# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214028Orig1s000

# NON-CLINICAL REVIEW(S)

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

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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| Application number: | 214028 |
| Supporting document/s: | SDN001 |
| Applicant's letter date: | 2-22-2021 |
| CDER stamp date: | 2-22-2021 |
| Product: | Vuity® (Pilocarpine hydrochloride ophthalmic solution, 1.25%) |
| Indication: | For the treatment of presbyopia in adults |
| Applicant: | Abbvie Inc (North Chicago, IL) |
| Review Division: | DPT- ORPURM/OSM, supporting the Division of Ophthalmology Products (DO) |
| Reviewer: | Erin Ruhland, PhD |
| Supervisor/Team Leader: | Lori Kotch, PhD, DABT |
| Division Director: | Mukesh Summan, PhD, DABT |
| Project Manager: | Diana Willard |

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# TABLE OF CONTENTS

# 1 Executive Summary

## 1.1 Introduction

The Applicant has filed a 505(b)(2) NDA for Vuity® (pilocarpine hydrochloride ophthalmic solution, 1.25%) for the treatment of presbyopia in adults. All nonclinical elements of the NDA were referenced from NDA 020237 (Salagen), literature references or through the conduct of GLP studies. The NDA is approvable from a Nonclinical Pharmacology/Toxicology perspective.

## 1.2 Brief Discussion of Nonclinical Findings

- For nonclinical systemic safety, pharmacology and drug metabolism, the Applicant references NDA 020237 (Salagen). The Applicant also references Isopto carpine (NDA 200890). No nonclinical information was derived from NDA 200890.

- Salagen labeling has not undergone PLLR conversion, however most information required by guidance for the PLLR formatted label for this application are present in the Salagen labeling.

- The Applicant provided all nonclinical ocular toxicity studies.

- The ocular toxicity studies performed by the Applicant used a combination (fixed or unfixed) of pilocarpine and oxymetazoline. (b) (4) .

- No adverse toxicity was associated with the combination of pilocarpine/oxymetazoline and oxymetazoline did not appear to influence the absorption or ocular distribution of pilocarpine when administered in combination. Formulations used in the nonclinical studies were identical or very similar to the to-be-marketed formulation in excipient content. Therefore, these studies should be adequate to assess risk of pilocarpine as monotherapy in the to-be-marketed formulation.

## 1.3 Recommendations

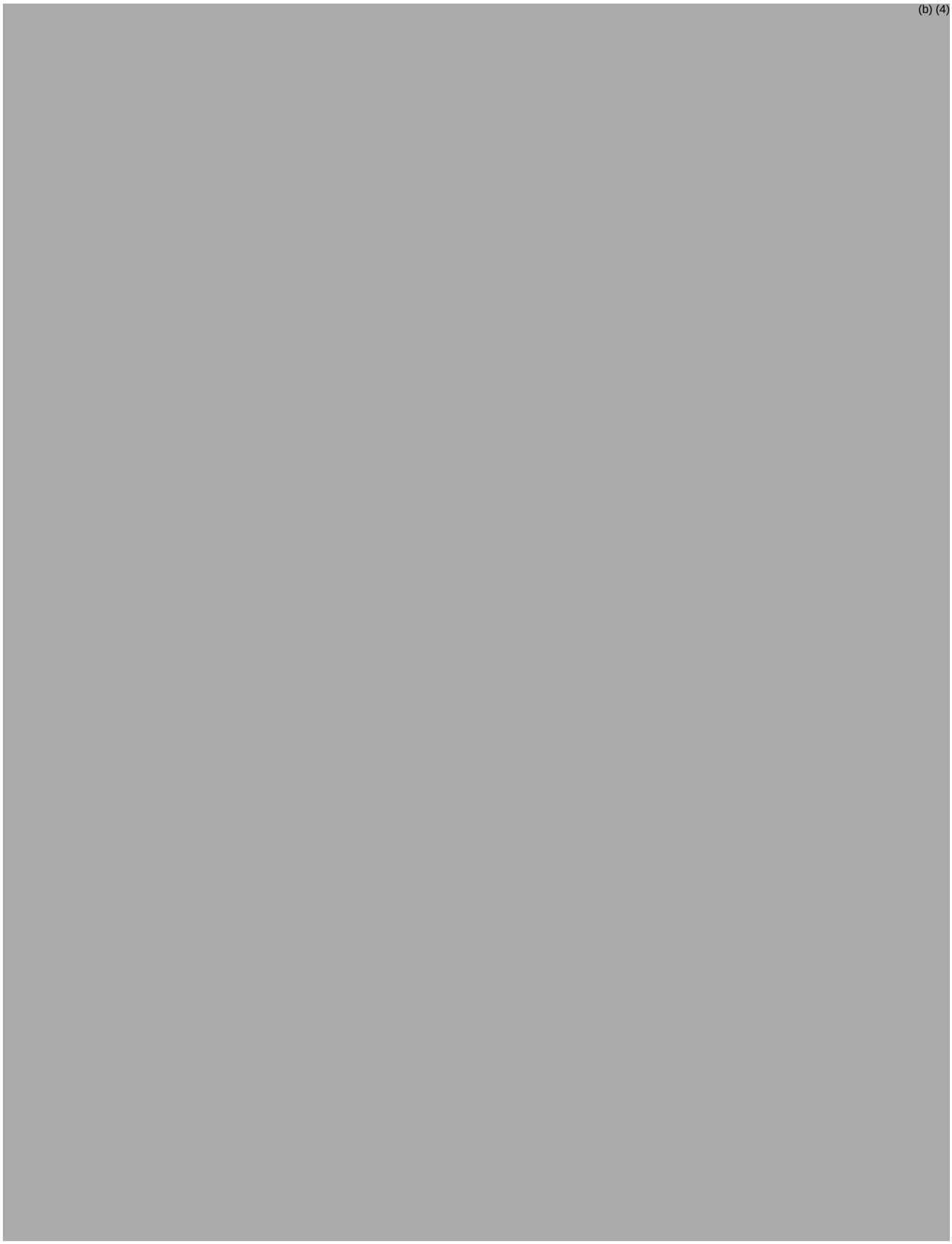
- **1.3.1 Approvability**

  - **NDA 214028 is approvable at the proposed dose indicated from the nonclinical pharmacology/toxicology discipline standpoint.**

- **1.3.3 Labeling**

### 1.3.3.1 Applicant's Proposed Labeling (Nonclinical sections only)

(b) (4)





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

(b) (4)

### 1.3.3.3 FDA's Proposed PLLR Labeling for PRODUCT® (nonclinical sections only)



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

# 2 Drug Information

## 2.1 Drug

CAS Registry Number: 54-71-7

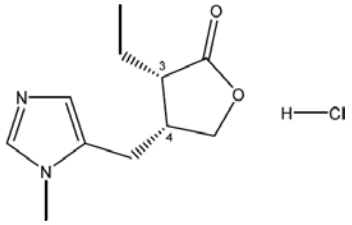
Generic Name: Pilocarpine hydrochloride

Code Name: AGN-190584

Chemical Name: 3-Ethyldihydro-4-[(1-methyl-1H-imidazol-5-yl)-methyl]-2(3*H*)-furanone hydrochloride *or* 2(3H)-Furanone, 3-ethyldihydro-4-[(1-methyl-1*H*imidazol-5-yl)-methyl]-monohydrochloride, (3*S*-*cis*)

