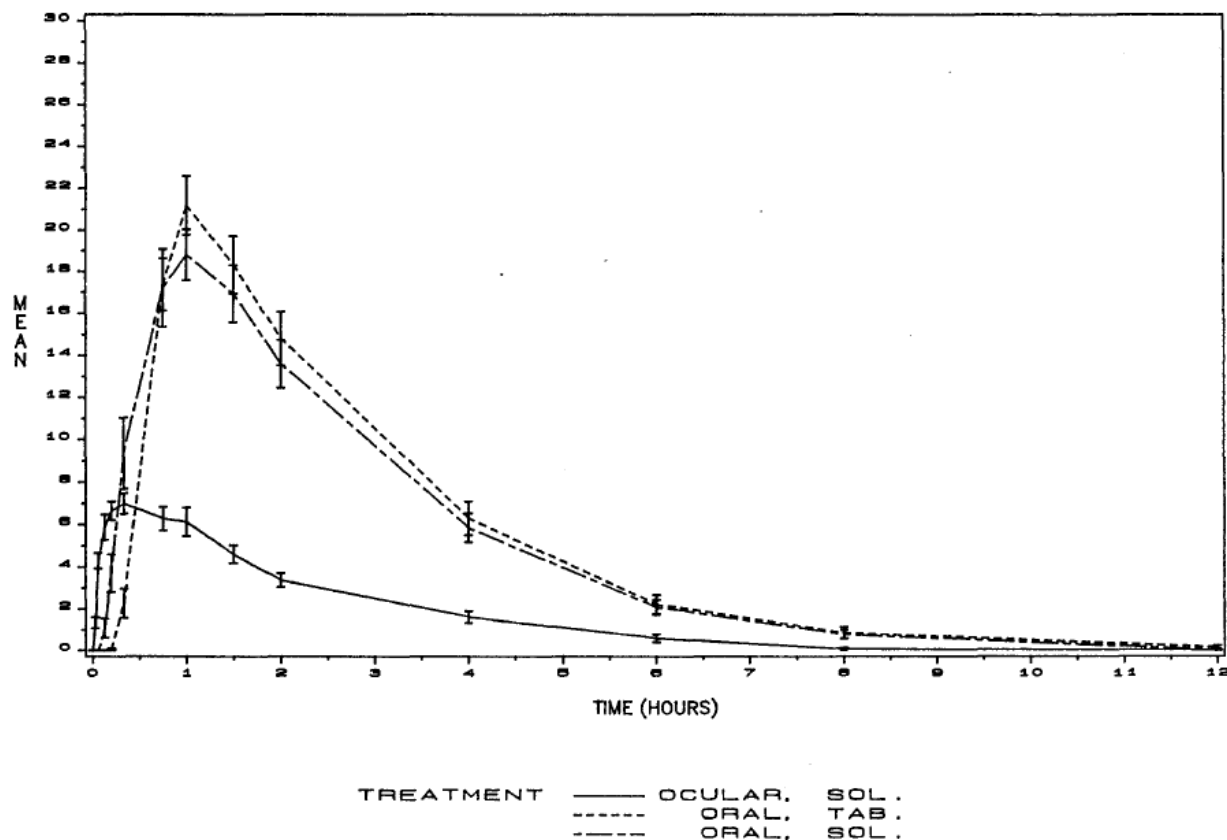


Figure 2. Mean pilocarpine concentrations in Study 647.83.P90-05

Source: Figure 1 in Report MGI 647.83.CR91-06

Table 5. Mean values for PK variable estimates

Source: From Table 4.2 in Report MGI 647.83.CR91-06

PK parameter	Salagen oral tablet 5 mg	Ophthalmic solution 8 %
Dose (mg)	5	5
C _{max} (ng/mL)	22.25 (1.42)	7.57 (0.54)
AUC (hr.ng/mL)	62.18 (5.93)	18.65 (2.04)
T _{max} (h)	1.00 (0.05)	0.37 (0.05)
T _{1/2}	1.33 (0.11)	1.41 (0.11)

Study 647.83.P89-04 was a Phase 1 single-center, randomized, double-blind, placebo controlled, parallel group, multiple-dose safety and PK study in 30 healthy male subjects. Volunteers were randomly assigned to receive 5 mg or 10 mg pilocarpine HCl tablets or placebo (10 subjects/group). Treatments were administered 3 times daily (TID): 4 hours between morning and noon doses, 6 hours between noon and evening doses, for 2 consecutive days. PK variables including C_{max}, T_{max}, AUC, absorption half-life, elimination half-life, and lag time were analyzed using a non-linear, one compartment, first-order-input, first-order-output, lag time model. The PK parameters are shown in Table 6.

