CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206966Orig1s000

CLINICAL REVIEW(S)

Clinical Memorandum: Approval of Resubmission NDA 206966

On September 14, 2015, the Applicant (Dr. Reddy's Laboratories, SA) submitted NDA 206966 for Xeglyze (abametapir) lotion, 0.74% for the treatment of head lice infestation in patients 6 months of age and older. On August 30, 2016, the Agency issued a Complete Response Letter because of deficiencies discovered during an inspection of Dr. Reddy's Lab Ltd. CTO Unit VI (FEI 3002949085) manufacturing facility.

On November 12, 2019, the Applicant resubmitted NDA 206966. The resubmission included a new site as an alternative drug substance manufacturing facility, additional drug product information and stability data, and updated manufacturing process and facilities information. The resubmission contained no new clinical information. On April 23, 2020, the Office of Pharmaceutical Quality (OPQ) issued an Integrated Quality Assessment. On May 4, 2020, the OPQ issued a memorandum with final recommendations and conclusions regarding approvability. The major deficiency was that "the required preapproval inspection of the drug substance testing facility, (b) (4) is still pending due to travel restrictions associated with the COVID-19 pandemic, and OPMA has made a final recommendation of (b) (4) for the facility." This deficiency was conveyed to the Applicant in a Discipline Review Letter date May 4, 2020.

On May 11, 2020, the Applicant submitted an Information Amendment which included alternative drug substance testing facilities which have been recently inspected. After discussion, the review team agreed to a 3 month extension of the goal date. The extended user fee goal date is now August 12, 2020. This was conveyed to the Applicant in a letter dated May 12, 2020. The letter also requested that the Applicant:

> "…update your NDA by May 19, 2020 with the name(s) of facility(ies) that you plan on using to replace Lucid Laboratories. Additionally, include a statement that you plan to rely only on the data from the newly added facility(ies) for (b) (4) testing for the release of the drug substance."

On May 19, 2020, the Applicant submitted a Quality Module Information Amendment containing the requested information. Per the OPQ memorandum by Dr. Hamid Shafiei, dated June 5, 2020:

"The proposed two new drug substance testing facilities have been reviewed by the facilities reviewer, Dr. Aditi Thakur. Dr. Thakur has found the proposed new testing facilities adequate to support the approval of this application.

Also, on June 1, 2020, the Applicant submitted updated PI labeling and carton/container labels. The updated PI labeling, and carton/container labels have adequately addressed all CMC deficiencies that were noted during the second review cycle for this application.

Therefore, from the OPQ perspective, this NDA is now recommended for **approval** with the expiration dating period of **36 months**."

Therefore, I also recommend approval of NDA 206966 for Xeglyze lotion for the treatment of head lice infestation in patients 6 months of age and older.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KEVIN L CLARK
06/05/2020 05:12:56 PM

GORDANA DIGLISIC
06/08/2020 11:24:13 AM

Clinical Memorandum: Extension of NDA 206966

On May 5, 2020, I filed a Clinical Memorandum in DARRTS stating my agreement with Complete Response to the resubmission of NDA 206966. The Complete Response was based on the inability to complete a required preapproval inspection of a drug substance testing facility, (b) (4) This deficiency was conveyed to the Applicant in a Discipline Review Letter date May 4, 2020.

On May 11, 2020, the Applicant submitted an Information Amendment which included alternative drug substance testing facilities which have been recently inspected. After discussion, the review team agreed to a 3 month extension of the goal date. The extended user fee goal date is now August 12, 2020. This was conveyed to the Applicant in a letter dated May 12, 2020. The letter also requested that the Applicant:

> "…update your NDA by May 19, 2020 with the name(s) of facility(ies) that you plan on using to replace (b) (4). Additionally, include a statement that you plan to rely only on the data from the newly added facility(ies) for (b) (4) testing for the release of the drug substance."

In summary, the plan for Complete Response has been withdrawn and an extension granted to review additional information to be submitted by the Applicant.

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/s/

KEVIN L CLARK
05/12/2020 04:29:39 PM

GORDANA DIGLISIC
05/14/2020 06:06:32 PM

Clinical Memorandum: Resubmission of NDA 206966

On September 14, 2015, the Applicant (Dr. Reddy's Laboratories, SA) submitted NDA 206966 for Xeglyze (abametapir) lotion, 0.74% for the treatment of head lice infestation in patients 6 months of age and older. On August 30, 2016, the Agency issued a Complete Response Letter because of deficiencies discovered during an inspection of Dr. Reddy's Lab Ltd. CTO Unit VI (FEI 3002949085) manufacturing facility.

On November 12, 2019, the Applicant resubmitted NDA 206966. The resubmission included a new site as an alternative drug substance manufacturing facility, additional drug product information and stability data, and updated manufacturing process and facilities information. The resubmission contained no new clinical information. On April 23, 2020, the Office of Pharmaceutical Quality (OPQ) issued an Integrated Quality Assessment. On May 4, 2020, the OPQ issued a memorandum with final final recommendations and conclusions regarding approvability:

> "At the time of the review of the resubmission of this NDA, the Office (of) Pharmaceutical manufacturing Assessment had made a recommendation of "Withhold" for the drug substance manufacturing facility, Dr. Reddy's Lab Ltd. CTO Unit VI (FEI 3002949085). As of April 30, the status for this manufacturing facility has been changed to "Compliant". However, the following deficiencies still exist:
>
> 1) The required preapproval inspection of the drug substance testing facility, (b) (4) is still pending due to travel restrictions associated with the COVID-19 pandemic, and OPMA has made a final recommendation of (b) (4) for the facility.
> 2) The resolution of the currently pending CMC labels/labeling issues have been deferred to (the) next review cycle.
>
> Therefore, from the OPQ perspective, this NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(6),(13) until the above issues are satisfactorily resolved."

I concur with the recommendations and conclusion from OPQ recommending a Complete Response to the resubmission of NDA 206966.

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/s/

KEVIN L CLARK
05/05/2020 02:48:14 PM

GORDANA DIGLISIC
05/05/2020 05:49:55 PM

Office Deputy Director Decisional Memo

Date	August 25, 2016
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director Decisional Memo
NDA/BLA #	NDA 206966
Applicant Name	Dr. Reddy's Laboratories
Date of Submission	September 14, 2015
PDUFA Goal Date	September 14, 2016
Proprietary Name / **Established (USAN) Name**	Xeglyze/ abametapir
Dosage Forms / Strength	Lotion/0.74%
Applicant Proposed Indication(s)	[redacted] (b) (4) indicated for the topical treatment of head lice infestation [redacted] (b) (4) in patients 6 months of age and older. (b) (4) [redacted]
Action:	Complete response
Approved Indication(s)/Populations	N.A.

Material Reviewed/Consulted	Names of discipline reviewers
Medical Officer Review	Kevin Clark, MD
CDTL Review	Gordana Diglisic, MD
Division Director Review	Kendall Marcus, MD
Statistical Review	Carin Kim, PhD
Pharmacology Toxicology Review	Jill Merrill, PhD
CMC Review/ONDQA Review	Yichun Sun, PhD
ONDQA Biopharmaceutics Review	Vidula Kolhatkar, PhD
Microbiology Review	Eric Adeeku, PhD
Clinical Pharmacology Review	Doanh Tran, PhD
DPMH	Erica Radden, MD (pediatrics); Christos Mastroyannis, MD (maternal health)
OPDP	Tara Turner, PharmD, MPH
OSI	Roy Blay, PhD
OSE/DMEPA	Hina Mehta, PharmD
OSE/DRISK	Erin Hachey, Pharm.D.

CDTL=Cross-Discipline Team Leader
CMC=Chemistry Manufacturing and Controls
ONDQA=Office of New Drug Quality Assurance
DPMH=Division of Pediatric and Maternal Health
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Benefit-Risk Summary and Assessment

Xeglyze (abametapir) lotion is a topically administered metalloproteinase inhibitor. This memo documents my concurrence with the Division of Dermatology and Dental Products Complete Response (CR) recommendation for NDA 206966 for Xeglyze (abametapir) lotion, 0.74%, a pediculicide for the topical treatment of head lice infestation in patients 6 months of age and older.

Efficacy was established in two double-blind, vehicle-controlled trials in 216 head-lice infested subjects, age 6 months and older, on the primary endpoint of proportion of index subjects who were lice free at all follow-up visits through Day 14. In both trials, Xeglyze lotion demonstrated a statistically significant improvement, relative to vehicle control, in the primary endpoint. In Trial 1, 81% of Xeglyze-treated subjects versus 51% of vehicle-treated subjects achieved the primary endpoint ($p=0.001$), while in Trial 2, 82% of Xeglyze-treated subjects versus 47% of vehicle-treated subjects achieved the primary endpoint ($p<0.001$).

The safety of Xeglyze was assessed in two Phase 3 trials in 349 head lice-infested subjects, age 6 months and older, who received a 10 minute application of Xeglyze. Supportive data were provided from seven Phase 2 trials (4 PK trials; 2 dermal safety trials; 1 TQT trial) in 95 subjects, who were administered Xeglyze, including under maximal use conditions. The most common adverse reactions reported with Xeglyze were erythema, rash, skin burning sensation, contact dermatitis, vomiting, eye irritation, and hair color changes.

The major approvability issue for this application was a failed inspection at the active pharmaceutical ingredient (API) manufacturing site. Significant deviations from current good manufacturing practices (cGMP) were observed, resulting in a warning letter and a withhold recommendation from the Office of Pharmaceutical Quality (OPQ).

The primary reviewers from the clinical, statistical and clinical pharmacology disciplines have not identified any issues that preclude approval; however, this application cannot be approved at this time due to significant GMP deficiencies at the drug substance manufacturing site. The applicant will need to have an API manufacturing site in cGMP compliance before this application can be approved.

Further discussions regarding product labeling, and postmarketing study requirements and commitments will be deferred to a future review cycle.		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	The human head louse is an ectoparasite that relies on humans for its survival. The louse must take a blood meal from its host regularly. Head lice rarely survive longer than 36 hours without a host. Certain biological functions of the louse, including digestion of the blood meal, hatching of the nit, and molting, utilize metalloproteinase enzymes. The diagnosis of an active infestation relies on the identification of live lice on the hair or scalp of the patient. The presence of nits alone is not diagnostic of active infestation. Symptoms of head lice infestation include pruritus, erythema, and excoriations of the scalp. Head lice infestation is a common problem, affecting between 6 and 12 million individuals per year. Infestations occur most commonly in children ages 3 to 11 years. Infestations occur more frequently in females, and are uncommon in African-Americans. While not severe or life-threatening, head lice infestation is a significant cause of lost school and work days for affected children and their caregivers.	Head lice infestation is a common problem, especially in children. Active infestation is diagnosed on the basis of the identification of head lice on the hair or scalp. Symptoms include pruritus, erythema, and excoriations of the scalp. While not severe or life-threatening, head lice infestation is a significant cause of lost school and work days for affected children and their caregivers.

Current Treatment Options	Pharmacologic treatments include both over-the-counter (OTC) and prescription medications. OTC products include permethrin and pyrethrin with piperonyl butoxide. Resistance to pyrethroids is common. Prescription medications include Lindane shampoo 1%, Ovide (malathion) lotion 0.5%, Ulesfia (benzyl alcohol) lotion 5%, Natroba (spinosad) suspension 0.9%, and Sklice (ivermectin) lotion 0.5%. Lindane shampoo, approved in 1975, carries a boxed warning for neurologic toxicity, with seizures and death reported following use with repeat or prolonged application, or in rare circumstances with a single application. The use of Ovide lotion, approved in 1982, is limited to children 6 years and older. Resistance has been reported outside the U.S. Natroba (approved in 2011), Ulesfia (approved in 2009), and Sklice (approved in 2012) are approved for use in children 6 months and older, and no resistance has been seen. Ulesfia labeling recommends a second treatment one week after the first; Natroba labeling recommends a second treatment after one week if live lice are still present; Sklice requires only a single application. Because Natroba and Ulesfia contain benzyl alcohol, they pose additional risk for infants younger than 6 months of age due to the association of benzyl alcohol with neonatal gasping syndrome.	Non-pharmacologic and pharmacologic treatments, both OTC and prescription, are available for the treatment of head lice infestation. Toxicities and resistance limit the use of many currently available therapies. Therefore, the development of safe and effective new treatments remains important.

	Non-pharmacologic methods for treating lice include devices (e.g., Lice Comb, Lockomb, Licemeister), hair removal and occlusion (petroleum jelly, olive oil, mayonnaise, etc.). The American Academy of Pediatrics 2015 guidance for the treatment of head lice infestation recommends 1% permethrin or pyrethrins as first-line therapy for active infestations, provided resistance to these products has not been seen in the community. If resistance in the community is present, manual removal of lice/nits by "wet-combing" or an occlusive method can be considered. Where resistance to permethrin or pyrethrins has been demonstrated, or if a patient has not adequately responded to permethrin or pyrethrins, benzyl alcohol 5% can be used for children older than 6 months, or malthion 0.5% for children 2 years or older. Natroba and Sklice may be helpful in difficult cases.	
Benefit	The subject of this NDA, Xeglyze (abametapir) is a metalloproteinase inhibitor, which chelates metal cations at the active center of metalloproteinases critical to louse egg development, hatching and survival. Efficacy was assessed in two double-blind, vehicle-controlled trials in 216 subjects, age 6 months and older, randomized 1:1 to a single application of abemetapir lotion, 0.74% or vehicle. The primary efficacy endpoint was the proportion of index subjects who were lice free at all follow-up visits through Day 14 (i.e., Days 1, 7, 14). The two secondary endpoints were the	Relative to vehicle control, Xeglyze lotion achieved statistically significant response rates, defined as the proportion of index subjects who were lice free at all follow-up visits through Day 14, in two identical double-blind trials. Additional analyses using a per-protocol population achieved similar results to the ITT population analyses. Sensitivity analyses using LOCF were

	proportion of index subjects who were lice free at the Day 1 visit, and the proportion of index subjects who were lice free at the Day 7 visit. These secondary endpoints were not agreed to in the Special Protocol Assessment (SPA). In the trials, 85% of participants were female, and 95% were Caucasian. Approximately 95% of the index subjects were between the ages of 6 months and less than 18 years of age; there were no index subjects 65 years of age or older. Both trials were conducted exclusively in the U.S. In both trials, Xeglyze lotion showed a superior difference in the proportion of index subjects who were lice-free at all visits through 14 days after treatment. In Trial 1, 81% of Xeglyze-treated subjects versus 51% of vehicle-treated subjects achieved the primary endpoint (p=0.001), while in Trial 2, 82% of Xeglyze-treated subjects versus 47% of vehicle-treated subjects achieved the primary endpoint (p<0.001). The results of the secondary endpoint of the proportion of lice-free subjects at Day 1 were not statistically significant; however, the results of the secondary endpoint of the proportion of lice-free subjects at Day 7 were statistically significant. These secondary endpoints were not agreed upon with the Agency per the SPA agreement letter. The results of supportive analyses using a per protocol population were consistent with the primary analysis using the ITT population.	conducted, and the results were similar to the primary imputation method of imputing missing values as treatment failures. Sub-group analyses on gender, race, and age could not be reliably conducted due to the majority of enrolled subjects being Caucasian females age 6 months to 12 years.

	Sensitivity analyses using LOCF were conducted, and the results were similar to the primary imputation method of imputing missing values as treatment failures. The majority of the enrolled index subjects were female and Caucasian, therefore efficacy by these subgroups could not be assessed. In addition, approximately 89% of the index subjects were between the ages of 6 months and less than 12 years of age, therefore differences in efficacy between subjects less than 12 years of age and those 12 years of age and greater would be difficult to detect.	
Risk	The safety of Xeglyze was assessed in two Phase 3 trials in 349 head lice-infested subjects aged 6 months and older, who received a 10 minute application of Xeglyze. Supportive data were provided from seven Phase 2 trials (4 PK trials; 2 dermal safety trials; 1 TQT trial) in 95 subjects, who were administered Xeglyze, including under maximal use conditions (defined as a single application of one whole container, ~200 mL). The most common adverse reactions reported with Xeglyze were erythema, rash, skin burning sensation, contact dermatitis, vomiting, eye irritation, and hair color changes. There were no deaths in the Xeglyze clinical development program. There were 2 SAE's, neither of which was deemed to be treatment related. No subjects discontinued due to an AE in any of the Phase 2 or 3 trials.	No deaths, treatment-related SAEs or DAEs occurred in the Xeglyze clinical development program. Xeglyze contains benzyl alcohol (b) (4) as an excipient, thus there is potential toxicity (neonatal gasping syndrome) if infants under 6 months of age were to be treated with Xeglyze, or in case of accidental ingestion. The most common adverse reactions reported with Xeglyze were erythema, rash, skin burning sensation, contact dermatitis, vomiting, eye irritation, and hair color changes. Adverse events of special interest were

	Xeglyze contains benzyl alcohol (b) (4) as an excipient. This raises concern regarding potential toxicity (neonatal gasping syndrome) if infants under 6 months of age were to be treated with Xeglyze, or in case of accidental ingestion. Adverse events of special interest included erythema/edema, pruritus, excoriation/pyoderma, and eye irritation. In patients in the Phase 3 trials without erythema/edema at baseline, 3.2% of Xeglyze-treated subjects had developed erythema/edema on Day 1, compared to 1.4% of vehicle-treated subjects. In patients in the Phase 3 trials without scalp pruritus at baseline, 1.4% of Xeglyze-treated subjects had developed pruritus on Day 1, compared to 0.7% of vehicle-treated subjects. In patients in the Phase 3 trials without scalp excoriation/pyoderma at baseline, no Xeglyze-treated subjects had developed excoriation/pyoderma on Day 1, compared to 0.9% of vehicle-treated subjects. In patients in the Phase 3 trials without eye irritation at baseline, 1.7% of Xeglyze-treated subjects had developed eye irritation on Day 1, compared to 1.4% of vehicle-treated subjects. Hair color changes (pink/red) were observed in 1% of Xeglyze-treated subjects in one of the Phase 3 trials, versus	observed more frequently in Xeglyze-treated subjects relative to vehicle-treated subjects, including scalp erythema/edema, scalp pruritus, and eye irritation. There has been no suggestion of a clinically significant contact sensitization risk with Xeglyze, when used as directed. Xeglyze has shown no evidence suggestive of irritation or cumulative irritation potential, under exaggerated conditions of use. The elimination half-life of the metabolite, abametapir carboxyl, has not been well characterized There is a potential risk of inhibition of CYP 3A4, 2B6 and 1A2 following a single application of Xeglyze lotion. There is an unknown risk of neonatal benzyl alcohol toxicity in babies being breastfed by women receiving treatment with Xeglyze.

	no vehicle-treated subjects. All events resolved within 7 days. The frequency of TEAEs was analyzed by gender and age strata (6 months to <2 years; 2 years to <4 years; 4 years to <12 years; 12 years to <18 years; and ≥18 years). The rates of occurrence of TEAEs were evenly distributed across these age strata. The number of non-Caucasian subjects was insufficient to conduct meaningful racial subgroup analyses. Overall, there were no treatment-related abnormal laboratory values, vital sign measurements, or clinically significant effect on cardiac electrical activity. In the dermal sensitization trial, there was no suggestion of a clinically significant contact sensitization risk with Xeglyze, when used as directed (a single 10-minute application). Analysis of cumulative irritation revealed that under exaggerated conditions of use (continuous application under occlusion for 21 days), Xeglyze showed no evidence suggestive of irritation or cumulative irritation potential. The unconjugated abametapir carboxyl accounts for the vast majority of drug related plasma exposure in humans. Abametapir carboxyl is cleared slowly from the systemic circulation and results in plasma concentration significantly higher than that of abametapir. Based on data in adults, where samplings were carried out to 72 hours, the ratios of C_{max} and $AUC_{0\text{-}72h}$ between abametapir carboxyl and abametapir were about 30 and 250, respectively. The	

	elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be approximately (mean ± SD) 71 ± 40 hours or longer. *In vitro* studies suggest that there is a potential risk of CYP 3A4, 2B6, and 1A2 enzyme inhibition due to high and sustained concentrations of the metabolite, abametapir carboxyl, following application of abametapir lotion, 0.74%. The risk of neonatal benzyl alcohol toxicity in babies being breastfed by women receiving treatment with Xeglyze is unknown.	
Risk Management	1. Risk of neonatal benzyl alcohol toxicity 2. Risk of benzyl alcohol toxicity from accidental ingestion 3. Unknown risk of neonatal benzyl alcohol toxicity in babies being breastfed by women receiving treatment with Xeglyze 4. Inadequate characterization of the elimination half-life of the metabolite, abametapir carboxyl. 5. Potential risk of CYP 3A4, 2B6, and 1A2 enzyme inhibition	1. W&P section and Pediatric Use subsection of the PI: Use of Xeglyze is not recommended in pediatric patients under 6 months of age because of the potential for increased systemic absorption and "gasping syndrome". 2. W&P section and Pediatric Use subsection of the PI: Xeglyze should only be administered under direct supervision of an adult. 3. A PMR for a pharmacokinetic clinical trial in lactating women who require treatment with Xeglyze lotion, 0.74%. 4. A PMR for a maximal use pharmacokinetic trial of Xeglyze lotion, 0.74% in pediatric subjects 6

		months to 3 years 11 months of age with head lice infestation to fully characterize the concentration time profile of abametapir and its metabolite, abametapir carboxyl. 5. A PMR for a clinical trial in adult subjects to evaluate the potential for Xeglyze lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing, at systemic exposures of abametapir and abametapir carboxyl similar to those observed under maximal use conditions in pediatric subjects. Additional drug interaction trials may be needed depending on the results of this trial. There are no serious safety concerns that warrant the need for a REMS.

Other Background

Regulatory History

In December 2007, IND 77510 was opened for abametapir lotion for the treatment of head lice infestation.

In August 2012, an End-of-Phase 2 meeting was scheduled. (The meeting was subsequently canceled by the applicant upon receipt of the Agency's responses, which the applicant determined to be sufficient.) The Agency requested that the applicant develop a container/closure design to reduce the risk of accidental ingestion. Due to the inclusion of benzyl alcohol (b) (4) in the vehicle, the Agency requested that the applicant evaluate the potential systemic exposure of benzyl alcohol in the pediatric pharmacokinetics (PK) trial. Finally, because *in vitro* studies showed that abametapir induced inhibitory effects on the hERG current, which raised concerns about QTc prolongation, the Agency recommended cardiac safety monitoring (ECG) during the pediatric PK trial.

In October 2013, the applicant submitted a special protocol assessment (SPA). The Agency issued a SPA agreement letter in December 2013. Specifically, the Agency noted that the design of the phase 3 trial was acceptable; the proposal to conduct two identical phase 3 trials in parallel was acceptable; the proposed study population, dosing regimen, primary efficacy endpoint, and testing methods were acceptable.

In December 2013 and April 2014, an Initial Pediatric Study Plan (iPSP) was submitted. An agreed PSP letter was issued to the applicant in May 2014.

A pre-NDA meeting was held in January 2015. The Agency informed the applicant that the *ex vivo* method for determining ovicidal activity may not be predictive of *in vivo* ovicidal activity, (b) (4)

The NDA was submitted on September 14, 2015 and granted a standard review. A major issue at the time of filing was the OAI status of the drug substance manufacturing site.

Product Quality

OPQ concluded that "the applicant had provided sufficient CMC information to assure the identity, purity, strength and quality of the drug product. However, the Office of Process and Facility has made a "**Withhold**" recommendation for the drug substance manufacturing site due to unresolved cGMP issues."

The manufacturing site (Dr. Reddy's Lab, Unit VI in Srikakulam, India) was inspected November 21, 2014 and was classified OAI and a 9-item FDA Form 483 was issued. The deficiencies included several quality systems and data integrity issues. The firm responded to

the observations; however, the Office of Compliance review determined that the responses lacked sufficient corrective actions. A subsequent response was also deemed inadequate. A Warning Letter issued on November 5, 2015.

Non-clinical Pharmacology/Toxicology

There are no pharmacology/toxicology issues that preclude approval.

The Pharmacology/Toxicology reviewer noted that "All nonclinical studies enormously exaggerated exposure under clinical conditions of use. The drug-related nonclinical effects observed after extended repeat testing would not be a cause for concern for this drug product under the clinical conditions of use which is one time use on scalp and hair for 10 minutes and then rinsed off."

In the 28-day repeat-dose dermal study in minipigs, dermal effects (erythema, flaking) and histological effects (epidermal hyperplasia, hyperkeratosis, erosion and/or ulceration) were dependent on the strength, frequency and contact time of dosing, and were reversible. Systemic effects (tremors, decreased activity and decreased feed consumption) occurred, but it is unclear how much of the systemic exposure may have been due to oral ingestion of the topically applied abametapir lotion.

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Xeglyze lotion or abametapir. Abametapir was not mutagenic or clastogenic based on the results of two *in vitro* genotoxicity tests (Ames test and human lymphocyte chromosomal aberration assay) and one *in vivo* genotoxicity test (rat micronucleus assay).

No effects on fertility have been observed in rats following repeated oral doses of up to 75 mg/kg/day abametapir (50 times the MRHD based on C_{max} comparisons).

In vitro studies showed that abametapir induced inhibitory effects on the hERG current, which raised concerns about QTc prolongation. The applicant conducted a study to evaluate the effects of abametapir on electrocardiographic parameters in anesthetized male rats. Abametapir did not appear to cause acute effects on cardiovascular variables; however, the study was suboptimal. The sponsor subsequently conducted a cardiovascular study in minipigs using telemetry. While this study was not acceptable for regulatory use, no significant changes were observed in ECG parameters with abametapir plasma concentrations as high as 329 ng/mL at 60 minutes after application of abametapir 8.0% treatment. While these studies were considered less than ideal, there was no non-clinical cause for concern for potential cardiovascular effects associated with abametapir.

Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval.

Pharmacokinetics (PK) were evaluated in 6 adult and 12 pediatric subjects aged 3 to 12 years of age. The mean (%CV) abametapir C_{max} and AUC_{0-8h} in the adult group were 41 (66%) ng/mL and 121 (50%) ng*h/mL, respectively. The mean (%CV) C_{max} and AUC_{0-8h} in the pediatric group were 73 (57%) ng/mL and 264 (62%) ng*h/mL, respectively. The mean (%CV) terminal half-life in adults was 21 (11%) hours. Abametapir absorption was rapid with a median T_{max} of 0.57 to 1.54 hours.

Serum concentration of benzyl alcohol, an excipient in the formulation of abametapir lotion, 0.74%, was assessed. Benzyl alcohol in serum was measurable (limit of quantitation = 0.5 μg/mL) in 7 subjects out of 39 evaluable subjects. The C_{max} of benzyl alcohol in these 7 subjects ranged from 0.52 to 3.57 μg/mL.

In vitro studies using liver microsomes showed that abametapir is extensively metabolized, primarily by CYP1A2 and to a lesser extent CYP2B6.

In vitro studies suggest there is a low risk of *in vivo* cytochrome P450 (CYP) inhibition for abametapir and a low risk of CYP induction for both abametapir and abametapir carboxyl.

QT prolongation potential. Abametapir lotion, 0.74% for 60 minutes to the scalp and back area in healthy adults without head lice did not prolong cardiac repolarization (QTc interval). The mean observed abametapir C_{max} in the TQT study exceeded those observed under maximal use conditions in subjects with active head lice infestation. There is no concern regarding QTc prolongation with abametapir lotion, 0.74% in the treatment of head lice.

Effect of age. Abametapir exposure increased as the age of the subject decreased.

Renal impairment. The effect of renal impairment on abametapir lotion, 0.74% PK was not evaluated by the applicant.

Hepatic impairment. The effect of hepatic impairment on abametapir lotion, 0.74% PK was not evaluated by the applicant.

Clinical/Statistical – Efficacy

Pivotal trials.

The table below provides a summary of the primary efficacy results from the pivotal trials.

Table 1: Proportion of Lice-free Index Subjects at Day 14 (Primary Endpoint), and at Days 1, 7 (Secondary Endpoints) (ITT population)

	Trial 001			Trial 002		
	Abametapir N=53	**Vehicle N=55**	**p-value**	**Abametapir N=55**	**Vehicle N=53**	**p-value**
Primary Endpoint (Day 14)	43 (81%)	28 (51%)	0.001	45 (82%)	25 (47%)	<0.001
Secondary endpoints						
Day 1	49 (93%)	46[(1)] (84%)	0.10	48 (87%)	44 (83%)	0.45
Day 7	48 (91%)	34 (62%)	0.001	47 (86%)	36 (68%)	0.025

Source: Table 7 of FDA Statistical Review
P-value from CMH test stratified by pooled sites; the protocol-specified imputation method was to impute missing as last observation carried forward (LOCF), except for missing data at Day 14 that was imputed as treatment failure.
(1) Subject (b) (6) had a missing Day 1 assessment; however, per the SAP, this subject was considered to be a success as Days 7 and 14 were treatment success.

The Office of Scientific Investigations (OSI) conducted inspections of two clinical investigator sites. OSI concluded that "The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication."

Advisory Committee

There were no complex scientific or regulatory issues that required the input of an Advisory Committee.

Pregnancy Considerations

Consistent with the Pregnancy and Lactation Labeling Rule guidelines, The **Use in Specific Populations** section, **Pregnancy** subsection, of the product label will state that there are no available data on Xeglyze lotion use in pregnant women to inform a drug-associated risk.

In embryo-fetal development studies conducted with oral administration of abametapir during organogenesis, no evidence of fetal harm or malformations, independent of maternal toxicity, were observed in pregnant rats and rabbits at doses that produced exposures up to 50 times and equivalent to the maximum recommended human dose (MRHD) in rats and rabbits, respectively. The highest dose evaluated in rabbits was limited due to maternal toxicity associated with the vehicle used in the study.