Molecular Formula/Molecular Weight: $C_{11}H_{16}N_2O_2 \cdot HCl$ / 244.72 g/mol

Structure:




Pharmacologic Class: Cholinergic receptor agonist

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 122483: AGN-199201 (Allergan; oxymetazoline/pilocarpine fixed combination)
- NDA 020237 (listed drug on Form 356h): Salagen, tablet; oral
  - Approved 3-22-1994
  - A Pharmacology/Toxicology review of the initial NDA application was not found online.
  - Indicated for the treatment of symptoms of dry mouth from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck; and the treatment of symptoms of dry mouth in patients with Sjogren's Syndrome.
  - Approved dose range 15-30 mg per day (not to exceed 10 mg per dose).
- NDA 200890 (listed drug on Form 356h
  - Approved 6-22-2010
  - Nonclinical review dated 5-17-2010 (Dr. Conrad Chen)
  - Indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension, the management of acute angle-closure glaucoma, the prevention of

postoperative elevated IOP associated with laser surgery, and the induction of miosis
- Maximum approved dose: 4% QID
- NOTE: No nonclinical information for this review was derived from NDA 200890.

- DMF (b) (4): Pilocarpine HCl

## 2.3 Drug Formulation

**Composition of Pilocarpine Hydrochloride 1.25% Ophthalmic Solution**

| Component | Function | Quality Standard | Concentration | |
|---|---|---|---|---|
| | | | % w/w | mg/mL |
| Pilocarpine Hydrochloride | Drug substance | USP | 1.25 | 12.5 |
| Benzalkonium Chloride | Preservative | NF | 0.0075 | 0.075 |
| Boric Acid | (b) (4) | NF | (b) (4) | |
| Sodium Citrate Dihydrate | | USP | | |
| Sodium Chloride | | USP | | |
| Hydrochloric Acid and/or Sodium Hydroxide | pH adjustment | NF | q.s | q.s. |
| Purified Water | (b) (4) | USP | q.s. | q.s. |

## 2.4 Comments on Novel Excipients

- All excipients are qualified for topical ocular administration.

## 2.5 Comments on Impurities/Degradants of Concern

- (b) (4)
  - The Applicant proposes a specification of (b) (4)% (of % labeled strength*) for the degradant impurity (a daily dose of (b) (4) mg/eye/day at MRHOD).
  - The Applicant qualified (b) (4) up to (b) (4)% (of drug product*) or (b) (4) mg/eye/day in the chronic (6-month) ocular toxicity study reviewed below.
  - The Applicant's specification is qualified from a toxicologic perspective.

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  - The Applicant qualified (b) (4) up to (b) (4)% (of drug product) or (b) (4) mg/eye/day in the chronic (6-month) ocular toxicity study reviewed below.
  - The Applicant's specification is qualified from a toxicologic perspective.

**Reviewer's note: It is important to distinguish the impurity specifications proposed by the Applicant when expressed as "of % of labeled strength" versus the spiked impurity content of the dosing solutions in the nonclinical study when expressed as "% of drug product". The former is calculated as a percent of the impurity when based on the API content of the drug product (e.g. (b) (4)% of the MRHOD of (b) (4) mg/eye/day is equivalent to (b) (4) mg/eye/day) while the latter is calculated based on addition of the impurity to the final dosing solution such that the content is absolute (e.g. (b) (4)% of the dosing solution is equivalent to (b) (4) mg/mL of the impurity or (b) (4) mg/eye/day based on a (b) (4) mL drop BID—NOAEL dose in the qualifying study).*

***Leachables***

The Applicant proposes a limit of (b) (4) ppm for (b) (4), a leachable observed during primary stability in the physician and standard trade configuration (carton) at levels higher than the unknown leachable limit. The leachable was identified and determined to have originated from (b) (4).

The Applicant cites (b) (4) to support the systemic safety of (b) (4). The oral reference dose (lifetime daily dose without an appreciable risk of deleterious effects) for (b) (4) was determined by the Environmental Protection Agency to be (b) (4) µg/kg/day. Assuming average body weight (60 kg), the acceptable chronic oral dose of (b) (4) µg is approximately (b) (4)-fold the estimated dose from administering two drops of pilo HCl 1.25% into the eyes each day (1 drop/eye/day x (b) (4) mL/drop x 2 eyes x (b) (4) µg/mL) based on the proposed limit of (b) (4) ppm (b) (4).

To support the ocular safety of (b) (4), the Sponsor cites the following published articles:

(b) (4)

(b) (4)

In this article, the investigators instilled 0.1mL of a dilution of (b) (4) into the eyes of New Zealand White rabbits. Irritancy in the eyes was scored by Draize with scoring using the Texaco single-digit toxicity classification system as follows: minimally irritating 0-15, slightly irritating >15-25, moderately irritating >25-50, severely irritating >50-80, extremely irritating >80-110. Corneal thickness was measured and expressed as a percentage of the thickness of the control eye (% swell). Measurements were taken at

24, 48, and 72 hours post-dose. Additionally, if irritancy continued, measurements were taken on Days 7, 10, 14 and 21.

| Solvent | Concentration (% vol) | Draize score | % Swell |
|---|---|---|---|
| (b) (4) | (b) (4) | 66 | 181 |
| | | 49 | 146 |
| | | 39 | 114 |
| | | 2 | 113 |
| | | 1 | 91 |

A dose dependent increase in irritancy and corneal swelling was observed with (b) (4)% (b) (4) being considered an irritant but only minimal findings at (b) (4)% (b) (4). (b) (4)% (b) (4) ((b) (4) mg/mL; (b) (4)mg/eye) represents a (b) (4)-fold margin over (b) (4) ppm (b) (4) ( mg/mL; (b) (4) µg/eye) when administered as the dose of Vuity® proposed for approval ( (b) (4) QD).

(b) (4)

*review article

Undiluted (b) (4) ( (b) (4) ml), (b) (4)% (b) (4) ( (b) (4)ml; (b) (4)mg/eye) and (b) (4)% (b) (4) ((b) (4) ml; (b) (4) mg/eye) were instilled into the conjunctival sac of five rabbits (strain not stated). Reactions were scored immediately after instillation and again at 24 h post-instillation after staining with fluorescein. Undiluted (b) (4) caused severe corneal injury and iritis. Moderate corneal injury and no corneal injury were observed after the instillation of (b) (4)%. A (b) (4)% solution (b) (4) mg/mL; (b) (4) mg/eye) represents a (b) (4)-fold margin over (b) (4) ppm instilled with the drug product ( (b) (4) mg/mL; (b) (4)µg/eye).

The Applicant's specification of NMT (b) (4)ppm (b) (4) is supported by the data provided.

## 2.6 Proposed Clinical Population and Dosing Regimen

- Vuity® is indicated for the treatment of presbyopia in adults.
- The recommended dosage of Vuity® is one drop in each eye once daily.
- With a drop volume of (b) (4)mL/drop, the total daily ocular dose is (b) (4) mg/eye/day or (b) (4) mg/day total daily dose when administered bilaterally and assuming 100% absorption.