Table 6. PK Parameters for SALAGEN Tablets in Study 647.83.P89-04

Source: Table 4 in 2.7.2 Summary of Clinical Pharmacology Studies

PK parameter	Salagen oral tablet	
	5	10
Dose (mg)	5	10
C _{max} (ng/mL)	14.61 (1.63)	41.35 (6.69)
AUC (hr*ng/mL)	33.04 (5.14)	107.96 (19.87)
T _{max} (hr)	1.25 (0.13)	0.85 (0.13)
T _{lag} (hr)	0.48 (0.08)	0.40 (0.04)
t _{1/2} (hr)	0.76 (0.10)	1.35 (0.15)

AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration;

PK = pharmacokinetic(s); t_{1/2} = terminal half-life; T_{lag} = time between dosing and the first measurable concentration; T_{max} = time to reach maximum plasma concentration.

AUC and C_{max} increased by a factor of approximately three when dose was doubled from 5 mg to 10 mg, suggesting that these pharmacokinetic variables increased approximately in proportion to dose. The trough concentrations remained relatively stable for comparable dose times and groups between Day 1 and Day 2. Mean plasma pilocarpine HCl concentrations exhibited similar profiles during both dosing days, returning to levels below detectable limits within 24 hours and showing no tendency to carryover from Day 1 to Day 2.

Comparison of Pilocarpine Exposure

A comparison of doses, systemic exposure from the CSF-1 and SALAGEN PK studies, as well as exposure ratios (SALAGEN data over CSF-1) are presented in Table 7.

Table 7. Comparison of Pilocarpine Exposure and Exposure Ratios

Source: Table 5 in 2.7.2 Summary of Clinical Pharmacology Studies

Parameter	Salagen Oral Tablet (647.83.P90-05)	Salagen Oral Tablet (647.83.P89-04)		CSF-1 Ophthalmic Solution ^a (21-100-0004)
N	24	10	9	15
Dose (mg)	5	5	10	0.672
Regimen	Single dose	Multiple dose (TID, 2 days) ^b		Multiple dose (BID, 8 days)
C _{max} (ng/mL)	22.255 (1.425)	14.61 (1.63)	41.35 (6.69)	0.8972 [0.287]
AUC (hr*ng/mL)	62.185 (5.929)	33.04 (5.14)	107.96 (19.87)	2.991 [0.888]
Ratio_C _{max}	24.8	16.2	46.1	NA
Ratio_AUC	20.8	11.0	36.1	NA

^a Results obtained after BID administration over 8 consecutive days.

^b Doses administered at 8AM, 12PM, 18 PM on Days 1-2.

AUC = area under the concentration vs. time curve; BID = twice daily; C_{max} = maximum observed plasma concentration; NA = not available; PK = pharmacokinetic(s); SD = standard deviation; SE = standard error; TID = 3 times a day.

Sources: Salagen: Initial NDA, Volume 11, Section 6.6.2, Study protocol P89-04, Study report MGI 647.83.CR91-03, Table 4.2 and Volume 16, Section 6.6.5, Study protocol P90-05, Study report MGI 647.83 CR91-06, Table 4.2; CSF-1: Study 21-100-0004, [Table 14.4.2](#)

Reviewer's comments: Systemic exposure to pilocarpine HCl following SALAGEN tablets was significantly higher than with CSF-1. Exposure in terms of C_{max} was around 16-fold higher for 5 mg tablet administered TID and 46-fold higher for 10 mg tablet administered TID as compared to CSF-1 administered as two drops once daily. Similarly, AUC was 11-fold higher for 5 mg tablet administered TID and around 36-fold higher for 10 mg tablet administered TID as compared to CSF-1 administered as two drops once daily. SALAGEN is currently approved in strengths of 5 mg and 7.5 mg per tablet. So, for the purpose of comparison, 5 mg tablet data is relevant. The results indicated that pilocarpine systemic exposure (AUC and C_{max}) after dosing with the proposed intraocular dose was lower than the approved dose of orally administered listed drug, SALAGEN (5 mg oral tablet).

