# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214028Orig1s000

# SUMMARY REVIEW

# Cross-Discipline Team Leader and Division Director Review of NDA 214028

| | |
|---|---|
| **Review Completion Date** | See DARRTS Stamp Date |
| **From** | William M. Boyd, M.D., Wiley Chambers, M.D. |
| **Subject** | Cross-Discipline Team Leader and Division Director Review |
| **NDA #** | 214028 |
| **Applicant** | AbbVie Inc. |
| **Date of Submission** | February 22, 2021 |
| **PDUFA Goal Date** | December 22, 2021 |
| **Proprietary Name** | Vuity |
| **Established or Proper Name** | Pilocarpine hydrochloride ophthalmic solution 1.25% |
| **Dosage Form(s)** | Ophthalmic solution |
| **Dosing Regimen(s)** | One drop in both eyes once daily |
| **Regulatory Action** | Approval |
| **Indication(s)/Population(s)** | Treatment of presbyopia in adults |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Regulatory Project Manager | Diana Willard |
| Medical Officer Review | Sonal Wadhwa |
| Statistical Review | Sungwoo Choi |
| Pharmacology Toxicology Review | Erin Ruhland, |
| OPQ Review | Chunchun Zhang, Zhengfu Wang, Milton Sloan, Rose Xu, Jesse Wells |
| Clinical Pharmacology Review | Qianni Wu |
| OPDP | Carrie Newcomer |
| OSI | Roy Blay |
| CDTL Review | William M. Boyd |
| Division Director | Wiley A. Chambers |
| OSE/DMEPA | Nasim Roosta |

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

# 1. Summary

Pilocarpine hydrochloride is a cholinergic muscarinic agonist that activates muscarinic receptors located at smooth muscles such as the iris sphincter muscle and ciliary muscle. Pilocarpine HCl 1.25% contracts the iris sphincter muscle therefore constricting the pupil to enhance the depth of focus and improve near and intermediate visual acuity while maintaining some pupillary response to light. Pilocarpine hydrochloride ophthalmic solution 1.25% also contracts the ciliary muscle potentially shifting the eye to a more myopic state.

The application for Pilocarpine is submitted as a 505(b)(2) application listing Salagen NDA 20-237 and Isopto Carpine NDA 200-890 as reference drug products.

NDA 214028 Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25% will be approved for the treatment of presbyopia in adults. Two trials, Gemini 1 (1883-301-013) and Gemini 2 (1883-302-013), were submitted with this NDA to support the approval of Vuity. The results of these two clinical trials support the use of pilocarpine hydrochloride ophthalmic solution 1.25% for the treatment of presbyopia in adults. The most common adverse reactions reported in (>5%) patients are headache and conjunctival hyperemia.

## 2. Benefit-Risk Assessment

**NDA 214028 Benefit-Risk Integrated Assessment**

The data contained in this submission establishes that administration of Pilocarpine OU QD improves presbyopia in adults. Studies Gemini 1 (1883-301-013) and Gemini 2 (1883-302-013) demonstrate ability of Pilocarpine 1.25% to temporarily improve presbyopia. The most common ocular adverse events for pilocarpine at > 5% are headache and conjunctival hyperemia. The benefit of pilocarpine hydrochloride ophthalmic solution 1.25% OU QD in treating patients with presbyopia outweighs the risks to patients with presbyopia.

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**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Presbyopia is a condition in which the eye exhibits a diminished ability to focus on near objects with increasing age.<br>• Both non-surgical (reading glasses) and surgical methods (i.e., IOL exchange) for the correction of presbyopia are available.<br>• Currently there is no pharmacologic treatment for presbyopia. | Without the use of pilocarpine or reading glasses older patients will have difficulty reading small text or doing activities (e.g., sewing) at close proximity. |
| **Current Treatment Options** | • The current standard of care is use of refractive correction, i.e., reading glasses.<br>• There are no approved drug products for the treatment of presbyopia | Will give patients an option of non-invasive, reversible, pharmacologic treatment for presbyopia. |
| **Benefit** | • Will provide another treatment option for presbyopia. | Will give patients an option of non-invasive, reversible, pharmacologic treatment for presbyopia. |
| **Risk and Risk Management** | • Labeling will identify the expected adverse reactions. Pilocarpine risks are well known. | Pilocarpine in concentrations from 0.5% though 8% have been marketed for decades. Routine monitoring and reporting of all adverse events are expected to be adequate. |

# 3. Background

Presbyopia is a condition in which the eye exhibits a diminished ability to focus on near objects with increasing age. In 2005, 1.044 billion people globally were estimated to have presbyopia, and prevalence is expected to increase to 1.782 billion by 2050 (Holden 2008).