# 3 Studies Submitted

## 3.1 Studies Reviewed

- Study PK15030: Ocular and systemic pharmacokinetics of oxymetazoline and pilocarpine following a single topical administration of mono- and combination therapies and repeat topical administration of combination therapy to Dutch Belted rabbits
- Study 1883-T02-057: AGN-190584-A: 5-day topical ocular tolerability study in rabbits
- Study (b) (4)-123169: AGN-190584-A/AGN-199201: 1-month topical ocular toxicity study with systemic evaluation in rabbits
- Study 1883-T01-057: AGN-190584- and AGN-199201: 6-month topical ocular toxicity study in rabbits

## 3.2 Studies Not Reviewed

- Study PK14095-PK: Ocular pharmacokinetics of oxymetazoline and pilocarpine hydrochloride in 5 test formulations following a single topical administration to Dutch Belted rabbits
- Study AN13082-BM: Validation of a method for the determination of AGN-199201 and AGN-190584 in rabbit plasma by HPLC with MS/MS detection
- Study 1883-B01-050: Bioanalytical validation report for the determination of oxymetazoline and pilocarpine in rabbit plasma ($K_2$ EDTA) by LC-MS/MS
- Study TX14097: AGN-190584-A and AGN-199201: 14-day topical ocular tolerability study in rabbits
    - Formulations studied do not match to-be-marketed formulation in excipient content
- Bourrié, M., *et al*., 1996, “Cytochrome P450 isoform inhibitors as a tool for the investigation of metabolic reactions catalyzed by human liver microsomes”, *J Pharmacol Exp Ther*, 277: 321 – 332.
- Chu, T., *et al*., 1996, “Oxymetazoline: Potential mechanisms of inhibitory effects on aqueous humor dynamics”, *Pharmacology*, 53: 259 – 270.
- Ellis, P., *et al*., 1972, “Enzymatic hydrolysis of pilocarpine”, *Invest Ophthalmol*, 11: 747 – 751.
- Endo, T., *et al*., 2007, “Involvement of CYP2A6 in the formation of a novel metabolite, 3-hydroxypilocarpine, from pilocarpine in human liver microsomes”, *Drug Metab Dispos*, 35: 476 – 483.
- Garcia-Lázaro, S., *et al*., 2012, “Visual function through 4 contact lens-based pinhole systems for presbyopia”, *J Cataract Refract Surg*, 38: 858 – 865.
- Holden, B., *et al*., 2008, “Global vision impairment due to uncorrected presbyopia”, *Arch Ophthalmol*, 126: 1731 – 1739.
- Kinonen, T., *et al*., 1995, “Competitive inhibition of coumain 7-hydroxylation by pilocarpine and its interaction with mouse CYP 2A5 and human CYP 2A6”, *Br J Pharmacol*, 116: 2625 – 2630.

- Laibovitz, R., *et al*., 1996, "Dorzolamide versus pilocarpine as adjunctive therapies to timolol: A comparison of patient preference and impact on daily life", *Clin Ther*, 18: 821-832.
- Lee, V., *et al*., 1980, "Corneal metabolism of pilocarpine in pigmented rabbits", *Invest Ophthalmol Vis Sci*, 19: 210- 213.
- Li, Y., *et al*., 1997, "Comparison of CYP2A6 catalytic activity on coumarin 7-hydroxylation in human and monkey liver microsomes", *Eur J Drug Metab Pharmacokinet*, 22: 295 – 304.
- Miller, S. and T. Patton, 1982, "Age-related differences in ophthalmic drug disposition II: Drug-protein interactions of pilocarpine and chloramphenicol", *Biopharm Drug Dispos*, 3: 115 – 128.
- Murray, D. and I. Leopold, 1985, "Alpha-adrenergic receptors in rabbits eyes", *J Ocul Pharmacol*, 1: 3 – 18.
- Newsom, D. and R. Stern, 1974, "Pilocarpine adsorption by serum and ocular tissues", *Am J Ophthalmol*, 77: 918 – 922.
- Osmori, Y., *et al*., 2004, "Absorption, distribution and excretion of $^{14}$C-pilocarpine following oral administration to rats", *Arzneim Forsch Drug Res*, 3: 171 – 178.
- Ostrin, L. and A. Glasser, 2004, "Accomodation measurements in a prepresbyopic and presbyopic population, *J Cataract Refract Surg*, 30: 1435 – 1444.
- Radhakrishnan H. and W. Charman, 2007, "Age-related changes in static accommodation and accommodative miosis", *Ophthal Physiol Opt*, 27: 342 – 352.
- Ruiz, L., *et al*., 2009, "Intrastromal correction of presbyopia using a femtosecond laser system", *J Refract Surg*, 25: 847 – 854.
- Schwarz, R., *et al*., 1993, "Characterization of muscarinic agonists in recombinant cell lines", *Life Sci*, 52: 465 – 472.
- Sendelbeck, L., *et al*., 1975, "Comparative distribution of pilocarpine in ocular tissues of the rabbits during administration by eyedrop or by membrane-controlled delivery systems", *Am J Ophthalmol*, 80: 274 – 283.
- Skyes, D., *et al*., 2009, "Exploring the mechanism of agonist efficacy: A relationship between efficacy and agonist dissociation rate at the muscarinic $M_3$ receptor", *Mol Pharmacol*, 76: 543 – 550.
- (b) (4)


# 4 Pharmacology

## 4.1 Primary Pharmacology

- Pilocarpine hydrochloride (Pilo HCl) is a cholinergic muscarinic agonist that activates muscarinic receptors located at smooth muscles such as the iris sphincter muscle and ciliary muscle. 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 while maintaining some pupillary response to light.

- Pilocarpine also contracts the ciliary muscle, facilitating accommodation.

# 5 Pharmacokinetics/ADME/Toxicokinetics

## 5.1 PK/ADME

Study PK15030: Ocular and systemic pharmacokinetics of oxymetazoline and pilocarpine following a single topical administration of mono- and combination therapies and repeat topical administration of combination therapy to Dutch Belted rabbits

- This study determined ocular and systemic pharmacokinetics of pilocarpine and oxymetazoline following single or repeated administration to female Dutch Belted (DB) rabbits as monotherapies versus combination therapies.
  - Group 1: bilateral topical instillation ( (b) (4) mL) 1.5% pilocarpine and 0.125% oxymetazoline daily for 14 days.
  - Groups 2 and 3: single bilateral topical instillation of 1.5% pilocarpine or 0.125% oxymetazoline monotherapies, respectively.
  - Group 4: single bilateral topical installation of an unfixed combination (0.125% oxymetazoline followed 5 minutes later by 1.5% pilocarpine).