The elimination half-life (t_{1/2}) of pilocarpine HCl was approximately 3 to 4 hours. The 2 administrations of CSF-1 were given 2 h apart in the PK study, and plasma levels after the second administration were higher than those measured after the first. The PK assessment is adequate from a clinical pharmacology perspective. The plasma levels of pilocarpine are not expected to contribute to the clinical effects of CSF-1.

It is also noted that pilocarpine HCl 1.25% ophthalmic solution (Vuity) was approved in 2021 to treat presbyopia in adults (similar indication as the current proposed product with same active ingredient). The approved dosing regimen is one drop in each eye once daily. The steady state C_{max} at day 30 (C_{max,ss}) was around 1.9 ng/mL and AUC_{0-t,ss} was 4.14 ng.hr/mL. The systemic

exposure of the proposed pilocarpine HCl 0.4% ophthalmic solution in the current submission is noted to be less than that of VUITY.¹

4.3 Study 18-150-0006

Pharmacodynamics of CSF-1

The Applicant assessed reduction in pupil diameter (miosis) as a PD marker in the Phase 2b (Study 18-150-0006) and Phase 3 studies (NEAR-1 and NEAR-2). However, it is noted that pupil diameter is not considered an acceptable efficacy endpoint or a PD marker. The applicant's analysis of pupil diameter is discussed below for completeness.

The dose-response effect was tested in Phase 2b study (Study 18-150-0006). This study was conducted to evaluate the effect of each active ingredient of the (b) (4) fixed-dose combination (FDC) formulation of CSF-1 (called CSF-1-FDC, containing pilocarpine HCl and diclofenac sodium), and to test the efficacy and safety of increasing pilocarpine HCl concentrations (0.2% to 0.4%). Approximately 150 subjects were randomized to 3 arms (50 subjects per treatment arm):

1. CSF-1 (pilocarpine hydrochloride [0.2%] and diclofenac sodium [0.006%]) / CSF-1 (pilocarpine hydrochloride [0.4%] and diclofenac sodium [0.006%]).
2. Pilocarpine hydrochloride (0.2%) / Pilocarpine hydrochloride (0.4%) alone.
3. Diclofenac sodium (0.006%) alone

All subjects were instructed to dose twice daily (BID) in both eyes with a single drop for approximately 1 week until the afternoon before Visit 3 (Day 8). At Visit 3 (Day 8), subjects initially randomized to the CSF-1 arm now received pilocarpine hydrochloride 0.4%/diclofenac sodium 0.006% (CSF-1 0.4%/0.006%); subjects randomized to the pilocarpine hydrochloride alone arm now received pilocarpine hydrochloride (0.4%) alone; and subjects randomized to diclofenac sodium alone arm continued dosing with diclofenac sodium (0.006%) alone. Subjects were instructed to dose twice daily (BID) in both eyes with a single drop for approximately 1 week until the afternoon before Visit 4 (Day 15). One of the secondary efficacy endpoints was Mean change in pupil diameter under near VA at 40 cm testing conditions at each time point at Visit 3 and Visit 4.

CSF-1-FDC and the pilocarpine-only groups demonstrated statistically significant reduction in pupil diameter at both pilocarpine concentrations compared to the vehicle throughout all timepoints (from 20 minutes to 6 hours post dosing). Additionally, in both CSF-1-FDC and pilocarpine-only groups the 0.4% strength showed a statistically significant greater effect than the 0.2%, as shown in Figure 3.

¹ DARRTS, NDA 214028, REV-CLINPHARM-21 (Primary Review), Original-1 (Type 5- New Formulation or New Manufacturer), dated 10/12/2021