The exact cause of presbyopia is not known. The most likely cause of progressive presbyopia is a loss of elasticity of the crystalline lens, although changes in the lens's curvature from continual growth and loss of power of the ciliary muscles have also been postulated to contribute to its pathogenesis. The ability to focus on near objects declines throughout life, from an accommodation of about 20 D (ability to focus at 50 mm away) in a child, to 10 D at age 25 years (100 mm), and plateaus at 0.5 to 1 D at age 60 years (ability to focus down to 1 to 2 meters only). The first signs of presbyopia are eye strain, difficulty seeing in dim light, and problems focusing on small objects and/or fine print and are usually first noticed between the ages of 40 and 50 years. Uncorrected near-vision impairment caused by presbyopia may have a negative impact on activities of daily living, career options, and self-esteem.

There are currently no approved therapeutic products in the US for presbyopia. Both non-surgical and surgical methods for the correction of presbyopia are available. Traditional non-surgical methods of refractive correction for presbyopia include the use of dedicated reading spectacles, bifocal or multifocal spectacles, and monovision or multifocal contact lenses. A number of surgical techniques are also used for the treatment of presbyopia, which include monovision PRK or LASIK, conductive keratoplasty, intraocular lenses, and corneal inlays. However, for each of the existing technologies mentioned above, visual quality is reduced at one or more viewing distances (near, 40 cm; intermediate, 66 cm; distance, 4 m or more) and each comes with its own unique safety risks and complications. Commonly used reading glasses help with near vision but reduce vision at all other distances. Bifocals and progressive lenses (i.e., glasses, contacts) produce optical aberrations especially at intermediate distances, may compromise intermediate vision, and can increase the risk of falls. Multifocal optics reduce image quality uniformly at all viewing distances. The widespread number of surgical technologies is limited due to surgical risks, the need for repositioning, explantation, or regression of effect. Thus, there remains a need for improved methods for correcting presbyopia.

(b) (4)

(b) (4) The applicant conducted 3 Phase 2 studies evaluating the safety and efficacy of pilocarpine, oxymetazoline, and/or pilocarpine and oxymetazoline combination therapies (Studies 199201-007, 199201-009, and 199201-010). Results from these studies led to the conclusion that the early indications of an efficacy contribution from oxymetazoline in Study 199201-007 were not substantial or reproducible, and that oxymetazoline did not offer additional clinically meaningful improvements in safety or efficacy when combined with pilocarpine to improve uncorrected near visual acuity (UNVA) in Studies 199201-009 and 199201-010. Therefore, the applicant proceeded with the development of pilocarpine monotherapy for the treatment of presbyopia. Through modeling and evaluation of the Phase 2 study results, the sponsor believes the optimal dose of pilocarpine hydrochloride ophthalmic solution monotherapy to be 1.25% for

the treatment of presbyopia.

The Phase 3 clinical development program in support of the proposed indication consists of 2 Phase 3 studies [Gemini 1 (Study 1883-301-013) and Gemini 2 (1883-302-013)], which used the intended commercial formulation. The objectives of these studies were to evaluate the efficacy and safety of pilocarpine hydrochloride ophthalmic solution 1.25% versus vehicle when administered bilaterally, once daily for 30 days in participants with presbyopia. The 2 studies are broadly identical in design, except in Study 1883-301-013 (Gemini 1) the systemic pharmacokinetics of pilocarpine hydrochloride ophthalmic solution 1.25% were characterized in a subset of approximately 10% of all enrolled participants.

The following meetings were conducted under IND 122483 for this application:
- End of Phase 2 Meeting 11/30/18
- Pre-NDA Meeting 12/11/19
- Type C Meeting 7/21/20.

Pilocarpine is not approved in any country for the treatment of presbyopia.

# 4. Product Quality

OPQ completed their integrated review of the original application on 10/22/2021.

## 4.1. Drug Substance

Pilocarpine hydrochloride, USP drug substance is the subject of the Type II DMF No. (b) (4) by (b) (4)

**Specifications for Pilocarpine hydrochloride, USP Drug Substance**

| Test | Acceptance Criteria | Method |
|---|---|---|
| Physical appearance | Colorless, translucent, odorless, faintly bitter crystals | Visual |
| Residual solvents (%) | | GC (USP) |
| (b) (4) | NMT (b) (4) | |
| (b) (4) | NMT (b) (4) | |
| (b) (4) | NMT (b) (4) | |
| (b) (4) | NMT (b) (4) | |
| Microbial enumeration (CFU/g) | | |
| Total aerobic microbial count | (b) (4) | USP <61> |
| Total combined yeasts and molds count | (b) (4) | |

Source: Module 3.2.S.4.1

## 4.2. Drug Product

The drug product is a clear, colorless, sterile ophthalmic solution containing 1.25% of pilocarpine hydrochloride.

**Composition of Drug Product**

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

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

[a] Per Type II DMF No. (b) (4)

Source: Module 3.2.P.1

## 4.3. Drug Product Specification

The pilocarpine hydrochloride 1.25% ophthalmic solution specification is provided below.