No data are available regarding the presence of abametapir in human milk, or the effects of abametapir on the breastfed infant or on milk production.

Pediatrics

Pediatric Use. The **Use in Specific Populations** section, **Pediatric Use** subsection, of the product label will state that the safety and effectiveness of Xeglyze have been established in patients 6 months of age and older.

Required Pediatric Studies. An agreed iPSP letter was issued on May 8, 2014, in which the Agency agreed that studies should be waived in patients <6 months of age because: (1) necessary studies are impossible or highly impracticable due to the low prevalence of head lice infestation in infants less than 6 months of age, and (2) the potential of increased systemic absorption due to a high ratio of skin surface to body mass and the potential for an immature skin barrier in pediatric subjects from birth to 6 months. The applicant completed pediatric studies in patients 6 months and older, and the pediatric assessment is complete.

Other Relevant Regulatory Issues

Tradename Review

The applicant's proposed tradename "Xeglyze" is acceptable from both a safety and misbranding perspective. The applicant was informed of this determination on November 30, 2015.

Consults

Division of Medical Policy Programs (DMPP)/Office of Prescription Drug Promotion (OPDP)

DMPP and OPDP reviewed the Patient Package Insert (PPI) and Instructions for Use (IFU) for Xeglyze. In their collaborative review, DMPP and OPDP simplified wording and clarified concepts where possible; ensured that the PPI and IFU were consistent with the package insert (PI); removed unnecessary or redundant information; and ensured that the PPI and IFU were free of promotional language. OPDP also reviewed the draft PI and carton and container labeling and provided suggestions to improve the clarity of the PI, as well as to remove potentially promotional language.

Division of Medication Error, Prevention, and Analysis (DMEPA)

DMEPA was consulted to review the proposed prescribing information (PI) and carton and container labels for vulnerabilities that could lead to medication errors. DMEPA identified areas in the labels and labeling that could be improved to increase the readability and prominence of important information and promote the safe use and handling of the product, and provided recommendations to the PI and container label and carton labeling to address the deficiencies.

Division of Pediatric and Maternal Health (DPMH)

DPMH was consulted to provide input on pediatric use labeling, particularly regarding the (b) (4) benzyl alcohol excipient and the associated neonatal toxicity. DPMH recommended that language regarding the association between benzyl alcohol and neonatal toxicity, i.e., "gasping syndrome", be included in the Warnings and Precautions section and the Pediatric Use subsection of product labeling. Additionally, because of the risk of accidental ingestion, product labeling will state that Xeglyze lotion should be administered to pediatric patients only under direct adult supervision.

DPMH also provided input for appropriate labeling of the pregnancy and lactation subsections of Xeglyze to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format requirements.

DPMH concluded: *A review of the literature revealed no data with Xeglyze use in pregnant or lactating women. From the clinical studies during the development cycle of the drug, limited data exists for Xeglyze exposure in pregnant women. There is no data on lactation in humans or animals with use of Xeglyze. The existing data are not sufficient to determine any drug-associated risk. However, Xeglyze Lotion is rapidly systemically absorbed and contains benzyl alcohol, which with systemic exposure, has been associated with serious adverse reactions and death in neonates and low birth-weight infants.*

DPMH recommended a PMR for a Clinical Lactation Study to assess concentrations of abametapir in maternal plasma and breast milk so as to estimate potential infant exposure.

Risk Evaluation and Mitigation Strategies (REMS)

The Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology provided a consultative review to determine if a risk evaluation and mitigation strategy (REMS) is needed for Xeglyze (abametapir), a new molecular entity. DRISK concluded that "At this time, risk mitigation measures beyond professional labeling are not warranted for Xeglyze for the treatment of head lice infestation in patients 6 months of age and older."

Postmarketing Requirements and Commitments

Prior to the determination that this product could not be approved, the following PMRs/PMCs had been agreed to with the applicant:

Post Marketing Requirements

1. A single dose, open-label pharmacokinetic clinical trial to evaluate plasma and breastmilk concentrations of abametapir, abametapir carboxyl, and benzyl alcohol in lactating women who require treatment with Xeglyze lotion, 0.74%.

2. A maximal use pharmacokinetic trial of Xeglyze lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age with head lice infestation to fully characterize the concentration time profile of abametapir and metabolite abametapir carboxyl.

3. A clinical trial in adult subjects to evaluate the potential for Xeglyze lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatric subjects. Additional drug interaction trials may be needed depending on the results of this trial.

Post Marketing Commitments

4. A study to evaluate the long-term storage stability of abametapir carboxyl in plasma stored at -80°C for a duration of at least 1,251 days.

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/s/

AMY G EGAN
08/25/2016

Division Director Summary Review for Regulatory Action

Date	August 23, 2016
From	Kendall A. Marcus, M.D.
Subject	Division Director Summary Review
NDA/BLA # Supplement #	NDA 206966
Applicant	Dr. Reddy's Laboratories
Date of Submission	September 14, 2015
PDUFA Goal Date	September 14, 2016
Proprietary Name / Non-Proprietary Name	XEGLYZE/abametapir
Dosage Form(s) / Strength(s)	Lotion, 0.74%
Applicant Proposed Indication(s)/Population(s)	[redacted] (b) (4) indicated for the topical treatment of head lice infestation [redacted] (b) (4) in patients 6 months of age and older. (b) (4)
Action/Recommended Action for NME:	*Complete Response*
Approved/Recommended Indication/Population(s) (if applicable)	*Treatment of head lice infestation in patients 6 months of age and older*

Xeglyze (abametapir) Review Team:

Discipline	Reviewer	Team Leader
Clinical	Kevin Clark	Gordana Diglisic
Stats	Carin Kim	Mohamed Alosh
Clin Pharm	Donny Tran	Dennis Bashaw
Nonclinical	Jill Merrill	Barbara Hill
OSI	Roy Blay	Janice Pohlman

Maternal Health	Christos Mastroyannis	Tamara Johnson
Pediatrics	Erica Radden	Donna Snyder
OPDP	Tara Turner	Melinda McLawhorn
PLT	Rowell Medina	Barbara Fuller
Product Quality		
DS	Xavier Ysern	Donna Christner
DP	Bhavishya Mittal	Moo-Jhong Rhee
Process	Tony (Yaodong) Huang	Nallaperumal Chidambaram
Micro	Eric Adeeku	Jesse Wells
Facility	Quallyna Porte	Christina Capacci-Daniel
ATL	Yichun Sun	Moo-Jhong Rhee
EA	Raanan Bloom	Scott Furness
RBPM	Maria Cowan	

I. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pediculus humanus capitis, known as the head louse, is an obligate ectoparasite that feeds exclusively on human blood. The average life span of a head louse from the time the nit is laid until the adult louse dies is thirty days. The head louse does not have wings or legs capable of jumping, so they are transferred only through close contact between individuals. Head-to-head contact is by far the most common route of lice transmission. While the head louse feeds up to 4-5 times a day, they are capable of living off the head for periods up to 48 hours. The head louse is a distinct species from the body louse and pubic louse and is generally not considered to be a vector of other diseases.

Visualization of a live louse in the hair or on the scalp is required to establish that an individual has an active infection. Pruritis, and erythema and excoriations of the scalp are common signs and symptoms of lice infestation. Pruritis is usually the first manifestation of head lice infestation and results from an allergic reaction to lice saliva injected during feeding. Lice have a predilection for the nape of the neck and the post-auricular area of the scalp so excoriations and nits may be concentrated in those areas.

In the United States, roughly 6-12 million people, predominantly children, are treated each year for head lice. Children between the ages of 3 and 11 years are the most frequently infested group and females are more frequently affected.

Currently available over-the counter (OTC) treatments include permethrin and pyrethrins with piperonyl butoxide, although resistance to pyrethroids is common. Products available by prescription include Lindane shampoo 1%; Ovide (malathion) lotion, 0.5%; Ulesfia (benzyl alcohol) lotion, 5%; Natroba (spinosad) topical suspension, 0.9% and Sklice (ivermectin) lotion, 0.5%. Mechanical measures aimed at eradication include combing with a lice comb or shaving of the scalp.

Certain biologic functions of the louse, including digestion of the blood meal, hatching of the nit and molting utilize metalloproteinase enzymes. Abametapir, the active ingredient in Xeglyze lotion is a metalloproteinase inhibitor from the class of bipyridinium molecules. The proposed dosing of Xeglyze lotion is a single, 10-minute application of an amount sufficient to saturate the hair and scalp, followed by rinsing with water.

Two pivotal trials were submitted in support of the efficacy of Xeglyze. Trials Ha03-001 (Trial 001) and Ha03-002 (Trial 002) enrolled 704 subjects, 6 months of age and older, with head lice infestation. All subjects received a single application of either Xeglyze lotion or vehicle control. For the evaluation of efficacy, the youngest subject from each household was considered to be the index subject of the household (N=216). A significantly greater proportion of index subjects who received Xeglyze lotion demonstrated success on the primary endpoint of the proportion of index subjects who are lice free at all follow-up visits through Day14 compared to subjects who received vehicle.

Adverse reactions that occurred in at least 1% of subjects in the Xeglyze lotion group and at a greater frequency than in the vehicle group include erythema (4%), rash (3.2%), burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), scalp pruritis (1.4%), and hair color changes (1%). These adverse reactions were all mild to moderate in severity and reversible. No differences in the frequencies of adverse reactions were observed across all age groups.

The temporal relationship of the application of Xeglyze lotion and the onset of vomiting in 4 of the 6 subjects who reported vomiting make the potential association of the event to Xeglyze lotion unlikely at best. However, because the half-life of abametapir in adults is 21 hours and the half-life of the carboxyl metabolite is about 71 hours, a relationship to study drug cannot be excluded.

Hair color changes represent a unique adverse event related to the mechanism of action of abametapir, which chelates metal cations such as iron and zinc. In the presence of the ferrous (Fe+2) ion, abametapir forms a water-soluble pink/red colored complex at iron concentrations as low as 1 ppm. Iron is commonly found in both well and tap water at varying concentrations. Pink/red hair discoloration which resolved within 7 days was reported in a total of 3 subjects treated with Xeglyze lotion 10 minute applications. Hair discoloration lasting approximately 2.5 months was also reported in 1 subject in a Phase 1 trial who applied Xeglyze lotion for one hour.

The requirement to evaluate this product in infants below the age of 6 months is waived because benzyl alcohol, which is one of the excipients, is known to cause neonatal gasping syndrome. Product labeling contains a warning about the risk of neonatal gasping syndrome.
Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

Based on a review of the application, manufacturing capability, and inspectional documents of Dr. Reddy's Labs Unit VI (FEI 3002949085), the facility review team from the Office of Process and Facilities (OPF) determined that this facility is not considered acceptable to manufacture the drug substance for this application. Deficiencies were noted in laboratory control records, computerized systems, batch production and control records, document control system, training records, process validation, specification failure investigations, water standards and personnel hygiene. Therefore, based on deficiencies noted in product quality, a complete response will be issued.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Head lice is a common infection in the United States that affects 6-12 million people, primarily children, each year. Head lice infestation has a significant impact on affected households in terms of school and work absences, anxiety, and embarrassment. While multiple treatments are currently available for treatment, resistance is increasing to some products.	Head lice is a common disease of childhood that can have substantial impact on productivity in terms of days missed from work and on learning in terms of school days missed. Multiple treatment options increase the likelihood that effective options will be available to households.
Current Treatment Options	• Currently available over-the counter (OTC) treatments include permethrin and pyrethrins with piperonyl butoxide, although resistance to pyrethroids is common. Products available by prescription include Lindane shampoo 1%; Ovide (malathion) lotion, 0.5%; Ulesfia (benzyl alcohol) lotion, 5%; Natroba (spinosad) topical suspension, 0.9% and Sklice (ivermectin) lotion, 0.5%. Mechanical measures aimed at eradication include combing with a lice comb or shaving of the scalp.	Multiple treatments options are currently available, although resistance to some is increasing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Two Phase 3 randomized, double-blind, multicenter, vehicle-controlled trials were submitted in support of the efficacy of Xeglyze (abametapir) lotion, 0.74%. The primary objective of each trial was to evaluate the efficacy of at-home administration of a single application of abametapir lotion on the index subject of a household. Trial subjects were enrolled by household. The index subject was defined as the youngest member of the household and had to have at least 3 live lice. All other members of the household needed to have at least 1 live louse identified. Households were enrolled at 7 centers located in the United States. In both trials, abametapir lotion was statistically superior to vehicle lotion ($p \leq 0.001$) for the primary endpoint of the proportion of lice-free index subjects at Day 14.	Efficacy was convincingly demonstrated in two adequate and well-controlled clinical trials under conditions of actual use.
Risk	• Adverse reactions that occurred in at least 1% of subjects in the Xeglyze lotion group and at a greater frequency than in the vehicle group include erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), eye irritation (1.2%), and hair color changes (1%). These adverse reactions were all mild to moderate in severity and reversible. No differences in the frequencies of adverse reactions were observed across all age groups.	The safety profile has been adequately characterized. Observed adverse reactions were mild to moderate in severity and reversible.
Risk Management	• Professional and patient labeling adequately convey observed adverse reactions and the potential adverse reactions of neonatal gasping syndrome and accidental benzyl alcohol ingestion. The product is recommended for single use in order to minimize the potential risk of accidental ingestion.	Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

1. Background

Pediculus humanus capitis, known as the head louse, is an obligate ectoparasite that feeds exclusively on human blood. The average life span of a head louse from the time the nit is laid until the adult louse dies is thirty days. The head louse does not have wings or legs capable of jumping, so it is transferred only through close contact between individuals. Head-to-head contact is by far the most common route of lice transmission. While the head louse feeds up to 4-5 times a day, it is capable of living off the head for periods up to 48 hours. The head louse is a distinct species from the body louse and pubic louse and is generally not considered to be a vector of other diseases.

Visualization of a live louse in the hair or on the scalp is required to establish that an individual has an active infection. Pruritis, and erythema and excoriations of the scalp are common symptoms and signs of lice infestation. Pruritis is usually the first manifestation of head lice infestation and results from an allergic reaction to lice saliva injected during feeding. Lice have a predilection for the nape of the neck and the post-auricular area of the scalp so excoriations and eggs may be concentrated in those areas.

In the United States, roughly 6-12 million people, predominantly children, are treated each year for head lice. Children between the ages of 3 and 11 years are the most frequently infested group and females are more frequently affected.

Currently available over-the counter (OTC) treatments include permethrin and pyrethrins with piperonyl butoxide, although resistance to pyrethroids is common. Products available by prescription include Lindane shampoo 1%; Ovide (malathion) lotion, 0.5%; Ulesfia (benzyl alcohol) lotion, 5%; Natroba (spinosad) topical suspension, 0.9% and Sklice (ivermectin) lotion, 0.5%. Mechanical measures aimed at eradication include combing with a lice comb or shaving of the scalp.

Certain biologic functions of the louse, including digestion of the blood meal, hatching of the nit and molting utilize metalloproteinase enzymes. Abametapir, the active ingredient in Xeglyze lotion, 0.74% is a metalloproteinase inhibitor from the class of bipyridinium molecules. The proposed dosing of Xeglyze lotion is a single, 10-minute application of an amount sufficient to saturate the hair and scalp, followed by rinsing with water.

2. Product Quality

For detailed information about the product quality review of this application, please see reviews completed by Xavier Ysern, PhD.; Branch II; Division of New Drug API/ONDP; dated December, 29, 2015; Bhavishya Mittal, PhD; Branch V; Division of New Drug Products II/ONDP; dated April 18, 2016; Yaodong (Tony) Huang, PhD; Branch VIII, Division of Process Assessment III/OPF dated March 1, 2016; Quallyna Porte, Biologist, OPQ/OPF/DIA/BII dated April 12, 2016; Vidula Kolhatkar, PhD, Branch II, Division of Biopharmaceutics/ONDP dated April 12, 2016; Eric Adeeku, PhD, Branch I, Division of Microbiology Assessment/OPF, Raanan Bloom, PhD, Environmental Assessment Team/ONDP.

Xeglyze lotion, 0.74% contains abametapir as the active ingredient. The chemical name of abametapir is: 5, 5'-dimethyl-2, 2'-bipyridinyl. The identity, strength, purity and quality of the drug substance are deemed assured by the drug substance specification. Drug substance potential impurities have been well characterized and adequately controlled.

(b) (4). The expiration dating period of 24 months is recommended for the drug product when stored at controlled room temperature based on long-term and accelerated stability data obtained from 3 registration batches of the drug product, and 6 supportive batches of the drug product. The Environmental Assessment (EA) team finds that the NDA applicant's request for a categorical exclusion from an EA acceptable.

Accidental ingestion of Xeglyze lotion, particularly by children, poses a safety concern because of the benzyl alcohol excipient. During the drug development program, the Agency advised the applicant to choose a container/closure design for commercialization which is more in line with topical products, and refrain from using a design which is typical for oral liquids. (b) (4) therefore, the applicant selected a USP Type (b) (4) amber glass bottle

Final packaging for Xeglyze lotion consists of a PVC safety-coated round amber glass bottle affixed with a white polypropylene child resistant cap featuring a tri-foil inner liner. Each bottle contains about 7 oz. or 210 mL (200 g) of the lotion.

Based on a review of the application, manufacturing capability, and inspectional documents of Dr. Reddy's Labs Unit VI (FEI 3002949085), the facility review team from the Office of Process and Facilities (OPF) determined that this facility is not considered acceptable to manufacture the drug substance for this application. Deficiencies were noted in laboratory control records, computerized systems, batch production and control records, document control system, training records, process validation, specification failure investigations, water standards and personnel hygiene. Therefore, a Complete Response is recommended from the OPQ perspective.

3. Nonclinical Pharmacology/Toxicology

For full details of the pharmacology/toxicology review of this application, please see the review completed by Dr. Jill Merrill, pharmacology/toxicology reviewer. This application is considered approvable from the pharmacology/toxicology perspective.

Abametapir, the active pharmaceutical ingredient in Xeglyze lotion, 0.74%, is a metalloproteinase inhibitor, which exerts its inhibitory effects by chelating metal cations at the active center of metalloproteinases that are critical to louse egg development, hatching and survival of the head louse.

The conducted nonclinical studies greatly exaggerated the expected exposure under clinical conditions of use. Drug-related nonclinical effects observed after extended repeat testing would not be a cause for concern under the expected clinical conditions of use, which would be one time use on the scalp or hair for 10 minutes. Key findings of the non-clinical review are summarized here.

Dermal effects associated with topical administration of Xeglyze lotion in a 28-day repeat-dose dermal study in minipigs included erythema and flaking and were associated with histological observations of epidermal hyperplasia, hyperkeratosis, erosion and/or ulceration. These effects were dependent on dosing parameters (i.e., strength, frequency and contact time) and were reversible. Systemic effects included tremors, decreased activity and decreased feed consumption in both males and females. Reversibility of these systemic effects could not be assessed in males due to early termination in affected animals based on ethical considerations. Reversibility of clinical signs was demonstrated in females. No clinical signs consistent with gastrointestinal targets or smooth muscle function were observed in the clinical program. Therefore, the systemic effects noted in the dermal minipig study are not a cause for concern for the clinical single topical application of abametapir lotion which is subsequently washed off after 10 minutes.

Abametapir and abametapir-COOH, the major human metabolite, were not mutagenic in the Ames test. Abametapir caused increases in chromosome aberrations in human lymphocytes at cytotoxic concentrations and was negative in the in vivo rat micronucleus assay when administered orally at doses up to 160 mg/kg/day. The overall interpretation of the conducted genotoxicity studies is that abametapir and abametapir-COOH do not exhibit a genotoxic signal.

Abametapir has been tested for reproductive and developmental toxicology in rats and rabbits after oral administration with no significant findings independent of maternal toxicity.

4. Clinical Pharmacology

For full details of the clinical pharmacology review of this application, please see the review completed by Dr. Doanh C. Tran, PhD. From a clinical pharmacology perspective, this application is approvable.

The abametapir lotion formulation was evaluated as a 0.37% and a 0.74% strength. Based on superior efficacy and similar safety findings, the higher concentration (0.74%) was chosen for evaluation as the proposed dose for commercial development.

The pharmacokinetics of abametapir were evaluated under clinical conditions of use in lice-infested subjects from the ages of 6 months to 17 years. As expected, abametapir exposure increased as the age of subjects decreased.

The metabolic pathway of abametapir involves the sequential formation of abametapir hydroxyl and abametapir carboxyl with glucuronidation of both metabolites catalyzed by UDP glucuronosyltransferases. In vitro studies showed that abametapir is extensively metabolized, primarily by CYP1A2 and to a lesser extent CYP2B6. In vivo data suggests that unconjugated

abametapir carboxyl accounts for the vast majority of drug-related plasma exposure in humans. Abametapir carboxyl is cleared slowly from the systemic circulation and results in plasma concentration significantly higher than that of abametapir. The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be about 71 hours or longer.

Benzyl alcohol is an excipient in the formulation of Xeglyze lotion, 0.74%. Because systemic exposure to benzyl alcohol can lead to neonatal gasping syndrome, serum benzyl alcohol levels were measured following application of the lotion to assess this risk. In the two clinical trials in which benzyl alcohol levels were measured, a minority of subjects (7/39) had a single measurable concentration of benzyl alcohol only at 30 minutes or one hour post dose; the levels observed were about 30-200 fold lower than a level reported to be associated with neonatal gasping syndrome. The observed concentrations do not appear to pose a safety concern.

The clinical pharmacology reviewer recommends two postmarketing requirements to further evaluate the clinical pharmacology of Xeglyze lotion, 0.74%; a maximal use pk trial in pediatric subjects 6 months to 3 years 11 months of age, and a clinical trial to evaluate the potential inhibitory activity of cytochrome P450 3A4.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

For a complete review of the statistical analyses of efficacy for this application, see the statistical review by Dr. Carin Kim. From a statistical perspective, this application is approvable. The applicant provided convincing demonstration of efficacy in the clinical trials described below.

Two Phase 3 randomized, double-blind, multicenter, vehicle-controlled trials were submitted in support of the efficacy of Xeglyze lotion, 0.74%. The primary objective of each trial was to evaluate the efficacy of at-home administration of a single application the lotion for the treatment of head lice. Trial subjects were enrolled by household. For a household to be enrolled, the index subject needed to be the youngest member of the household and have at least 3 live lice. All other members of the household needed to have at least 1 live louse identified. The agreed upon primary endpoint was the proportion of index subjects who were lice free at all follow-up visits through Day 14. Households were enrolled at 7 centers located in the United States.

Baseline demographics and characteristics were consistent with known infection patterns of head lice. About 85% of index subjects were females between the ages of 6 months and 12 years and over 90% were white. All subjects had nits and all but 1 vehicle subject had 3 live lice present at baseline.

In both trials, Xeglyze lotion was statistically superior to vehicle lotion ($p \leq 0.001$) for the primary endpoint of the proportion of lice-free index subjects at Day 14. For the secondary

endpoints of the proportion of lice-free subjects at Day 1 and at Day 7, while the results were not statistically significant at Day 1, they were at Day 7. Findings for the intent-to-treat (ITT) analysis and the per protocol analysis were similar. ITT efficacy results are reported in Table 1.

Table 1: Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Day 14 (Primary Endpoint) and at Days 1, 7 (Secondary Endpoints)

	Trial 001			Trial 002		
	Abametapir N=53	Vehicle N=55	p-value	Abametapir N=55	Vehicle N=53	p-value
Primary Endpoint (Day 14)	43 (81%)	28 (51%)	0.001	45 (82%)	25 (47%)	<0.001
Secondary endpoints						
Day 1	49 (93%)	46(1) (84%)	0.10	48 (87%)	44 (83%)	0.45
Day 7	48 (91%)	34 (62%)	0.001	47 (86%)	36 (68%)	0.025

Source: P-value from CMH test stratified by pooled sites; the protocol-specified imputation method was to impute missing as last observation carried forward (LOCF), except for missing data at Day 14 that was imputed as treatment failure.

(1) Subject (b) (6) had a missing Day 1 assessment; however, per the SAP, this subject was considered to be a success as Days 7 and 14 were treatment success.

Because the majority of the enrolled subjects were Caucasian females between the ages of 6 months and 12 years, any differences in efficacy by gender, race or age would be difficult to detect.

7. Safety

As previously noted, the applicant evaluated Xeglyze lotion, 0.74% under actual use conditions in two identical multi-center, randomized, double-blind, vehicle-controlled trials. A total of 704 subjects 6 months of age and older with head lice infestation were enrolled, of whom all but 5 subjects were confirmed to have received the study medication. Additional data collected during Phase 2 clinical trials provided supportive safety data of use of the product in a clinical setting.

The safety database under actual conditions therefore included 349 subjects treated with Xeglyze lotion and 350 subjects treated with vehicle. Of these subjects, 21 were 6 months to 4 years of age, 166 subjects were 4 to 12 years of age, 57 subjects were 12 to 18 years of age, and 105 subjects were 18 years of age or older. The size of the safety database is considered adequate to characterize adverse events.

All subjects received a single application of either Xeglyze lotion or vehicle control. The study product was administered at home by the subject or caregiver (Day 0). The subjects were instructed to apply study product to dry hair in an amount sufficient (up to the full content of one bottle) to thoroughly coat the hair and scalp, leave on the hair and scalp for 10 minutes and then rinse off with warm water. The subjects were evaluated in the trial center on Day 1, 7 and 14. Safety evaluation included assessment of vital signs, physical examination, active assessment of local adverse reaction (eyes and scalp), laboratory evaluation (Day 1 and 14), and recording of all adverse events (AE). Scalp irritation was assessed by the investigator at

each study visit using scales for erythema, edema, pruritus, excoriation and pyoderma. Eye irritation was also assessed and rated by the investigator at each study visit.

No subject discontinued the trials due to adverse events. No deaths were reported, and no serious adverse events attributable to study product were reported.

The most common adverse reactions observed in the Phase 3 trials were application site erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), eye irritation (1.2%), and hair color changes (0.9%).

Table 2 provides adverse reactions that occurred in at least 1% of subjects in the Xeglyze lotion group and at a greater frequency than in the vehicle group. These adverse reactions were all mild to moderate in severity and reversible. The frequencies of adverse reactions were similar across all age groups.

Table 2: Adverse Reactions Occurring in ≥1% of the Xeglyze (abametapir) lotion, 0.74% Group and at a Greater Frequency than the Vehicle Group

Adverse Reactions	XEGLYZE Lotion N=349 Subjects (%)	Vehicle Lotion N=350 Subjects (%)
Erythema	14 (4.0)	6 (1.7)
Rash	11 (3.2)	8 (2.3)
Skin burning sensation	9 (2.6)	0 (0.0)
Contact dermatitis	6 (1.7)	4 (1.1)
Vomiting	6 (1.7)	2 (0.6)
Eye irritation	4 (1.2)	2 (0.6)
Hair color changes	3 (1)	0 (0.0)

I agree that the adverse reactions listed in Table 2, with the exception of vomiting, are related to the use of Xeglyze lotion. The temporal relationship of the onset of vomiting in 4 of the 6 subjects who reported vomiting make the potential association of the event to Xeglyze lotion unlikely at best. However, because the half-life of abametapir in adults is 21 hours and the half-life of the carboxyl metabolite is about 71 hours, a relationship to study drug cannot be excluded. Of note, contact dermatitis was also observed in 2/206 healthy subjects who participated in a dermal safety trial to evaluate the potential of Xeglyze lotion to induce contact sensitization.

Hair color changes represent a unique adverse event related to the mechanism of action of abametapir, which chelates metal cations such as iron and zinc. In the presence of the ferrous (Fe+2) ion, abametapir forms a water-soluble pink/red colored complex at iron concentrations as low as 1 ppm. Iron is commonly found in both well and tap water at varying concentrations.

In the Phase 3 clinical trials, investigators reported pink/red hair discoloration in a total of 3 subjects treated with Xeglyze lotion at the same trial site in Mississippi. One subject had blond hair and the other 2 had brown hair. The lotion was applied to and left on their hair for 10 minutes as per application instructions. All events resolved within 7 days. Hair discoloration was also reported in 1 subject in a Phase 1 trial. The subject had chemically-treated blond hair. Xeglyze lotion was applied to and left on the hair for 60 minutes. This event resolved within approximately 2.5 months. It is possible that the longer persistence of discoloration than occurred in Phase 3 is a result of the much longer application time in the Phase 1 trial.

No evidence of a treatment-related effect on any clinical chemistry measurement and no clinically meaningful trends were observed across the treatment groups.

Pregnant women were not excluded from enrollment in the Phase 3 clinical trials, however, only 2 pregnant subjects were enrolled. Therefore, the Division of Pediatric and Maternal Health (DPMH) Team recommended a postmarketing clinical lactation study in lactating

women who require treatment with Xeglyze lotion, 0.74% to better characterize the amount of abametapir, abametapir carboxyl and benzyl alcohol transferred into breastmilk and any potential risk associated with breastfeeding.

8. Advisory Committee Meeting

No regulatory issues requiring advisory committee input were identified during the review of this application.

9. Pediatrics

The applicant conducted Phase 3 trials in subjects 6 months of age and older, the relevant population for head lice infestation and the population for whom the applicant seeks labeling.

The applicant requested a pediatric waiver for Xeglyze lotion, 0.74% for the pediatric study requirement for ages birth through 6 months of age because necessary studies are impossible or highly impracticable; limited data is publically available to demonstrate the prevalence of head lice infestation in infants less than 6 months of age. In addition, the applicant requested a pediatric waiver for Xeglyze lotion for subjects aged 0 – 6 months because there is evidence to suggest that there is the potential of increased systemic absorption due to a high ratio of skin surface to body mass and the potential for an immature skin barrier in pediatric subjects from birth to 6 months. The Agency's Pediatric Review Committee concurred with the Pediatric Study Plan on April 30, 2014.