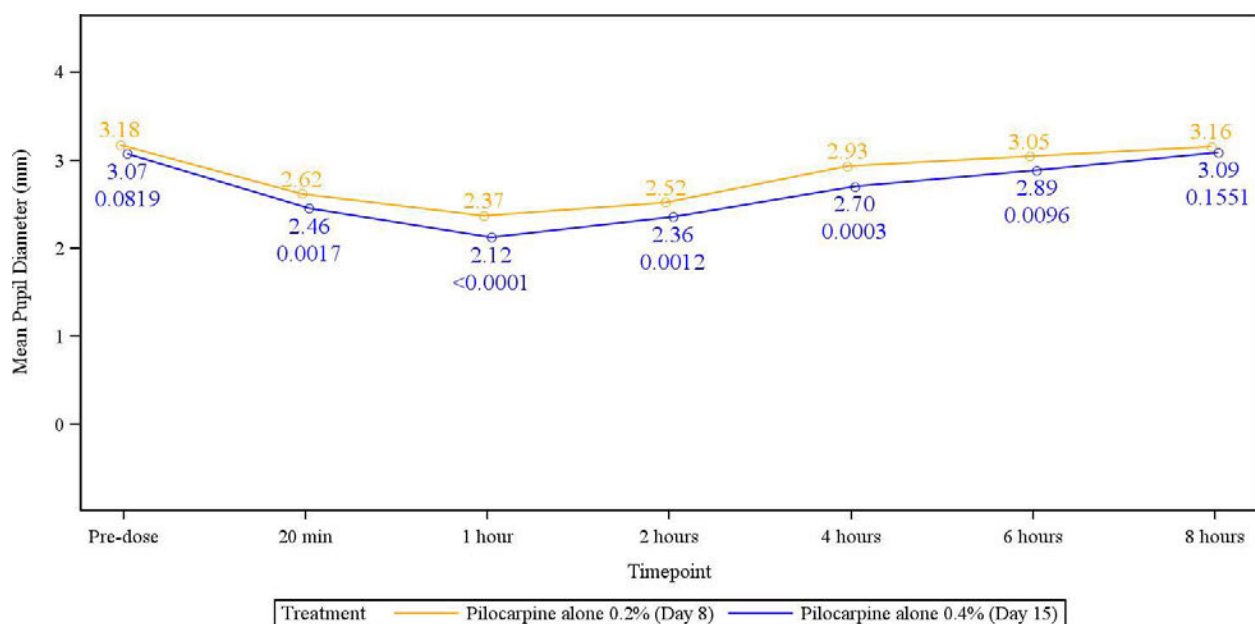


Figure 3. Mean Change in PD Under Near VA at 40 cm Testing Conditions at Each Timepoint (Study 18-150-0006).

Source: Figure 2 in 2.7.2 Summary of Clinical Pharmacology Studies

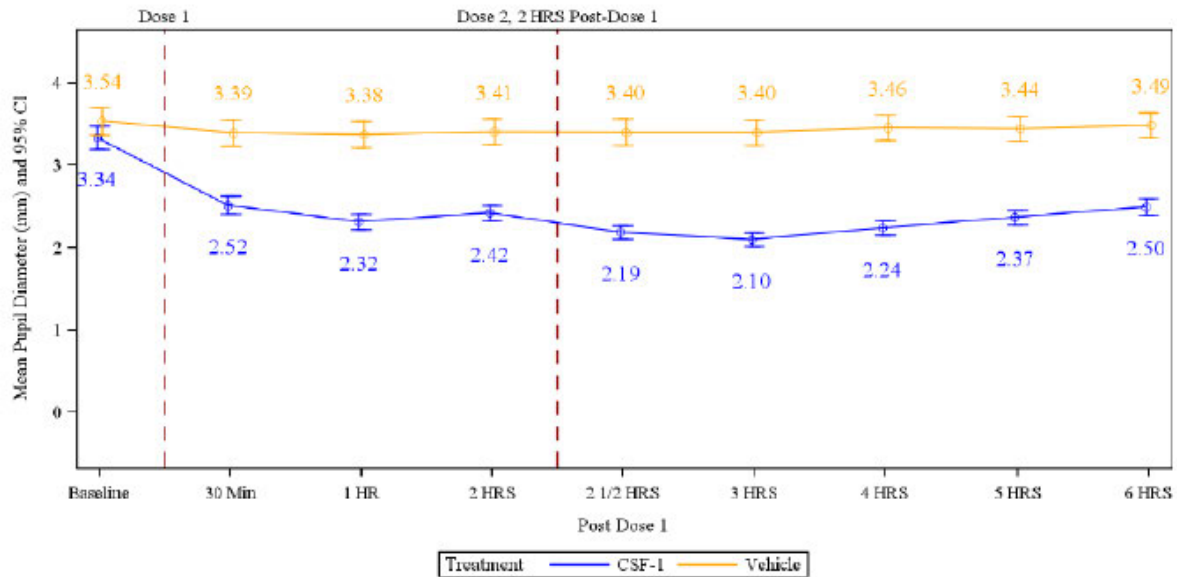
4.4 Study 21-150-0002 (NEAR-1) and Study 21-150-0003 (NEAR-2)

Study 21-150-0002 (NEAR-1) and Study 21-150-0003 (NEAR-2) also demonstrated miotic effect over time. Both studies had identical, multi-center, randomized, double-masked, vehicle-controlled designs to evaluate the efficacy and safety of CSF-1 in the treatment of presbyopia. Pupil diameter reduction was an exploratory endpoint in both studies.