**Specifications for Pilocarpine Hydrochloride 1.25% Ophthalmic Solution**

| Test Parameter | Acceptance Criteria | Analytical Procedure | Where Applied | |
|---|---|---|---|---|
| | | | Release | Stability |
| Physical Appearance | Clear and colorless solution. Free of particulate matter. | Visual | X | X |
| Pilocarpine HCl Identification | | DP-LC-0933 | X | |
| HPLC (retention time) | Positive for Pilocarpine | HPLC - UV | | |
| HPLC (UV spectrum) | Positive for Pilocarpine | HPLC - PDA | | |
| Pilocarpine HCl Concentration (% label claim) | (b) (4) | DP-LC-0933<br>HPLC - UV | X | X |
| Individual Pilocarpine Impurity (% LS) | | DP-LC-0933<br>HPLC - UV | X | X |
| (b) (4) | NMT (b) (4) | | | |
| (b) (4) | NMT (b) (4) | | | |
| Individual Unspecified | NMT (b) (4) | | | |

| | | | | |
|---|---|---|---|---|
| Total Impurities (%LS) | NMT (b) (4) | | | |
| Benzalkonium Chloride Concentration (% label claim) | (b) (4) | DP-LC-0932<br>HPLC - UV | X | X |
| Osmolality (mOsm/kg) | (b) (4) | Freezing Point Depression<br>USP <785> | X | X |
| pH | (b) (4) | Electric Potential<br>USP <791> | X | X |
| Particulate Matter (count) | NMT (b) (4) Particles/mL ≥ (b) (4) µm<br>NMT (b) (4) Particles/mL ≥ (b) (4) µm<br>NMT Particles/mL ≥ (b) (4) µm | Light Obscuration<br>USP <789> | X | X |
| Sterility | Meets compendial requirement | USP <71> | X | X |

[1] Corresponds to (b) (4) % w/w
[2] Corresponds to (b) (4) % w/w

Source: Module 3.2.P.5

## 4.4. Drug Product Container Closure

Pilocarpine hydrochloride 1.25% ophthalmic solution is supplied sterile in a colorless low density polyethylene bottle, tip and high impact polystyrene dark green cap in 1.5 mL fill in a 5 mL (physician sample) container and 2.5 mL fill in a 5 mL container (commercial product). (b) (4) Primary packaging components are described in the table below.

**Primary Packaging Components**

| | Fill Volume | Bottle | Tip | Cap | Label Adhesive |
|---|---|---|---|---|---|
| Description | 1.5 mL<br>2.5 mL | 5 mL round bottle, (b) (4) | 15 mm dropper, (b) (4) | 15 mm cap, (b) (4) | (b) (4) |
| (b) (4) | | Low density polyethylene | Low density polyethylene | High impact polystyrene | Not applicable |
| Color | | Colorless | Colorless | Dark green | Not applicable |
| Sterilization | | (b) (4) | (b) (4) | (b) (4) | Not applicable |

Source: Module 3.2.P.7

## 4.5. Microbiology

Pilocarpine hydrochloride 1.25% ophthalmic solution is a sterile solution intended for topical ophthalmic administration. (b) (4) material is sampled and assayed according to a validated test method in order to determine the total viable bioburden of the formulation. Antimicrobial preservative effectiveness testing (APET) is performed according to USP <51> and ICH guideline Q1A (R2) during stability studies.

All batches of finished product are subjected to a release sterility test. Subsequent testing of the stability batches is performed annually.

(b) (4) bioburden test is performed (b) (4) (b) (4) to ensure that the (b) (4) bioburden levels do not exceed levels per current GMP and EMA/CHMP/CVMP/QWP/850374/2015, CPMP/QWP/486/95. Results are tested against established internal acceptance criteria.

Antimicrobial preservative effectiveness results for development and primary batches indicate that the drug product met USP antimicrobial preservative effectiveness criteria for topical ophthalmic drug products at all test timepoints.

## 4.6. Establishment Information

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on 10/14//2021.

**Facility Level Evaluation of Drug Substance Manufacturer**

| **Facility name/FEI** | (b) (4) |
|---|---|
| **DMF#** | (b) (4) |
| **Any special manufacturing/storage condition?** | No |
| **Previous OPMA evaluation** | Relevant and acceptable. |
| **Initial Facility Assessment** | |
| **Process experience** | Experience manufacturing the proposed DS with no significant process/facility |
| **Quality oversight** | Recent, relevant 483s with adequate CAPAs |
| **Other potential contributing risk factors** | No additional risk factors identified |
| **Data concerns** | No unique concerns about batch data |
| **PAI / 704(a)(4)** | No |
| **Facility Status Assessment: Approve - Based on Previous History**<br>The firm is acceptable based on the previous inspection history and the firm's manufacturing capability. | |

**List of Testing Facilities**

The following commercial DS/DP Control Testing Laboratories have been proposed by the applicant to support external testing function of the pending drug product. The facilities proposed below, unless noted otherwise, are within compliance standards and have the ability to perform the function and responsibilities outline in the application following assessment:

| Facility Name/FEI | Responsibilities | Previous OPMA evaluation |
|---|---|---|
| Allergan Pharmaceuticals Ireland / FEI 3002806285 | Drug product stability testing | Relevant and acceptable. |

### 4.7. Office of Product Quality Recommendation

From the OPQ integrated review dated 10/22/2021:

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality microbiology and manufacturing process aspects.