Each bottle (200 g) of Xeglyze lotion, 0.74% contains (b) (4) of benzyl alcohol as a (b) (4) Benzyl alcohol 0.9% when used in flush solutions has been shown to cause severe metabolic acidosis, encephalopathy and respiratory depression with gasping leading to death in infants at doses of 99 to 234 mg/kg/day. Benzyl alcohol toxicity has been particularly associated with low birth-weight infants, because of the greater dose of benzyl alcohol relative to body weight, and because the metabolic and excretory pathways for benzyl alcohol are still immature. In two clinical trials in which benzyl alcohol levels were measured in subjects ranging in age from 3 years to adult, benzyl alcohol levels were detected in a minority of subjects (7/39) with Cmax ranging from 0.52 to 3.57 µg/ml. The levels observed were about 30-200 fold lower than a level reported to be associated with neonatal gasping syndrome. The observed concentrations do not appear to pose a safety concern.

Language regarding the associated potential for neonatal gasping syndrome will be included in the Warnings and Precautions section and the Pediatric Use subsection of the labeling.

The design of the container (an amber glass bottle selected due to (b) (4)) and viscosity of the product limited the use of additional preventive measures for accidental ingestion, such as an orifice-reducing plug, or a squeezable container with flow restrictor. Therefore, labeling will include a recommendation to administer the drug to pediatric patients only under direct adult supervision. The risk of accidental ingestion will be described in the Warnings and Precautions section of the labeling.

10. Other Relevant Regulatory Issues

Two investigator sites were inspected in support of this application. No deficiencies were found that would preclude reliance upon the data that was submitted. The reader is referred to the Clinical Inspection Summary by Roy Blay, Ph.D.; Good Clinical Practice Assessment Branch; Division of Clinical Compliance Evaluation; Office of Scientific Investigations; dated June 16, 2016.

11. Labeling

Professional and patient labeling were reviewed and labeling was finalized following minor modifications. Important elements of labeling are as follows:

- **Indications and Usage**:

Xeglyze lotion, 0.74% is indicated for the topical treatment of head lice infestation in patients 6 months and older in the context of an overall lice management program.

- **Dosage and Administration**:

Xeglyze lotion is for topical use only. (b) (4)
Treatment with Xeglyze lotion involves a single application.

- **Warnings and Precautions**:

Systemic exposure to benzyl alcohol has been associated with serious and fatal adverse reactions including "gasping syndrome" in neonates and low birth weight infants. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth weight infants may be more likely to develop toxicity.

In order to prevent accidental ingestion in pediatric patients, Xeglyze lotion should only be administered under direct supervision of an adult.

12. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

Prescription status, routine pharmacovigilance, and professional and patient labeling are adequate risk management measures for the product. A Risk Evaluation and Mitigation Strategy (REMS) is not required.

- Other Postmarketing Requirements and Commitments

Three clinical trials will be required as Postmarketing Requirements (PMRs) under Food and Drug Administration Amendments Act (FDAAA). The rationales for these PMRs are discussed in the Safety section and Pediatric section of this memo.

1. Conduct a maximal use pharmacokinetic trial of XEGLYZE Lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age with head lice infestation to fully characterize the concentration time profile of abametapir and metabolite abametapir carboxyl.

2. Conduct a clinical trial in adult subjects to evaluate the potential for XEGLYZE Lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatrics. Additional drug interaction trials may be needed depending on the results of this trial.

3. A Clinical Lactation Study: A single dose, pharmacokinetic, open-label, clinical study to evaluate plasma and breastmilk concentrations of abametapir, abametapir carboxyl, and benzyl alcohol in lactating women who require treatment with XEGLYZE Lotion, 0.74%.

The applicant has agreed to conduct the following postmarketing commitment.

4. Conduct a study to evaluate the long-term storage stability of abametapir carboxyl in plasma stored at -80 ºC for duration of at least 1251 days.

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/s/

KENDALL A MARCUS
08/24/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206966
Priority or Standard	Standard
Submit Date(s)	09/14/2015
Received Date(s)	09/14/2015
PDUFA Goal Date	09/14/2016
Division/Office	DDDP/ODEIII
Reviewer Name(s)	Kevin L. Clark, MD
Review Completion Date	04/27/16
Established Name	Abametapir
(Proposed) Trade Name	Xeglyze
Applicant	Dr. Reddy's Laboratories
Formulation(s)	Lotion, 0.74%
Dosing Regimen	Apply XEGLYZE Lotion to dry hair in an amount (up to the full content of one bottle) sufficient to thoroughly coat the hair and scalp. Leave on the hair and scalp for 10 minutes and then rinse off with warm water.
Applicant Proposed Indication(s)/Population(s)	Treatment of head lice infestation in patients 6 months of age and older
Recommendation on Regulatory Action	Approval pending
Recommended Indication(s)/Population(s) (if applicable)	Treatment of head lice infestation in patients 6 months of age and older

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APPEARS THIS WAY ON ORIGINAL

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ABC	ATP binding cassette
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration time curve
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CYP	cytochrome P450
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GGT	gamma glutamyl transferase
GRMP	good review management practice

(b) (4)

ICH	International Conference on Harmonization
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

(b) (4)

LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NP	nurse practitioner
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	over-the-counter
PA	physician's assistant
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QT-IRT	QT Interdisciplinary Review Team
QTcB	QTc with Bazett correction
QTcF	QTc with Fridericia correction
RBC	red blood cells
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee

SLC	solute carrier
SLS	sodium lauryl sulfate
SOC	standard of care, system organ class (MedDRA)
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event
UGT	uridine diphosphate glucuronosyltransferase
WBC	white blood cells

1 Executive Summary

1.1. Product Introduction

Xeglyze (abametapir) Lotion, 0.74% is a pediculocide in the class of metalloproteinase inhibitors. Abametapir, the active moiety, is a new molecular entity (NME). Xeglyze is intended as a single-application topical therapy for head lice infestation. The proposed indication is treatment of head lice infestation in patients 6 months of age and older. The proposed dosing regimen is: Apply Xeglyze to dry hair in an amount (up to the full content of one bottle) sufficient to thoroughly coat the hair and scalp, leave on the hair and scalp for 10 minutes, then rinse off with warm water.

Xeglyze contains benzyl alcohol (b) (4) as an excipient to serve as (b) (4) Each bottle (200 g) of Xeglyze contains (b) (4) of benzyl alcohol. Systemic exposure to benzyl alcohol has been associated with serious and fatal adverse reactions including "gasping syndrome" in neonates and low birth weight infants. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants may be more likely to develop toxicity. Use not recommended in pediatric patients under 6 months of age because of the potential for increased systemic absorption.

See Section 4.2 for a more detailed discussion of CMC information regarding this drug product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant submitted evidence from two adequate and well controlled trials in support of this New Drug Application (NDA) submission. The data from these trials showed substantial evidence of the effectiveness of Xeglyze for the treatment of head lice infestation in patients 6 months of age and older. These trials were conducted under conditions of actual use, in geographically diverse sites. Therefore, the efficacy results are generalizable to the target population. The applicant has demonstrated that Xeglyze is effective for its intended use. In my opinion, the applicant has met the evidentiary standard required by 21 CFR 314.126(a)(b).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Xeglyze (abametapir) Lotion, 0.74% is a pediculocide and a new molecular entity (NME) in the class of metalloproteinase inhibitors. The proposed indication is treatment of head lice infestation in patients 6 months of age and older. The proposed dosing regimen is a single, 10 minute application of an amount sufficient to saturate the hair and scalp, followed by rinsing with water. Based on evidence from two adequate and well- controlled trials, Xeglyze is safe and effective for its intended use. Therefore, I recommend approval of Xeglyze, pending successful labeling negotiation and favorable outcome of facilities inspection.

Head lice infestation is a common problem; according to the Centers for Disease Control and Prevention, between 6 and 12 million people per year are affected. Infestations occur most commonly in children aged 3 to 11 years. Although not severe or life-threatening, head lice infestation is nevertheless a significant cause of lost school and work days for affected children and their caregivers. There are multiple drugs approved for treatment of head lice infestation. However, resistance to the available over-the-counter pediculocides has been reported. A new product, requiring only a single treatment, with a favorable safety and efficacy profile would be a useful addition to currently available treatments.

Two adequate and well-controlled trials, Ha03-001 and Ha03-002, evaluated Xeglyze under actual-use conditions in subjects 6 months of age and older with head lice infestation. For both trials, Xeglyze was statistically superior to Vehicle ($p \leq 0.001$) for the primary efficacy endpoint, which was the proportion of index subjects (i.e. the youngest household member with at least 3 live lice present at screening) who were lice-free at all follow-up visits through to the Day 14 Visit. In Trial Ha03-001, 81% of subjects treated with Xeglyze were lice free at all follow-up visits compared to 51% of subjects treated with Vehicle. In Trial Ha03-002, 82% of subjects treated with Xeglyze were lice free at all follow-up visits, compared to 47% in the Vehicle group.

The safety profile demonstrated for Xeglyze was adequately characterized during the drug development program. Adverse reactions include local manifestations of scalp erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), eye irritation (1.2%), scalp pruritus (1.4%), and hair color changes (1%). The adverse reactions were mild to moderate in severity and reversible. The frequencies of adverse reactions were similar across all age groups.

The primary metabolite of the active ingredient, abametapir carboxyl is cleared slowly from the circulation. Because pediatric PK data were only collected up to 8 hours post-dose, and because concentrations of abametapir carboxyl were continuing to rise at that time, C_{max} and T_{max} could not be characterized in pediatric subjects. However, available data indicate that exposure to abametapir carboxyl is

greater in pediatric subjects and is inversely proportional to weight. Studies using human hepatocytes showed concentration dependent inhibition by abametapir carboxyl of CYP3A4 and to a lesser extent CYP2B6 and CYP1A2. Because of this, the following postmarketing requirements will be requested: 1. Conduct a maximal use pharmacokinetic trial of Xeglyze lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age to fully characterize the concentration time profile of abametapir and metabolite abametapir carboxyl, and 2. Conduct a clinical trial to evaluate the potential for Xeglyze lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatrics. Additional drug interaction trials may be needed depending on the results of this trial.

The available evidence of safety and efficacy supports the approval of Xeglyze for treatment of head lice infestation in patients 6 months of age and older. Although there are safe and effective treatments currently available, only Sklice (ivermectin) lotion 0.5% is indicated for a single application treatment and Natroba (spinosad) Topical suspension 0.9% is indicated for 1-2 applications (a second application is needed only if live lice are seen 7 days after the first treatment). Xeglyze is effective after a single application, with an acceptable safety profile; however, the potential inhibition of CYP3A4 by the carboxyl metabolite of the active ingredient, as well as systemic exposure to this metabolite in pediatric subjects needs to be further characterized. PMRs will be requested to address these concerns (see Risk framework below). In conclusion, I recommend approval of Xeglyze for the treatment of head lice infestation in patients 6 months of age and older, pending successful labeling negotiations and a favorable site inspection report.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Head lice infestation is a common problem; according to the Centers for Disease Control and Prevention, between 6 and 12 million people per year are diagnosed. Infestations occur most commonly in children aged 3 to 11 years. • Although not severe or life-threatening, head lice infestation is a significant cause of lost school and work days for affected children and their caregivers.	Head lice infestation is a common problem, and is extremely disruptive to the lives of parents and children.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Currently approved over-the-counter products approved in the US for treatment of head lice infestation include Rid (pyrethrins and piperonyl butoxide) Mousse 4% and NIX (permethrin) Lotion 1%. • Currently approved prescription products approved in the US for treatment of head lice infestation include Lindane Shampoo 1%, Ovide (malathion) Lotion 0.5%, Ulesfia (benzyl alcohol) lotion 5%, Natroba(spinosad) topical suspension 0.9%, and Sklice (Ivermectin) Lotion 0.5%. • Pyrethrins and piperonyl butoxide is approved for children age 2 years and older, and permethrin is approved for children 6 months of age and older. Ovide is approved for children 6 years and older. Ulesfia, Natroba, and Sklice are approved for children 6 months of age and older. • Lindane Shampoo carries a boxed warning for neurologic toxicity, with seizures and death reported following use with repeat or prolonged application, but also in rare cases following a single application according to directions. Lindane Shampoo should be used with caution in infants, children, the elderly, and individuals with other skin conditions, and those who weigh < 110 lbs (50 kg) as they may be at risk of serious neurotoxicity. Lindane Shampoo is contraindicated in premature infants and individuals with known uncontrolled seizure disorders. The boxed warning also states that Lindane Shampoo should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of lice. • Resistance to over-the-counter pediculocides has been reported.	Resistance to over-the-counter pediculocides has been reported. Among currently approved prescription treatments, Natroba (spinosad) topical suspension 0.9%, requires 1-2 treatments and Sklice (ivermectin) lotion 0.5% only a single treatment; both are approved for children 6 months of age and older. Ulesfia (benzyl alcohol) lotion 5%, is also approved for children age 6 months and older, and requires 2 treatments 7 days apart. Safety of Ovide in children less than 6 years of age has not been established. Although effective, Lindane carries significant risk of neurotoxicity. Although there are safe and effective drugs currently available in the US for the treatment of head lice infestation for patients 6 months of age and older, there is a role for additional therapeutic options, particularly if they are effective after only a single treatment and have an acceptable safety profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Resistance has not yet been noted in the US to any of the approved prescription drugs; however, resistance to Ovide has been reported in the United Kingdom and Denmark. • Ulesfia contains benzyl alcohol 5% as the active ingredient and Natroba contains benzyl alcohol 10% as an excipient. Systemic exposure to benzyl alcohol has been associated with serious and fatal adverse reactions including "gasping syndrome" in neonates and low birth weight infants. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants may be more likely to develop toxicity because of the potential for increased systemic absorption.	
Benefit	• Trials Ha03-001 and Ha03-002 evaluated Xeglyze under actual-use conditions in subjects with head lice infestation. A total of 349 subjects were treated with a single, 10 minute application of Xeglyze in these pivotal Phase 3 trials. These multicenter trials were conducted in geographically diverse sites. • The primary efficacy endpoint was proportion of index subjects (i.e. the youngest household member with at least 3 live lice present at screening) who were lice-free at the Day 1, 7, and 14 Visit. • For both trials, Xeglyze was statistically superior to Vehicle ($p \leq 0.001$) for the primary efficacy endpoint. In Trial Ha03-001, 81% of subjects treated with Xeglyze were lice free at all follow-up visits compared to 51% of subjects treated with vehicle lotion. In Trial Ha03-002, 82% of subjects treated with Xeglyze were ice free at all follow-up	The evidence submitted by the applicant to support the approval of Xeglyze has met the evidentiary standard for providing substantial evidence of effectiveness under the proposed conditions of use. Only one product is currently approved for single dose therapy; therefore, Xeglyze will be a useful addition to the therapeutic armamentarium. The rate of adverse reactions was similar in children and adults. The trials were adequate and well-controlled. The geographic distribution of trial sites ensures that results are generalizable to the population. Because Xeglyze is effective

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	visits, compared to 47% in the Vehicle group. • Subjects who had scalp erythema/edema, scalp pruritus, scalp excoriation/pyoderma, and eye irritation at baseline had improvement of these symptoms after treatment with Xeglyze.	after a single treatment, children should be able to return to school one day after treatment, resulting in fewer missed school days as well as fewer missed days of work by parents or caregivers.
Risk	• The safety database for Xeglyze consists of 2 Phase 3 trials, which enrolled 244 pediatric subjects (6 months to <18 years of age). Supportive safety data was provided by 4 Phase 2 PK trials, 2 Dermal Safety trials, and a Thorough QT trial. The Phase 2 trials included 95 pediatric subjects. • Treatment-related adverse events include scalp erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), eye irritation (1.7%), vomiting (1.7%), scalp pruritus (1.4%), and hair color changes (0.9%). The adverse reactions were mild to moderate in severity and were reversible. The frequency of adverse events in adults and children were similar. • Xeglyze contains benzyl alcohol (b) (4) as an excipient. This poses a risk for infants less than 6 months of age and premature infants for neonatal gasping syndrome resulting from increased systemic absorption through the immature skin barrier. In the event of accidental ingestion, systemic toxicity may result as well. • The primary metabolite of the active ingredient, abametapir carboxyl is cleared slowly from the circulation. Because pediatric PK data were only collected up to 8 hours post-dose, and because concentrations of abametapir carboxyl were continuing to rise at that time, C_{max} and T_{max} could not be characterized in pediatric	The safety profile for Xeglyze was adequately characterized during the drug development program. Adverse events include mostly local reactions. Subjects who experienced vomiting had no abnormalities of laboratory data or on physical examination. The toxicity risk posed by the excipient benzyl alcohol (b) (4) will be addressed in the Warnings and Precautions section of product labeling, a childproof container/closure system, and printed warnings on the carton and container. Also, the potential of the metabolite abametapir carboxyl to inhibit CYP3A4 should be further evaluated and the pediatric exposure to abametapir carboxyl should be characterized. The following Post-Marketing Requirements (PMR) are recommended: 1. Conduct a maximal use pharmacokinetic trial of Xeglyze lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age to fully characterize the concentration time

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	subjects. However, available data indicate that exposure to abametapir carboxyl is greater in pediatric subjects and is inversely proportional to weight. • Studies using hepatocytes showed concentration dependent inhibition by abametapir carboxyl of CYP3A4 and to a lesser extent CYP2B6 and CYP1A2.	profile of abametapir and metabolite abametapir carboxyl. 2. Conduct a clinical trial to evaluate the potential for Xeglyze lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatrics. Additional drug interaction trials may be needed depending on the results of this trial.
Risk Management	Not applicable.	Not applicable

2 Therapeutic Context

2.1. Analysis of Condition

Infestations of the human head louse (*Pediculus humanus capitis*) continue to be commonly diagnosed. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that between 6 and 12 million people per year are diagnosed with head lice infestation. Infestations occur most commonly in children aged 3 to 11 years. Although not a cause of serious illness, nor a carrier of pathogens to humans, the head louse is nevertheless a costly burden because of lost time from school or child care, with concomitant lost productivity as working parents stay home to treat their affected children.

Head lice infestations occur more frequently in girls; this is thought to be due to the tendency to have longer hair, have more and longer head-to-head contact, and to exchange hair care accessories.[1] Head lice are uncommon in African-Americans because anatomic differences in American lice do not allow for proper positioning of the female in order to lay eggs on coarse, curly hair.[2,3]

The human head louse is an ectoparasite that relies on humans as their host for survival. The louse must take a blood meal from the host regularly, and are highly vulnerable to dehydration and death if they become detached from the host. Head lice rarely survive longer than 36 hours without a host. Certain biological functions of the louse, including digestion of the blood meal, hatching of the nit, and molting utilize metalloproteinase enzymes. These enzymes utilize metal cations at the active site and are potentially important targets for antiparasitic drugs.

The entire life cycle of *Pediculus humanus capitis* lasts 30 days. It begins when an egg (nit) is laid by an adult female at the base of the hair shaft, generally within 1 cm of the scalp. This is necessary because the warmth of the scalp helps the egg to incubate. The nits hatch after 6-9

[1] Jacobson CC and Abel EA. Periodic Synopsis: Parasitic Infections. Journal of the American Academy of Dermatology 2007;56:1026-43.

[2] 2 Burkhart CN and Burkhart CG. Head lice: Scientific assessment of the nit sheath with clinical ramifications and therapeutic options. Journal of the American Academy of Dermatology 2005; 53:129-133.

[3] Meinking TL et al. Chapter 83. Infestations in Dermatology e-edition, 2nd Edition: Bolognia JL and Jorizzo JL, Elsevier, Inc. © 2009.

days, releasing a nymph which undergoes 3 molting cycles of 3-4 days each, developing into an adult louse. The mature adult louse is tan to grayish white in color, and is approximately the size of a sesame seed. After mating, the female louse can lay up to 8 eggs per day and may reproduce for 2-3 weeks.

The diagnosis of an active infestation depends on the identification of live lice on the hair or scalp of the patient. Therefore, accurate diagnosis depends on the skill and patience of the examining clinician in locating these tiny insects. The presence of nits alone is not diagnostic of active infestation, because it is not possible to distinguish hatched vs unhatched nits with the naked eye. Symptoms of head lice infestation include pruritus, erythema, and excoriations of the scalp.

2.2. Analysis of Current Treatment Options

Pharmacologic treatments approved for the treatment of head lice infestation, and available over-the-counter (OTC), include permethrin and pyrethrin with piperonyl butoxide. As treatments for head lice infestation have been developed, resistance has also developed. In the United States, resistance to pyrethroids is common.

The following drugs have been approved for the treatment of head lice infestation and are available by prescription: Lindane shampoo 1%, Ovide (malathion) lotion 0.5%, Ulesfia (benzyl alcohol) lotion 5%, Natroba (spinosad) suspension 0.9%, and Sklice (ivermectin) lotion 0.5%.

Lindane Shampoo was approved January 22, 1975. The labeling carries a boxed warning which states that Lindane Shampoo should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of head lice infestation. The boxed warning also covers neurologic toxicity, with seizures and death reported following use with repeat or prolonged application, but also in rare cases following a single application according to directions. The warning further states that Lindane Shampoo should be used with caution in infants, children, the elderly, individuals with other skin conditions, and those who weigh < 110 pounds (50 kg) as they may be at risk of serious neurotoxicity. Lindane Shampoo is contraindicated in premature infants and individuals with known uncontrolled seizure disorders.

Ovide lotion was approved August 2, 1982, and is limited to use in children 6 years and older. Resistance has been reported in the United Kingdom and Denmark[4]. In contrast, Natroba,

[4] Wadowski L, Balasuriya L, Price HN, and O'Haver J. Lice Update: New solutions to an old problem. Clinics in

Ulesfia, and Sklice are currently approved for use in children 6 months and older; no resistance to these products has been documented. Ulesfia labeling recommends a second treatment 1 week after the first; in contrast, Natroba labeling only recommends a second treatment after 1 week if live lice are still present. Sklice requires only a single application. Although no resistance has been documented in the United States to these 3 drugs at this time, resistance has historically developed to older drugs over time and after repeated use. Therefore, the development of safe and effective new treatments for head lice infestation remains important.

Ulesfia was approved April 9, 2009 containing benzyl alcohol 5% as the active ingredient. The indication is topical treatment of head lice infestation in patients 6 months of age and older. As stated in product labeling, Ulesfia works by opening the respiratory spiracles, allowing the mineral oil containing vehicle to penetrate, thus leading to asphyxiation of the louse. According to labeling for Ulesfia, the most common adverse reactions (> 1% and more common than with placebo) are: pruritus, erythema, pyoderma, ocular irritation, applicant site irritation, and application site anesthesia and hypoesthesia.

Natroba was approved Jan 18, 2011. The indication is topical treatment of head lice infestation in patients 6 months of age and older. As stated in product labeling, Natroba causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die. According to the labeling for Natroba, the most common adverse reactions are application site erythema, ocular erythema and application site irritation.

Although now approved for use in children 6 months of age or older, Natroba (which contains benzyl alcohol 10% as an excipient) and Ulesfia pose additional risk for infants younger than 6 months of age because of the association of benzyl alcohol with neonatal gasping syndrome. This information is included in the approved labeling for both of these products.

Sklice was approved in February 7, 2012. It is indicated for the topical treatment of head lice infestation in patients 6 months of age and older. As stated in product labeling, Sklice binds the glutamate-gated chloride channels, inducing paralysis and death of the louse. Per product labeling, the most common adverse events reported with this drug include application site pruritus, excoriation, and erythema.

Physical, non-pharmacologic methods for treating lice include devices, hair removal and occlusion (petroleum jelly, olive oil, mayonnaise, etc.). Devices approved for the treatment of head lice include Lice Comb, (b) (4), Licemeister, and others.

Table 1: Currently available products approved by the FDA for the treatment of head lice infestation

Product (s) Name	Relevant Indication	Rx or OTC	Dosing/ Administration	Important Safety and Tolerability Issues
Rid (pyrethrins and piperonyl butoxide) Mousse, 4% (eq 0.33% base) NDA 21043 Approved 3/7/2000	Topical treatment of head lice infestation in patients 2 years of age and older	OTC	Apply to dry hair for 10 minutes, remove by shampooing after 10 minutes; requires 2nd treatment in 7-10 days	Local reactions including erythema, pruritus, and edema as well as allergic reactions have been reported.
NIX (permethrin) Lotion, 1% NDA 19435 Approved 3/31/1986	Topical treatment of head lice infestation in patients 2 months of age and older	OTC	Apply to damp hair for 10 minutes; repeat in 7 days if needed	Local reactions including erythema, pruritus, and edema as well as allergic reactions have been reported.
Lindane Shampoo, 1% ANDA 84219 Approved 1/22/1975	Topical treatment of head lice infestation only in patients who: 1. cannot tolerate other approved therapies, or 2. have failed treatment with other approved therapies.	Rx	Apply to dry hair for 4 minutes	Seizures and deaths have been reported following Lindane Shampoo use with repeat or prolonged application, but also in rare cases following a single application according to directions. Lindane Shampoo should be used with caution in infants, children, the elderly, and individuals with other skin conditions, and those who weigh < 110 lbs (50 kg) as they may be at risk of serious neurotoxicity.
Ovide (malathion) Lotion, 0.5% NDA 18613 Approved 8/2/1982	Head lice infestation of scalp hair	Rx	Apply for 8-12 hours and repeat in 7 days if live lice are present.	Chemical burns including second-degree burns and stinging sensations may occur with the use of OVIDE Lotion. Safety and effectiveness in children less than 6 years of age has not been established. Product is flammable.
Ulesfia (benzyl alcohol) lotion, 5% NDA 22129 Approved 4/9/2009	for topical treatment of head lice infestation in patients 6 months of age and older	Rx	2 ten minute applications 7 days apart	Intravenous administration of products containing benzyl alcohol has been associated with neonatal gasping syndrome consisting of severe metabolic acidosis, gasping respirations, progressive hypotension, seizures, central nervous system depression, intraventricular hemorrhage, and death in preterm, low birth weight infants. Neonates (i.e. patients less than 1 month of age or preterm infants with a corrected age of less than 44 weeks) could be at risk for gasping syndrome if treated with ULESFIA® Lotion No teratogenic effects in animal studies.

Product (s) Name	Relevant Indication	Rx or OTC	Dosing/ Administration	Important Safety and Tolerability Issues
Natroba (spinosad) topical suspension, 0.9% NDA 22408 Approved 1/18/2011	for topical treatment of head lice infestation in patients 6 months of age and older	Rx	10 minute application which is repeated in 7 days if live lice are noted on examination	NATROBA Topical Suspension contains benzyl alcohol and is not recommended for use in neonates and infants below the age of 6 months. Systemic exposure to benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants No teratogenic effects in animal studies.
Sklice (Ivermectin) Lotion, 0.5% NDA 202736 Approved 2/7/2012	for topical treatment of head lice infestation in patients 6 months of age and older	Rx	Single 10 minute application	Adverse reactions, reported in less than 1% of subjects treated with SKLICE Lotion, include conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin burning sensation.

Source: Table created by reviewer, data taken from product labelling.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Xeglyze is a new molecular entity (NME), and therefore is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Xeglyze was developed under the IND 77510, which was submitted on December 20, 2007.

A **Pre-IND** meeting was held June 20, 2007. The purpose of this meeting was to provide general guidance on the content and format of the proposed Investigational New Drug Application under 21 CFR 312.

End of Phase 2 Meeting was scheduled for **August 1, 2012**. The applicant cancelled this meeting after deeming the Agency's response to pre-meeting questions to be sufficient. The Agency requested that the applicant develop a container/closure design to reduce the risk of accidental ingestion, using a design more typical for topical products. The inclusion of benzyl alcohol (b) (4) in the Vehicle prompted additional requests from the Agency. The applicant was asked to evaluate the potential systemic exposure of benzyl alcohol in the pediatric pharmacokinetics (PK) trial. Also, the applicant was asked to comment on the potential effect of benzyl alcohol on efficacy data in light of the fact that benzyl alcohol 5% is the active ingredient in an approved product for treatment of head lice infestation. Finally, the Agency recommended cardiac safety monitoring (ECG) during the pediatric PK trial.

Special Protocol Assessment (SPA) was submitted by the applicant on **October 23, 2013**. The Special Protocol Agreement letter was sent on **December 4, 2013**. The Agency agreed that the planned design and analysis presented was adequate to address the objectives necessary to support a regulatory submission. The Agency also specified the following specific agreements (excerpted from SPA letter of 12/4/2013):

1 . The general design of your Phase 3 trial (Ha03-001(entitled "A Randomized, Double- Blind, Multicenter, Vehicle-Controlled Study of the Efficacy and Safety of Abametapir Lotion 0.74% Administered for the treatment of Head Lice Infestation" is acceptable.

2. Your proposal to conduct 2 identical, well-controlled Phase 3 trials in parallel to support the efficacy and safety of abametapir lotion 0.74% is acceptable. However, the trials should not have common investigators or common subjects in order to have independent replication of trial findings.

3. The proposed study population (males or females 6 month of age or older with active head lice infestation defined as at least three live lice for the index subject and at least one live louse for the other household members) is acceptable.

4. The proposed dosing regimen (single application of abametapir lotion 0.74% for 10 minutes) is acceptable.

5. Your proposed primary efficacy endpoint of the proportion of all index subjects who are lice free at all follow-up visits through the Day 14 visit (e.g. Days I,7, 14) is acceptable.

6. Your proposal to define the Intent to Treat (ITT) subjects as all index subjects who were randomized, and to use such analysis set as the primary analysis population is acceptable.

7. Your proposal to use the Cochran-Mantel-Haenszel test stratified by site as the primary analysis method is acceptable.