Each study enrolled approximately 300 presbyopic subjects, aged between 45 and 64 years, randomized (1:1) to either CSF-1 or vehicle. Subjects were treated for 2 weeks with either CSF-1 or vehicle BID in the morning, with a 2 h interval between doses during the first treatment week and a 3 h interval during the second treatment week.

In study Near-1 mean change in pupil diameter at 40 cm testing conditions at each time point at Visit 2 (Day 1), Visit 3 (Day 8), and Visit 4 (Day 15) showed statistically significant decrease in mean pupil diameter in the CSF-1 group compared to Vehicle group throughout all time points. The statistically significant decrease in pupil diameter was noted in the CSF-1 arm as early as 30 minutes after the initial treatment on Day 1 and the effect was sustained over 6 h observation period (Figure 4). Day 15 showed that this statistically significant effect started 20 minutes post-Dose 1 and was maintained throughout the day over the 8 h of observation (Figure 5).

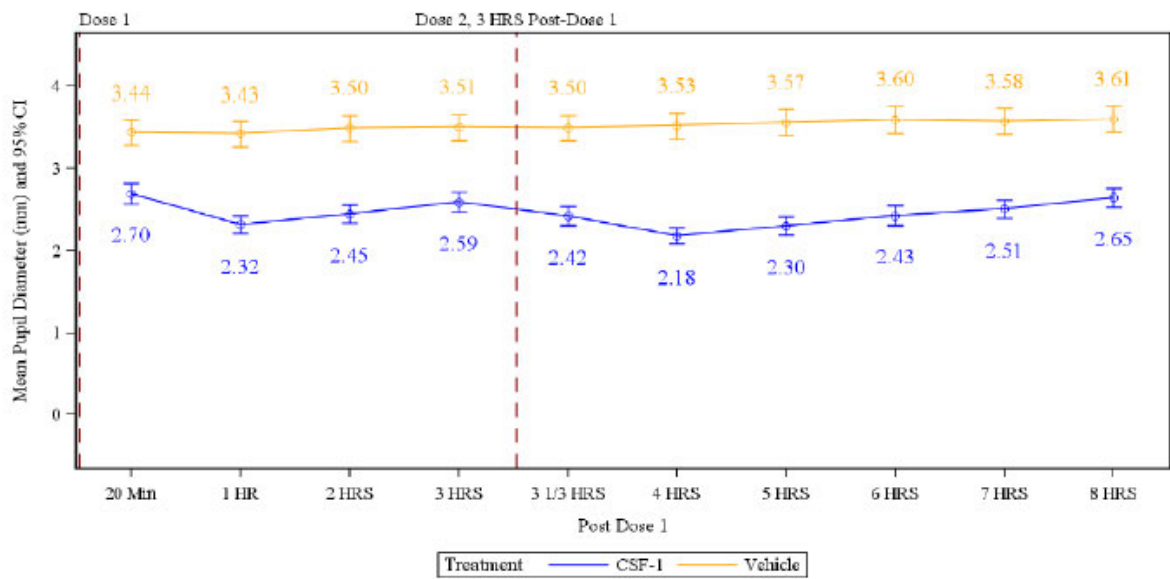
Mean Pupil Diameter (mm) Under Near VA at 40 cm Testing Conditions from Baseline at Each Time Point at Visit 2 (Day 1) - Study Eye
Full Analysis Set (Observed Data Only)



Abbreviations: CI = Confidence Interval; HR = Hour; VA = Visual Acuity.
Note: Observed means and the 95% CIs are shown.
Reference: Table 14.2.3.9.2
Source: SDC-P:\Projects\Orasis\20-150-0002\Statistics\Programs\Primary Programs\TLF\line.sas 20OCT2022 6:37:57

Figure 4. Visit 2 (Day 1): Mean Pupil Diameter in NEAR-1
Source: Figure 7 in Clinical Study Report: 20-150-0002 NEAR-1

Mean Pupil Diameter (mm) Under Near VA at 40 cm Testing Conditions at Each Time Point at Visit 4 (Day 15) - Study Eye
Full Analysis Set (Observed Data Only)