**Composition of Formulations**

| Ingredient (%w/v) | Group 1 Fixed-dose Combination | Group 2 Pilocarpine Monotherapy | Group 3 Oxymetazoline Monotherapy | Group 4 Unfixed Combination |
|---|---|---|---|---|
| Pilocarpine HCl | 1.5 | 1.5 | - | Formulations from Groups 2 and 3 were used to dose Group 4. |
| (b) (4) | | | | |
| Benzalkonium Chloride | 0.0075 | 0.0075 | 0.0075 | |
| Sodium Citrate Dihydrate | | | | |
| Boric Acid | | | | |
| Sodium Chloride | | | | |
| pH | | | | |
| Purified Water | QS | QS | QS | |
| Lot Number | E-000029-060-1 | E-000029-060-2 | E-000029-060-3 | |

QS = Quantity Sufficient; ' – ' = Not Applicable

- At designated timepoints, cornea, bulbar conjunctiva, aqueous humor, iris-ciliary body (ICB), and plasma were collected. Concentrations of pilocarpine and oxymetazoline were measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

**Pharmacokinetic Parameters of Pilocarpine in Ocular Tissues and Plasma Following Topical Administration of Combination (1.5% Pilocarpine and 0.125% Oxymetazoline) and Mono- (1.5% Pilocarpine) Therapy to Dutch Belted Rabbits**

| Pilocarpine | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Matrix | Group | Day | $T_{max}$ (hr) | $C_{max}$ (ng/mL or ng/g) | | $AUC_{0\text{-tlast}}$ (ng·hr/mL or ng·hr/g) | | $AUC_{0\text{-}24}$ (ng·hr/mL or ng·hr/g) | | $T_{1/2}$ (hr)[a] |
| | | | | Mean | SE | Mean | SE | Mean | SE | |
| Aqueous Humor | Fixed | 1 | 0.5 | 1780 | 450 | 4070 | 520 | 4070 | 520 | 5.29 |
| | | 14 | 0.5 | 160 | 53 | 2630 | 630 | 1760 | NA | 6.15 |
| | Mono | 1 | 0.5 | 2120 | 420 | 3860 | 780 | 3860 | 780 | NC |
| | Unfixed | 1 | 0.5 | 3660 | 430 | 4110 | 340 | 4110 | 340 | 5.38 |
| Bulbar Conjunctiva | Fixed | 1 | 0.5 | 613 | 173 | 2330 | 460 | 2330 | 460 | 6.98 |
| | | 14 | 0.5 | 619 | 315 | 8590 | 1780 | 3630 | NA | 8.11 |
| | Mono | 1 | 1 | 1020 | 470 | 4660 | 1570 | 4660 | 1570 | NC |
| | Unfixed | 1 | 0.5 | 1300 | 450 | 1350 | 300 | 1350 | 300 | NC |
| Cornea | Fixed | 1 | 0.5 | 6380 | 1080 | 16,300 | 2400 | 16,300 | 2400 | 6.54 |
| | | 14 | 0.5 | 5330 | 970 | 55,100 | 13,200 | 30,300 | NA | 8.58 |
| | Mono | 1 | 0.5 | 6050 | 750 | 25,900 | 6500 | 25,900 | 6500 | NC |
| | Unfixed | 1 | 0.5 | 9540 | 1360 | 16,100 | 2500 | 16,100 | 2500 | 8.64 |
| Iris-Ciliary Body | Fixed | 1 | 0.5 | 8800 | 1860 | 70,200 | 11,500 | 70,200 | 11,500 | 4.37 |
| | | 14 | 1 | 11,900 | 2300 | 69,500 | 8400 | 58,900 | NA | 5.13 |
| | Mono | 1 | 0.5 | 11,500 | 1300 | 38,400 | 4000 | 38,400 | 4000 | 4.73 |
| | Unfixed | 1 | 0.5 | 17,700 | 1400 | 62,500 | 5800 | 62,500 | 5800 | 4.62 |
| Plasma | Fixed | 1 | 0.5 | 40.5 | 8.7 | 56.7 | 7.7 | 56.7 | 7.7 | NC |
| | | 14 | 0.5 | 68.3 | 22.1 | 101 | 25 | 59.8 | NA | NC |
| | Mono | 1 | 0.5 | 49.2 | 9.4 | 38.4 | 6.0 | 38.4 | 6.0 | NC |
| | Unfixed | 1 | 0.5 | 46.7 | 6.30 | 39.5 | 6.2 | 39.5 | 6.2 | NC |

a – Day 14 half-life values represent the functional half-life (calculated from 0-24h postdose).
OU = both eyes; SE = standard error; hr = hour; NA = not applicable; NC = not calculable
Fixed = Group 1 = 1.5% pilocarpine and 0.125% oxymetazoline in a fixed combination formulation
Mono = Group 2 = 1.5% pilocarpine in a monotherapy
Unfixed = Group 4 = 0.125% oxymetazoline and 1.5% pilocarpine in an unfixed formulation administered 5 minutes apart

- Pilocarpine exposure ($AUC_{0\text{-tlast}}$) was similar in most ocular tissues following a single dose as an unfixed combo, a fixed combo, or a monotherapy.
  - Reviewer's note: The to-be-marketed formulation proposed by the Applicant contains only pilocarpine as the active ingredient. The pivotal ocular toxicity studies were performed with a combination of oxymetazoline and pilocarpine (fixed and unfixed combinations; see below). The addition of oxymetazoline did not significantly increase or decrease exposure to pilocarpine systemically or in the ocular tissues examined.

# 6 General Toxicology

## 6.2 Repeat-Dose Toxicity

**Study title: AGN-190584-A: 5-day topical ocular tolerability study in rabbits**

| | |
|---|---|
| Study no.: | 1883-T02-057 |
| Study report location: | \\CDSESUB1\evsprod\nda214028\0001\m4\42-stud-rep\423-tox\4236-loc-tol\1883-t02-057.pdf |
| Conducting laboratory and location: | Allergan Inc (Irvine, CA) |
| Date of study initiation: | 2-20-2018 |
| GLP compliance: | No |
| QA statement: | No |
| Drug, lot #, and % purity: | AGN-190584-A, Lot E-000029-097 |

- **Key Study Findings**

- Female NZW rabbits were administered vehicle or 1.25% AGN-190584-A by topical ocular instillation in the left eye once daily for 5 consecutive days.
- AGN-190584-A was considered well tolerated.
- Treatment related effects were reported as minimal discomfort and mild conjunctival hyperemia with similar incidence/grade to vehicle treated eyes.
- Pupil diameters in eyes treated with 1.25% AGN-190584-A were reduced.

Methods

| | |
|---|---|
| Doses: | 1.25% |
| Frequency of dosing: | Once daily; left eye only |
| Route of administration: | Topical ocular instillation |
| Dose volume: | (b) (4) mL/drop |
| Formulation/Vehicle: | To-be-marketed formulation (see above) |
| Species/Strain: | Rabbit / New Zealand White |
| Number/Sex/Group: | 5/group (females only) |
| Age: | 8 – 12 months |
| Weight: | 3.83 – 4.46 kg |
| Deviation from study protocol: | None reported. |

**Observations and Results**

- **Mortality**
  - No animals died or were sacrificed prior to schedule.

- **Clinical Signs**
  - No treatment related changes in clinical signs attributed to the test article.