The product is regulated as a drug device combination product per the Genus decision. The drug product is packaged in a multi-dose LDPE eyedropper, and OPPQ considered it as a class 2 combination product and no CDRH quality system (QS)/GMP consult is necessary. The 356h form was updated including all the device facilities per the Agency's request on Oct 12, 2021. OPMA has issued an overall acceptable recommendation for all the facilities on Oct 14, 2021.

Therefore, NDA 214028 is recommended approval from Product Quality perspective.

## 5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 10/22/2021:

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.

From the labeling from the product:


## 6. Clinical Pharmacology

From the original Clinical Pharmacology review dated 10/12/2021:

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.

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<br>10 mg: 41 | 3.7±3.2 |
| AUC (ng*h/mL) | 4.14±2.16 [c] | 5 mg: 33 [d]<br>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. $AUC_{0\text{-}10hr,ss}$
d. $AUC_{0\text{-}6hr,ss}$
e. $AUC_{0\text{-}6hr,ss}$ (timepoints were measured up to 6 hours post dose on Day 8)

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 Cmax 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.

## 7. Clinical/Statistical- Efficacy

From the original Medical Officer Review dated 10/28/2021:

The two studies which provide the main support for efficacy were: Gemini 1 (1883-301-013) and Gemini 2 (1883-302-013).

Gemini 1 was a multicenter, double-masked, randomized, parallel-group, vehicle-controlled, Phase 3 study in participants with presbyopia. Participants received AGN-190584 1.25% or vehicle dosed once daily, bilaterally, for 30 days. Approximately 300 participants with presbyopia were to be enrolled at approximately 50 sites in the US.

Gemini 2 was a multicenter, double-masked, randomized, parallel-group, vehicle-controlled, Phase 3 study in participants with presbyopia. Participants received AGN-190584 1.25% or vehicle dosed once daily, bilaterally, for 30 days. Approximately 400 participants with presbyopia were to be enrolled at approximately 50 sites in the US.

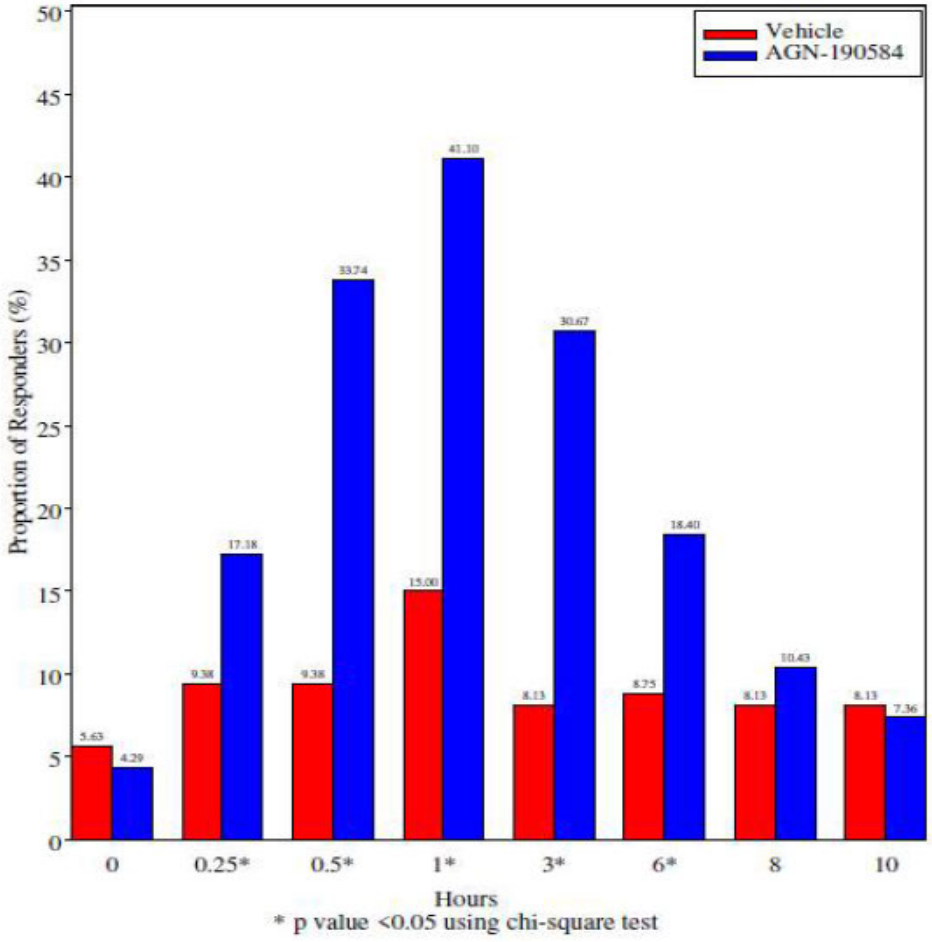
The primary efficacy endpoint in both studies was the proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA at Day 30, Hour 3. The primary efficacy endpoint was analyzed using a chi-square test with a 2-sided 95% confidence interval (CI); missing data was imputed as 3-line gain failure.