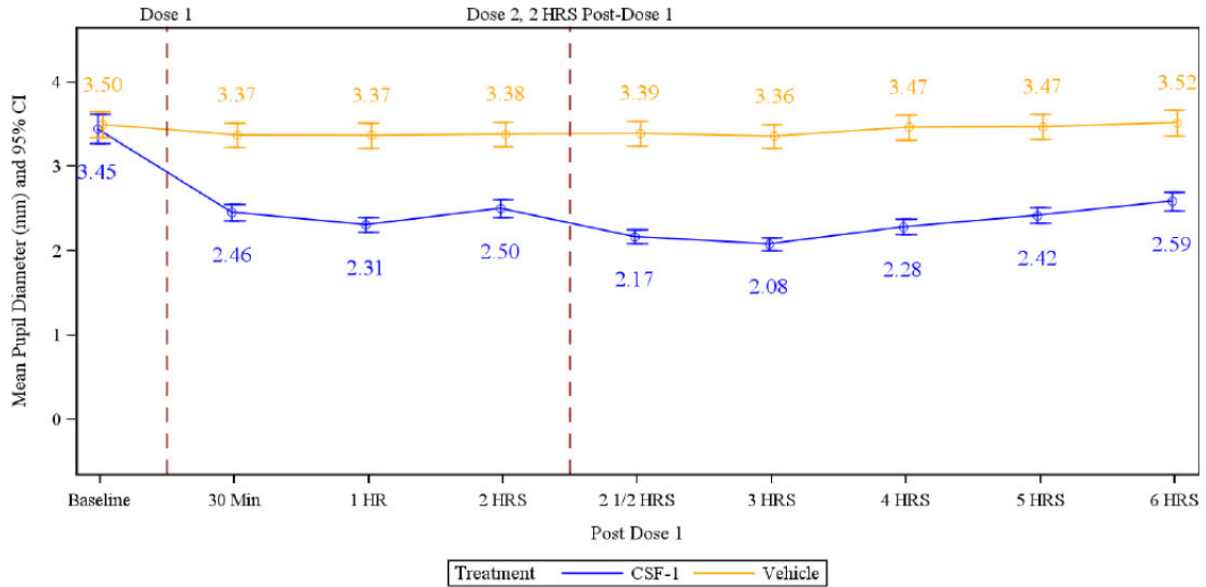
Abbreviations: CI = Confidence Interval; HR = Hour; VA = Visual Acuity.
Note: Observed means and the 95% CIs are shown.
Reference: Table 14.2.3.9.2
Source: SDC-P:\Projects\Orasis\20-150-0002\Statistics\Programs\Primary Programs\TLF\line.sas 20OCT2022 6:38:03

Figure 5. Visit 4 (Day 15): Mean Pupil Diameter in NEAR-1

Source: Figure 9 in Clinical Study Report: 20-150-0002 NEAR-1

Similar results were obtained in NEAR-2 study. Figures 6 and 7 show mean pupil diameter at Day 1 and Day 15 in NEAR-2 study, respectively.

Mean Pupil Diameter (mm) Under Near VA at 40 cm Testing Conditions from Baseline at Each Time Point at Visit 2 (Day 1) - Study Eye Full Analysis Set (Observed Data Only)



Abbreviations: CI = Confidence Interval; HR = Hour; VA = Visual Acuity.
 Note: Observed means and the 95% CIs are shown.
 Reference: Table 14.2.3.9.2
 Source: SDC-P:\Projects\Orasis\20-150-0003\Statistics\Programs\Primary Programs\TLF\line.sas 15AUG2022 14:38:26

Figure 6. Visit 2 (Day 1): Mean Pupil Diameter in NEAR-2

Source: Figure 7 in Clinical Study Report: 20-150-0003 NEAR-2

Mean Pupil Diameter (mm) Under Near VA at 40 cm Testing Conditions at Each Time Point at Visit 4 (Day 15) - Study Eye
Full Analysis Set (Observed Data Only)