8. Your proposed rescue therapy (NIX®) is acceptable.

9. Your proposed active assessment of cutaneous and ocular irritation is acceptable. See Additional Comment #7.

The Agency also communicated the following non-agreements, along with suggested resolution:

1. You proposed to impute missing data using the last observation carried forward (LOCF), "except for the subjects without follow up lice-evaluation at the Day 14 visit who will be

considered as treatment failures". It is not clear whether your imputation method is intended for the primary as well as the secondary endpoints. You should propose an imputation method that is consistent for handling both the primary and the secondary endpoints so that the study findings can be reasonably interpreted. Note that your proposed approach might inflate the success rate of the secondary endpoint at Day 7 (i.e., lice-free index subjects at Day 7) if a subject was a success at Day **1** and missed the Day 7 visit.

Analyses of efficacy were performed using both LOCF and missing value treated as failure (MVTF). Each of the analyses revealed similar results. These analyses are discussed in Section 6.1.2 and 6.2.2 of this review.

2. Your proposed secondary endpoints are:

- Proportion of all index subjects who are lice free at visit Day 1.
- Proportion of all index subjects who are lice free at visit Day 7.

Based on the life cycle of the louse, an evaluation of the proportion of index subjects who are lice free on Day 1 or Day 7 may not be clinically meaningful. As you proposed two secondary endpoints, testing each endpoint at a-0.05 would inflate the Type I error rate. The protocol needs to include a method of controlling multiplicity among the secondary endpoints. Secondary endpoints should be clinically relevant.

The applicant did not change the secondary endpoints in response to this non-agreement. This did not ultimately affect my review recommendation because only the primary endpoint was clinically relevant, and the applicant met the evidentiary standard for efficacy with the primary endpoint.

3. Because your product is a new molecular entity, the safety monitoring in your Phase 3 trial(s) should include periodic laboratory assessments (e.g. hematology and chemistry).

Initial Pediatric Study Plan was submitted on **December 11, 2013** and **April 10, 2014**. An **Agreed Pediatric Study Plan** was sent to the applicant on **May 8, 2014**.

Pre-NDA meeting was held on **January 21, 2015**. The content and format of the pending NDA submission were discussed. The Agency advised the applicant regarding the need for consistency in handling missing data between primary and secondary endpoints. The Agency also informed the applicant that the ex-vivo method for determining ovicidal activity may not be predictive of in-vivo ovicidal activity, (b) (4) However, the Agency also stated that the final determination of whether the ex-vivo trial is adequate (b) (4) would be decided during the NDA review process.

NDA was submitted on September 14, 2015.

3.3. Foreign Regulatory Actions and Marketing History

This moiety is a NME, not marketed elsewhere.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Because of a relatively high number of index subjects enrolled, combined with high treatment response, the review team chose Site 107 from Trial Ha03-001 and Site 207 from Trial Ha03-002 for Office of Scientific Investigations (OSI) site inspections. OSI investigators completed inspections of the respective sites; both were classified as "No Action Indicated".

4.2. Product Quality

Xeglyze is a white to off-white oil in water emulsion, containing 0.74% w/w of abametapir, intended for topical administration. The formulation of Xeglyze used in the drug development program was the to-be-marketed formulation. Xeglyze contains no novel excipients. The composition of Xeglyze is displayed in Table 2. For a comprehensive review of the drug substance and drug product, please refer to Dr. Xavier Ysern's review and Dr. Bhavishya Mittal's review in the Integrated Quality Assessment, dated April 22, 2016.

Table 2: Xeglyze Drug Product Composition

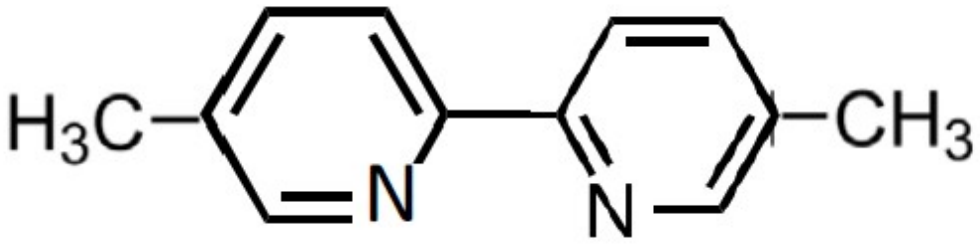
Component	Quantity		Function	Quality Standard
	Amount per unit (g/bottle)	%w/w		
Abametapir (5,5'-Dimethyl-2,2'-dipyridyl)	(b) (4)	0.74	Active	In-house
Light mineral oil	(b) (4)			NF

Component	Quantity		Function	Quality Standard
	Amount per unit (g/bottle)	%w/w		
Polysorbate 20	(b) (4)		(b) (4)	NF
Benzyl Alcohol				NF
Butylated hydroxytoluene				NF
Carbomer 980 (b) (4)				NF
Trolamine				NF
Purified Water				USP

Source: Applicant's submission, 2.3 Quality Overall Summary, Table 1

The structural formula of the active ingredient, abametapir, is displayed in Figure 1 below.

Figure 1: Structural Formula of Abametapir



Drug Substance Quality Summary

Abametapir is a white to pale yellow solid that has an empirical formula of $C_{12}H_{12}N_2$ and a molecular weight of 184.24. Abametapir melts in the temperature range of 114°C -117°C. Abametapir is insoluble in water; sparingly soluble in hexane and petroleum ether; soluble in acetonitrile, diethyl ether, dimethyl sulfoxide, isopropyl alcohol, and propylene glycol; freely soluble in acetic acid, acetone, benzene, benzyl alcohol, chloroform, dimethylformamide, dioxane, ethanol, ethyl acetate, methanol and tetrahydrofuran. The partition coefficient (logP) of the drug is determined to be 2.13 at pH 7.0. Abametapir drug substance is not hygroscopic.

The drug substance is (b) (4)

(b) (4)

The identity, strength, purity and quality of the drug substance are deemed assured by the drug substance specification. (b) (4) A re-test period of (b) (4) months is recommended for the drug substance when stored at (b) (4) in the proposed package.

Drug Product Quality Summary

The drug product, Xeglyze (abametapir) Lotion, is a viscous, white to off-white oil in water emulsion, containing 0.74% w/w of abametapir. Abametapir is a pediculocide and is indicated for the topical treatment of head lice infestation (Pediculosis humanis capitis) in patients 6 months of age and older. The inactive ingredients used in XEGLYZE lotion are water, light mineral oil, polysorbate 20, carbomer 980, trolamine, butylated hydroxytoluene and benzyl alcohol.

The identity, strength, purity including microbial limits, and quality of the drug product are deemed assured by the drug product specification. (b) (4) The expiration dating period of 24 months is recommended for the drug product when stored at controlled room temperature based on long-term and accelerated stability data obtained from 3 registration batches of the drug product, and 6 supportive batches of the drug product. The Environmental Assessment (EA) team finds that the NDA applicant's request for a categorical exclusion from an EA is acceptable.

Benzyl Alcohol and Selection of Container/Closure Design

There is a safety concern related to the excipient benzyl alcohol involving accidental ingestion, particularly by children. During the drug development program, at the end of Phase 2 meeting, the Agency advised the applicant: "To reduce medication errors due to accidental ingestion, we strongly recommend that you choose a container/closure design for commercialization which is more in line with topical products, and refrain from using a design which is typical for oral liquids. We encourage you to include a consideration of child resistance when selecting the to-be-marketed container/closure system for this product." During the development program for Xeglyze, (b) (4)

[redacted] therefore, the applicant selected the USP Type [redacted] amber glass bottle because [redacted]
Furthermore, the design of the glass container required modification to widen the container opening after the Phase 2 studies. Widening of the container opening was necessary because investigators had difficulty removing Xeglyze from the non-compressible glass container because of the viscosity of Xeglyze. The to-be-marketed container closure features a 45mm white polypropylene child resistant closure cap with a tri-foil inner liner.

In order to mitigate the risk of accidental ingestion, Xeglyze will be marketed with a childproof container/closure system as discussed above. Additionally, language recommending that Xeglyze "should only be administered to pediatric patients under the direct supervision of an adult" is included in Section 5 Warnings and Precautions and 17 Patient Counseling Information of product labeling.

Facilities

Please refer to the comprehensive facilities review by Quallyna Porte in the OPQ Integrated Quality Assessment of April 22, 2016. From this review: " Although Dr. Reddy's Lab (Unit VI) has historically manufactured non-sterile APIs (active pharmaceutical ingredients), its recent inspectional history of non-compliance particularly related to data integrity and quality systems issues, provides no confidence in their capability to commercially manufacture APIs. Therefore a recommendation of Withhold is made for NDA 206966."

Conclusion and Recommendations

In conclusion, the Office of Product Quality issued these comments and recommendations:

"The applicant of this NDA has provided sufficient CMC information to assure the identity, purity, strength and quality of the drug product.

However, the Office of Process and Facility has made a [redacted] recommendation for the drug substance manufacturing site due to unresolved cGMP issues.

Also, the issues on labels/labeling are not completely resolved at this time. Therefore, from the OPQ perspective, this NDA is recommended for **Complete Response** per 21 CFR 314.125(b)(6),(13) until the above issues are satisfactorily resolved."

4.3. Clinical Microbiology

The Microbiology division of the Office of Product Quality reviewed microbial testing of the drug substance and drug product for this NDA. In their final review, the Microbiology reviewer found the applicant's test results "acceptable" and recommended approval from the microbiology perspective. Please refer to the comprehensive review by Dr. Eric Adeeku in the Integrated Quality Assessment of April 22, 2016.

4.4. Nonclinical Pharmacology/Toxicology

The applicant submitted a battery of nonclinical pharmacology/toxicology studies in support of this NDA; those most relevant to product labeling will be discussed here. Xeglyze contains no novel excipients; the composition of the drug product is discussed in detail in Section 4.2 of this review. Please refer to Dr. Jill Merrill's comprehensive Pharmacology/Toxicology review 4/12/2016 in DARRTS. The following paragraphs contain excerpts from Dr. Merrill's review unless otherwise specified.

A single dose oral abametapir toxicity study was conducted in rats (0 {vehicle control; (b) (4) 150, 175, 200, 250 mg/kg; n=1/sex/dose; (b) (4) 0005). Clinical signs included body tremors at all dose levels and piloerection, fast respiration and abnormal gait or convulsions at the higher dose levels. Both males dosed at 200 and 250 mg/kg died within 4 hours of dosing.

The repeat-dose toxicity of abametapir was investigated in groups of Sprague-Dawley rats (3/sex/dose) at 0 (vehicle control; (b) (4) 5, or 20 mg/kg/day in a 7-day intraperitoneal toxicity study (b) (4) 612). At the end of the experimental period all animals were terminated and blood samples were taken for hematology and serum chemistry analysis. Under the conditions of this study abametapir did not produce any toxic effects when compared with the vehicle control animals.

A 2-week repeat-dose oral toxicity study (0 {vehicle control; (b) (4) 8, 25, 75 or 100 mg/kg/day) was conducted in CD rats (b) (4) 0006). The kidney and red blood cells were identified as target organs for toxicity. Under the conditions of this study the NOAEL for abametapir was determined to be 8 mg/kg/day.

Abametapir was administered to juvenile rats orally for 8 weeks at oral doses of 0 (vehicle control; (b) (4) 5, 12, or 30 mg/kg/day beginning on PND 7. Body weight

gain, crown-rump and tibial lengths, were unaffected by treatment. There were no adverse effects on the development or maturation of the central nervous system or reproductive organs. The primary effects noted in this study included decreased red blood cell parameters (associated with the pharmacological activity of abametapir), slightly increased creatinine (1.1 to 1.3-fold above control values at the end of the treatment and recovery periods), with no histopathological correlates at any dose. Although a dosing error during Week 4 precluded development of a NOAEL, no new target organs were identified.

Cardiovascular safety was originally evaluated in an in vitro hERG assay (b) (4) 0017/072680). Inhibitory effects on the hERG current raised concerns about QTc prolongation (IC50 =~56 µM). The applicant had also conducted a study to evaluate the effects of abametapir on electrocardiographic parameters in anesthetized male rats and although it was concluded that abametapir did not appear to cause acute effects on cardiovascular variables, the study did not meet minimal standards and the sponsor was advised to conduct a cardiovascular safety study in an unanesthetized nonrodent species with a sufficient number of animals of both sexes. The sponsor subsequently conducted a cardiovascular study in minipigs using telemetry (71456) which was too flawed for regulatory use. Although the minipig study lacked acceptable dose formulation analysis, no significant changes were observed in ECG parameters with abametapir plasma concentrations as high as 329 ng/mL at 60 minutes after application of the 8.0% abametapir treatment. These studies are less than ideal, but do not present nonclinical causes for concern for potential cardiovascular effects associated with abametapir. Cardiovascular safety was ultimately evaluated and confirmed in Trial Ha02-005, the thorough QT trial. The thorough QT trial is discussed in more detail in Section 8.4.9 of this review.

Study number 20049509 was a 28-day toxicity study of Abametapir Lotion by dermal administration to minipigs with a 16-day recovery. Once daily dermal administration of abametapir lotion, 0.74% in female minipigs for 28 days was without systemic effects (correlates to a Cmax value of 294 ng/mL and an AUClast value of 622 ng●h/mL on Day 28; 14.2 mg/kg/day). Females treated twice daily with abametapir lotion, 0.74% or once daily with abametapir lotion, 3.7% had tremors and distended abdomen (≥28.2 mg/kg/day). In males, general signs of toxicity and penile prolapse were observed with once daily administration of abametapir lotion, 0.74% (correlates to a Cmax value of 534 ng/mL and an AUClast value of 1297 ng●h/mL on Day 13; 14.2 mg/kg/day). The penile prolapse observations required early termination for humane reasons and no underlying cause of the protrusion was demonstrated. Under the conditions of this study, the NOAEL in females is once daily dermal administration of abametapir lotion, 0.74% (14.2 mg/kg/day) and a NOAEL in males could not be determined. Dr. Merrill noted that “These treatment-related effects noted after extended repeat dose testing would not be a cause for concern under the proposed clinical conditions of use which is for a one time 10-minute application and then washed off.”

The applicant has performed the complete ICH genotoxicity battery for abametapir. These genotoxicity studies were reviewed under the IND submission and briefly described below. Abametapir (≤500 µg/plate) with or without metabolic activation was not mutagenic in the bacterial reverse mutation test. Higher concentrations were limited by toxicity. In the in vitro chromosomal aberration test in Human lymphocytes, chromosomal aberrations were observed, but only at cytotoxic concentrations (230.3 µg/mL). This result was considered equivocal. Abametapir (<160 mg/kg/day) did not induce micronucleus formation in the in vivo rat micronucleus assay. Abametapir is considered to be negative for genotoxic potential.

The applicant also conducted an *in vitro* Reverse Mutation Assay in Bacterial Cells (Ames test) to evaluate the genotoxicity of abametapir carboxyl. The mutagenic effect of abametapir-COOH was tested in the Ames test using the plate incorporation method in TA98, TA100, TA102, TA1535, and TA1537 *Salmonella typhimurium* tester strains with 5 dose concentrations (7.9, 25, 79, 250, and 790 µg/plate) in both the presence and absence of metabolic activation. Abametapir-COOH elicited cytotoxicity at 2500 µg/plate in a dose range finding study. Abametapir-COOH was negative for both cytotoxicity and mutagenicity at dose concentrations of 7.9-790 µg/plate for each of the five tester strains both with and without metabolic activation (±S9).

No carcinogenicity studies were included in this NDA submission. Abametapir lotion is intended as a single application drug product for the treatment of head lice infestation in patients 6 months of age and older, and the product is not intended for chronic use.

Oral doses of abametapir (0 {vehicle; (b) (4) 10, 25, 75 mg/kg/day) were evaluated for effects on fertility and early embryonic development in the CD rat (b) (4) 0006). Treatment-related findings were observed at all dose levels, but at 10 and 25 mg/kg/day none of the changes were considered to be of toxicological importance. The NOAEL for parental toxicity was 25 mg/kg/day abametapir and the NOAEL for fertility and early embryonic development was 75 mg/kg/day abametapir in CD rats.

Oral administration of abametapir in (b) (4) (0 {vehicle control}, 10, 20, or 40 mg/kg/day) to New Zealand White rabbits during the organogenesis phase of gestation (gestation days 6 - 19) did not produce any statistically significant adverse effects when compared with vehicle control animals (b) (4) 0004). However, the vehicle itself caused reduced maternal weight gain and the NOAEL for maternal toxicity is considered to be 10 mg/kg/day based on a reduced maternal weight gain at the end of treatment (Day 20) of 23% and 46% at 20 and 40 mg/kg/day, respectively. Although there were no differences in maternal body weight at termination (Day 29), does in the high dose group took longer to catch up with the control group body weight during the post treatment period. No treatment-related effects were observed on the mean number of corpora lutea, implantation sites, resorptions (early, late), dead fetuses, viable fetuses, fetal sex ratio, fetal and placental weights, and external,

visceral and skeletal morphology. The NOAEL for developmental toxicity was 40 mg/kg/day, the highest dose tested.

The applicant used The EpiOcular™ Human Cell Construct was used to assess the potential ocular irritation of abametapir lotion, 0.74% (Study # 14AB04-AB05.015001). The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) conversion assay, which measures the NAD(P)H-dependent microsomal enzyme reduction of MTT (and to a lesser extent, the succinate dehydrogenase reduction of MTT) to a blue formazan precipitate, was used to assess the cellular metabolism after exposure to each test article for six exposure times (0.33, 1, 2, 4, 8, and 24 hours). One hundred microliters of the test article was applied to each EpiOcular™ human cell construct. Duplicate cultures of the negative control (exposure time control), 100 µL of sterile deionized water, were exposed for 0.25, 4, 8 and 24 hours. Duplicate cultures of the positive control, 100 µL of 0.3% Triton®-X-100, were exposed for 15 and 45 minutes. The exposed cultures were then incubated for the appropriate amount of time at standard culture conditions. The duration of exposure resulting in a 50% decrease in MTT conversion in test article-treated EpiOcular™ human cell constructs, relative to control cultures, was determined (ET50). Since the positive control fell within two standard deviations of the historical mean (18.5 – 35.4 minutes), and the corrected mean OD550 value for the negative control exposure time (1.448) was within 20% of the corrected mean OD550 value for the maximum negative control exposure time (up to 4 hours) (1.333), the assay was accepted. The ET50 values of both of these test articles represent mild ocular irritation potential.

In conclusion, upon review of the data presented above in addition to other studies, Dr. Merrill finds that Xeglyze is approvable for the treatment of head lice infestation in children six months of age and older from a Pharmacology/Toxicology perspective. Furthermore, Dr. Merrill proposed the following modifications to the applicant's proposed labeling:

1. 1.3.3 Labeling

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. With the exception of titles which are underlined based on the label template, nonclinical recommendations are shown as underlined text. It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the XEGLYZE label text. A clean copy of these revised labeling sections is provided in Appendix #2.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Xeglyze [redacted] is a [redacted] pediculicide [redacted] indicated for the topical treatment of head lice infestation [redacted] in patients 6 months of age and older. [redacted]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

[redacted] There are no available data [redacted] on Xeglyze [redacted] use in pregnant women to inform a drug associated risk. In embryofetal development studies conducted with oral administration of abametapir during organogenesis no evidence of fetal harm or malformations, independent of maternal toxicity, were observed in pregnant rats and rabbits at doses that produced exposures up to 50 times and equivalent to the maximum recommended human dose (MRHD) in rats and rabbits, respectively. The highest dose evaluated in rabbits was limited due to maternal toxicity associated with the vehicle used in the study *[see Data]*. [redacted]

Data

Animal Data

Systemic ~~E~~embryofetal development studies were performed in rats [redacted] and rabbits. Oral doses of 10, 25, and 75 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 17) to pregnant rats. In the presence of maternal toxicity, embryofetal toxicity (lower fetal body weights and delayed ossification) was noted at 75 mg/kg/day. No treatment related effects on malformations were noted at 75 mg/kg/day (50 times the exposure at the MRHD based on C_{max} comparisons). [redacted]

Oral doses of 4, 16 and 40 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 19) to pregnant rabbits. No treatment related effects on embryofetal toxicity or malformations were noted at 40 mg/kg/day (~1 times the MRHD based on C_{max} comparisons). Maternal toxicity related to the vehicle limited the maximum dose in pregnant rabbits.

(b) (4)

In a perinatal and postnatal development study in rats, oral doses of 10, 25, and 75 mg/kg/day were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal lethality and decreased fetal body weight gain were noted at 75 mg/kg/day. No treatment related effects on postnatal development were noted at 75 mg/kg/day (47 times the MRHD based on C_{max} comparisons).

Lactation

Risk Summary

No data are available regarding the presence of (b) (4) abametapir (b) (4) in human milk, or the effects of abametapir on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xeglyze (b) (4) and any potential adverse effects on the breastfed child from Xeglyze (b) (4) or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abametapir (5,5'-dimethyl 2,2'-bipyridinyl) is a metalloproteinase inhibitor (b) (4) (b) (4) Metalloproteinases have (b) (4) physiological processes (b) (4) critical to egg development and survival of (b) (4) lice. (b) (4)

12.3 Pharmacokinetics

Excretion

Excretion of abametapir and its human metabolites was not examined in patients. (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term (b) (4) studies in animals have not been conducted to evaluate the carcinogenic potential (b) (4) of Xeglyze (b) (4) or abametapir.

Abametapir was not mutagenic or clastogenic based on the results of two in vitro genotoxicity tests (Ames test and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay). (b) (4)

No effects on fertility have been observed in rats following repeated oral doses of up to 75 mg/kg/day abametapir (50 times the MRHD based on C_{max} comparisons).

4.5. Clinical Pharmacology

Please refer to the comprehensive review by Dr. Doanh Tran. As per his review, "The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 206966 acceptable pending agreement on recommended labeling changes and post marketing requirements and commitments."

4.5.1. Mechanism of Action

The active ingredient in Xeglyze is abametapir. Abametapir is a metalloproteinase inhibitor. The mechanism of action as a pediculocide of metalloproteinase inhibitors is the interruption of physiological processes critical to egg development and survival of lice.

4.5.2. Pharmacodynamics

From the Clinical Pharmacology Review by Dr. Doanh Tran:

"The Applicant conducted a thorough QT study Ha02-005 and reported that administration of Abametapir lotion, 0.74% for 60 minutes in healthy adults without head lice did not prolong cardiac repolarization (QTc interval). The results of this study were reviewed by interdisciplinary review team for QT (IRT-QT) under IND 77510 on 6/14/2013, which concurred with the Applicant's conclusion. The mean observed abametapir Cmax in this study was 432 ± 137 ng/mL, which exceeded those observed under maximal use conditions in subjects with active head lice infestation. Therefore, the results of this study are applicable to the target population and it can be concluded that there is no concern regarding QTc prolongation with Abametapir

lotion, 0.74% for treatment of head lice infestation."

The thorough QT study is reviewed in more detail in Section 8.4.9 of this review. Otherwise, the applicant did not study the pharmacodynamics of Xeglyze (from section 12.2 of applicant's proposed labeling).

4.5.3. Pharmacokinetics

The clinical development program for Xeglyze included 3 human pharmacokinetic (PK) trials:

- Trial Ha02-003: evaluated PK in 6 adult and 12 pediatric subjects, aged 3 to 12 years
- Trial Ha03-003: evaluated PK in 22 pediatric subjects aged 6 months to 17 years
- Trial Ha03-004: evaluated PK in 38 pediatric subjects aged 6 months to 17 years

Each trial enrolled subjects with head lice infestation and each subject was treated with a 10 minute application of Xeglyze at the 0.74% strength. Pharmacokinetic samplings were carried out to 72 hours post dose in adults and 8 hours post dose in pediatric subjects for all trials. The PK parameters for the active ingredient, abametapir, were characterized as described below.

From Dr. Tran's Review:

Bioavailability (Absorption):

"Trial Ha02-003 evaluated pharmacokinetics in 6 adult and 12 pediatric subjects aged 3 to 12 years of age. The mean (%CV) abametapir plasma maximum concentration (Cmax) and area under the concentration time curve from 0 to 8 hours post dose (AUC0-8h) in the adult group were 41 (66%) ng/mL and 121 (50%) ng*h/mL, respectively. The mean (%CV) Cmax and AUC0-8h in the pediatric group were 73 (57%) ng/mL and 264 (67%) ng*h/mL, respectively, and were higher compared to the values for adults. The mean (%CV) terminal half-life in adults was 21 (11%) hours.

Trials Ha03-003 and Ha03-004 evaluated pharmacokinetics in pediatric subjects aged 6 months to 17 years of age. The pharmacokinetic results for plasma abametapir are shown in table below. As expected, even though the values varied between the 2 trials, abametapir exposure increased as the age of the subject decreased. Abametapir absorption was rapid with a median Tmax of 0.57 to 1.54 hours."

Table 3 displays the PK parameters of abametapir in pediatric subjects from Trials Ha03-003 and Ha03-004, stratified by age.

Table 3: Abametapir Pharmacokinetic Parameters in Pediatric Subjects with Head Lice Infestation

Study	Age Group	n	C_{max} (ng/mL) Mean (%CV)	AUC_{0-8} (ng*h/mL) Mean (%CV)
Ha03-003	6 months to <1 year	1	418	1057
Ha03-004		5	228 (50%)	688 (43%)
Ha03-003	1 year to <2 years	3	209 (62%)	446 (65%)
Ha03-004		8	147 (49%)	406 (37%)
Ha03-003	2 years to <3 years	6	206 (66%)	633 (57%)
Ha03-004		8	160 (48%)	602 (51%)
Ha03-003	3 years to 17 years	12	121 (60%)	330 (49%)
Ha03-004		7	52 (45%)	254 (67%)

Source: Dr. Tran's Clinical Pharmacology Review, Table 1

Benzyl Alcohol

"Xeglyze contains benzyl alcohol (b) (4)% as an excipient to serve as (b) (4) . Each bottle (200 g) of XEGLYZE Lotion contains (b) (4) of benzyl alcohol. Systemic exposure to benzyl alcohol has been associated with serious and fatal adverse reactions including "gasping syndrome" in neonates and low birth weight infants. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants may be more likely to develop toxicity. The risk of systemic absorption is higher in children because children have a higher surface area to body mass ratio, and also because of an immature skin barrier. Because of the risk of systemic absorption of benzyl alcohol, the Agency requested in the End-of-Phase 2 communication that the applicant evaluate the potential systemic exposure of benzyl alcohol in the pediatric PK trial. Serum benzyl alcohol concentrations were assessed in Trials Ha-03-003 and Ha03-004. According to Dr. Tran, "Benzyl alcohol in serum was measurable (limit of quantitation = 0.5 µg/mL) in 7 subjects out of 39 evaluable subjects. The Cmax of benzyl alcohol in these 7 subjects ranged from 0.52 to 3.57 µg/mL… These observed concentrations of benzyl alcohol do

not appear to be a safety concern. Systemic exposure to benzyl alcohol at concentration of ~109.2 µg/mL (1.01 mmol/L) has been associated with neonatal gasping syndrome." In other words, the maximum serum concentration of benzyl alcohol observed in the pediatric PK study is approximately 30-fold less than the serum concentration associated with neonatal gasping syndrome.

Distribution

"Abametapir plasma protein binding ranged from 91.3 – 92.3% and was concentration independent within the tested concentration range of 50 – 800 ng/mL. Metabolite abametapir carboxyl plasma protein binding ranged from 96.0 – 97.5% and was concentration independent within the tested concentration range of 1000 – 13000 ng/mL."

Metabolism

"The metabolic pathway of abametapir involves the sequential formation of abametapir hydroxyl followed by abametapir carboxyl catalyzed by phase I oxidative metabolism enzymes with glucuronidation of both metabolites mediated by Phase II metabolism catalyzed by UDP-Glucuronosyltransferases (UGTs). In vitro studies using liver microsomes showed that abametapir is extensively metabolized, primarily by CYP1A2 and to a lesser extent CYP2B6. In vivo data suggests glucuronidated metabolites contribute only a small proportion of total drug related exposure and their overall levels are low. The unconjugated abametapir carboxyl accounts for the vast majority of drug related plasma exposure in humans.

Abametapir carboxyl is cleared slowly from the systemic circulation and results in plasma concentration significantly higher than that of abametapir. Based on data in adults in Trial Ha02-003, where samplings was carried out to 72 hours, the ratios of Cmax and AUC0-72h between abametapir carboxyl and abametapir were about 30 and 250, respectively. The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be approximately (mean ± SD) 71 ± 40 hours or longer. In vitro data suggest that abametapir carboxyl is not further metabolized by CYP450s or other NADPH-dependent microsomal enzymes."

Drug-drug interactions

"In vitro studies suggest there is low risk of in vivo cytochrome P450 (CYP) inhibition for abametapir and low risk of CYP induction for both abametapir and abametapir carboxyl. However, there is a potential risk of CYP 3A4 inhibition due to high and sustained concentration of abametapir carboxyl following application of Abametapir lotion, 0.74%. Results of microsomes studies suggests that abametapir carboxyl at concentrations observed in clinical trials would not inhibit CYP enzymes. However, studies using hepatocytes showed

concentration dependent inhibition of CYP3A4 and to a lesser extent CYP2B6 and CYP1A2. The potential of Abametapir lotion, 0.74% to inhibit CYP3A4 should be further evaluated in vivo."

"Abametapir and abametapir carboxyl are not substrates for ABC (ATP binding cassette) efflux transporters MDR1 and BCRP and SLC (solute carrier) uptake transporters OATP1B1, OATP1B3, OAT1, OAT3 and OCT2… Overall, the data suggest low risk of interaction with drug transporters following topical application of Abametapir lotion, 0.74% for treatment of head lice infestation."