**Gemini 1 (1883 301 013) Efficacy Results – Primary Endpoint**

Gemini 1 (1883-301-013): Mesopic, High Contrast, Binocular DCNVA: Analysis of Participants With 3-Line Improvement (ITT Population)

| | Vehicle<br>N=160 | AGN-190584<br>N=163 |
|---|---|---|
| Day 1, 0.25 Hour | | |
| Responder Rate | 5/159 (3.1%) | 11/161 (6.8%) |
| Difference % | | 3.7% |
| 95% CI | | (-1.1, 8.4) |
| P-value | | 0.1302 |
| | | |
| Day 30, 3 Hour | | |
| Responder Rate | 13/153 (8.5%) | 50/163 (30.7%) |
| Difference % | | 22.5% |
| 95% CI | | (14.3, 30.8) |
| P-value | | <0.0001 |

Figure 11-1 Proportion of Participants with at Least Three Line Improvement from Baseline at Day 30: Mesopic, High-contrast, Binocular DCNVA (ITT Population)




Source: Figure 14.2-5.3

At Day 30, Hour 3, the proportion of participants with a 3-line, mesopic DCNVA improvement was 30.7% (50/163) in the AGN-190584 group compared with 8.1% (13/160) in the vehicle group. The percent rate difference between groups (95% CI) of 22.5% (14.3, 30.8) was statistically significant ($p < 0.0001$) in favor of the AGN-190584 group.

Post-hoc analysis

An additional analysis of the primary efficacy endpoint was performed with the added criterion that participants did not lose more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3.

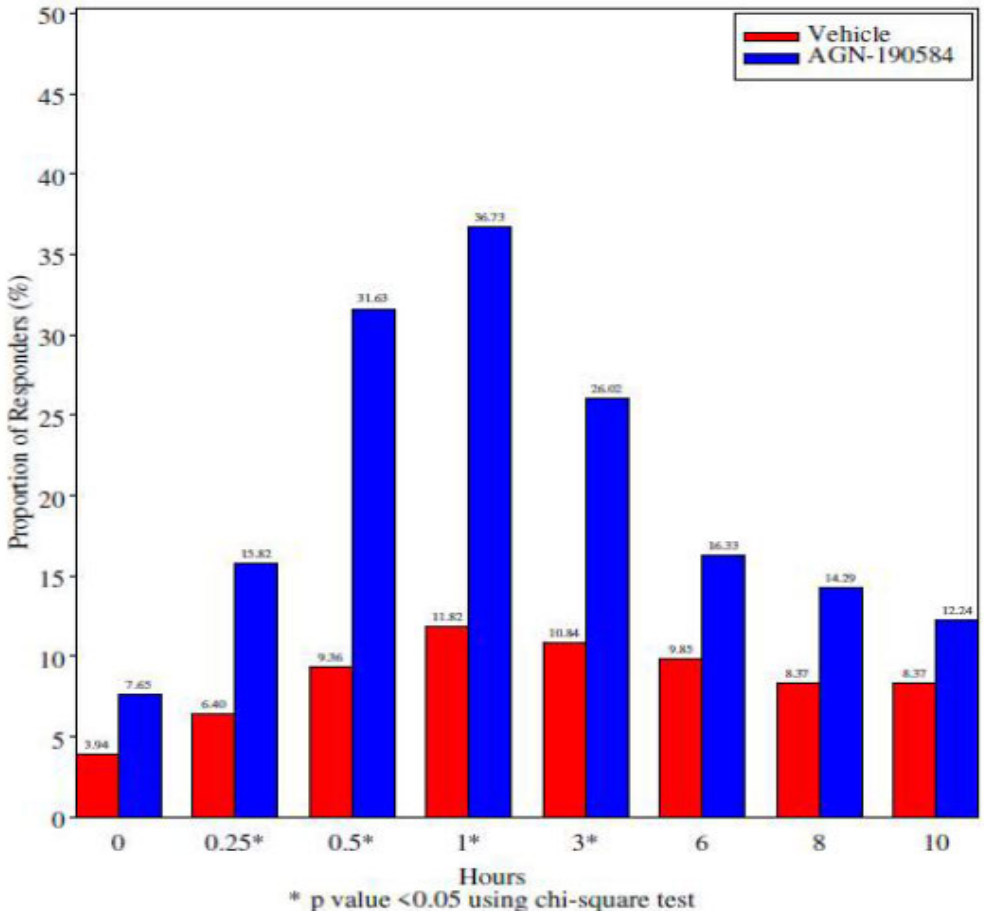
At Day 30, Hour 3, the proportion of participants that achieved a 3-line, mesopic DCNVA improvement without losing more than 5 letters of CDVA with the same refractive correction was 30.7% (50/163) in the AGN-190594 group compared with 8.1% (13/160) in the vehicle group. The percent rate difference between groups (95% CI) of 22.5% (14.3, 30.8) was statistically significant ($p < 0.0001$) in favor of the AGN-190584 group. This post-hoc analysis demonstrated an identical outcome to the primary efficacy analysis.