- **Gross Ocular Observations and Ocular Discomfort Assessment**
  - "Discomfort observations"
    - Transient, minimal (Grade 1)
    - Noted only in the treated eyes in both AGN 190584-A and vehicle groups with similar severity and incidence
  - Hyperemia
    - Transient, minimal
    - Noted only in the treated eyes in both AGN 190584-A and vehicle groups with similar severity and incidence

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

**Study title: AGN-190584-A/AGN-199201: 1-month topical ocular toxicity study with systemic evaluation in rabbits**

| | |
|---|---|
| Study no.: | TX13119 / (b) (4)-123169 |
| Study report location: | \\CDSESUB1\evsprod\nda214028\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\tx13119-tx.pdf |
| Conducting laboratory and location: | (b) (4) |
| Date of study initiation: | 11-25-2013 |
| GLP compliance: | Yes |
| QA statement: | Yes; signed |
| Drug, lot #, and % purity: | AGN-190584-A (pilocarpine): Lot 210282F; described as commercially available product characterized per its label; purity not reported<br>AGN-199201 (oxymetazoline): Lot 010419AX21 / R20751; purity 99.8% |

**Key Study Findings**

- Unilateral ocular instillation of pilocarpine (1%) / oxymetazoline (0.05% - 0.25%), BID for 30 days, did not cause adverse toxicity in the rabbit eye

Methods

Doses:

| Group Number | Test Formulation 1 | Test Formulation 2 (Formulation No.) | Frequency of Instillation |
|---|---|---|---|
| 1 | AGN-199201 Vehicle | Sham | 1 drop 2 times/day[a] |
| 2 | 0.05% AGN-199201 | 1% AGN-190584-A | 1 drop of each test formulation 2 times/day[a] |
| 3 | 0.125% AGN-199201 | 1% AGN-190584-A | 1 drop of each test formulation 2 times/day[a] |
| 4 | 0.25% AGN-199201 | 1% AGN-190584-A | 1 drop of each test formulation 2 times/day[a] |

- AGN-190584 (oxymetazoline) dose range: 0.05% - 0.25%.
- AGN-190584-A (pilocarpine) dose was constant (1%)

Route of administration: Topical ocular instillation; left eye only

Dose volume: (b) (4) mL

Formulation/Vehicle: To-be-marketed formulation of pilocarpine (AGN-190584-A; see above); AGN-199201 dosing solution formulated / administered separately:

| Formulation Ingredients (%w/v) | Placebo | AGN-199201 0.05% | AGN-199201 0.125% | AGN-199201 0.25% |
|---|---|---|---|---|
| Lot Number | AN13086-112613-01 | AN13086-112613-04 | AN13086-112613-03 | AN13086-112613-02 |
| | | | | (b) (4) |
| Benzalkonium Chloride | | | | (b) (4) |
| | | | | (b) (4) |
| Boric Acid | | | | (b) (4) |
| | | | | (b) (4) |
| Sodium Chloride | | | | (b) (4) |
| (b) Hydrochloric Acid | | | | |
| (b) Sodium Hydroxide | | | | |
| (b) (4 | | | | |

Species/Strain: Rabbit / New Zealand White

Number/Sex/Group: Vehicle / sham and high-dose AGN-199201 (oxymetazoline): 7/sex/group
Low- and mid- dose AGN-199201: 5/sex/group

Age: 5 – 6 months

Weight: 2.6 – 3.6 kg (Day 0)

Unique study design: Dosing procedure: Rabbits were treated in the left eye with the AGN-199201 ophthalmic solution, followed 2 minutes ± 1 minute later by instillation of 1% AGN-190584-A.

Deviation from study protocol: No deviations impacted study conduct or interpretation of results.

- **Observations and Results**

- **Mortality (twice daily)**
    - No animals died or were euthanized prior to scheduled sacrifice.

- **Clinical Signs (At the time of the first daily dose instillation of AGN-190584-A, and 1-2 hours following the first daily dose instillation of AGN-190584-A. Recovery period: once daily).**
    - Dilated pupil; left (treated) eye
        - Males and females from the 0.125% and 0.25% AGN-199201-treated groups.
        - Attributed to the pharmacology of AGN-199201.
        - By 1-2 hours following the first daily dose instillation, the number of animals affected and instances of the finding per animal were less.

- **Body Weights (weekly)**
    - No changes in body weights attributed to the test article.

- **Feed Consumption (daily)**
    - No changes in feed consumption attributed to the test article.

**Ophthalmoscopy (prior to randomization, prior to the first daily instillation at the end of the dosing period, and once near the end of the recovery period; slit lamp biomicroscopy, indirect ophthalmoscopy; modified Hackett and McDonald scoring).** An additional standard eye examination was conducted on Study Day 18 to confirm the observations of abnormal iris in some animals.

- Pupil diameter
    - Increased in the high-dose group by up to 2.1 mm for males and 2.6 mm for females
    - Noted at all treatment levels during the dosing period at 1-2 hours following the second daily dose instillation.
    - Correlated with the clinical observations of dilated pupil
    - Attributed to alpha-1 agonist properties of AGN-199201
- Iris
    - Noted as “slow to react” in the treated females at frequencies up to 28.6% in high dose females
    - Noted at 1-2 hours following the second daily dose instillation on Study Day 14
    - Attributed to the pharmacology of AGN-199201.
- Both the larger pupil size and slow iris response observations did not appear to persist to the next daily dose administration and were not noted

during the two remaining ocular observation intervals during the dosing period (Study Days 21 and 27).

- **Intraocular pressure (weekly)**
  - No changes in intraocular pressure attributed to the test article.
- **Gross Pathology**
  - No macroscopic changes attributed to the test article.
- **Histopathology**

  Adequate Battery: eyes, optic nerve, extraocular muscles, eyelids, Harderian glands, lacrimal glands, nictitating membrane, gross lesions

  Peer Review: Yes

  Histological Findings: No microscopic findings attributed to the test article.

- **Toxicokinetics**

**Summary of Toxicokinetic Parameters on Study Day 27 (AGN-199201 and AGN-190584-A)**

| Dosage[a] | $C_{max1}$ (ng/mL) | $C_{max2}$ (ng/mL) | $t_{max1}$ (hr) | $t_{max2}$ (hr) | $AUC_{0-6}$ Interval (hr) | $AUC_{6-24}$ Interval (hr) | $AUC_{0-24}$ Interval (hr) |
|---|---|---|---|---|---|---|---|
| **AGN-199201** | | | | | | | |
| Overall (Both Genders Combined) | | | | | | | |
| 0.05% | 0.335 | 0.141 | 0.25 | 0.50 | 0.664 | 0.217 | 0.773 |
| 0.125% | 0.515 | 0.310 | 0.25 | 0.25 | 0.776 | 0.708 | 1.49 |
| 0.25% | 1.23 | 0.667 | 0.25 | 0.25 | 1.75 | 1.62 | 3.37 |
| **AGN-190584-A** | | | | | | | |
| Overall (All Groups and Both Genders Combined) | 6.78 | 8.78 | 0.25 | 0.25 | 5.93 | 11.0 | 16.7 |

Day 27 = 28th day of treatment

a – Rabbits were treated with each dose unilaterally 2 times daily followed 2 minutes ± 1 minute later by one topical ocular drop (approximately (b)(4) µL) of 1% AGN-190584-A.