Recommendations Regarding Phase IV Requirements and Commitments

As discussed above, the carboxyl metabolite of abametapir is cleared slowly from the systemic circulation and results in plasma concentration significantly higher than that of abametapir. In addition, studies using hepatocytes showed concentration-dependent inhibition of Cytochrome P450 3A4. Therefore, the clinical pharmacology team recommends the following post-marketing requirements:

- Conduct a maximal use pharmacokinetic trial of Xeglyze lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age to fully characterize the concentration time profile of abametapir and metabolite abametapir carboxyl.
- Conduct a clinical trial to evaluate the potential for Xeglyze lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatrics. Additional drug interaction trials may be needed depending on the results of this trial.

In order to verify the accuracy of analyses performed on abametapir carboxyl concentrations after prolonged storage of samples at -80 degrees centigrade, the clinical pharmacy team recommends the following postmarketing commitment:

- Conduct a study to evaluate the long-term storage stability of abametapir carboxyl in plasma stored at -80 ºC for duration of at least 1251 days.

Dr. Tran and the clinical pharmacology team propose the following changes for sections 7 and 12 of the applicant's proposed labeling:

Deletions are noted as ~~strikethrough~~ and additions are noted as double underline.

7 DRUG INTERACTIONS

In vitro studies suggest there is a potential for inhibition of cytochrome P450 3A4 enzyme following application of XEGLYZE (b) (4). XEGLYZE (b) (4) with drugs that are substrate of (b) (4) may lead to increased systemic concentration of the interacting drugs. Avoid (b) (4) administration of drugs that are CYP3A4 substrates within 2 weeks after application XEGLYZE (b) (4).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abametapir (5,5'-dimethyl 2,2'-bipyridinyl) is a metalloproteinase inhibitor (b) (4). Metalloproteinases (b) (4) have a (b) (4) role in (b) (4) physiological processes (b) (4) critical to egg development and survival of (b) (4) lice. (b) (4)

(b) (4)

12.3 Pharmacokinetics

Absorption

(b) (4)

(b) (4)

The pharmacokinetics of XEGLYZE (b) (4) were evaluated in 3 trials, namely Trials A, B, and C. Each trial enrolled lice infested subjects who received a single 10 minute application of XEGLYZE (b) (4). Pharmacokinetic samplings were carried out to 72 hours post dose in adults and 8 hours post dose in pediatrics for all trials.

Trial A evaluated pharmacokinetics in 6 adult and 12 pediatric subjects 3 to 12 years of age. The mean (%CV) abametapir plasma maximum concentration (Cmax) and area under the concentration time curve from 0 to 8 hours post dose (AUC0-8h) in the adult group were 41 (66%) ng/mL and 121 (50%) ng*h/mL, respectively. The mean (%CV) Cmax and AUC0-8h in the pediatric group were 73 (57%) ng/mL and 264 (b) (4) %) ng*h/mL, respectively, (b) (4) The mean (%CV) terminal half-life in adults was 21 (11%) hours.

Trials B and C evaluated pharmacokinetics in pediatric subjects 6 months to 17 years (b) (4) The pharmacokinetic results for plasma abametapir are shown in Table (b) (4) even though the values varied between the 2 trials, abametapir exposure increased as the age of the subject decreased. Abametapir absorption was rapid with a median Tmax of 0.57 to 1.54 hours.

Abametapir pharmacokinetic parameters in subjects with head lice infestation

Study	Age Group	n	C_{max} (ng/mL) Mean (%CV)	AUC_{0-8} (ng*h/mL) Mean (%CV)
(b) (4)	6 months to <1 year	1	418	1057
		5	228 (50%)	688 (43%)
	1 year to <2 years	3	209 (62%)	446 (65%)

Study	Age Group	n	C_{max} (ng/mL) Mean (%CV)	AUC_{0-8} (ng*h/mL) Mean (%CV)
(b) (4)		8	147 (49%)	406 (37%)
	2 years to <3 years	6	206 (66%)	633 (57%)
		8	160 (48%)	602 (51%)
	3 years to 17 years	12	121 (60%)	330 (49%)
		7	52 (45%)	(b) (4)

Serum concentration of benzyl alcohol, an excipient in the formulation of XEGLYZE (b) (4), was assessed in Trials B and C. Benzyl alcohol in serum was measurable (limit of quantitation = 0.5 µg/mL) in 7 subjects out of 39 evaluable subjects. The Cmax of benzyl alcohol in these 7 subjects ranged from 0.52 to 3.57 µg/mL *[see Warnings and Precautions (5.X) and Use in Specific Populations (8.4)].*

Distribution

Abametapir and its primary human metabolite, abametapir carboxyl, are highly bound to proteins in (b) (4) plasma. Abametapir is 91.3 – 92.3% bound to plasma proteins, and abametapir carboxyl is 96.0% – 97.5% bound to plasma proteins.

Elimination

~~Metabolism~~Metabolism

Abametapir is extensively (b) (4) metabolized, primarily by the cytochrome P450 enzyme CYP1A2 to a mono-hydroxylated metabolite (abametapir hydroxyl) and further to a mono-carboxylated metabolite (abametapir carboxyl). Abametapir carboxyl is cleared slowly from the systemic circulation resulting in plasma concentration (b) (4) higher than that of abametapir. Based on data in adults in Trial A above, where samplings was carried out to 72 hours, the ratios of Cmax and AUC0-72h between abametapir carboxyl and abametapir were about 30 and 250, respectively. The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be approximately (mean ± SD) 71 ± 40 hours in adults.

~~Excretion~~Excretion

Excretion of abametapir and its human metabolites was not examined in patients. (b) (4)

Drug interaction:

In vitro studies suggest that there is a potential for inhibition of cytochrome P450 3A4 enzyme following application of XEGLYZE (b) (4) due to high and prolonged systemic exposure of the metabolite abametapir carboxyl.

4.6. Devices and Companion Diagnostic Issues

This section is not applicable to this NDA.

4.7. Consumer Study Reviews

This section is not applicable to this NDA.

5 Sources of Clinical Data and Review Strategy

Table of Clinical Studies

Table 4: Tabular Listing of All Clinical Studies Relevant to NDA 206966

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
Ha03-001	Randomized, Double Blind, Vehicle-controlled, Parallel	Xeglyze 0.74%, Single Dose, Topical	Primary: % of index subjects lice-free at all follow-up visits through Day 14. Secondary: % of index subjects lice-free at Day 1 & Day 7 Visits.	10 minutes	108 Index, 379	Head lice infestation, Adults, Pediatrics (6 months and older)	7, US (2 in California, 1 each in Florida, Nevada, Ohio, Tennessee, and Texas).
Ha03-002	Randomized, Double Blind , Vehicle-controlled, Parallel	Xeglyze 0.74%, Single Dose, Topical	Primary: % of index subjects lice-free at all follow-up visits through Day 14. Secondary: % of index subjects lice-free at Day 1 & Day 7 Visits	10 minutes	108 Index, 325	Head lice infestation, Adults, Pediatrics (6 months and older)	7, US (1 each in Arizona, California, Florida, Mississippi, North Carolina, Tennessee, and Utah).
Studies to Support Safety							
Ha02-005	Randomized, Double Blind, Vehicle, AC, Crossover (TQT Trial)	Xeglyze, 0.74%, Single Dose, Topical	Part 1: assess the safety & tolerability of single doses of Xeglyze w/ increasing Tx durations to determine dose for use in Part 2. Part 2: assess effect supratherapeutic dose of Xeglyze on cardiac repolarization.	20, 40 or 60 minutes	24 (part 1), 57 (part 2)	Healthy adults, male and female	1, USA
Ha02-002	Randomized, Double Blind, Vehicle (dose ranging)	Xeglyze 0.37%, Single Dose, Topical; Xeglyze 0.74%, Single Dose, Topical	Primary: To determine safety & tolerability of Xeglyze after a single topical application to hair & scalp of adult subjects with head lice infestation. Secondary: To investigate the PK of Xeglyze following single dose topical application to hair and scalp of adult subjects with head lice infestation, & to investigate the ovicidal and lousicidal activity of Xeglyze in adult subjects with head lice infestation.	10 or 20 minutes	30	Head lice Infestation, Adults	1, India

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Ha03-003	Open label	Xeglyze 0.74%, Single Dose, Topical	Primary objective: To evaluate the safety and tolerability of a single application of Xeglyze for the treatment of head lice Secondary objective: To evaluate the pharmacokinetics of Xeglyze, its metabolites and benzyl alcohol (contained in the Xeglyze vehicle) under conditions of maximal exposure in a pediatric population	10 minutes	22	Head lice infestation, Pediatrics (0.9 to < 18 years of age)	2 sites, USA (both in California)
Ha03-004	Open label, Maximal Use	Xeglyze 0.74%, Single Dose, Topical	Primary objective: To evaluate the safety and tolerability of a single application of Xeglyze under maximal use conditions for the treatment of head lice. Secondary objective: To evaluate the pharmacokinetics of both Xeglyze and benzyl alcohol (contained in the Xeglyze vehicle) under maximal use conditions	10 minutes	38	Head lice infestation, Pediatrics (6 months- 17 years)	3 sites, USA, (2 in California, 1 in Florida)
Ha03-006	Randomized, Vehicle, Negative and Positive controls (dermal sensitization)	Xeglyze, 0.2mL, Topical	To determine the sensitization potential of Xeglyze on normal skin.	48 hours for each patch	238	Healthy adults without head lice infestation	1 site, USA
Ha03-007	Randomized, Vehicle, Negative and Positive controls (dermal irritation)	Xeglyze, 0.2mL, Topical	The primary objective of this trial was to determine the potential of Xeglyze to cause irritation after repeated topical application to the healthy skin of humans under controlled conditions.	24 hours per patch, 21 continuous days	40	Healthy adults without head lice infestation	1 site, USA
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Ha01-001	Randomized, Double Blind, Vehicle, Dose ESC	Xeglyze 0.37%, Single Dose, Topical; Xeglyze 0.74%, Single Dose, Topical	To determine safety & tolerability of Xeglyze when applied topically to hair & scalp of healthy volunteers; to measure plasma & urine levels of Xeglyze after topical admin of Xeglyze to hair and scalp.	10 or 20 minutes	32	Healthy adults without head lice infestation	1, Australia
Ha02-003	Randomized, Double Blind, Vehicle, Parallel	Xeglyze 0.37%, Single Dose, Topical Xeglyze 0.74%, Single Dose, Topical	Primary objective: To evaluate the efficacy of Xeglyze Secondary objective: To evaluate the safety, tolerability and the pharmacokinetics of Xeglyze	10 minutes	142	Lice Infestation, Adults, Pediatrics (age 2 years and older)	2 sites, USA (both in California)

Source: 2015 Clinical Reviewer Template; data from applicant submission.

5.2. Review Strategy

This review will focus primarily on evaluation of safety and efficacy data from two adequate and well-controlled Phase 3 trials, Ha03-001 and Ha03-002. Supportive safety data from four Phase 2 trials, which included dose-ranging, pharmacokinetics (PK), and maximal use trials will also be considered. Two dermal safety studies and a Thorough QT trial will also be reviewed. Trial Ha03-008, which evaluated the mechanism of action of Xeglyze using a mixed *in vivo/in vitro* protocol will be discussed but not considered in the evaluation of efficacy because the applicability of *in vitro* data is of limited clinical value.

This review will present some analyses performed by the applicant (with my commentary), some analyses by the biostatistics reviewer, and some of my own analyses. My analyses were performed using applicant datasets and the JReview software tool. Tables in which the data is presented will clearly identify the source of the data analyzed.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial Ha03-001- A Randomized, Double-Blind, Multicenter, Vehicle-Controlled Study of the Efficacy and Safety of Abametapir Lotion 0.74% Administered for the Treatment of Head Lice Infestation

Trial Design

Overview and Objective

Trial Ha03-001, "A Randomized, Double-Blind, Multicenter, Vehicle-Controlled Study of the Efficacy and Safety of Abametapir Lotion 0.74% Administered for the Treatment of Head Lice Infestation" is a Phase 3 safety and efficacy trial. The primary objective of this trial was to evaluate the efficacy of at-home administration of a single application of Xeglyze for the treatment of head lice infestation in subjects 6 months of age and older. The secondary objectives were to evaluate the safety and tolerability of at-home administration of a single application of Xeglyze for the treatment of head lice infestation.

Trial Design

Trial Ha03-001 was a randomized, double-blind, multicenter, vehicle-controlled, parallel-group trial in subjects 6 months of age and older with active head lice infestation. The trial was conducted in 7 centers in the United States; 2 in California, and 1 each in Florida, Nevada, Ohio, Tennessee, and Texas. The centers are well distributed geographically; this is important because resistance to permethrin and pyrethroids has shown geographic variability in the United States.

All members of a household who were 6 months of age and older were considered for enrollment in the trial. The index subject of each household was the youngest person within that household with at least 3 live lice present as assessed at Screening. Non-index household members were defined as the remaining members of the household with at least 1 live louse present as assessed at Screening.

The main inclusion criteria for this trail included:

- Male or female, 6 months of age or older, in good general health
- Had active head lice infestation at Screening as determined by a trained evaluator with at least 3 live lice for the index subject and at least 1 live louse for the other household members.
- The subject and/or their caregiver was physically able and willing to apply the study product at home.
- Belonged to a household with an eligible index subject with active head lice infestation.
- Agreed to an examination for head lice and to all visits and procedures throughout the study.

The main exclusion criteria for this trial were as follows:

- Had treatment (over-the-counter, home remedy or prescription medication) for head lice within 14 days prior to Day 0.
- Intended to use any other form of lice treatment from Day 0 through the Day 14 Visit, unless provided as rescue therapy to this Protocol.
- Intended to use a lice comb from the Day 0 through the Day 14 Visit unless provided as rescue therapy to this Protocol.
- Intended to cut their hair, use hair dye/bleach or have permanent wave hairstyling from Day 0 through the Day 14 Visit.
- Had a household member(s) who was infested with lice but was not willing or not eligible for enrollment.

- Had visible skin/scalp condition(s) that were not attributable to head lice infestation, such as an erythema score that was >2, blisters or vesicles which, in the opinion of the investigative personnel or Sponsor, interfered with safety and/or efficacy evaluations.
- Had eczema or atopic dermatitis of skin/scalp.
- Had a prior reaction to Nix® or products containing permethrin.
- Was receiving systemic or topical medication, which in the opinion of the investigator, would compromise the integrity of the safety and/or efficacy assessments.

Index and non-index subjects completed a Screening Visit within 7 days (Day -7 to Day 0) prior to treatment to determine eligibility for participation in the trial. Each household had to contain 1 eligible index subject to be eligible for enrollment. A child <6 months of age in a household who was known to be infested was referred to their primary care physician for evaluation and treatment. A Baseline visit was conducted on Day 0 to confirm eligibility, to conduct baseline safety and efficacy assessments, and to randomize index subjects in a 1:1 ratio to receive study product which was either Xeglyze or the matching Vehicle. Vehicle was identical to Xeglyze but without the active ingredient. Eligible non-index subjects within each household were randomized to the same treatment group as the index subject. A permuted block design stratified by site was used for randomization of households. The assigned study product was dispensed to subjects on Day 0 for self-administration at home on the same day. Each bottle contained 200 grams of study product. The administration of the study product at home by the patient or caregiver represents actual-use conditions. All subjects were required to return to the trial site for follow-up visits on Day 1, Day 7 and Day 14 for the conduct of safety and efficacy assessments.

Subjects were provided with administration instructions and administered the study product at home. Adult subjects were instructed to administer the study product to the eligible children in their household. At the time of dispensing, each bottle was marked with the respective subject's initials and clear tape placed over the initials. Each subject was instructed to use the bottle that was allocated to them and sharing or exchange of study product bottles was prohibited.

Administration instructions included applying the product directly to a subject’s dry scalp and hair. The study product was then massaged into the scalp and hair, starting with the hairline area behind the ears and back of the neck, extending to the end of the hair. Subjects were instructed to apply a sufficient amount to saturate the scalp and hair, up to a maximum of 1 bottle (200 grams). Caregivers were instructed to apply study product to each subject’s scalp and hair while avoiding exposure to the neck, eyes, ears and face. Once saturation of the scalp and hair was achieved, the subject was instructed to leave the study product on the scalp and hair for 10 minutes. At the end of the 10 minute treatment period, the subjects were instructed to rinse their hair with warm water until all study product was removed from the scalp and hair. Hair could then be dried with a towel or air dried and then washed with

shampoo any time after removing the study product. No adjunctive measures (e.g. nit combing) were included in the study protocol.

A total of 108 index subjects were enrolled in the trial, along with 271 eligible household members. The 108 enrolled and randomized index subjects comprised the Intent-to Treat (ITT) population, which was the population used for the efficacy analysis. The 379 enrolled subjects comprised the All Randomized population. The safety population consisted of all subjects who were randomized and received study product (374 subjects).

Table 5: Trial Schedule of Assessments

	Screening Visit[1]	Baseline Visit[1]	Follow-Up Visit 1	Follow-Up Visit 2	Follow-Up Visit 3
	Day -7 to Day 0	Day 0	Day 1	Day 7 (±1 day)	Day 14 (+2 days)
Screening/Safety					
Informed Consent/Assent	X				
Eligibility evaluation	X	X*			
Demographics	X				
Medical History	X	X*			
Vital Signs[2]	X	X*	X	X	X
Physical Examination[3]	X	X*	X	X	X
Scalp and Eye Irritation Assessment	X	X*	X	X	X
Laboratory assessments[4]		X*			X
Prior/Concomitant Medications	X	X*	X	X	X
Adverse Events			X	X	X
Efficacy					
Head Lice Assessment[5]	X	X*	X	X	X
Investigational Product					
Randomization		X			
Weigh IP bottle		X	X[6]	X[6]	X[6]
Dispense IP for application at home		X			
Return of IP			X	X[7]	X[7]

Source: Applicant's submission; Ha03-001 Study Report
Abbreviations: IP = investigational product.

1 Screening and Baseline visit could occur on the same day (Day 0). Procedures with an asterisk (*) were repeated if Screening and Baseline were split to 2 separate visits.
2 Vital signs included pulse, blood pressure, and temperature.
3 Full physical examination at Screening, Day 0 and Day 14. Brief physical examination at Day 1 and 7. If clinically indicated, a symptom-focused examination could be performed at any other visit.
4 Safety laboratory assessments were performed at Baseline visit(pre-dose Day 0) and on Day 14.
5 If any live lice were identified at a follow-up visit, the subject was considered a treatment failure and provided with rescue therapy.
6 All returned IP bottles were weighed.
7 If not already returned at previous visit.

Trial Endpoints

Statistical Analysis Plan

The following populations were used when analyzing trial data:

- The Intent to Treat (ITT) population consisted of all index subjects who were enrolled and randomized.
- The Per Protocol (PP) population was defined as all subjects in the ITT population without a significant protocol deviation.
- The All Randomized population included all subjects who were enrolled and randomized.
- The Safety population included all subjects who were randomized and received study product.

Descriptive statistics were used to summarize the continuous variables of number (n), mean, median, standard deviation (SD), minimum and maximum. Frequency tabulations were used to summarize the categorical variables of frequency counts and percentages.

No substitutions for missing values were made for the analysis of disposition, demographics, and safety data.

The primary imputation method for missing data for the primary, secondary, and exploratory efficacy analyses was the pre-defined Last Observation Carried Forward (LOCF) method except for subjects without a follow up lice evaluation at Day 14 Visit who were considered as treatment failures. Pre-treatment assessment was not used to impute any post-baseline missing data. Subjects who were assessed having live lice and received rescue therapy at any trial visit were set to treatment failures at all subsequent trial visits.

The number of randomized, completed, and discontinued subjects and reason for discontinuations were summarized using descriptive statistics. The disposition of index subjects and all subjects were presented separately.

Subject demographics and hair characteristics were summarized by descriptive statistics for

continuous data and frequency tabulations for categorical data. The data were summarized for index subjects and all subjects separately. Summaries of baseline and demographic data were produced for the ITT, PP, Safety, and All Randomized populations. The amount of study product administered to index subjects (ITT and PP populations) and to all subjects (All Randomized population) was summarized separately using descriptive statistics.

Efficacy analyses

Primary Efficacy Analysis

The primary efficacy endpoint was defined as the overall proportion of index subjects who were lice-free at all follow-up visits through to the Day 14 Visit. Subjects who were treated with study product and were lice-free **at all visits** post-treatment (i.e., Day 1, 7, 14 or an unscheduled visit) were considered as treatment successes. Subjects who were treated with study product and had any live lice detected at any visit post-treatment were considered as treatment failures. The primary analysis population was the ITT population.

The presence of live lice (treatment failure versus success) at each scheduled visit (Day 1 and 7) and overall (lice-free at Day 1, 7, and 14) is presented by frequency tabulations. In addition, the number of live lice present (3 or more and 1 or 2) along with whether there were nits (eggs) present is summarized. The number of subjects requiring rescue therapy is summarized.

The overall proportion of index subjects who were lice-free at all follow-up visits through to the Day 14 Visit was analyzed using a Cochran-Mantel-Haenszel test, stratified by site at a 5% level of significance. Sites with <8 index subjects per treatment group were pooled, within geographical region, starting from the smallest site, until each pooled site had at least 8 index subjects per treatment group. The odds ratio and 95% confidence interval (CI) for the odds ratio are presented.

Treatment group by site interaction was tested separately at a 10% level of significance (Breslow-Day), using a logit model to check whether any site had a large impact on the analysis. If the Breslow-Day test yielded a significant result ($p<0.10$), a logit model was fitted to the data to investigate the treatment group by site interaction. The odds ratios and 95% CI for the odds ratios are presented for each site. The model investigated was as follows:

success/failure = treatment site treatment*site.

As a sensitivity analysis (secondary analysis on the primary endpoint) the analysis above was repeated on the PP population.

Secondary Efficacy Analyses

The secondary efficacy endpoints were defined as:

- Proportion of all index subjects who were lice-free at visit Day 1.
- Proportion of all index subjects who are lice-free at visit Day 7.

Secondary efficacy endpoints were analyzed using the same method and populations as for the primary efficacy analysis. To adjust for multiple testing, the step down Bonferroni method was used for the secondary analysis.

The secondary efficacy endpoint is not clinically relevant because of the life cycle of the human head louse. As such it was the subject of a Special Protocol Assessment (SPA) nonagreement (see section 3.2 of this review).

Exploratory Efficacy Analysis

The exploratory endpoint was defined as the proportion of all subjects who were lice-free at all follow-up visits through to the Day 14 Visit.

The analysis method used for the primary and secondary efficacy described above was conducted on the All Randomized population as an exploratory efficacy analysis.

Sensitivity analyses

Finally, the primary efficacy analysis was repeated on the ITT population using 3 different imputation methods for missing data: Observed Case Sensitivity, LOCF Sensitivity, and Treatment Failure Sensitivity (see Table 6 which displays a comparison of each):

1. Observed Case Sensitivity (treatment success approach) in which all missing data was imputed as treatment successes.
2. LOCF Sensitivity in which the last observation carried forward including the use of pre-treatment assessments (baseline value) to impute missing data post-treatment was used.
3. Treatment Failure Sensitivity in which all missing data was imputed as treatment failures.

Table 6: Analysis Imputation Scheme Algorithm for Missing Data

Imputation Method	Day 1 Visit	Day 7 Visit	Day 14 Visit
Observed Case Sensitivity	Missing = success	Missing = success	Missing = success
LOCF Sensitivity	Missing = failure	If Day 1 = failure, missing Day 7 = failure. If Day 1 = success, missing Day 7 = success.	If Day 7 = failure, missing Day 14 = failure If Day 7 = success, missing Day 14 = success.
Treatment Failure Sensitivity	Missing = failure	Missing = failure	Missing = failure

Abbreviations: LOCF = last observation carried forward.
Source of Table: Ha03-001 Study Report

Protocol Amendments

All subjects were recruited under the Trial protocol of December 16, 2013; there were no changes made in the conduct of the trial. As recommended by the Agency, the applicant modified the imputation method for missing data, such that the method was consistent for both primary and secondary endpoints.

Data Quality and Integrity: Applicant's Assurance

All case report forms (CRF) were electronic and utilized Electronic Data Capture (EDC). The eCRFs were completed at the trial site. The trial monitor reviewed the data entered on the eCRFs against the source documents for completeness and accuracy at each monitoring visit. Data that were not entered directly onto the eCRFs, such as laboratory results from a central laboratory, were also verified by review of the source documents. The trial monitor was also responsible for monitoring adherence to the protocol, good clinical practice (GCP), and applicable region-specific requirements.

Data on the eCRFs was verified and validated by the data management team as described in the data validation manual. All validations and queries were managed within the EDC system and required completion, correction or confirmation of the data by the site. Data was cleaned on an ongoing basis, and all analyses were performed once the database was locked.

6.1.2. Study Results

Compliance with Good Clinical Practices

Attestation from the clinical study report (CSR) (Section 5.2, p.9):"This study was conducted in accordance with the Declaration of Helsinki, the International Conference of Harmonization (ICH) guideline for Good Clinical Practice (GCP), Food and Drug Administration (FDA) regulations and other applicable local laws and regulations."

Financial Disclosure

The applicant submitted FDA form 3454 certifying that they, the applicant, had not entered into any financial arrangements with the clinical investigators. A list of clinical investigators for the Xeglyze clinical development was provided. The financial disclosure review template is located in Appendix 13.2.

Patient Disposition

ITT Population: Index Subjects

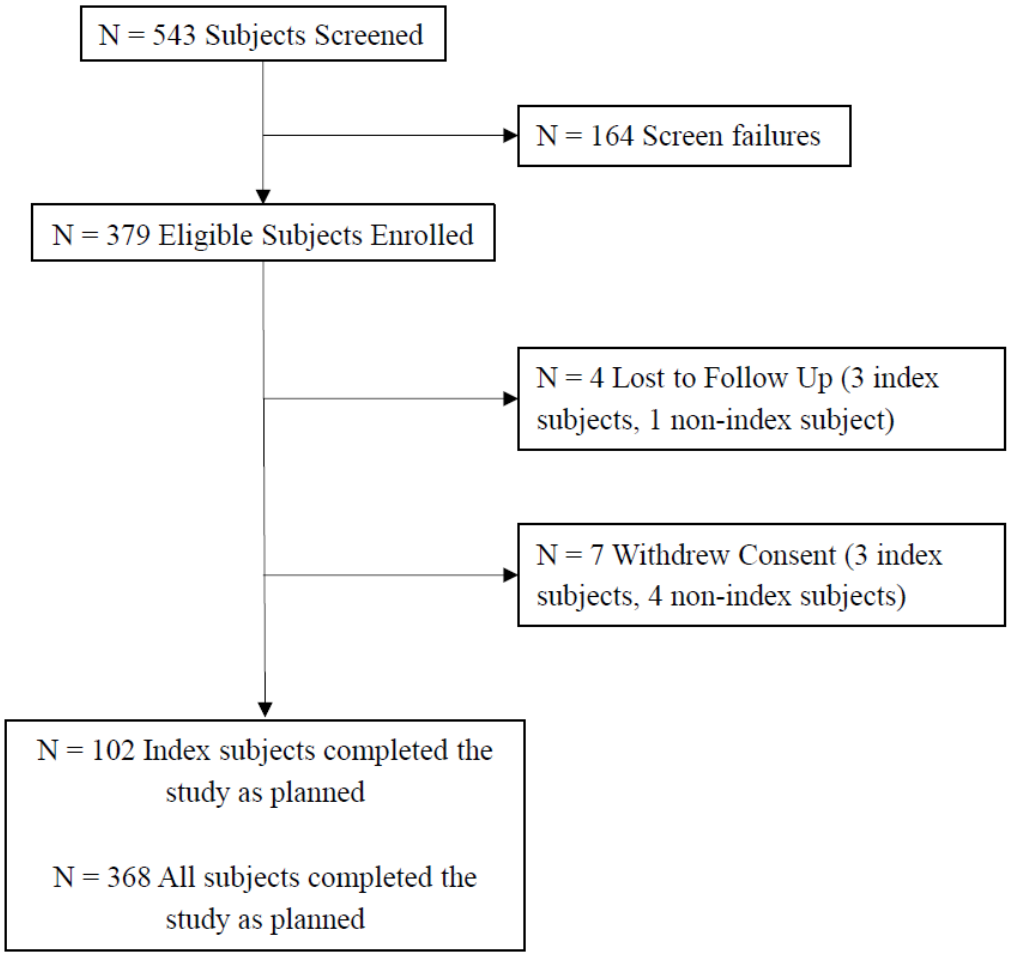
A total of 108 eligible index subjects were enrolled and randomized using a 1:1 allocation ratio to receive either Xeglyze (53 index subjects) or Vehicle (55 index subjects). All 108 randomized index subjects received study product and 102 index subjects completed the trial.

Xeglyze group: A total of 53 index subjects were enrolled and included in the ITT Population (100%), and 52 index subjects were included in the PP population (98.1%). One index subject was excluded from the PP population due to a protocol deviation. A total of 3 index subjects were lost to follow-up (Subjects: (b) (6)), resulting in 50 (94.3%) index subjects completing the trial as planned.

Vehicle group: A total of 55 index subjects were enrolled and included in the in the ITT Population, and 53 index subjects were included in the PP population (96.4%). Two index subjects were excluded from the PP population due to protocol deviations. A total of 3 index subjects withdrew consent (Subjects: (b) (6) resulting in 52 (94.5%) index subjects completing the trial as planned.

Figure 2 graphically displays the overall disposition of subjects that provided assent/consent to participate in the trial.

Figure 2: Disposition of Subjects



Protocol Violations/Deviations

Most of the reported protocol deviations were minor, such as missed assessments or trial visits occurring outside the time window specified in the protocol. Visits occurring outside the time window specified in the protocol did not affect the evaluation of safety or efficacy. In some cases, investigators were unable to successfully obtain blood samples for laboratory studies. Although the missing lab data may somewhat affect the evaluation of safety, it does not impair the evaluation of efficacy.