**Gemini 2 (1883 301 013) Efficacy Results – Primary Endpoint**

Gemini 2 (1883-302-013): Mesopic, High Contrast, Binocular DCNVA: Analysis Of Participants With 3-Line Improvement in DCNVA Without Losing More Than 5 Letters of CDVA (ITT Population)

| | Vehicle N=215 | AGN-190584 N=212 |
|---|---|---|
| Day 1, 0.25 Hour | | |
| Responder Rate | 3/203 (1.5%) | 10/196 (5.1%) |
| Difference % | | 3.6% |
| 95% CI | | 0.1, 7.1 |
| P-value | | 0.0415 |
| | | |
| Day 30, 3 Hour | | |
| Responder Rate | 22/198 (10.8%) | 51/196 (26.0%) |
| Difference % | | 15.2% |
| 95% CI | | 7.7, 22.7 |
| P-value | | <0.0001 |

**Figure 11-1** **Proportion of Participants with at Least 3-line Improvement from Baseline at Day 30: Mesopic, High-contrast, Binocular DCNVA (ITT Population)**



At Day 30, Hour 3, the proportion of participants with a 3-line, mesopic DCNVA improvement without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction was 26.0% (51/196) in the AGN-190584 group compared with 10.8% (22/203) in the vehicle group. The percent rate difference between groups (95% CI) of 15.2% (7.7, 22.7) was statistically significant ($p < 0.0001$) in favor of the AGN-190584 group.

## Efficacy Summary Statement

Studies Gemini 1 and Gemini 2 demonstrated efficacy in their primary endpoints, i.e., the proportion of participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA without losing more than 5 letters of mesopic, high-contrast, binocular CDVA with the same refractive correction at Day 30, Hour 3.

# 8. Safety

From the original Medical Officer Review dated 10/28/2021:

## 8.1. Safety Database

The two studies which provide the main support for safety and efficacy were:
Gemini 1 (1883-301-013) and Gemini 2 (1883-302-013).

Gemini 1 (1883-301-013): Extent of Exposure (Safety Population)

| | Vehicle N=159 | AGN-190584 N=163 |
|---|---|---|
| Treatment Duration (Days) | | |
| >= 7 Days | 155 | 161 |
| >= 14 Days | 153 | 161 |
| >= 21 Days | 153 | 161 |
| >= 28 Days | 143 | 153 |
| | | |
| Mean (sd) | 28.8 (5.1) | 29.3 (3.2) |
| Min, Max | 1, 39 | 3, 39 |

Gemini 2 (1883-302-013): Extent of Exposure (Safety Population)

| | Vehicle N=215 | AGN-190584 N=212 |
|---|---|---|
| Treatment Duration (Days) | | |
| >= 7 Days | 213 | 209 |
| >= 14 Days | 210 | 208 |
| >= 21 Days | 209 | 207 |
| >= 28 Days | 193 | 193 |
| | | |
| Mean (sd) | 29.0 (4.1) | 29.2 (4.4) |
| Min, Max | 1, 46 | 1, 43 |

## 8.2. Deaths

There were no deaths in either Study Gemini 1 or Gemini 2.

## 8.3. Serious Adverse Events

Gemini 1(1883-301-013)
No serious TEAEs were reported in the safety population. One 46-year-old, female participant (b) (6) had a serious adverse event (porphyria) during screening, which was moderate in intensity and resolved. This participant was not enrolled or included in the safety population; thus, a narrative was not prepared.

Gemini 2 (1883-302-013)
No serious TEAEs were reported in the AGN-190584 group. Two participants in the vehicle group had serious TEAEs of dysphagia and Guillain-Barre syndrome.

## 8.4. Treatment Emergent Adverse Events and Adverse Reactions

Gemini 1(1883-301-013): Ocular Treatment Emergent AEs

| | Vehicle N=159 | AGN-190584 N=163 |
|---|---|---|
| Headache | 6 | 7 |
| Visual impairment | 1 | 7 |
| Conjunctival hyperemia | 4 | 4 |
| Vision blurred | 2 | 4 |
| Eye irritation | 1 | 4 |
| Eye pain | 1 | 4 |
| Lacrimation increased | 0 | 4 |
| Dry eye | 3 | 2 |
| Asthenopia | 0 | 2 |
| Photophobia | 0 | 2 |
| Punctate keratitis | 5 | 1 |
| Vital dye staining cornea present | 2 | 1 |
| Meibomian gland dysfunction | 1 | 1 |
| Chalazion | 0 | 1 |
| Dyschromatopsia | 0 | 1 |
| FBS in eyes | 0 | 1 |
| Glare | 0 | 1 |
| Lacrimation decreased | 0 | 1 |
| Migraine with aura | 0 | 1 |
| Paranasal sinus discomfort | 0 | 1 |
| Visual field defect | 0 | 1 |
| Vitreous floaters | 0 | 1 |
| Conjunctival disorder | 1 | 0 |

| | Vehicle N=159 | AGN-190584 N=163 |
|---|---|---|
| Conjunctival hemorrhage | 1 | 0 |
| Conjunctival edema | 1 | 0 |
| Eye pruritis | 1 | 0 |