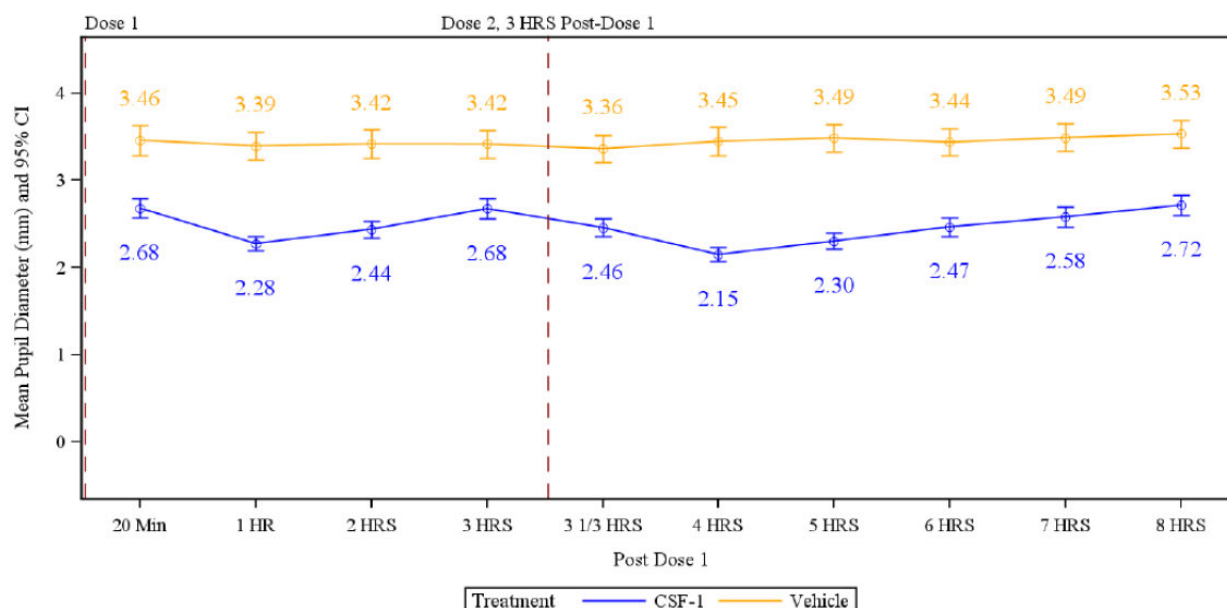


Figure 7. Visit 4 (Day 15): Mean Pupil Diameter in NEAR-2

Source: Figure 7 in Clinical Study Report: 20-150-0003 NEAR-2

In the Phase 2b (Study 18-150-0006) and Phase 3 studies (NEAR-1 and NEAR-2), PD data of CSF-1 demonstrated significant reduction in pupil diameter seen at the first timepoints obtained (20 to 30 minutes post first dose). In the NEAR-1 and NEAR-2 studies, CSF-1 reached its maximal miotic effect approximately 1 h after each daily CSF-1 administrations, and the effect following the second dose was slightly larger than that seen after the first dose. PK and PD data were not collected in the same studies; therefore, the sponsor did not perform any formal PK/PD analysis.

Reviewer's comment: In the Phase 2b study (Study 18-150-0006), a dose-response was noted, where pilocarpine HCl 0.4% alone resulted in statistically greater decreases in mean pupil diameter than pilocarpine HCl 0.2%. The Phase 3 placebo-controlled studies showed early onset of miosis (maximal miotic effect approximately 1 h after each daily CSF-1 administrations), and the effect following the second dose was slightly larger than that seen after the first dose. The miotic effect was sustained over at least 8 h. As noted earlier, pupil diameter is not considered an acceptable efficacy endpoint or a PD marker.

No dedicated studies have been conducted on PD dose range and dose-response with CSF-1. The plasma levels of pilocarpine are not expected to contribute to the clinical effects of CSF-1.

4.5 Bioanalytical Method

The bioanalytical method that was used for determination of pilocarpine in human plasma (K2EDTA) by LC-MS/MS in Study 21-100-0004. The performance and validation parameters of the analytical method are summarized in Table 8.