- **Dosing Solution Analysis**
  - Dosing solutions remained within acceptance criteria for the duration of the study (± 10% nominal concentration)

**Study title: AGN-190584- and AGN-199201: 6-month topical ocular toxicity study in rabbits**

| | |
|---|---|
| Study no.: | **1883-T01-057** |
| Study report location: | \\CDSESUB1\evsprod\nda214028\0001\m4\42-stud-rep\423-tox\4232-repeat-dose-tox\1883-t01-057-a1.pdf |
| Conducting laboratory and location: | Allergan Inc (Irvine, CA) |
| Date of study initiation: | 9-19-2017 |
| GLP compliance: | Yes |
| QA statement: | Yes; signed |
| Drug, lot #, and % purity: | AGN-190584 (pilocarpine): Lot 2309I0807; purity of drug substance not found in report<br>AGN199201 (oxymetazoline): Lot R21832; purity of drug substance not found in report |

**Key Study Findings**

- This study determined the ocular toxicity of a pilocarpine / oxymetazoline combination following topical ocular instillation in rabbits; otherwise, the formulation excipients were identical to the to-be-marketed formulation. A pilocarpine alone treatment group was not included.
- The dosing solutions additionally were spiked with the degradant impurities (b) (4) to qualify these compounds above their respective specifications (see above).
- Dosing related effects were limited to non-adverse, mild ocular redness at all dose levels
- The no-observed-adverse-effect level (NOAEL) is considered to be the high-dose 3.0%/0.3% AGN-190584 (pilocarpine)/AGN-199201 (oxymetazoline).

Methods

Doses:

| Group No. | Test Material[b] | |
|---|---|---|
| | AGN-190584 | AGN-199201 |
| 1 | 0% | 0% |
| 2 | 1.5% | 0.125% |
| 3 | 2.0% | 0.2% |
| 4 | 3.0% | 0.3% |

Low dose = 1.5% AGN-190584 and 0.125% AGN-199201.
Mid dose =2.0% AGN-190584 and 0.2% AGN-199201.
High dose = 3.0% AGN-190584 and 0.3% AGN-199201.

Total daily ocular doses (pilocarpine / oxymetazoline)
Right eye (QD):
- Low dose: 0.525 / 0.0438 mg/eye/day
- Mid dose: untreated
- High dose: 1.05 / 0.105 mg/day

Left eye (BID):
- Low dose: 1.05 / 0.0875 mg/day
- Mid dose: 1.4 / 0.14 mg/day
- High dose: 2.1 / 0.21 mg/day

`Frequency of dosing: Right eye (Groups 1,3,4): once daily
Right eye (Group 2): untreated
Left eye: twice daily

Route of administration: Topical ocular instillation

Dose volume: (b) (4) mL/drop

Formulation/Vehicle: Formulation was identical to clinical formulation except for the addition of oxymetazoline

Species/Strain: Rabbit / New Zealand White

Number/Sex/Group: Main Study: 10/sex/group (5 + 5: interim / terminal sacrifice)
Recovery (Vehicle control and High dose only): 3/sex/group

Age: 6 – 7 months

Weight: 2.6 – 3.4

Deviation from study protocol: None which affected conduct or interpretation of study results.

- **Observations and Results**
- **Mortality (twice daily, once in the morning and once in the afternoon)**
  - No animals died prior to scheduled sacrifice.
- **Clinical Signs (cageside: once daily, target 1 hour postdose; Detailed: weekly)**
  - Ocular redness
    - Incidence similar between eyes receiving one or two drops per day.

- Observed between Days 42 and 168 in most eyes.
- Considered to be slight in general.

Incidence of Red Eyeball

| Group | Control | | Low Dose | | Mid Dose | | High Dose | |
|---|---|---|---|---|---|---|---|---|
| | M | F | M | F | M | F | M | F |
| Number of Animals: | 13 | 13 | 10 | 10 | 10 | 10 | 13 | 13 |
| Redness of the Eyes – Right Eye* | 0 | 0 | 1 (1) | 1 (1) | 4 (7) | 3 (7) | 4 (12) | 3 (3) |
| Redness of the Eyes – Left Eye* | 3 (8) | 0 | 1 (4) | 4 (15) | 3 (6) | 1 (4) | 4 (13) | 3 (5) |

* Number of eyes affected (Number of observations). The observations were performed weekly at detailed examinations, or at unscheduled occasions when observed.
Low dose = 1.5% AGN-190584 and 0.125% AGN-199201.
Mid dose =2.0% AGN-190584 and 0.2% AGN-199201.
High dose = 3.0% AGN-190584 and 0.3% AGN-199201.

- Protruding nictitating membrane
  - Low dose:
    - Single occasion in one animal (Day 17; left eye only)
  - Mid-dose
    - Ongoing observation in two different animals; resolved (Days 77 – 91; both eyes)
  - High Dose
    - Single occasion in two different animals (Day 84: both eyes, Day 91: left eye only).

- **Body Weights (weekly)**
  - No changes in body weight attributed to the test article.

- **Feed Consumption (twice weekly)**
  - No changes in feed consumption attributed to the test article.

- **Ophthalmoscopy (once prestudy, Week 4, 13, 26 and end of recovery)**
  - Gross observations
    - Redness
      - Slight to moderate
      - Overall, slight redness was observed in a total of 82 of 112 eyes (73%) and moderate redness was observed in a total of 4 of 112 eyes (4%) administered the test Item; also present at a low incidence in control eyes (slight or moderate redness in 12 of 52 eyes; 23%) that received vehicle only and Group 2 right eyes (slight redness in 8 of 20 eyes) that were not dosed.
        - Findings could be related to mechanical manipulation during ophthalmic observation.

Incidence of Redness

| Group | Control | | Low Dose | | Mid Dose | | High Dose | |
|---|---|---|---|---|---|---|---|---|
| | M | F | M | F | M | F | M | F |
| Number of Animals: | 13 | 13 | 10 | 10 | 10 | 10 | 13 | 13 |
| Slight Redness of the Eyes* | | | | | | | | |
| Right Eye | 1 (1) | 4 (18) | 4 (7) | 4 (7) | 5 (40) | 8 (57) | 9 (48) | 13 (91) |
| Left Eye | 2 (14) | 4 (8) | 6 (38) | 7 (47) | 5 (22) | 8 (48) | 8 (42) | 13 (67) |
| Moderate Redness of the Eyes* | | | | | | | | |
| Right Eye | 0 | 0 | 0 | 0 | 0 | 1 (5) | 0 | 1 (1) |
| Left Eye | 1 (2) | 0 | 0 | 1 (1) | 1 (1) | 0 | 0 | 0 |

* Number of eyes affected (Number of observations). The observations were performed weekly starting Day 71/ Week 11.
Low dose = 1.5% AGN-190584 and 0.125% AGN-199201.
Mid dose =2.0% AGN-190584 and 0.2% AGN-199201.
High dose = 3.0% AGN-190584 and 0.3% AGN-199201.

- **Gross Pathology**
  - No changes in macroscopic observations attributed to the test article.

- **Histopathology**

  Adequate Battery: Nasal cavity, eye (five sagittal sections of each eye), eyelids, Harderian gland, lacrimal gland, gross lesions, parotid lymph nide, optic nerve, nictitating membrane, tongue

  Peer Review: Yes

  Histological Findings: No microscopic changes attributed to the test article.