For Gemini 1, the TEAEs were reported for 35.0% (57/163) of participants in the AGN-190584 group compared with 23.3% (37/159) of participants in the vehicle group. The TEAEs reported for at least 2 participants (≥ 1%) in either treatment group, in order of descending incidence, were: headache, visual impairment, conjunctival hyperemia, vision blurred, eye irritation, eye pain, lacrimation increased, nausea, dry eye, asthenopia, photophobia, and hypertension in the AGN-190584 group; and headache, punctate keratitis, conjunctival hyperemia, dry eye, vision blurred, and vital dye staining cornea present in the vehicle group.

Gemini 2 (1883-302-013): Ocular Treatment Emergent AEs

| | Vehicle N=215 | AGN-190584 N=212 |
|---|---|---|
| Conjunctival hyperemia | 11 | 15 |
| Vision blurred | 1 | 13 |
| Eye pain | 3 | 12 |
| Eye irritation | 1 | 5 |
| Punctate keratitis | 6 | 3 |
| FBS in eyes | 2 | 3 |
| Visual acuity reduced | 1 | 3 |
| Visual impairment | 0 | 3 |
| Lacrimation increased | 2 | 2 |
| Abnormal sensation in eye | 0 | 2 |
| Vitreous floaters | 0 | 2 |
| Keratitis | 2 | 1 |
| Cataract | 0 | 1 |
| Conjunctival edema | 0 | 1 |
| Dry eye | 0 | 1 |
| Eyelid margin crusting | 0 | 1 |
| Glare | 0 | 1 |
| Halo vision | 0 | 1 |
| Metamorphopsia | 0 | 1 |
| Photopsia | 0 | 1 |
| Psuedomyopia | 0 | 1 |
| Swelling of eyelid | 0 | 1 |
| Vitreous degeneration | 0 | 1 |
| Vitreous detachment | 0 | 1 |
| Eye discharge | 2 | 0 |
| Chalazion | 1 | 0 |
| Corneal cyst | 1 | 0 |

| | Vehicle N=215 | AGN-190584 N=212 |
|---|---|---|
| Eye pruritis | 1 | 0 |
| Eyelid edema | 1 | 0 |
| Lacrimal disorder | 1 | 0 |
| Lacrimation decreased | 1 | 0 |

For Gemini 2, the TEAEs reported in the AGN-190584 group (34.4%, 73/212), compared with the vehicle group (23.7%, 51/215). The TEAEs reported for at least 1% of participants in either treatment group, in order of descending incidence, were: headache, conjunctival hyperemia, vision blurred, eye pain, eye irritation, punctate keratitis, foreign body sensation in eyes, visual acuity reduced, visual impairment, and nausea in the AGN-190584 group; and conjunctival hyperemia, headache, punctate keratitis, eye pain, and nasopharyngitis in the vehicle group.

Gemini 1(1883-301-013): Non-Ocular Treatment Emergent AEs reported in more than 1 subject

| | Vehicle N=159 | AGN-190584 N=163 |
|---|---|---|
| Nausea | 0 | 4 |
| Headache | 9 | 16 |
| HTN | 1 | 2 |

Gemini 2 (1883-302-013): Non-Ocular Treatment Emergent AEs reported in more than 1 subject

| | Vehicle N=215 | AGN-190584 N=212 |
|---|---|---|
| Nausea | 0 | 3 |
| Nasopharyngitis | 3 | 1 |
| Headache | 9 | 23 |
| Dizziness | 0 | 2 |
| Sinus headache | 1 | 1 |
| Cough | 1 | 1 |

Headache and nausea were the only non-ocular TEAEs were reported in 1% or more of subjects in either treatment group in the Gemini 1 or Gemini 2 study.

## Safety Summary Statement

The safety database contained in this submission establishes the safety of Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25% dosed once daily in both eyes for the treatment of presbyopia in adults.

The following TEAEs of special interest were examined: headache TEAEs with preferred terms of headache, migraine, migraine with aura, and sinus headache; and vision impairment TEAEs with preferred terms of vision blurred, visual impairment, and visual field defect. Findings indicated that all TEAEs of special interest were numerically more common in the AGN-190584

group compared with the vehicle group. See the original Medical Officer Review dated 10/28/2021, Section 8.5.1.