Investigators excluded the following index subjects from the per protocol (PP) population:

- Subject (b) (6), randomized to the Xeglyze group, as there was insufficient evidence of study product administration due to being lost to follow up after study product was dispensed.
- Subject (b) (6), randomized to the Vehicle group, as there was insufficient evidence of study product administration as the family withdrew consent to participate in the trial.
- Subject (b) (6), randomized to the Vehicle group, was found to be ineligible, because of the member of the family and after the Day 7 Visit due to a hospitalization for a pre-existing condition which in the Medical Monitor's opinion should have rendered the subject ineligible to participate in the trial (failure to meet inclusion criteria #2).

Investigators excluded the following subjects (from the All Subject population) from the safety population:

- Subject (b) (6), randomized to the Xeglyze group, as there was insufficient evidence of study product administration due to lost to follow up after study product was dispensed.
- Subjects (b) (6) randomized to the Vehicle group, due to insufficient evidence of study product administration as the family withdrew consent to participate in the trial.

Table of Demographic Characteristics

Table 7 displays the demographic characteristics of the index subjects (ITT Population). The distribution by race and gender is similar to the patterns of head lice infestation observed in the clinical setting.

Table 7: Demographic characteristics of the primary efficacy (index) population

Demographic Parameters	Treatment Groups		Total (N=108) n (%)
	Xeglyze (N=53) n (%)	Vehicle (N=55) n (%)	
Sex			
Male	5/53 (9.4%)	10/55 (18.2%)	15/108 (13.9%)
Female	48/53 (90.6%)	45/55 (81.8%)	93/108 (86.1%)
Age			
Mean years (SD)	7.47 (4.20)	7.36 (6.66)	
Median (years)	6.80	6.00	
Min, max (years)	0.5, 19.2	1.2, 49.1	
Age Group			
6 months to <4 years	11/53 (20.8%)	11/55 (20%)	22/108 (20.4%)
4 to <12 years	36/53 (67.9%)	39/55 (70.9%)	75/108 (69.4%)
12 to <18 years	4/53 (7.5%)	3/55 (5.5%)	7/108 (6.5%)
18 years and older	2/53 (3.8%)	2/55 (3.6%)	4/108 (3.7%)
Race			
White	50 (94.3%)	55 (100.0%)	105/108 (97.2%)
Black or African American	2 (3.8%)	0 (0.0%)	2/108 (1.9%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other[1]	1 (1.9%)	0 (0.0%)	1/108 (0.9%)
Ethnicity			
Hispanic or Latino	41/53 (77.4%)	46/55 (83.6%)	87/108 (80.6%)
Not Hispanic or Latino	12/53 (22.6%)	9/55 (16.4%)	21/108 (19.4%)
Region (optional)			
United States	53	55	108/108 (100%)
Rest of the World			
Canada	0 (0.0%)	0 (0.0%)	0 (0.0%)
South America	0 (0.0%)	0 (0.0%)	0 (0.0%)
Europe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asia	0 (0.0%)	0 (0.0%)	0 (0.0%)
Africa	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Applicant submission; Adapted from Table 14.1.2.1 and Table 21, Ha03-001 CSR

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Hair characteristics such as length and texture can affect the efficacy of treatment for head lice infestation. Consequently, investigators recorded details of the hair characteristics of each subject. The hair characteristics for the index subjects were comparable between the treatment groups with regards to length, texture, and volume. The hair characteristics were reasonably comparable with regards to shape; more index subjects with curly hair were randomized to the Xeglyze group, and more index subjects with straight hair were randomized to the Vehicle group. Hair characteristics for the index subjects are presented in Table 8.

Table 8: Hair Characteristics, Index Subjects

Hair Characteristic	Xeglyze (N = 53)	Vehicle (N = 55)
Length, n (%)		
Short (Ear Length or Shorter)	13 (24.5%)	12 (21.8%)
Medium (Shoulder Length)	15 (28.3%)	14 (25.5%)
Long (Past Shoulder Length to Mid-back)	13 (24.5%)	16 (29.1%)
Very Long (Past Mid-back)	12 (22.6%)	13 (23.6%)
Texture, n (%)		
Coarse	9 (17.0%)	9 (16.4%)
Medium	31 (58.5%)	36 (65.5%)
Fine	13 (24.5%)	10 (18.2%)
Volume, n (%)		
Thick	18 (34.0%)	21 (38.2%)
Medium	25 (47.2%)	25 (45.5%)
Thin	10 (18.9%)	9 (16.4%)
Shape, n (%)		
Curly	9 (17.0%)	3 (5.5%)
Wavy	17 (32.1%)	19 (34.5%)
Straight	27 (50.9%)	33 (60.0%)

Source: Applicant's submission; Table 10, Ha03-001 CSR

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

To ensure compliance, investigators weighed bottles of the study product (Xeglyze or Vehicle) before use. Subjects returned the bottles on Day 1; investigators weighed the bottles again to determine the amount of study product used for each subject. One index subject (Xeglyze

group) and 4 subjects (the index subject and 3 siblings, Vehicle group) did not return for evaluation on Day 1, 7, or 14 and were lost to follow up. Therefore, compliance could not be verified and this subject was excluded from analyses of safety and efficacy. The mean weight (and range of weight) of study product administered per subject was similar between the treatment groups. Tables 9 and 10 display a summary of study product administration in index subjects and all subjects. Table 11 displays a summary of study product administration, stratified by age group.

Table 9: Summary of Study Product Administration – Index Subjects (ITT Population)

Study Product Administered (g)	**Xeglyze (N=53)**	**Vehicle Lotion (N=55)**
n	52	54
Mean (SD)	116.0 (63.6)	116.1 (61.6)
Median	124.5	126.8
Min, Max	6.0, 208.1	7.0, 214.0

Source: Applicant's submission; Table 14.1.4.1, Ha03-001 CSR

Table 10: Summary of Study Product Administration – All Subjects

Study Product Administered (g)	**Xeglyze (N=187)**	**Vehicle Lotion (N=192)**
n	186	188
Mean (SD)	118.5 (59.9)	132.8 (59.8)
Median	125.8	145
Min, Max	6.0, 208.1	6.0, 215.0

Source: Applicant's submission; Table 14.1.4.3, Ha03-001 CSR

Table 11: Trial Ha03-001: Summary of Exposure by Age – All Randomized Subjects

Age		**Xeglyze (g)**	**Vehicle (g)**
6 months to <2 years	N	4	3
	Mean (SD)	79.95 (88.6)	22.30 (16.6)
	Min, Max	6.0, 195.4	7.0, 39.9
2 to <4 years	N	9	13
	Mean (SD)	109.4 (66.4)	85.0 (56.1)
	Min, Max	10.0, 208.1	24.0, 201.0

Age		Xeglyze (g)	Vehicle (g)
4 to <12 years	N	84	87
	Mean (SD)	120.89 (57.3)	139.4 (55.9)
	Min, Max	12.0, 205.3	14.0, 214.0
12 to <18 years	N	28	30
	Mean (SD)	131.8 (62.3)	160.0 (55.2)
	Min, Max	6.0, 194.1	9.0, 210.0
≥18 years	N	61	55
	Mean (SD)	112.9 (59.7)	125.0 (57.3)
	Min, Max	12.0, 205.0	6.00, 215.0

Source: Applicant's submission: Summary of Clinical Efficacy, Table 12

During the trial, investigators prohibited concomitant medications or treatments that could potentially interfere with the evaluation of efficacy, such as use of lice combs, home remedies, and OTC or prescription medications for head lice infestation (unless provided by investigators as rescue therapy per protocol). These prohibitions began 14 days prior to Day 0, and ended on Day 14. Other prohibited medications included treatment with an investigational agent within 30 days prior to Day 0. Use of systemic or topical medications which, in the opinion of the investigator, could have interfered with the safety and/or efficacy results was also prohibited from Day 0 until the end of the Day 14 Visit.

The most commonly used concomitant medications (taken by at least 3 subjects) are summarized in Table 12. Concomitant medications were used infrequently during the trial and there appeared to be no appreciable difference in the concomitant medications used by treatment group.

Table 12: Summary of Concomitant Medications used by ≥3 Subjects

Medication	Xeglyze (N=186)	Vehicle (N=188)
Subjects with at least one concomitant medication	**45 (24.2%)**	**49 (26.1%)**
Albuterol	7 (3.8%)	11 (5.9%)
Loratadine	4 (2.2%)	0 (0.0%)
Permethrin	4 (2.2%)	16 (8.5%)
Amoxicillin	4 (2.2%)	1 (0.5%)
Ibuprofen	2 (1.1%)	5 (2.7%)
Hydrocodone/Acetaminophen	2 (1.1%)	1 (0.5%)

Medication	Xeglyze (N=186)	Vehicle (N=188)
Acetylsalicylic acid	1 (0.5%)	2 (1.1%)
Guaifenesin	0 (0.0%)	3 (1.6%)
Hydrocortisone	0 (0.0%)	3 (1.6%)

Source: Applicant's Submission; Table 37, Ha03-001 CSR

Investigators provided permethrin as rescue therapy to all treatment failures (defined as subjects with live lice present at any follow-up visit). As such, the use of rescue therapy did not impact the evaluation of efficacy. On the Day 1 Visit, 6 subjects in the Xeglyze group and 20 subjects in the Vehicle group were provided with rescue therapy. On the Day 7 Visit, 2 subjects in the Xeglyze group and 30 in the Vehicle group were provided with rescue therapy. On the Day 14 Visit, 7 subjects in the Xeglyze and 19 subjects in the Vehicle group were provided with rescue therapy.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint, agreed to by the Agency in a Special Protocol Assessment (SPA), was the proportion of Index subjects who were lice free at all follow-up visits (Day 1, 7, and 14). According to the Biometrics Review by Dr. Carin Kim (dated 4/22/2016 in DARRTS) : "(Xeglyze) was statistically superior to vehicle lotion ($p<0.001$) for the primary endpoint of the proportion of lice-free subjects at Day 14. As a supportive analysis, the primary and the secondary efficacy results were analyzed using the Per Protocol (PP) population. The results from the PP analysis yielded very similar results to those of the index ITT population as 105 of the 108 index ITT subjects in Trial 001, and 106 of the 108 index ITT subjects were included in the PP population." Table 13 displays the primary efficacy results from the index ITT subjects; table 14 displays the efficacy analysis using the PP population. The primary efficacy results from the index ITT population are included in product labeling.

Table 13: Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Day 14 (Primary Endpoint); Trial Ha03-001

	Xeglyze N=53	Vehicle N=55	p-value
Primary Endpoint (Day 14)	43 (81%)	28 (51%)	0.001

Source: Adapted from Table 7, Biostatistics review

Table 14: Proportion of Lice-free Per Protocol (PP) Index Subjects at Day 14 (Primary Endpoint) in Trial Ha03-001

	Xeglyze N=52	Vehicle N=53
Primary Endpoint (Day 14)	43 (83%)	28 (53%)

Source: Adapted from Table 8, Biostatistics review

As an exploratory analysis per the protocol, the following Table 15 presents the results for the primary endpoint at Day 14 trials in all randomized subjects (all ITT) in Trial Ha03-001 which included all subjects in the household with at least 1 live louse at the Baseline Visit. The response rates were slightly higher than those of the index ITT population.

Table 15: Proportion of all Intent to Treat (all ITT) Lice-free Subjects at Day 14 (Primary Endpoint)

	Xeglyze N=187	Vehicle N=191
Primary Endpoint (Day 14)	165 (88%)	119 (62%)

Source: Adapted from Table 9, Biostatistics review

Table 16 presents a comparison of results for the primary efficacy endpoint at Day 14 by using the last observation carried forward (LOCF) as well as missing value treated as failure (MVTF) to impute missing data for Trial Ha03-001. The results were similar for each of the imputation methods for missing data. It should be noted that the amount of missing data in each trial was minimal.

Table 16: Results for the Primary Efficacy Endpoint at Day 14 with Last Observation Carried Forward and Missing Value Treated as Failure (Index ITT) in Trial Ha03-001

	Xeglyze N=53	Vehicle N=55	p-value
MVTF (1)	43 (81%)	28[(1)] (51%)	0.001
LOCF (2)	45 (85%)	29 (53%)	0.001

Source: Biostatistics Reviewer analysis; p-value based on a CMH test stratified by pooled sites.

(1) MVTF: Missing value treated as failure – primary imputation method; (2) LOCF: last observation carried forward.

Analysis by Subgroup and Site

From the biostatistics review by Dr. Carin Kim: "The majority of the enrolled index ITT subjects were female (85%), and Caucasian (95%), therefore, any differences in efficacy for the male subjects, and non-Caucasians would be difficult to detect. Furthermore, approximately 89% of the index subjects were between the ages of 6 months and less than 12 years of age. Therefore, any differences in efficacy for those subjects ≥12 years of age would be difficult to detect."

Table 17 presents the results for the primary efficacy endpoint at Day 14 by age groups, gender, race (white vs. non-white) for TrialHa03-001.

Table 17: Primary Efficacy Results by Gender, Race, and Age Group in Trial Ha03-001

	Xeglyze N=53	**Vehicle N=55**
Gender		
Female	38/48 (79%)	22/45 (49%)
Male	5/5 (100%)	6/10 (6%)
Race		
White	41/50 (82%)	28/55 (51%)
Black	1/2 (50%)	-
Other	1/1 (100%)	-
Age Group		
6 months – 4 years	10/11 (91%)	7/11 (64%)
4-12 years	28/36 (78%)	18/39 (46%)
12-18 years	3/4 (75%)	1/3 (33%)
>=18, <65 years	2/2 (100%)	2/2 (100%)
≥ 65 years	-	-

Source: Adapted from Table 13, Biostatistics review

From the biostatistics review by Dr. Carin Kim: "For Site #106 in Trial 001, while the response rate for the vehicle was higher than that of (Xeglyze), this could occur due to chance alone. Note that given the number of subjects in each center was relatively small, the findings from centers were expected to have large variability due to chance."

Table 18 below presents the results for the primary efficacy endpoint at Day 14 in Trial Ha03-001, by the center.

Table 18: Primary Efficacy at Day 14 by Center (index ITT), Trial Ha03-001

Site	Xeglyze N=53	Vehicle N=55
101	7/8 (88%)	4/8 (50%)
102	2/3 (67%)	3/4 (75%)
103	6/8 (75%)	5/8 (63%)
104	10/12 (83%)	4/12 (33%)
105	6/7 (86%)	1/8 (13%)
106	1/3 (33%)	2/3 (67%)
107	11/12 (92%)	9/12 (75%)

Source: Adapted from Table 13, Biostatistics review

Data Quality and Integrity – Reviewers' Assessment

From the biostatistics review by Dr. Carin Kim: "The databases for the studies required minimal data management prior to performing analyses and no request for additional datasets were made to the applicant." As displayed in table xx, there is large variability in treatment effect between trial sites. Dr. Kim's review states:"… given the number of subjects in each center was relatively small, the findings from centers were expected to have large variability due to chance." I concur with her analyses.

Efficacy Results – Secondary and other relevant endpoints

The protocol-specified secondary endpoints were:

- Proportion of index subjects who are lice free at Day 1 visit

- Proportion of index subjects who are lice free at Day 7 visit

As discussed in Section 3.2 of this review, the secondary endpoints were the subjects of a SPA non-agreement. Because of the life cycle of the head louse, these endpoints are not clinically relevant or meaningful.

From the biostatistics review: "For the secondary endpoints of the proportion of lice-free subjects at Day 1 and at Day 7, while the results were not statistically significant at Day 1, they were at Day 7. Although the results for the secondary endpoint at Day 7 were statistically significant, these secondary endpoints were not agreed upon with the Agency per the SPA agreement letter (12/4/2013)."

Table 19 displays the results for the secondary endpoint for the ITT population in Trial Ha03-001.

Table 19: Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Days 1, 7 (Secondary Endpoints), Trial Ha03-001

	Xeglyze N=53	**Vehicle N=55**	**p-value**
Day 1	49 (93%)	46(1) (84%)	0.10
Day 7	48 (91%)	34 (62%)	0.001

Source: Adapted from Table 7, Biostatistics Review

(1) Subject (b) (6) had a missing Day 1 assessment; however, per the SAP, this subject was considered to be a success as Days 7 and 14 were treatment success.

Table 20 displays results for the secondary efficacy endpoint for the PP index subjects, and table 21 displays the results for the secondary efficacy endpoint for all ITT subjects. The secondary endpoint response rates were slightly higher than those for the primary endpoint. However, as agreed in the SPA, only the primary efficacy endpoint will be considered in judging the potential therapeutic benefit of Xeglyze.

Table 20: Proportion of Lice-free Per Protocol (PP) Subjects at Day 1, 7 (Secondary Endpoints); Trial Ha03-001

	Xeglyze N=52	**Vehicle N=53**
Day 1	49 (94%)	45 (85%)
Day 7	48 (92%)	33 (62%)

Source: Adapted from Table 8, Biostatistics review

Table 21: Proportion of Lice-free Intent to Treat (index ITT) Subjects at Day 1, 7 (Secondary Endpoints), Trial Ha03-001

	Xeglyze N=187	**Vehicle N=191**
Day 1	175 (94%)	167 (87%)
Day 7	175 (94%)	138 (72%)

Source: Adapted from Table 9, Biostatistics review

Dose/Dose Response

Dose and dose response were not studied in Trial Ha03-001.

Durability of Response

Analyses of durability were not performed in Trial Ha03-001. Efficacy beyond 14 days post-treatment was not evaluated.

Persistence of Effect

Analyses of persistence of effect were not performed in Trial Ha03-001. Efficacy beyond 14 days post-treatment was not evaluated.

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted on Trial Ha03-001.

6.2. Trial Ha03-002: A Randomized, Double-Blind, Multicenter, Vehicle-Controlled Study of the Efficacy and Safety of Abametapir Lotion 0.74% Administered for the Treatment of Head Lice Infestation

6.2.1. Trial Design

Overview and Objective

Study Ha03-002, "A Randomized, Double-Blind, Multicenter, Vehicle-Controlled Study of the Efficacy and Safety of Abametapir Lotion 0.74% Administered for the Treatment of Head Lice Infestation" is also a Phase 3 safety and efficacy trial. The objectives of this trial are identical to those of the previously discussed Phase 3 Trial, Ha03-001. The primary objective of this trial was to evaluate the efficacy of at-home administration of a single application of Xeglyze for the treatment of head lice infestation in subjects 6 months of age and older. The secondary

objectives were to evaluate the safety and tolerability of at-home administration of a single application of Xeglyze for the treatment of head lice infestation.

Trial Design

Trial Ha03-002 was a randomized, double-blind, multicenter, vehicle-controlled, parallel-group trial in subjects with active head lice infestation. The protocol for Trial Ha03-002 was identical to the protocol for Trial Ha03-001, including subject enrollment, study plan, safety assessments, and rescue therapy. Trial Ha03-002 was conducted in 7 centers in the United States. These were well distributed geographically with 1 center each in Arizona, California, Florida, Mississippi, North Carolina, Tennessee, and Utah.

A total of 325 eligible subjects (including 108 index subjects) were enrolled and allocated a study treatment based on the randomization of the index subject in that family. Of these, 163 subjects were allocated to receive Xeglyze and 162 subjects were allocated to receive Vehicle. The 108 index subjects comprised the ITT population, with 106 completing the trial and included in the PP population. A total of 318 subjects completed the trial and comprised the All Randomized and Safety populations. The 7 subjects who did not complete the trial were all lost to follow up.

Inclusion and exclusion criteria were the same for both Pivotal Phase 3 trials. Also identical were the test product, Vehicle, and application instructions. The schedule of assessments for trial Ha03-002 was also identical to Ha03-001 and is shown in Table 3.

Trial Endpoints

The trial endpoints for Trial Ha03-002 were identical to those in Ha03-001. As in the other Pivotal trial, the primary endpoint was to determine the proportion of index subjects who were lice-free at all follow-up visits through to the Day 14 Visit. The secondary endpoints were as follows: for efficacy, the proportion of index subjects who were lice free at the Day 1 and Day 7 visits; for safety, the proportion of subjects with changes in irritation scores on scalp and eye assessments from Baseline through Day 14 visits, and the proportion of all subjects reporting TEAE at all follow-up visits through to Day 14. The exploratory endpoint of this trial was to determine the proportion of all subjects who were lice-free at all follow-up visits through to the Day 14 Visit.

Statistical Analysis Plan

The Statistical Analysis plan is identical to that used for Trial Ha03-001; Section 6.1 contains a detailed discussion of the SAP.

Protocol Amendments

All subjects were recruited under the Trial protocol of December 16, 2013; there were no changes made in the conduct of the trial. As recommended by the Agency, the applicant modified the imputation method for missing data, such that the method was consistent for both primary and secondary endpoints.

Data Quality and Integrity: Applicant's Assurance

All CRFs were electronic and utilized Electronic Data Capture (EDC). The eCRFs were completed at the trial site. The trial monitor reviewed the data entered on the eCRFs against the source documents for completeness and accuracy at each monitoring visit. Data that were not entered directly onto the eCRFs, such as laboratory results from a central laboratory, were also verified by review of the source documents. The trial monitor was also responsible for monitoring adherence to the protocol, GCP, and applicable region-specific requirements.

6.2.2. Study Results

Compliance with Good Clinical Practices

Attestation from the CSR (Section 5.2, p.9):"This study was conducted in accordance with the Declaration of Helsinki, the International Conference of Harmonization (ICH) guideline for Good Clinical Practice (GCP), Food and Drug Administration (FDA) regulations and other applicable local laws and regulations."

Financial Disclosure

The applicant submitted FDA form 3454 certifying that they, the applicant, had not entered into any financial arrangements with the clinical investigators. A list of clinical investigators for the Xeglyze clinical development was provided. The financial disclosure review template is located in Appendix 13.2.

Patient Disposition

ITT Population: Index Subjects

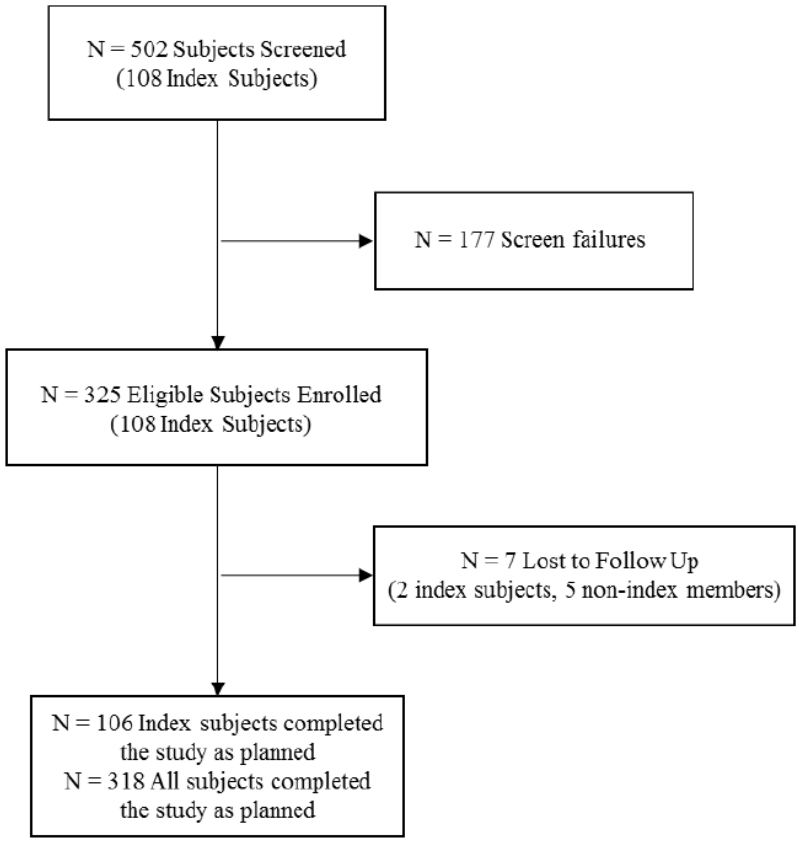
A total of 108 eligible index subjects were enrolled and randomized using a 1:1 allocation ratio to receive either Xeglyze (55 index subjects) or Vehicle (53 index subjects). All 108 randomized index subjects received study product and 106 index subjects completed the trial.

Xeglyze group: A total of 55 index subjects were enrolled and included in the ITT Population (100%), and 53 index subjects were included in the PP population (98.1%). Two index subjects were excluded from the PP population due to a protocol deviation (b) (6) One index subject was lost to follow-up (Subject (b) (6)), resulting in 54 (54/55; 98.2%) index subjects completing the trial as planned.

Vehicle group: A total of 53 index subjects were enrolled and included in the in the ITT and PP populations (100%). One index subject was lost to follow-up (Subject (b) (6)), resulting in 52 (53/53; 98.1%) index subjects completing the trial as planned.

Figure 3 graphically displays the overall disposition of subjects that provided assent/consent to participate in the trial.

Figure 3: Disposition of Subjects



Protocol Violations/Deviations

Most of the reported protocol deviations were minor, such as missed assessments or trial visits occurring outside the time window specified in the protocol. Visits occurring outside the time

window specified in the protocol did not affect the evaluation of safety or efficacy. In some cases, investigators were unable to successfully obtain blood samples for laboratory studies. Although the missing lab data may somewhat affect the evaluation of safety, it does not impair the evaluation of efficacy.

Investigators excluded the following index subjects from the per protocol (PP) population:

- Subject (b) (6), randomized to the Xeglyze group, received a prohibited treatment.
- Subject (b) (6), randomized to the Vehicle group, and did not follow study product administration instructions.

Table of Demographic Characteristics

Table 22 displays the demographic characteristics of the index subjects (ITT Population). The distribution by race and gender is similar to the patterns of head lice infestation observed in the clinical setting.

Table 22: Demographic characteristics of the primary efficacy (index) population

Demographic Parameters	Treatment Groups		Total (N=108) n (%)
	Xeglyze (N=55) n (%)	Vehicle (N=53) n (%)	
Sex			
Male	7/55 (12.7%)	10/53 (18.9%)	17/108 (15.7%)
Female	48/55 (87.3%)	43/53 (81.1%)	91/108 (84.3%)
Age			
Mean years (SD)	9.80 (10.50)	7.76 (7.74)	
Median (years)	7.00	6.50	
Min, max (years)	1.6, 58.5	1.1, 56.9	
Age Group			
6 months to <4 years	7/55 (12.7%)	11/53 (20.8%)	18/108 (16.7%)
4 to <12 years	41/55 (74.5%)	36/53 (67.9%)	77/108 (71.3%)
12 to <18 years	2/55 (3.6%)	4/53 (7.5%)	6/108 (5.6%)
18 years and older	5/55 (9.1%)	2/53 (3.8%)	7/108 (6.5%)
Race			
White	51/55 (92.7%)	49/53 (92.5%)	100/108 (92.6%)
Black or African American	0 (0.0%)	2/53 (3.8%)	2/108 (1.9%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian or Alaska Native	1/55 (1.8%)	0 (0.0%)	1/108 (0.9%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	1/53 (1.9%)	1/108 (0.9%)

Demographic Parameters	Treatment Groups		Total (N=108) n (%)
	Xeglyze (N=55) n (%)	Vehicle (N=53) n (%)	
Other[1]	3/55 (5.5%)	1/53 (1.9%)	4/108 (3.7%)
Ethnicity			
Hispanic or Latino	26/55 (47.3%)	21/53 (39.6%)	47/108 (43.5%)
Not Hispanic or Latino	29/55 (52.7%)	31/53 (58.5%)	60/108 (55.6%)
Unknown	0 (0.0%)	1/53 (1.9%)	1/108 (0.9%)
Region (optional)			
United States	55	53	108

Source: Applicant's submission; Adapted from Table 14.1.2.1 and Table 26, Ha03-002 CSR

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Hair characteristics such as length and texture can affect the efficacy of treatment for head lice infestation. Consequently, investigators recorded details of the hair characteristics of each subject. The hair characteristics for the index subjects were comparable between the treatment groups with regards to length, texture, and volume. The hair characteristics were reasonably comparable with regards to shape; more index subjects with curly hair were randomized to the Xeglyze group, and more index subjects with straight hair were randomized to the Vehicle group. Hair characteristics for the index subjects are presented in Table 23.

Table 23: Hair Characteristics, Index Subjects

	Xeglyze (N=55)	Vehicle (N=53)
Length		
Short (Ear Length or Shorter)	12 (21.8%)	10 (18.9%)
Medium (Shoulder Length)	19 (34.5%)	23 (43.4%)
Long (Past Shoulder Length to Mid-back)	13 (23.6%)	15 (28.3%)
Very Long (Past Mid-back)	11 (20.0%)	5 (9.4%)
Texture		
Coarse	6 (10.9%)	5 (9.4%)
Medium	35 (63.6%)	27 (50.9%)
Fine	14 (25.5%)	21 (39.6%)

	Xeglyze (N=55)	Vehicle (N=53)
Volume		
Thick	17 (30.9%)	18 (34.0%)
Medium	30 (54.5%)	22 (41.5%)
Thin	8 (14.5%)	13 (24.5%)
Shape		
Curly	7 (12.7%)	3 (5.7%)
Wavy	12 (21.8%)	13 (24.5%)
Straight	36 (65.5%)	37 (69.8%)

Source: Applicant's submission; Table 14.1.3.1, Ha03-002 CSR

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

To ensure compliance, Investigators weighed bottles of the investigational product (IP; Xeglyze or Vehicle) before use. Subjects returned the bottles on Day 1; investigators weighed the bottles again to determine the amount of study product used for each subject. The mean weight (and range of weight) of study product administered per subject was similar between the treatment groups. Tables 24 and 25 display a summary of study product administration in index subjects and all subjects. Table 26 displays a summary of study product administration, stratified by age group.