- **Toxicokinetics**

Summary of Toxicokinetic Parameters

| Concentration | | AGN-190584 Day 1[a] Cmax (ng/mL) | AGN-190584 Day 1[a] $AUC_{0-t}$ (hr·ng/mL) | AGN-190584 Day 28[b] Cmax (ng/mL) | AGN-190584 Day 28[b] $AUC_{0-t}$ (hr·ng/mL) | AGN-190584 Day 182[b] Cmax (ng/mL) | AGN-190584 Day 182[b] $AUC_{0-t}$ (hr·ng/mL) |
|---|---|---|---|---|---|---|---|
| | | AGN-190584 | | | | | |
| M | Low | 8.01 ± 2.63 | 3.37 ± 0.876 | 11.4 ± 3.59 | 8.12 ± 4.48 | 9.85 ± 3.17 | 4.53 ± 1.24 |
| | Mid | 10.9 ± 1.86 | 5.34 ± 0.594 | 37.1 ± 22.4 | 18.2 ± 5.08 | 27.2 ± 7.38 | 20.7 ± 6.28 |
| | High | 20.1 ± 7.82 | 8.20 ± 2.12 | 53.2 ± 23.4 | 41.8 ± 22.3 | 53.5 ± 34.6 | 31.2 ± 12.5 |
| F | Low | 9.85 ± 2.96 | 3.35 ± 0.792 | 15.2 ± 2.74 | 6.64 ± 1.33 | 8.34 ± 6.80 | 4.79 ± 2.19 |
| | Mid | 10.4 ± 1.25 | 4.26 ± 0.389 | 25.1 ± 6.07 | 16.4 ± 4.06 | 19.0 ± 10.6 | 9.57 ± 7.74 |
| | High | 13.7 ± 4.08 | 5.75 ± 1.08 | 24.2 ± 18.4 | 15.1 ± 8.12 | 33.3 ± 8.97 | 19.8 ± 5.49 |
| | | AGN-199201 | | | | | |
| M | Low | 0.206 ± 0.0637 | 0.145 ± 0.0307 | 0.387 ± 0.00436 | 0.339 ± 0.168 | 0.277 ± 0.0892 | 0.359 ± NC |
| | Mid | 0.387 ± 0.0979 | 0.285 ± 0.0405 | 1.02 ± 0.540 | 1.56 ± 0.295 | 0.954 ± 0.531 | 1.32 ± 0.404 |
| | High | 0.465 ± 0.167 | 0.747 ± 0.0804 | 1.55 ± 0.840 | 3.03 ± 1.02 | 1.38 ± 0.595 | 2.40 ± 0.487 |
| F | Low | 0.425 ± 0.113 | NR | 0.446 ± 0.155 | 0.427 ± 0.246 | 0.312 ± 0.138 | 0.555 ± 0.319 |
| | Mid | 0.476 ± 0.0149 | 0.637 ± 0.0556 | 0.869 ± 0.243 | 1.77 ± 0.117 | 0.705 ± 0.281 | 1.35 ± 0.763 |
| | High | 0.443 ± 0.124 | 0.680 ± 0.113 | 0.895 ± 0.564 | 1.92 ± 1.00 | 0.923 ± 0.205 | 2.62 ± 0.964 |

Doses administered AGN-190584 / AGN-199201: Low dose = 1.5%/0.125% (1.05/0.0875 mg/day); Mid dose = 2%/0.2% (2.1/0.21 mg/day); High dose = 3%/0.3% (3.15/0.315 mg/day).
NR = Not reported because there were less than 3 quantifiable concentrations at consecutive time points.
M = Males; F = Females
NC = Not calculable
[a] Blood samples were collected (N=3/sex/group/time point) alternating at each time point on Day 1 (non-serial).
[b] Blood samples were collected from the first three animals of each group at the Days 28 and 182 time points (serial).

- **Dosing Solution Analysis**
  - Dosing solutions remained within acceptance criteria for the duration of the study (± 10% nominal concentration)

# 7 Genetic Toxicology

**Salagen® labeling:**

*No evidence that pilocarpine has the potential to cause genetic toxicity was obtained in a series of studies that included: 1) bacterial assays (Salmonella and E. coli) for reverse gene mutations; 2) an in vitro chromosome aberration assay in a Chinese hamster ovary cell line; 3) an in vivo chromosome aberration assay (micronucleus test) in mice; and 4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.*

**Applicant proposed labeling statement:**

(b) (4)

(b) (4)

# 8 Carcinogenicity

**Salagen® labeling:**

*Lifetime oral carcinogenicity studies were conducted in CD-1 mice and Sprague-Dawley rats. Pilocarpine did not induce tumors in mice at any dosage studied (up to 30 mg/kg/day, which yielded a systemic exposure approximately 50 times larger than the maximum systemic exposure observed clinically). In rats, a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both males and females, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats. The tumorigenicity observed in rats was observed only at a large multiple of the maximum labeled clinical dose, and may not be relevant to clinical use.*

**Applicant proposed labeling statement:**

(b) (4)

*Reviewer's note: The Applicant's calculation of the safety margins is incorrect. The Applicant did not take into account body surface area (BSA) differences between humans and the nonclinical species used in the study. The correct calculations are provided below:*

- Total daily human ocular dose: (b) (4)
  - For 60 kg adult = (b) (4)
  - BSA conversion: (b) (4)
- Rat tumorigenic dose: 18 mg/kg
  - BSA conversion: (b) (4)

- Dose margin calculation: (b) (4)
  - Rounded to 200-fold for labeling purposes.

- Mouse NOAEL dose (no increase in tumors): 30 mg/kg
  - BSA Conversion: (b) (4)
  - Dose margin calculation: (b) (4)
    - Rounded to 160-fold for labeling purposes.

# 9 Reproductive and Developmental Toxicology

## 9.1 Fertility and Early Embryonic Development

**Salagen® labeling:**

*Oral administration of pilocarpine to male and female rats at a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on male animals, female animals, or both males and females. In dogs, exposure to pilocarpine at a dosage of 3 mg/kg/day (approximately 3 times the maximum recommended human dose when compared on the basis of body surface area (mg/m2) estimates) for six months resulted in evidence of impaired spermatogenesis. The data obtained in these studies suggest that pilocarpine may impair the fertility of male and female humans. SALAGEN® Tablets should be administered to individuals who are attempting to conceive a child only if the potential benefit justifies potential impairment of fertility.*

**Applicant Labeling Statement:**

(b) (4)

(b) (4)

*Reviewer's note: The Applicant's calculation of the safety margins is incorrect. The Applicant did not convert the mg/kg dose to mg/m$^2$ dose to account for body surface area (BSA) differences between humans and the nonclinical species used in the study. The correct calculations are provided below:*

- Total daily human ocular dose: (b) (4)
  - For 60 kg adult = (b) (4)
  - BSA conversion (b) (4)
- Rat toxic dose (impaired fertility): 18 mg/kg
  - BSA conversion (b) (4)
  - Dose margin calculation: (b) (4)
    - Rounded to 200-fold for labeling purposes.
- Dog toxic dose (sperm motility): 3 mg/kg
  - BSA conversion (b) (4)
  - Dose margin calculation: (b) (4)
    - Rounded to 110-fold for labeling purposes.