## 9. Advisory Committee Meeting

The application did not raise any new efficacy or safety issues. There were no issues that were thought to benefit from a discussion at an advisory committee meeting. An Advisory Committee Meeting was not held for the NDA.

## 10. Pediatrics

Pilocarpine ophthalmic solution in multiple concentrations including those at least 4 times the concentration proposed in this application has been used in children for the treatment of elevated intraocular pressure for many decades. The safety profile in children is the same as the safety profile in adults.

The Applicant requested a full waiver for pediatric subjects 0 to 17 years of age because studies are impossible or highly impracticable. Presbyopia is included on the automatic waiver list as a condition that is rare in pediatric patients.

At the PeRC meeting on 8/24/21 Perc agreed with granting the full waiver for pediatric subjects 0 to 17 years of age because studies would be impossible or highly impractical as there are too few patients to study.

## 11. BIOSTATISTICS

Per the original Biostatistics review dated 10/21/2021:

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

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

The primary efficacy endpoint of the two studies is the proportion of the participants gaining 3 lines or more from baseline in mesopic, high-contrast, binocular DCNVA without losing more than 1 line (5 letters) of mesopic, high-contrast, binocular corrected distance visual acuity

(CDVA) with the same refraction, at Day 30, Hour 3. Table 1 summarizes the primary analysis results.

**Table 1: Primary analysis results for the primary efficacy endpoint**

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

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

## 12. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There were no investigators with disclosable financial interests/arrangements (Form FDA 3455). There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the Applicant for covered studies [i.e., Gemini 1, Gemini 2].

Covered Clinical Study (Name and/or Number): Gemini 1 (1883-301-013)

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 36 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be | | |

| | | |
|---|---|---|
| influenced by the outcome of the study: Not applicable<br>Significant payments of other sorts: Not applicable<br>Proprietary interest in the product tested held by investigator: Not applicable<br>Significant equity interest held by investigator in S: Not applicable<br>Sponsor of covered study: Not applicable | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

Covered Clinical Study (Name and/or Number): Gemini 2 (1883-302-013)

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 36 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Not applicable<br>Significant payments of other sorts: Not applicable<br>Proprietary interest in the product tested held by investigator: Not applicable<br>Significant equity interest held by investigator in S: Not applicable<br>Sponsor of covered study: Not applicable | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to | Yes ☐ | No ☐ (Request information |

| | | |
|---|---|---|
| minimize potential bias provided: | | from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

## 13. Study Integrity

A routine Office of Scientific Investigations (OSI) audit was requested. Per the OSI review dated 9/17/2021:

Inspections were requested for the following protocols in support of this application:

- Protocol 1883-301-013 (GEMINI 1): A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584in Participants with Presbyopia

- Protocol 1883-302-013 (GEMINI 2): A Phase 3, Multicenter, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety and Efficacy of AGN-190584 in Participants with Presbyopia

The studies are essentially identical Phase 3 multicenter, double-masked, randomized, parallel-group, vehicle-controlled studies in adult subjects meeting the study selection criteria for presbyopia.

The clinical sites of Drs. David Wirta and Jennifer Kim were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

## 14. DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed proprietary name, Vuity, and found the proposed name conditionally acceptable on 4/26/2021.

DMEPA finalized a review of the originally submitted labeling on 8/6/2021. They completed a review of the revised container label and carton labeling received on 10/12 2021, for Vuity and found the labeling acceptable.

## 15. OPDP

The Office of Prescription Drug Promotion (OPDP) completed a review of the product labeling dated 10/19/2021.

## 16. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

| | | | | |
|---|---|---|---|---|
| X | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | X | Clinical outcome assessment (COA) data, such as | | See Sec 7 Study endpoints |
| | | □ | Patient reported outcome (PRO) | |
| | | □ | Observer reported outcome (ObsRO) | |
| | | X | Clinician reported outcome (ClinRO) | |
| | | □ | Performance outcome (PerfO) | |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Natural history studies | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | □ | Other: (Please specify) | | |
| □ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | □ | Input informed from participation in meetings with patient stakeholders | |
| | | □ | Patient-focused drug development or other stakeholder meeting summary reports | |
| | | □ | Observational survey studies designed to capture patient experience data | |
| | | □ | Other: (Please specify) | |
| □ | Patient experience data was not submitted as part of this application. | | | |

## 17. Labeling

The application for NDA 214028 Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25% for the treatment of presbyopia in adults will be approved with the attached labeling [Section 19 Appendix of this review] submitted 10/27/2021 (package insert) and 10/12/2021 (carton and container labeling).

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## 18. Regulatory Action

NDA 214028 Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25% will be approved for the treatment of presbyopia in adults. There are no recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

## 19. Appendix

The application for NDA 214028 Vuity (pilocarpine hydrochloride ophthalmic solution) 1.25% for the treatment of presbyopia in adults will be approved with the attached labeling submitted 10/27/2021 (package insert) and 10/12/2021 (carton and container labeling).

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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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