Table 24: Summary of Study Product Administration – Index Subjects (ITT Population)

Study Product Administered (g)	Xeglyze (N=55)	Vehicle Lotion (N=53)
n	54	53
Mean (SD)	123.3 (57.1)	120.4 (57.6)
Min, Max	16.0, 206.3	22, 203.8

Source: Applicant's submission; Table 14.1.4.1, Ha03-002 CSR

Table 25: Summary of Study Product Administration – All Subjects

Study Product Administered (g)	Xeglyze (N=163)	Vehicle Lotion (N=162)
n	157	161
Mean (SD)	131.2 (55.9)	125.5 (55.1)
Min, Max	11.7, 206.9	14.7, 205.2

Source: Applicant's submission; Table 14.1.4.3, Ha03-002 CSR

Table 26: Trial Ha03-002: Summary of Exposure by Age – All Randomized Subjects

		Ha03-002	
Age		**Xeglyze (g)**	**Vehicle (g)**
6 months to <2 years	N	3	5
	Mean (SD)	49.8 (46.5)	44.2 (24.1)
	Min, Max	16.0, 102.8	22.0, 71.6
2 to <4 years	N	5	11
	Mean (SD)	115.0 (70.5)	81.5 (42.1)
	Min, Max	50.8, 191.9	28.6, 178.2
4 to <12 years	N	79	84
	Mean (SD)	124.1 (56.5)	128.50 (51.9)
	Min, Max	11.7, 206.3	31.10, 205.2
12 to <18 years	N	27	23
	Mean (SD)	137.9 (54.0)	139.62 (52.1)
	Min, Max	16.0, 205.7	46.6, 204.8
≥18 years	N	43	38
	Mean (SD)	147.6 (48.8)	133.74 (57.0)
	Min, Max	38.9, 206.9	14.7, 202.2

Source: Applicant's submission: Summary of Clinical Efficacy, Table 12

All subjects in this trial applied their assigned study product; however, the following subjects had protocol deviations with study product administration:

- Subject (b) (6) (treated with Xeglyze): excluded from the PP population because the father applied mayonnaise to the hair.
- Subject (b) (6) (treated with Xeglyze): excluded from the PP population, as the subject left the study product on for 15 minutes instead of 10 minutes.
- Subject (b) (6) (Vehicle): reported there was insufficient study product to saturate the hair. The subject was noted to have very long and thick hair.

During the trial, investigators prohibited concomitant medications or treatments that could potentially interfere with the evaluation of efficacy, such as lice combs, home remedies, and OTC or prescription medications for head lice infestation (unless provided by investigators as rescue therapy per protocol). These prohibitions began 14 days prior to Day 0, and ended on Day 14. Other prohibited medications included treatment with an investigational agent within 30 days prior to Day 0. Use of systemic or topical medications which, in the opinion of the investigator, could have interfered with the safety and/or efficacy results was also prohibited from Day 0 until the end of the Day 14 Visit.

The most commonly used concomitant medications (taken by at least 3 subjects) are summarized in Table 27. Concomitant medications were used infrequently during the trial and there appeared to be no appreciable difference in the concomitant medications used by treatment group.

Investigators provided permethrin as rescue therapy to all treatment failures (defined as subjects with live lice present at any follow-up visit). As such, the use of rescue therapy did not impact the evaluation of efficacy. On the Day 1 Visit, 15 subjects in the Xeglyze group and 17 subjects in the Vehicle group were provided with rescue therapy. On the Day 7 Visit, 8 subjects in the Xeglyze group and 24 in the Vehicle group were provided with rescue therapy. On the Day 14 Visit, 10 subjects in the Xeglyze group and 31 subjects in the Vehicle group were provided with rescue therapy.

Table 27: Summary of Concomitant Medications used by ≥3 Subjects

Preferred Term	Xeglyze (N=163)	Vehicle (N=162)
Ibuprofen	10 (6.1%)	0 (0.0%)
Permethrin	5 (3.1%)	5 (3.1%)
Albuterol	5 (3.1%)	7 (4.3%)
Hydrocortisone	3 (1.8%)	3 (1.9%)
Amphetamine mixed salts	3 (1.8%)	2 (1.2%)
Hydrochlorothiazide	2 (1.2%)	1 (0.6%)
Levothyroxine	2 (1.2%)	1 (0.6%)
Loratadine	2 (1.2%)	3 (1.9%)

Preferred Term	Xeglyze (N=163)	Vehicle (N=162)
Metformin	2 (1.2%)	1 (0.6%)
Montelukast	2 (1.2%)	1 (0.6%)
Acetaminophen	2 (1.2%)	1 (0.6%)

Source: Applicant's submission; Table 42, Ha03-002 CSR

Efficacy Results - Primary Endpoint

Trial Ha03-002 was identical in design to Trial Ha03-001. As in Trial Ha03-001, in Ha03-002, The primary efficacy endpoint, agreed to by the Agency in a Special Protocol Assessment (SPA), was the proportion of Index subjects who were lice free at all follow-up visits (Days 1, 7, and 14). According to Dr. Carin Kim, Biostatistics reviewer: "(Xeglyze) was statistically superior to vehicle lotion ($p<0.001$) for the primary endpoint of the proportion of lice-free subjects at Day 14. As a supportive analysis, the primary and the secondary efficacy results were analyzed using the Per Protocol (PP) population. The results from the PP analysis yielded very similar results to those of the index ITT population as 106 of the 108 index ITT subjects were included in the PP population (in Trial Ha03-002)." Table 28 displays the primary efficacy results from the index ITT subjects; table 29 displays the efficacy analysis using the PP population. The primary efficacy results from the index ITT population are included in product labeling.

Table 28: Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Day 14 (Primary Endpoint)

	Xeglyze N=55	Vehicle N=53	p-value
Primary Endpoint (Day 14)	45 (82%)	25 (47%)	<0.001

Source: Adapted from Table 7, Biostatistics Review

Table 29: Proportion of Lice-free Per Protocol (PP) Subjects at Day 14 (Primary Endpoint); Trial Ha03-002

	Xeglyze N=53	Vehicle N=53
Primary Endpoint (Day 14)	43 (81%)	25 (47%)

Source: Adapted from Table 8, Biostatistics Review

As an exploratory analysis per the protocol, the following Table 30 presents the results for the primary endpoint at Day 14 trials in all randomized subjects (all ITT) in Trial Ha03-002 which included all subjects in the household with at least 1 live louse at the Baseline Visit. The response rate to Vehicle was slightly higher than that of the index ITT population.

Table 30: Proportion of all Intent to Treat (all ITT) Lice-free Subjects at Day 14 (Primary Endpoint); Ha03-002

	Xeglyze N=163	**Vehicle N=162**
Primary Endpoint (Day 14)	132 (81%)	98 (60%)

Source: Adapted from Table 9, Biostatistics review

Table 31 presents a comparison of results for the primary efficacy endpoint at Day 14 by using the last observation carried forward (LOCF) as well as missing value treated as failure (MVTF) to impute missing data for Trial Ha03-002. The results were similar for each of the imputation methods for missing data. It should be noted that the amount of missing data in each trial was minimal.

Table 31: Results for the Primary Efficacy Endpoint at Day 14 with Last Observation Carried Forward and Missing Value Treated as Failure (index ITT); Trial Ha03-002

	Xeglyze N=55	**Vehicle N=53**	**p-value**
MVTF (1)	45 (82%)	25 (47%)	<0.001
LOCF (2)	46 (84%)	26 (49%)	<0.001

Source: Biostatistics Reviewer analysis; p-value based on a CMH test stratified by pooled sites.

(1) MVTF: Missing value treated as failure – primary imputation method; (2) LOCF: last observation carried forward.

Analysis by Subgroup and Site

From the Biometrics review by Dr. Carin Kim: "The majority of the enrolled index ITT subjects were female (85%), and Caucasian (95%), therefore, any differences in efficacy for the male subjects, and non-Caucasians would be difficult to detect. Furthermore, approximately 89% of the index subjects were between the ages of 6 months and less than 12 years of age. Therefore, any differences in efficacy for those subjects ≥12 years of age would be difficult to detect."

Table 32 presents the results for the primary efficacy endpoint at Day 14 by age groups, gender, race (white vs. non-white) for Trial Ha03-002.

Table 32: Primary Efficacy Results by Gender, Race, and Age Group in Trial Ha03-002

	Xeglyze N=55	**Vehicle N=53**
Gender		
Female	41/48 (85%)	19/43 (44%)
Male	4/7 (57%)	6/10 (60%)
Race		
White	44/51 (86%)	23/49 (47%)
Black	-	1/2 (50%)
Other	1/4 (25%)	1/2 (50%)
Age		
6 months – 4 years	5/7 (71%)	4/11 (36%)
4-12 years	33/41 (80%)	15/36 (42%)
12-18 years	2/2 (100%)	4/4 (100%)
>=18, <65 years	5/5 (100%)	2/2 (100%)
≥ 65 years	-	-

Source: Adapted from Table 13, Biostatistics Review

Table 33 below presents the results for the primary efficacy endpoint at Day 14 in Trial Ha03-002, by the original center. As discussed in Section 6.1.2 of this review, given the number of subjects in each center was relatively small, the findings from centers were expected to have large variability due to chance.

Table 33: Primary Efficacy at Day 14 by Center (index ITT), Trial Ha03-001

Site	**Xeglyze N=53**	**Vehicle N=55**
201	9/12 (75%)	7/12 (58%)
202	7/7 (100%)	3/7 (43%)
203	2/2 (100%)	0 (0%)
204	4/4 (100%)	3/4 (75%)

Site	Xeglyze N=53	Vehicle N=55
205	8/8 (100%)	2/8 (25%)
206	2/6 (50%)	4/12 (33%)
207	9/10 (90%)	6/10 (60%)

Source: Adapted from Table 13, Biostatistics review

Data Quality and Integrity - Reviewers' Assessment

From the biostatistics review by Dr. Carin Kim: "The databases for the studies required minimal data management prior to performing analyses and no request for additional datasets were made to the applicant." As displayed in table xx, there is large variability in treatment effect between trial sites. Dr. Kim's review states:"… given the number of subjects in each center was relatively small, the findings from centers were expected to have large variability due to chance." I concur with her analyses.

Efficacy Results - Secondary and other relevant endpoints

The protocol-specified secondary endpoints were:

- Proportion of index subjects who are lice free at Day 1 visit
- Proportion of index subjects who are lice free at Day 7 visit

As discussed in Section 3.2 of this review, the secondary endpoints were the subjects of a SPA non-agreement. Because of the life cycle of the head louse, these endpoints are not clinically relevant or meaningful.

From the biostatistics review: "For the secondary endpoints of the proportion of lice-free subjects at Day 1 and at Day 7, while the results were not statistically significant at Day 1, they were at Day 7. Although the results for the secondary endpoint at Day 7 were statistically significant, these secondary endpoints were not agreed upon with the Agency per the SPA agreement letter (12/4/2013)."

Table 34 displays the results for the secondary endpoint for the ITT population in Trial Ha03-002.

Table 34: Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Day 1 and 7 (Secondary Endpoints); Trial Ha03-002

	Xeglyze N=55	**Vehicle N=53**	**p-value**
Day 1	48 (87%)	44 (83%)	0.45
Day 7	47 (86%)	36 (68%)	0.025

Source: Adapted from Table 7, Biostatistics Review

Table 35 displays results for the secondary efficacy endpoint for the PP index subjects, and table 36 displays the results for the secondary efficacy endpoint for all ITT subjects. The secondary endpoint response rates were slightly higher than those for the primary endpoint. However, as agreed in the SPA, only the primary efficacy endpoint will be considered in judging the potential therapeutic benefit of Xeglyze.

Table 35: Proportion of Lice-free Per Protocol (PP) Index Subjects at Days 1, 7 (Secondary Endpoints); Trial Ha03-002

	Xeglyze N=53	**Vehicle N=53**
Day 1	46 (88%)	44 (83%)
Day 7	45 (85%)	36 (68%)

Source: Adapted from Table 8, Biostatistics review

Table 36: Proportion of all Intent to Treat (all ITT) Lice-free Subjects at Day 1 and 7 (Secondary Endpoints); Trial Ha03-002

	Xeglyze N=163	**Vehicle N=162**
Day 1	148 (91%)	143 (88%)
Day 7	142 (87%)	123 (76%)

Source: Adapted from Table 9, Biostatistics review

Dose/Dose Response

Dose and dose response were not studied in Trial Ha03-002.

Durability of Response

Analyses of durability were not performed in Trial Ha03-002. Efficacy beyond 14 days post-treatment was not evaluated.

Persistence of Effect

Analyses of persistence of effect were not performed in Trial Ha03-001. Efficacy beyond 14 days post-treatment was not evaluated.

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted on Trial Ha03-002.

6.3. Trial Ha03-008: "A Randomised, Double-Blind, Vehicle-Controlled Study of the Ovicidal Efficacy and Safety of Abametapir Lotion 0.74% Administered for the Treatment of Head Lice Infestation"

6.3.1. Study Design

Overview and Objective

The objective of Trial Ha03-008 was to evaluate the mechanism of action of a single application of Xeglyze for the treatment of head lice infestation. The Trial used *ex-vivo/in-vitro* techniques to evaluate the effect of Xeglyze on lice and their ova.

Trial Design

The study was a double-blind, randomized, vehicle-controlled, single dose study which enrolled 50 subjects. The main Inclusion Criteria for this Trial included being healthy, male or female, age 3 years and older. Each subject was also required to have an active head lice infestation with a minimum of 3 live head lice and at least 10 undamaged and unhatched head lice eggs in their hair. The main Exclusion Criteria prohibited participation by subjects with scalp disease or a condition that, in the opinion of the investigator, may interfere with the study; was receiving systemic or topical medication, which in the opinion of the investigator, may compromise the integrity of the safety and/or efficacy assessments; and had treatment (including over-the-counter [OTC] medication or home remedy) for head lice within 14 days prior to Day 0.

Once enrolled, investigators randomized subjects in a ratio of 1:1, into 1 of 2 treatment groups: Xeglyze or Vehicle. Prior to application of study product, a minimum of 5 undamaged eggs located on hair shafts less than 1 cm from the scalp were randomly selected and removed from each subject's head by clipping the hairs to which the eggs were attached. Study staff applied Xeglyze or Vehicle to the scalp and hair of subjects for 10 minutes. The hair and scalp was then washed thoroughly with water and a minimum of 5 undamaged eggs located on hair shafts less than 1cm from the scalp were then removed from the hair by clipping the hairs to which the eggs were attached. Eggs were evaluated for viability by the central laboratory and incubated for a 14 day period. To assess viability, investigators examined all eggs under a dissecting

microscope. Non-viable eggs, (those considered partially squashed, barren [no visible cells inside] or malformed cell masses), were discarded. At the end of the incubation period, investigators compared the hatch rate of eggs harvested pretreatment to the hatch rate of eggs harvested post treatment. The post treatment hatch rates of eggs after treatment with Xeglyze and Vehicle were also compared.

Subjects were randomized and treated by study staff on Day 0 with either Xeglyze or Vehicle. Investigators conducted follow up visits on Day 1 and 7 to evaluate for the presence of live lice and ascertain the need for rescue therapy. Investigators treated any subject who had live lice detected at the Day 1 or Day 7 visit with MooV Headlice Solution®, which is an over-the-counter head lice product consisting of Eucalyptus oil 11%, Lemon Tea Tree Oil 1.0%, and Benzyl Alcohol 0.5%. This product is available in Australia from Ego Pharmaceuticals Pty Ltd.

Study Endpoints

The primary efficacy endpoint was the proportion of hatched eggs pre-treatment relative to the proportion of hatched eggs post-treatment, following a 14-day incubation period.

6.3.2. Study Results

Patient Disposition

Fifty subjects meeting the inclusion criteria were enrolled at a single site and randomized in a ratio of 1:1 to receive treatment with Xeglyze or Vehicle. As planned, 25 subjects were randomized to each group. All 50 subjects completed the trial as planned. Investigators excluded 1 subject from the per-protocol population after the subject's mother revealed, after treatment with study product, that she had treated the subject with an over-the-counter head lice treatment 9 days prior to Day 0. This treatment violated an exclusion criterion.

Table of Demographic Characteristics

Table 37: Summary of Demographic Characteristics in Trial Ha03-008

	Xeglyze (N=25)	**Vehicle (N=25)**	**Total (N=50)**
Age (years)			
N	25	25	50
Mean (SD)	8.7 (3.43)	8.3 (2.95)	8.5 (3.18)
Min, Max	3, 17	3, 12	3, 17
Sex n (%)			
Male	4 (16.0)	1 (4.0)	5 (10.0)
Female	21 (84.0)	24 (96.0)	45 (90.0)

	Xeglyze (N=25)	Vehicle (N=25)	Total (N=50)
Ethnicity n (%)			
Not Hispanic or Latino	25 (100.0)	25 (100.0)	50 (100.0)
Race n (%)			
White	25 (100.0)	25 (100.0)	50 (100.0)

Source: Applicant's submission, Ha03-008 CSR

Other Baseline Characteristics

At baseline, the treatment groups were comparable with respect to the number of eggs collected, number of eggs received at the lab, the number of viable eggs incubated (90.8% in the Xeglyze group and 88.6% in the Vehicle group) as well as the number of and reasons for discarding of eggs.

Trial Results - Primary Endpoint

In the Xeglyze group, 111 (111/119; 93.3%) of eggs collected prior to treatment hatched after incubation. A total of 130 eggs were collected and incubated after treatment with Xeglyze; none (0/130; 0%) of these eggs hatched. In the Vehicle group, 93 (93/117; 79.5%) of eggs collected prior to treatment hatched after incubation. A total of 136 eggs were collected and incubated after treatment with Vehicle; 49 (49/136; 36%) of these eggs hatched and 87 (87/136; 64%) remained unhatched. Per the applicant, the difference in hatch rates after treatment with Xeglyze and treatment with Vehicle was statistically significant ($p<0.0001$).

Protocol Ha03-008 was reviewed under IND 77510 by Melinda McCord, MD on May 27, 2014. From Dr. McCord's review: "An *ex-vivo* assessment of ovicidal activity has limited utility. Findings of ovicidal activity *in vitro* cannot be extrapolated to findings of ovicidal activity *in vivo* since conditions which may impact the assessment of effect are different… the Agency has already conveyed the comment that this approach is not acceptable (End-of Phase 2 Communication, 8/7/2012)." Furthermore, in an Advice Letter to the applicant dated July 7, 2014, the Agency stated the following: "For the proposed indication of the treatment of head lice infestation, the primary efficacy endpoint in protocol Ha03-008 should be the proportion of index subjects who are lice free 14 days after the last treatment. As previously communicated August 7, 2012, the applicability of data from ***in vitro*** studies with head lice to support the indication of the "treatment of head lice infestation" is limited." Therefore, for product labeling, the approved indication will be "treatment of head lice infestation".

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The applicant presented data from 2 adequate and well controlled Phase 3 trials of identical design in support of this NDA. The SPA agreed-upon primary efficacy endpoint for each of these trials was the proportion of index subjects who were lice-free at the Day 1, 7, and 14 Visits. The index subjects were defined as the youngest subject in the household, age 6 months or older, with at least 3 live lice present at the Baseline Visit. The primary efficacy results are displayed in Table 38; this information will be included in Section 14 Clinical Studies in product labeling.

Table 38: Proportion of Index Subjects Free of Live Lice at all Visits (Days 1, 7, and 14) After Treatment

	Trial Ha-03-001			Trial Ha03-002		
	Xeglyze Lotion (N=53)	**Vehicle Lotion (N=55)**	**p-value**	**Xeglyze Lotion (N=55)**	**Vehicle Lotion (N=53)**	**p-value**
Treatment Success	43 (81.1%)	28 (50.9%)	0.001	45 (81.8%)	25 (47.2%)	<0.001

Source: Table 1, Biostatistics Review

The primary efficacy endpoint chosen is well-established for the indication of head lice infestation. The results obtained are statistically significant and clinically meaningful. Section 6.1 and 6.2 of this review discuss the individual trials in more detail.

7.1.2. Secondary and Other Endpoints

The protocol-specified secondary endpoints for the Phase 3 trials were:

- Proportion of index subjects who are lice free at Day 1 visit
- Proportion of index subjects who are lice free at Day 7 visit

As discussed in Sections 3.2 and 6.1.2 of this review, the secondary endpoints were the subjects of a SPA non-agreement. Because of the life cycle of the head louse, these endpoints are not clinically relevant or meaningful. However, this data is intriguing because of the treatment effect seen in subjects who were treated with Vehicle. Table 39 displays the efficacy results for the secondary efficacy endpoint.

Table 39: Proportion of Lice-free Index Intent to Treat (index ITT) Subjects at Days 1, 7 (Secondary Endpoints)

	Trial Ha03-001			Trial Ha03-002		
	Xeglyze N=53	**Vehicle N=55**	**p-value**	**Xeglyze N=55**	**Vehicle N=53**	**p-value**
Day 1	49 (93%)	46[(1)] (84%)	0.10	48 (87%)	44 (83%)	0.45
Day 7	48 (91%)	34 (62%)	0.001	47 (86%)	36 (68%)	0.025

Source: Adapted from Table 7, Biostatistics Review

(1) Subject [redacted] (b) (6) had a missing Day 1 assessment; however, per the SAP, this subject was considered to be a success as Days 7 and 14 were treatment success.

At Day 1, the difference in efficacy results was not statistically significant because of a high treatment effect in the Vehicle group. The treatment effect of the Vehicle diminished through Day 7 and 14; the difference between Xeglyze and Vehicle was statistically significant by Day 7.

7.1.3. Subpopulations

As discussed in the biostatistics review, most of the index ITT subjects were female (85%) and Caucasian (95%). Because of this, it would be difficult to detect meaningful differences in efficacy for male or non-Caucasian subjects. Additionally, approximately 89% of index subjects were less than 12 years of age. Therefore, it would be difficult to detect meaningful differences in efficacy for subjects over 12 years of age.

Table 40 presents the results for the primary efficacy endpoint at Day 14 by age groups, gender, race (white vs. non-white) for the Phase 3 trials.

Table 40: Primary Efficacy Results by Gender, Race, and Age (Index Subjects)

	Trial Ha03-001		Trial Ha03-002	
	Xeglyze N=53	**Vehicle N=55**	**Xeglyze N=55**	**Vehicle N=53**
Sex				
Female	38/48 (79%)	22/45 (49%)	41/48 (85%)	19/43 (44%)
Male	5/5 (100%)	6/10 (60%)	4/7 (57%)	6/10 (60%)
Race				
White	41/50 (82%)	28/55 (51%)	44/51 (86%)	23/49 (47%)
Black	1/2 (50%)	-	-	1/2 (50%)
Other	1/1 (100%)	-	1/4 (25%)	1/2 (50%)
Age				
6 months – 4 years	10/11 (91%)	7/11 (64%)	5/7 (71%)	4/11 (36%)
4-12 years	28/36 (78%)	18/39 (46%)	33/41 (80%)	15/36 (42%)
12-18 years	3/4 (75%)	1/3 (33%)	2/2 (100%)	4/4 (100%)
>=18, <65 years	2/2 (100%)	2/2 (100%)	5/5 (100%)	2/2 (100%)
≥ 65 years	-	-	-	-

Source: Biostatistics review, Table 13

7.1.4. Dose and Dose-Response

Trial Ha02-003 was a Phase 2, multicenter, double-blind, randomized, vehicle-controlled, parallel study which evaluated the safety and efficacy of Xeglyze 0.37%, Xeglyze 0.74%, and Vehicle. A total of 142 subjects, age 2 years and older, with head lice infestation were enrolled and randomized to one of the 3 treatment groups. Unlike Trial Ha02-002, all subjects in Ha02-003 were treated with a 10 minute application of study product, which is the dosing regimen with which Xeglyze is proposed to be marketed. The primary efficacy endpoint was the proportion of subjects who were lice free at all follow-up visits through the Day 14 visit.

The primary efficacy results demonstrated statistically significant and clinically relevant treatment success in both the Xeglyze 0.37% (67.4%) and the Xeglyze 0.74% (85.7%) treatment groups compared to the Vehicle group (23.4%, $p<0.001$). Overall, Xeglyze 0.74% showed higher treatment success than Xeglyze 0.37%; the rates of adverse events were similar in each group. Because of superior efficacy and equivalent safety, the applicant chose 0.74% w/w, applied for 10 minutes, as the to-be-marketed concentration and dosing regimen for Xeglyze.

Table 41 displays treatment success by treatment arm in Trial Ha02-003.

Table 41: Treatment Success in Trial Ha02-003

	Xeglyze 0.37% N=46	Xeglyze 0.74% N=49	Vehicle N=47
Treatment Success	31 (67.4%)	42 (85.7%)	11 (23.4%)

Source: Applicant's submission; Table 8, Ha02-003 CSR

7.1.5. Onset, Duration, and Durability of Efficacy Effects

During the Phase 3 trials, investigators evaluated safety and efficacy at the Day 1, 7, and 14 Visits. As seen in Tables 36 and 37 in this section, the therapeutic effect of Xeglyze was evident beginning at the Day 1 visit.

Analyses of persistence of efficacy and/or tolerance were not performed. Efficacy beyond 14 days post treatment was not evaluated.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the 2 Phase 3 trials from which the primary efficacy database is drawn, Xeglyze was administered in the home by the subjects or caregiver. Because Xeglyze was administered under conditions of actual use in these trials, the treatment benefit observed in the trials should be generalizable to the target population.

The index subjects, upon whom the primary efficacy endpoint is based, were mostly female, of Caucasian race, and less than 12 years of age. The numbers of male and non- Caucasian subjects, as well as subjects age 12 and older, were not sufficient for meaningful statistical analysis of results from these subgroups.

7.2.2. Other Relevant Benefits

Because treatment with Xeglyze requires only a single application, it represents a useful addition to the available therapeutic armamentarium. For products requiring 2 treatments, these treatments are usually administered 1 week apart; patients are not usually permitted to attend day care or school until after the second treatment. Products for head lice infestation that require only one treatment are beneficial because they allow patients to return to day care or school (and their caregiver to return to work) the day after treatment.

7.3. Integrated Assessment of Effectiveness

The applicant has submitted data from 2 adequate and well-controlled clinical trials in support of this NDA. These were Trial Ha03-001 and Ha03-002, which are reviewed in detail in Sections 6.1 and 6.2 of this review. The efficacy data from these trials is statistically significant and clinically meaningful, and demonstrates substantial evidence of effectiveness of Xeglyze in the treatment of head lice infestation in patients 6 months of age and older. Therefore, the applicant has met the evidentiary standard.

Xeglyze is effective after a single application; therefore it is a useful addition to the therapeutic armamentarium against head lice infestation. This allows affected children to return to day care or school, and their caregivers to work, more quickly than pediculocides requiring 2 treatments a week apart.

The data presented in Table 38 in Section 7.1.1 will be included in labeling in Section 14 Clinical Studies. This table displays the proportion of the ITT population of both Phase 3 studies who were lice-free at the Day 1, 7, and 14 Visits.

For a more comprehensive review of the statistical analysis of efficacy results, please see the primary Biometrics Review by Dr. Carin Kim, dated 4/22/2016 in DARRTS.

8 Review of Safety

Safety Review Approach

The 2 Phase 3 trials were conducted under actual-use conditions, with subjects or caregivers administering Xeglyze at home. Because of this, pooled data from these trials will make up the primary safety database. This review will also evaluate safety in specific subgroups, stratified by age and other demographic characteristics where appropriate. Data from the Phase 3 subjects to be considered include active assessment of local safety, evaluation of systemic safety including vital signs and laboratory studies, and reported adverse events.

Although the Phase 2 trials were conducted using the to-be-marketed formulation, Xeglyze was administered by investigators in a clinic setting. Because Xeglyze was administered in a clinic setting, the Phase 2 data will not be pooled with data from the Phase 3 trials. However, the Phase 2 trials will nevertheless provide supportive safety data in these categories also. This section will also include results and analysis of the cardiac safety monitoring, dermal sensitization, and dermal irritation studies. The cardiac safety monitoring consisted of ECG monitoring and a thorough QT trial to assess the potential of Xeglyze to affect cardiac electrical activity.

The applicant defined hair discoloration as an adverse event of special interest. Hair discoloration occurred in 3 subjects in Phase 3 Trial Ha03-002, and 1 subject in Phase 1 Trial Ha02-005. These AE are discussed in Section 8.4.5.2.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Phase 3 trials

The applicant submitted data from 2 pivotal Phase 3 trials, Ha03-001 and Ha03-002. These were randomized, double-blind, multicenter trials conducted in the US. For each of these trials, the study product was to be administered at home by the subject or caregiver on Trial Day 0. The subjects were evaluated in the trial center for screening, as well as assessments on Days 1, 7, and 14. This population will comprise the primary safety database.

In Trial Ha03-001, a total of 379 subjects were enrolled and randomized to receive either Xeglyze or Vehicle. The Xeglyze group consisted of 187 subjects, with 183 completing the trial. Of the 4 subjects that failed to complete the trial, 3 returned on Day 1 (i.e. were treated with the IP) but did not return for the day 7 or Day 14 visits and were lost to follow-up. These subjects were included in the Safety Population. One subject did not return for the Day 1, nor

the Day 7 and Day 14 visits. Because the investigator was unable to verify whether this subject used the study product or not, this subject was excluded from the Safety Population.

Trial Ha03-002 enrolled a total of 325 subjects and randomized the subjects similarly to those in Ha03-001. Of the 163 subjects assigned to the Xeglyze group, 158 completed the trial. One family of 5 subjects did not return for the Day 7 or Day 14 visit and were lost to follow-up; however, because they received study product and returned on Day 1, they were included in the Safety Population. 162 subjects were assigned to the Vehicle group. 2 subjects from this group were lost to follow-up; one subject did not return for the Day 1 or any subsequent visits and the other did not return for the day 14 visit. While the applicant included both subjects in the Safety Population, for this review we will exclude the subject who did not return on Day 1 since we cannot verify whether this subject applied the Vehicle. A total of 160 subjects completed the trial as planned.