## 9.2 Embryonic Fetal Development

**Salagen® labeling:**

*Pregnancy: Teratogenic Effects*
*Pilocarpine was associated with a reduction in the mean fetal body weight and an increase in the incidence of skeletal variations when given to pregnant rats at a dosage of 90 mg/kg/day (approximately 26 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m2) estimates). These effects may have been secondary to maternal toxicity.*

**Applicant Labeling Statement:**

(b) (4)

(b) (4)

*Reviewer's note: The Applicant's calculation of the safety margins is incorrect. The Applicant did not convert the mg/kg dose to mg/m$^2$ dose to account for body surface area (BSA) differences between humans and the nonclinical species used in the study. The correct calculations are provided below:*

- Total daily human ocular dose: (b) (4)
  - For 60 kg adult = (b) (4)
  - BSA conversion (b) (4)
- Rat toxic dose (increased skeletal variations): 90 mg/kg
  - BSA conversion (b) (4)
  - Dose margin calculation: (b) (4)
    - Rounded to 970-fold for labeling purposes.

## 9.3 Prenatal and Postnatal Development

**Salagen® labeling:**

*In another study, oral administration of pilocarpine to female rats during gestation and lactation at a dosage of 36 mg/kg/day (approximately 10 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m2) estimates) resulted in an increased incidence of stillbirths; decreased neonatal survival and reduced mean body weight of pups were observed at dosages of 18 mg/kg/day (approximately 5 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m2) estimates) and above.*

**Applicant Labeling Statement:**

(b) (4)

*Reviewer's note: The Applicant's calculation of the safety margins is incorrect. The Applicant did not convert the mg/kg dose to mg/m$^2$ dose to account for body surface area (BSA) differences between humans and the nonclinical species used in the study. The correct calculations are provided below:*

- Total daily human ocular dose: (b) (4)
  - For 60 kg adult = (b) (4)
  - BSA conversion (b) (4)
- Rat toxic dose (decreased survival and body weight of pups): 18 mg/kg
  - BSA conversion (b) (4)
  - Dose margin calculation: (b) (4)
    - Rounded to 200-fold for labeling purposes.
- Rat toxic dose (increased stillbirths): 36 mg/kg
  - BSA conversion (b) (4)
  - Dose margin calculation: (b) (4)
    - Rounded to 390-fold for labeling purposes.

**9.5. Lactation**

Salagen® labeling:

> *It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SALAGEN® Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.*

The Applicant proposes the following labeling statement which differs from the approved Salagen® labeling in Section 8.2:

(b) (4)

(b) (4)

*To support the labeling statement regarding the presence of pilocarpine in lactating rats, the Applicant references:
**Omori, Y., *et al*., 2004, "Absorption, distribution and excretion of 14C-pilocarpine following oral administration to rats", *Arzneim. Forsch Drug Res*, 54: 171 – 178.**

- After single oral doses to nursing rats (0.3 mg/kg), $^{14}$C-labeled pilocarpine was detected in milk and plasma (see below). Similar peak concentrations were observed in the milk and plasma at 0.5 h and concentrations declined subsequently at similar rates, both being still detectable at 24 h.

**Mean plasma and milk concentrations of radioactivity after single 0.3 mg/kg oral doses of $^{14}$C-pilocarpine hydrochloride to nursing rats.**

| Sampling time (h) | Concentration of radioactivity (ng equivalents/g) | |
|---|---|---|
| | Plasma | Milk |
| 0.5 | 126 ± 9 | 123 ± 13 |
| 2 | 36 ± 4 | 39 ± 2 |
| 8 | 4 ± 1 | 8 ± 1 |
| 24 | 1 ± 0 | 1 ± 0 |

# 11 Integrated Summary and Safety Evaluation

The Applicant has filed a 505(b)(2) NDA for Vuity® (pilocarpine hydrochloride ophthalmic solution, 1.25%) for the treatment of presbyopia in adults. All nonclinical elements of the NDA were either referenced from NDA 020237 (Salagen), literature references or through the conduct of GLP studies. Toxicity associated to the ocular instillation of pilocarpine was limited to hyperemia and pupil dilation (an expected pharmacologic effect of pilocarpine). The NDA is approvable from a Nonclinical Pharmacology/Toxicology perspective.

| Toxicity | Species | NOAEL (mg/eye) | Safety Margin Based on unilateral ocular dose (mg/eye)* |
|---|---|---|---|
| NOAEL dose | Rabbit | 2.1 mg/eye (3% pilocarpine BID, 6 months) | (b) (4) |

*Maximum recommended human ocular dose: (b) (4) mg/eye/day

# 12 Appendix/Attachments

**Current Salagen Labeling (Nonclinical information only)**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Lifetime oral carcinogenicity studies were conducted in CD-1 mice and Sprague-Dawley rats. Pilocarpine did not induce tumors in mice at any dosage studied (up to 30 mg/kg/day, which yielded a systemic exposure approximately 50 times larger than the maximum systemic exposure observed clinically). In rats, a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in a statistically significant increase in the incidence of benign pheochromocytomas in both males and females, and a statistically significant increase in the incidence of hepatocellular adenomas in female rats. The tumorigenicity observed in rats was observed only at a large multiple of the maximum labeled clinical dose, and may not be relevant to clinical use.

No evidence that pilocarpine has the potential to cause genetic toxicity was obtained in a series of studies that included: 1) bacterial assays (Salmonella and E. coli) for reverse gene mutations; 2) an in vitro chromosome aberration assay in a Chinese hamster ovary cell line; 3) an in vivo chromosome aberration assay (micronucleus test) in mice; and 4) a primary DNA damage assay (unscheduled DNA synthesis) in rat hepatocyte primary cultures.

Oral administration of pilocarpine to male and female rats at a dosage of 18 mg/kg/day, which yielded a systemic exposure approximately 100 times larger than the maximum systemic exposure observed clinically, resulted in impaired reproductive function, including reduced fertility, decreased sperm motility, and morphologic evidence of abnormal sperm. It is unclear whether the reduction in fertility was due to effects on male animals, female animals, or both males and females. In dogs, exposure to pilocarpine at a dosage of 3 mg/kg/day (approximately 3 times the maximum recommended human dose when compared on the basis of body surface area (mg/m2) estimates) for six months resulted in evidence of impaired spermatogenesis. The data obtained in these studies suggest that pilocarpine may impair the fertility of male and female humans. SALAGEN® Tablets should be administered to individuals who are

attempting to conceive a child only if the potential benefit justifies potential impairment of fertility.

**Pregnancy: Teratogenic Effects**
Pilocarpine was associated with a reduction in the mean fetal body weight and an increase in the incidence of skeletal variations when given to pregnant rats at a dosage of 90 mg/kg/day (approximately 26 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m2) estimates). These effects may have been secondary to maternal toxicity. In another study, oral administration of pilocarpine to female rats during gestation and lactation at a dosage of 36 mg/kg/day (approximately 10 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m2) estimates) resulted in an increased incidence of stillbirths; decreased neonatal survival and reduced mean body weight of pups were observed at dosages of 18 mg/kg/day (approximately 5 times the maximum recommended dose for a 50 kg human when compared on the basis of body surface area (mg/m2) estimates) and above. There are no adequate and well-controlled studies in pregnant women. SALAGEN® Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SALAGEN® Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

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**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.**

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/s/

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ERIN M RUHLAND
10/22/2021 01:15:12 PM

LORI E KOTCH
10/22/2021 04:06:18 PM