Table 8. Summary of Bioanalytical Method for Pilocarpine in Plasma

Pilocarpine in plasma			
Bioanalytical method review summary	Method validation was adequate		
Report title	Bioanalytical Validation Report for the Determination of Pilocarpine in Human Plasma (K2EDTA) by LC-MS/MS		
Matrix	K2EDTA Human plasma		
LC-MS/MS Instrumentation	MDS Sciex API 6500 QTRAP Shimadzu LC-30AD Shimadzu SIL-30AC		
Data Collection and Analysis Software	Analyst® version 1.6.3 WATSON LIMS version 7.6.1		
Extraction method	Liquid-liquid Extraction		
Detection method	HPLC-MS/MS		
Sample aliquot volume	75 µL		
Regression model and weighting	Linear 1/x ² weighting		
Calibration Range	5.00 (LLOQ) to 500 (ULOQ) pg/mL		
Calibration standard concentrations	5, 10, 25, 50, 100, 200, 500 pg/mL		
Validation parameters	Method validation summary		Acceptability
	Cumulative accuracy (%RE)	Cumulative precision (%CV)	
Intra-assay validation	-0.6 – 18.8 % (LLOQ)	≤ 9.7 %	Yes
Inter-assay validation	-2.0- 7.3 %	≤ 6.9%	Yes
Dilution factors	1/10, 1/20		Yes
Mean analyte and IS recovery	Pilocarpine (%CV)	72.0 (7.50)	Yes
	Pilocarpine-d3 (%CV)	72.2 (6.61)	Yes
Selectivity			
Matrix to Analyte & IS	- No significant interfering peaks (>20.0% of the average LLOQ response) at the retention time of Pilocarpine 4/6 sources met the criteria (Percent of mean LLOQ 0-209 %; percent of mean IS 0-5.71%), therefore, the assessment was repeated with 10 lots 9/10 sources had an analyte response ≤ 20% of the mean analyte response and 10/10 sources had an IS response ≤ 5% of the mean IS response in the acceptable LLOQ standards		Yes

IS to Analyte	1/1 source had an analyte response $\leq 20\%$ of the mean analyte response in the acceptable LLOQ standard	Yes
Analyte to IS	1/1 source had an IS response $\leq 5\%$ of the mean IS response in the acceptable LLOQ standard.	Yes
Matrix effect	6/6 sources (100%) spiked at the HQC were within $\pm 15\%$ and 4/6 sources (66.7%) spiked at the LLOQ were within $\pm 20\%$. The LLOQ did not meet the criteria, therefore, the assessment was repeated with 10 lots 9/10 sources (90%) spiked at the LLOQ were within $\pm 20\%$ (-9.40% to 64.0% RE and $\leq 13.4\%$ CV)	Yes
Carryover	Carryover response for the matrix blank samples were $\leq 20.0\%$ of the average LLOQ response	Yes
Hemolysis effect	1/1 source (100%) spiked at the LQC was within $\pm 15\%$ and 1/1 source (100%) spiked at the HQC was within $\pm 15\%$	Yes
Lipemic effect	1/1 source (100%) spiked at the LQC was within $\pm 15\%$ and 1/1 source (100%) spiked at the HQC was within $\pm 15\%$	Yes
Stability		
Ambient Temperature Matrix Stability	0.200 mg/mL Pilocarpine in 1:1 Methanol:Water 34 days at 4°C	
Refrigerated Storage Matrix Stability	0.200 mg/mL Pilocarpine in 1:1 Methanol:Water 4 h at room temperature	
Whole blood stability	4 h at ambient temperature (Run 10) 4 h on wet ice	
Freeze-thaw stability	3 freeze/thaw cycles at -20°C	
Long-term storage	46 days at -20°C	
Method performance in Study 21-100-0004		
Assay passing rate	88.2% (sample analysis runs only)	
Cumulative accuracy (%RE)	-1.60% to 1.00%	Yes
Cumulative precision (%CV)	$\leq 6.28\%$	Yes
Method reproducibility	Incurred sample re-analysis was performed on 71 study samples and 95.8% of the samples met the pre-specified criteria	Yes
Study sample analysis / stability		

Length of time samples were stored prior to analysis	105 days since collection	Yes
Maximum freeze / thaw cycles for samples	3 freeze/thaw cycles	Yes

Source: Bioanalytical Validation Report ([\\CDSESUB1\EVSPROD\nda217836\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\192230\192230.pdf](#)); Bioanalytical Sample Analysis Report for Study 21-100-0004 ([\\CDSESUB1\EVSPROD\nda217836\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\21-100-0004\192234.pdf](#)). Abbreviations: CV=coefficient of variation; RE=relative error; IS: Internal standard; LLOQ: Lower Limit of Quantitation; HQC: high Quality Control

Reviewer's comments:

- Plasma concentration of pilocarpine was determined using a validated LC-MS/MS method.
- The % recovery of analyte and the corresponding internal standards (IS) is on the lower end (70-72 %), however was shown to be consistent across QC concentrations (% CV <15 %).
- Precision and accuracy (within-run and between-run) were conducted per Guidance for Industry: Bioanalytical Method Validation (May 2018) and pass the acceptance criteria.
- The assay performance for sample analysis for Study 21-100-0004 were in line with Guidance for Industry: Bioanalytical Method Validation (May 2018).

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/

SNEHA DHAPARE
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