Therefore, the total number of subjects in the Phase 3 safety population treated with Xeglyze was 349. Characteristics of the Safety Population of the two Phase 3 studies are listed in Tables 42 and 43 below.

Table 42: Safety Population, Phase 3 Pivotal Trials, Xeglyze applied by subject/caregiver in-home

Phase 3 Trial	Trial Design	Xeglyze (n=)	Vehicle (n=)
Ha03-001	randomized, double-blind, multicenter, vehicle-controlled, parallel-group	187 enrolled 186 included in safety population 183 completed trial[1]	192 enrolled 188 included in safety population 185 completed trial[2]
Ha03-002	randomized, double-blind, multicenter, vehicle-controlled, parallel-group	163 enrolled and included in safety population 158 completed trial[3]	162 enrolled 161 included in safety population[4] 160 completed trial[5]
Total		350 enrolled 349 incl in safety population 341 completed trial	354 enrolled 350 incl in safety population 345 completed trial

Source: Applicant's submission; Ha03-001 and Ha03-002 CSR
[1] 4 subjects from this group were lost to follow-up.
[2] 7 subjects from this group withdrew consent
[3] 5 subjects from this group were lost to follow-up.
[4] 1 subject did not return for Day 1 evaluation
[5] A total of 2 subjects from this group were lost to follow-up

Table 43: Safety Population of Pivotal Trials Stratified by Subject Age

	Trial Ha03-001		Trial Ha03-002	
Age Group	**Xeglyze (n=)**	**Vehicle (n=)**	**Xeglyze (n=)**	**Vehicle (n=)**
6 months to < 2 years	4	3	3	5
2 years to < 4 years	9	13	6	11
4 years to < 12 years	84	87	81	86
12 to < 18 years	28	30	29	23
>= 18 years	61	55	44	37
Total	186	188	163	162

Source: Applicant's submission; Summary of Clinical Efficacy, Table 18

Phase 2 trials

In addition to the Phase 3 data, the applicant also submitted data from 4 Phase 2 trials (2 dose-ranging studies, a Pediatric PK trial, and a Pediatric Maximal use trial) also included the to-be-marketed concentration of the Xeglyze, and therefore will be included in the analysis of safety. Unlike the Pivotal trials, the study product in these studies was administered in a clinic setting by trial staff.

Trial Ha02-003 was a Phase 2b trial conducted in 2 centers in the US. The trial was a randomized, double-blind, vehicle-controlled, and single dose trial. Investigators enrolled 142 pediatric and adult subjects with head lice infestation. These were randomized to 3 groups, to be treated for 10 minutes with Xeglyze 0.37%, Xeglyze 0.74%, or Vehicle. A total of 49 subjects were treated with the to-be-marketed strength of Xeglyze 0.74%; 35 of these were pediatric subjects between 2 and 18 years of age. Trial staff administered the treatments in a clinic setting. A total of 8 subjects did not complete the trial; 4 subjects in the Xeglyze 0.37% group were lost to follow-up, 1 subject in the Xeglyze group was lost to follow-up and 3 subjects from the Vehicle group discontinued. The reasons given for the 3 who did not complete the trial from the control group were "subject decision" (2), and "non-compliance with trial drug" (1). Table 44 displays the treatment groups in Ha02-003, stratified by age group.

Table 44: Summary of Exposure in Trial Ha02-003, Subjects with Head Lice Infestation; Treatment Applied by Trial Staff in Clinic Setting

Trial	Trial Design	Subject age	Exposure Subgroups (10 minute application)		
			Xeglyze 0.37% (n=)	**Xeglyze 0.74% (n=)**	**Vehicle (n=)**
Ha02-003	Randomized, Double Blind, Vehicle, Parallel (dose ranging)	2-5 years	7	5	8
		6-12 years	25	24	17
		13-17 years	6	6	5
		18+ years	8	14	17
		Total	46	49	47

Source: Applicant's submission; Table 7, Ha02-003 CSR

Trial Ha02-002 was a randomized, double-blind, vehicle-controlled trial with 30 adult subjects with head lice infestation. This trial was conducted in India at a single center. 10 subjects were treated with Xeglyze 0.37% for 10 minutes, 10 were treated with Xeglyze for 20 minutes, and the remaining 10 were treated with vehicle control (5 for 10 minutes and 5 for 20 minutes). All subjects completed the trial.

Table 45 displays the treatment groups in Trial Ha02-002.

Table 45: Summary of Exposure in Trial Ha02-002, Subjects with Head Lice Infestation; Treatment Applied by Trial Staff in Clinic Setting

Trial	Trial Design	Subject age	Exposure Subgroups					
			Xeglyze 0.37% (n=)		Xeglyze 0.74% (n=)		Vehicle (n=)	
Ha02-002	Randomized, Double Blind, Vehicle (dose ranging)	Adults	10 min	20 min	10 min	20 min	10 min	20 min
			10	N/A	N/A	10	5	5

Source: Applicant's submission; Table 14.1.1, Ha02-002 Trial Report

Trial Ha03-003 was performed in 2 centers in the US and enrolled 22 pediatric subjects ages 6 months to <18 years of age with head lice infestation. All subjects were treated with a single 10 minute application of Xeglyze, and all subjects completed the trial. **Trial Ha03-004** was conducted in 3 centers in the US, and enrolled 38 pediatric subjects age 6 months to 17 years. As in Ha03-003, subjects were also treated with a single 10 minute application of Xeglyze, but in Ha03-004 this was under maximal use conditions. Maximal use was defined as a single application of one whole container (~200 mL) of Xeglyze to each subject where feasible. Otherwise, the maximum feasible volume was applied ensuring that there was complete saturation of the scalp and hair. The amount of product applied to each subject was recorded. All 38 subjects completed the trial. Details of these 2 trials, along with stratification of subjects by age, are located in Table 46.

Table 46: Summary of Exposure in Pediatric PK Trials: Product Applied by Trial Staff in Clinic Setting.

Trial	Trial Design	Subject Age	Xeglyze, 10 min application (n=)
Ha03-003	Open label (Pediatric PK)	< 12 months	1
		1 to <2 years	3
		2 to <3 years	6
		3 to <18 Years	12
Ha03-004	Open label, Maximal Use	6 to <12 months	8
		1 to <2 years	9
		2 to <3 years	11
		3 to 17 years	10

Source: Applicant's submission; Table 9, Ha03-003 CSR; Section 11.2.1, Ha03-004 CSR

Additionally, the applicant submitted data from a dermal sensitization trial with 238 healthy adult subjects and a dermal irritation trial with 40 healthy adult subjects.

8.2.2. Relevant characteristics of the safety population

Demographically the Phase 3 safety population, treated with Xeglyze, is predominantly female (298/349; 85.4%) and White (334/349; 95.7%). When compared to the US population, African-Americans, Asians, and male gender are relatively underrepresented. In contrast, Hispanic ethnicity is overrepresented. However, the over-representation of females, Hispanics, and Whites in the Phase 3 safety population is unlikely to affect the applicability of the safety data to the target population. Despite this demographic skew, the safety population bears some similarities to the target population. As previously discussed in Section2.1, head lice infestation is more common in females than males, and head lice infestation is less common in African-Americans.

As was also discussed earlier, head lice infestation most commonly occurs in children 3 to 11 years of age. A total of 187 (187/349; 53.6%) of the Phase 3 safety population, treated with Xeglyze, was 11 years of age or younger. The number of subjects in this age group is sufficient to characterize the safety profile of Xeglyze in this age group. Table 47 displays the demographic characteristics of the Phase 3 safety population.

Table 47: Demographic characteristics of the Phase 3 Safety Population

Demographic Parameters	Ha03-001		Ha03-002		
	Xeglyze (N=186) n (%)	Vehicle (N=188) n (%)	Xeglyze (N=163) n (%)	Vehicle (N=162) n (%)	
Sex					
Male	26 (13.9)	32 (17.0)	25 (15.3)	32 (19.8)	
Female	160 (86.0)	156 (83.3)	138 (84.7)	130 (80.2)	
Age					
Mean years (SD)	15.8	16.0	16.2	14.0	
Min, max (years)	0.5, 56	1.2, 61	1.6, 60	1.1, 57	
Age Group					
6 months to <4 years	13 (7.0)	16 (8.5)	9 (5.5)	16 (9.9)	
4 to <12 years	84 (45.2)	87 (46.3)	81 (49.7)	86 (53.1)	
12 to <18 years	28 (15.1)	30 (16.0)	29 (17.8)	23 (14.2)	
18 years and older	61 (32.8)	55 (29.3)	44 (27.0)	37 (22.8)	
Race					**U.S. Population[2]**
White	180 (96.8)	187 (99.5)	154 (94.5)	159 (98.2)	77.4%
Black or African American	4 (2.1)	1 (0.5)	0 (0.0)	2 (1.2)	13.2%
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5.4%
American Indian or Alaska Native	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)	1.2%
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0.2%
Other[1]	2 (1.1)	0 (0.0)	6 (3.7)	0 (0.0)	2.5%
Ethnicity					
Hispanic or Latino	141 (75.8)	158 (84.0)	89 (54.6)	74 (45.7)	17.4%
Not Hispanic or Latino	45 (24.2)	30 (16.0)	74 (45.4)	87 (53.7)	
Region					
United States	186 (100)	188 (100)	163 (100)	162 (100)	

Source: Reviewer's Table; Data from JReview analysis of Applicant datasets.
[1] reflects biracial or multiracial background; [2] from census.gov, data as of July 1, 2014

8.2.3. Adequacy of the safety database

The primary safety database is taken from the 2 Phase 3 studies. A total of 699 subjects comprise the safety population; 349 of these subjects were treated with Xeglyze for 10 minutes, and 350 were treated with Vehicle. Of the 699 total subjects, 495 were pediatric subjects (age 6 months to <18 years). A total of 239 pediatric subjects were treated with Xeglyze, and 256 with Vehicle lotion. The Phase 3 population is most appropriate for the primary analysis of safety because this population had the study product administered at home by the patient or caregiver, thus reflecting more closely conditions of actual use.

Supportive safety data were also obtained from Trials Ha02-003, Ha03-003, and Ha03-004. While these data reflect the to-be-marketed strength of Xeglyze and the proposed duration of treatment, the study product was administered by trial staff in a clinic setting. Therefore, exposures in these trials may not accurately reflect conditions of actual use. Tables 14 and 16 display the numbers of subjects and treatment received stratified by age where appropriate.

The safety database is adequate to characterize the safety profile of Xeglyze for the treatment of head lice infestation in patients 6 months of age and older.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data and the overall submission are adequate to characterize the safety and efficacy of Xeglyze. Data quality and fitness were evaluated in conjunction with the JumpStart team. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

8.3.2. Categorization of Adverse Events

The applicant defined an adverse event (AE) as any untoward medical occurrence in a subject participating in a clinical study. Specifically, an AE was any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study product, whether or not related to the study product. A pre-treatment AE or pre-existing medical condition that worsened in intensity after administration of study product was considered an AE. AEs were coded using Medical Dictionary for Regulatory Activities Version 16.1 (MedDRA) terminology. The coding of adverse events in the NDA submission appeared adequate and allowed for accurate estimation of adverse event risks.

Treatment-Emergent Adverse events (TEAE) were defined as AEs that began or worsened on or after administration of study product. TEAEs were summarized by system organ class (SOC) and preferred term per treatment group. The number and percentage of subjects with TEAEs and the number of TEAEs were summarized. Subjects who experienced the same AE (MedDRA preferred term) more than once were only counted once for that event. In addition, separate summaries were produced for TEAEs by severity, by relationship to study product and for Serious Adverse Events (SAE).

A Serious Adverse Event (SAE) was any untoward medical occurrence that at any dose:

- Resulted in death;

- Was life-threatening (i.e., an immediate risk of death);
- Required in-patient hospitalization or prolongation of existing hospitalization;
- Resulted in persistent or significant disability/incapacity;
- Was associated with a congenital anomaly/birth defect, or
- Was an important medical event that may not have resulted in death, may not have been life-threatening, or did not require hospitalization but may have been considered serious when, based upon appropriate medical judgment, may have jeopardized the subject's safety or may have required medical or surgical intervention to prevent any of the outcomes listed above.

SAEs also included any other event that the investigator or Sponsor judged to be serious or which was defined as serious by the regulatory agency. The definitions of TEAE and SAE used by the applicant are appropriate.

AEs and SAEs were recorded and reported from the time of study product application on Day 0 to study completion (Day 14) for all subjects who received at least 1 dose of the study product. This time period exceeds 5 times the half-life of Xeglyze and is therefore adequate.

Each subject was monitored regularly by the investigators for AEs or SAEs occurring throughout the study. The investigator enquired about any AEs by asking non-leading questions of the subjects or the caregivers of subjects too young to speak for themselves. All AEs or SAEs documented at a previous visit/contact that were designated as ongoing and were reviewed at subsequent visits/contacts. All AEs or SAEs were followed until resolution, until the condition stabilized, the event was otherwise explained, or the subject was lost to follow-up.

The investigator made an assessment of intensity for each AE and SAE reported during the study. The assessment was based on the investigator's clinical judgment. The severity of each AE and SAE was recorded on the eCRF and was assigned to one of the following categories:

- Mild: The subject was aware of the AE, but was still able to do all activities; no or minimal medical intervention/therapy required.
- Moderate: The subject had to discontinue some activities due to the AE; no or minimal medical intervention/therapy required.
- Severe: The subject was incapacitated by the AE and unable to perform normal activities; significant medical intervention/therapy required; hospitalization possible.

Severity was a category utilized for rating the intensity of an event; and both AEs and SAEs could be assessed as severe. An event was defined as "serious" when it met one of the pre-defined outcomes defined above.

The investigator made an assessment of the relationship between study product and the occurrence of each AE or SAE. The investigator used their clinical judgment and took into account possible alternative causes, such as natural history of any underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study product. Investigators assessed the causal relationship of the AE to the study product using the following classifications:

- Not Related: Onset of the AE had no reasonable temporal relationship to administration of the study product, a causal relationship to administration of the study product was biologically implausible, or the event was attributed to an alternative etiology.
- Unlikely: Onset of the AE had a reasonable temporal relationship to study product administration and although a causal relationship was unlikely, it was biologically plausible.
- Possible: Onset of the AE had a strong temporal relationship to administration of the study product, could not be explained by the subject's clinical state or other factors, and a causal relationship was biologically plausible.
- Probable: Onset of the AE showed a distinct temporal relationship to administration of the study product that could not be explained by the subject's clinical state or other factors, or the AE occurred on re-challenge, or the AE was a known reaction to the study product, or could be predicted by the product's pharmacology.

Investigators categorized AEs assessed as unrelated or unlikely as not related to study product. Investigators categorized AEs assessed as possible or probable as related to study product.

The definition of AE, TEAE, and SAE are acceptable. The classification system used by investigators to describe the severity of AE as well as the causal relationship between AE and study product are also acceptable.

8.3.3. Routine Clinical Tests

Safety assessments performed during the 2 Phase 3 trials included vital signs, physical examination, active assessment of local irritation (eyes and scalp), laboratory evaluation (chemistry and hematology testing), and recording of all AE. The 3 Phase 2 trials under consideration also monitored for renal toxicity with urinalysis; 2 of these trials also included ECG monitoring. The safety assessments conducted in these trials are shown in Table 48.

Table 48: Safety Assessments Performed in Phase 3 and Selected Phase 2 trials

Trial	Clinical Chemistry	Hematology	Urinalysis	ECG	Vital Signs	Physical Exam	Scalp and Eye Irritation	AE's
Ha03-001	X	X			X	X	X	X
Ha03-002	X	X			X	X	X	X
Ha02-003	X	X	X	X	X	X	X	X
Ha03-003	X	X	X	X	X	X	X	X
Ha03-004	X	X	X		X	X	X	X

Source: Applicant's submission; Table 2, Summary of Clinical Safety

Phase 3 Trials Ha03-001 and Ha03-002

Safety assessments during the 2 pivotal Phase 3 trials included assessment of vital signs, physical examination, active assessment of local safety (evaluation of eyes and scalp), laboratory evaluation (chemistry and hematology testing), and recording of all AE. Pregnancy testing, urinalysis, and ECG were not performed during the Phase 3 trials. The procedures that were performed were defined as follows:

Vital Signs

Assessment of vital signs was performed at every visit (Days 0, 1, 7, and 14) and included heart rate, blood pressure, and body temperature. Whenever possible, vital signs were measured in the seated position after the subject had rested for at least 5 minutes.

Physical Examination

A full physical examination was performed on Day 0 and Day 14, and included the following: evaluation of general appearance, skin, head (including face, neck, scalp, eyes, and ears), nose, mouth, throat, respiratory system, central and peripheral nervous system, cardiovascular system, gastrointestinal system, musculoskeletal system, skin, and lymph node palpation (head, neck, axillary, and inguinal). A brief physical examination was performed on Day 1 and Day 7, and included the following: evaluation of general appearance, skin, head (including face, neck, scalp, eyes, and ears), respiratory system, and cardiovascular system. Any physical condition changes since the previous visit were reported as an AE.

If clinically indicated, a symptom-focused examination could be performed at any other visit. All examinations were to be performed by a physician, physician's assistant (PA) or nurse practitioner (NP) and were to be performed by the same examiner each time whenever possible.

Local Safety Assessment: Scalp and Eye Irritation

At every trial visit (Days 0, 1, 7, and 14), scalp and eye assessments were performed to evaluate the severity of irritation on a 0-3 scale. The assessments were to be performed by a physician, PA or NP and were to be performed by the same evaluator each time whenever possible. Any increase in the severity score of scalp and eye assessments from baseline were reported as an AE.

The scalp was examined for erythema, excoriation, edema, and pyoderma. The scalp assessment included the skin of the ears, forehead, and posterior neck. Subjects or caregivers were queried regarding the presence of pruritus. Scalp irritation was scored as indicated in Table 49.

Table 49: Scalp Irritation Scores

Score	Definition
Erythema and Edema Scores	
0	No evidence of irritation or swelling.
1	Mild erythema and/or edema.
2	Moderate erythema with marked edema (area raised approximately 1 mm).
3	Severe erythema with edema and blistering.
Pruritus Scores	
0	There was no evidence of itching/scratching.
1	Some episodes of itching/scratching, slightly bothersome.
2	Frequent episodes of itching/scratching, several times a day, bothersome.
3	Nearly constant, frequent itching/scratching, very bothersome.
Excoriation and Pyoderma Scores	
0	No broken scalp and/or lesions.
1	Mild evidence of broken scalp and/or lesions (1 or 2 areas on the scalp).
2	Moderate to severe evidence of broken scalp and/or lesions (involving more 2 areas of broken skin or 2 lesions on scalp).
3	Severe intense evidence of broken scalp and/or lesions with crusting or infection.

Source: Applicant's submission; Ha03-001 CSR, Table 4, P. 25

The eyes (lids, sclera, and conjunctiva) were examined for irritation. Eye irritation was scored as indicated in Table 50.

Table 50: Eye Irritation Scores

Score	Definition
0	No irritation.
1	Mild scleral, lid and/or conjunctiva injection.
2	Moderate scleral and/or lid injection with conjunctival erythema.
3	Severe scleral and/or lid injection with conjunctival erythema and purulent drainage.

Source: Applicant's submission; Ha03-001 CSR, Table 5, P. 25

Assessments of Systemic Safety: Laboratory Testing

The clinical laboratory tests performed to assess systemic safety included monitoring of hematology and blood chemistries. These were performed on Day 0 and 14. Specific details are presented in Table 51. The investigator reviewed the laboratory test results and documented whether any abnormal results were clinically significant. Clinically significant abnormal laboratory results were to be reported as AEs.

Table 51: Clinical Laboratory Tests

Test	Parameters
Hematology	Hemoglobin, hematocrit, red blood cell count, mean cell volume, white blood cell count with differential, and platelet count.
Biochemistry	Sodium, potassium, bicarbonate, chloride, calcium, phosphate, blood urea nitrogen, creatinine, glucose, aspartate transaminase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase, total bilirubin, total protein, and albumin.

Source: Applicant's submission; Ha03-001 CSR, Table 6

The assessments performed during the 2 pivotal Phase 3 trials are adequate to assess the safety of Xeglyze for the topical treatment of head lice infestation in patients 6 months of age and older.

Phase 2 trials Ha02-003, Ha03-003, and Ha03-004

These 3 Phase 2 trials included subjects with head lice infestation who were treated with the Xeglyze at the to-be-marketed strength and duration of treatment. As such, data from these subjects will also be considered during the evaluation of safety. Like the pivotal trials, vital signs and local safety (eye and scalp irritation) were assessed at all visits. Key differences in the safety assessments performed during these trials are described below:

Ha02-003

Physical Examination

The schedule of physical examinations was slightly different from the pivotal trials; in this trial, a physical exam assessing the major body systems was performed on day 0 and 14. If clinically indicated, a symptom-focused examination could be performed at any other visit also.

Assessments of Systemic Safety: Laboratory Testing

As with the pivotal trials, chemistry and hematology testing was done on days 0 and 14; during this trial, they were performed on day 7 also. In this Phase 2 trial, PK parameters were drawn on day 0, and benzyl alcohol levels on day 1. Urinalysis was performed on day 0, 1, and 7. Urine pregnancy tests were performed at Screening and Day 14.

Cardiac Safety Monitoring

ECGs were obtained at the Screening/treatment visit and Day 1 (24 hours post-dose) follow-up visit. The ECG recordings were then sent to a central laboratory for final interpretation and reporting.

Ha03-003

Physical Examination

The schedule of physical exams for this trial was identical to that of the Phase 3 trials. A complete physical exam was performed on day 0 and 14, with a brief exam to assess interval change on day 1 and 7.

Assessments of Systemic Safety: Laboratory Testing

The schedule for hematology and blood chemistry monitoring for this trial was the same as the Phase 3 studies. Like the previous Phase 2 trial, urinalysis was also performed; however, in this trial urinalysis was obtained only on day 0 and 14. PK analyses of the Xeglyze and its metabolites in plasma and benzyl alcohol in serum were also performed on trial day 0. Pregnancy testing was not performed during this pediatric trial.

Cardiac Safety Monitoring

Trial Ha03-003 also included ECG monitoring, although on a slightly different schedule than Ha02-003. All ECG parameters, including heart rate (HR), QT interval, QTcB interval, QTcF

interval, QRS duration, PR interval and RR interval were summarized by descriptive statistics at screening (Day 0 pre-dose, 45 min and 7.5 hr post-dose) and Days 1, 7 and 14.

Subjects' overall assessments (normal or abnormal) were determined based on subject's QTc (QTcB or QTcF) values (average of three triplicate readings); if either of the average values of QTcB or QTcF > 450 msec they were considered abnormal.

Ha03-004

Physical Examination

The schedule of physical examinations was similar to that of trial Ha02-003. Physical examinations were performed at the Screening/treatment visit and on the Day 14 follow-up visit. Clinically significant abnormal findings at follow-up were reported as AEs.

Laboratory Safety Tests

The schedule for monitoring of hematology, blood chemistry, and urinalysis was the same as Trial Ha03-003, with testing on day 0 and 14. Urine pregnancy tests were performed in female subjects of childbearing potential for screening eligibility at Day 0 and Day 14. PK sampling was also done on trial day 0.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred during the development program for this drug.

8.4.2. Serious Adverse Events

During the development program for Xeglyze, there were 2 serious adverse events (SAE), both of which were nonfatal. One SAE occurred during Trial Ha03-001 (a Phase 3 trial), the other during Trial Ha03-006 (Phase 1, dermal sensitization trial). In both cases, the investigator determined that the events were not related to the Xeglyze.

In Trial Ha03-001, investigators reported that one subject (number (b) (6) received treatment with Vehicle), with a history of chronic kidney disease (CKD) experienced "renal impairment and was hospitalized for permanent placement of a dialysis catheter and renal dialysis." (from case narrative) The full medical history included type 1 diabetes (since 11 years of age), Stage 5 chronic kidney disease, anemia of CKD, diabetic gastroparesis with chronic vomiting, chronic pruritus, diabetic polyneuropathy and retinopathy, secondary

hyperparathyroidism, uncontrolled hyperphosphatemia, abdominal wall abscess and necrotizing fasciitis with multiple debridement and xenograft surgeries, wound infection (staphylococcal), and renal cancer (unconfirmed by physician). The investigator recorded this event as severe but not related to Xeglyze. No action was taken with the trial medication or trial conduct and the outcome of the event was recorded as recovered. In the opinion of the Medical Monitor, the subject was not in good general health at Screening and should have been deemed ineligible for trial participation (failure to meet inclusion criteria #2). I agree with the investigator that this event is unlikely to be related to treatment with Vehicle.

In Trial Ha03-006, a 23 year old female subject (subject (b) (6)) with a history of spontaneous abortions (2 of 3 pregnancies with 1 live birth) experienced a miscarriage. The subject reported a history of asthma but denied use of any concomitant medications. Neither respiratory complaints nor abnormal physical findings consistent with asthma were noted on her CRF. A pregnancy test administered at Screening was negative. The date of the subject's last menstrual period was not recorded in the narrative or CRF. This subject received 6th of 9 planned applications of test products on Day 15 before she was discontinued from the trial on Day 17 due to a positive pregnancy test. The subject experienced a miscarriage on Day 28, which was disclosed to trial staff 5 days later. The investigator judged the event of spontaneous abortion as severe in intensity and not related to Xeglyze. In the U.S. general population, the estimated background risk of miscarriage in clinically recognized pregnancies is 15-20%. I agree with the investigator that this event is unlikely to be related to study products applied during this dermal sensitization trial.

8.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

No subjects discontinued due to an AE in any of the Phase 3 or Phase 2 studies.

During the development program for Xeglyze, a total of 2 subjects discontinued due to an AE. Both cases occurred during Phase 1 trials. During Trial Ha02-005, a thorough QT study, 1 subject withdrew from the trial due to headache secondary to a sinus infection (treatment group ABC, Subject (b) (6)). This 25 year old Caucasian male subject received 2 of the 3 planned treatments. Treatment 1 was Xeglyze x 60 minutes to scalp and back plus Moxifloxacin placebo; Treatment 2 was Vehicle x 60 minutes to scalp and back plus Moxifloxacin placebo. On Day 6 after Treatment 2, the subject reported headache and sore throat, followed by fever and sinus congestion the following day. While the fever and sore throat resolved after 1 day, the headache and sinus congestion resolved after 9 and 10 days, respectively. The investigator determined these events were mild in severity and either not or unlikely related to Xeglyze. However, the investigator did not dose the subject for the third treatment period, and withdrew the subject due to headache presumed secondary to a sinus infection. Based on the most recent treatment received as well as the timing of the AE, I concur with the conclusion of the investigator and Applicant that the AE is not related to Xeglyze.

In Trial Ha03-006, 1 subject was discontinued from the trial due to an epididymal cyst on his left testicle on (b) (6) (Subject (b) (6)). This subject received Xeglyze between (b) (6) during the induction phase in this dermal sensitization trial. According to the CRF for this subject, the subject presented to the ER on (b) (6) with a complaint of hematuria and was initially (per his report) diagnosed with prostate cancer. A 51 year old Caucasian male, the subject underwent surgical removal of the cyst on (b) (6) no cancerous cells were detected. The investigator judged the event to be serious and not related to the Xeglyze. I agree with the investigator that this event is unlikely to be related to study products applied during this dermal sensitization trial.

8.4.4. Significant Adverse Events

Two serious adverse events (AE) occurred during the drug development program for Xeglyze; these are discussed in section 8.4.2. Two subjects discontinued due to adverse events; these are discussed in section 8.4.3. All of these AE were unrelated to treatment with Xeglyze. Aside from these, there were no other significant AE during the development program for Xeglyze.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Evaluation of Local Safety: Pooled Data from Phase 3 Trials

Active local safety assessments for erythema/edema, pruritus, excoriation/pyoderma, and eye irritation were performed and scored by Investigators at the Baseline visit, then on Day 1, 7, and 14. Investigators scored the assessments based on the scales below:

Table 52: Scalp Irritation Scoring System during Phase 3 Trials

Score	Definition
Erythema and Edema Scores	
0	No evidence of irritation or swelling.
1	Mild erythema and/or edema.
2	Moderate erythema with marked edema (area raised approximately 1 mm).
3	Severe erythema with edema and blistering.
Pruritus Scores	
0	There was no evidence of itching/scratching.
1	Some episodes of itching/scratching, slightly bothersome.
2	Frequent episodes of itching/scratching, several times a day, bothersome.
3	Nearly constant, frequent itching/scratching, very bothersome.
Excoriation and Pyoderma Scores	
0	No broken scalp and/or lesions.
1	Mild evidence of broken scalp and/or lesions (1 or 2 areas on the scalp).
2	Moderate to severe evidence of broken scalp and/or lesions (involving more 2 areas of broken skin or 2 lesions on scalp).
3	Severe intense evidence of broken scalp and/or lesions with crusting or infection.

Source: Applicant's submission: Ha03-001 CSR, Table 4

Table 53: Eye Irritation Scoring system during Phase 3 Trials

Score	Definition
0	No irritation.
1	Mild scleral, lid and/or conjunctiva injection.
2	Moderate scleral and/or lid injection with conjunctival erythema.
3	Severe scleral and/or lid injection with conjunctival erythema and purulent drainage.

Source: Applicant's submission; Ha03-001 CSR, Table 5,

Results of local safety evaluation are summarized in the following sections. The results of the Day 1 assessment will be particularly important to the evaluation of local safety because local reactions are most likely to manifest by this time.

Evaluation of Local Safety: Scalp Erythema and Edema

A total of 349 subjects comprised the Xeglyze treatment group. At the Baseline visit, 338 (338/349; 96.8%) had no erythema/edema, and 11 (11/349; 3.2%) had scalp erythema/edema.

On Day 1, of the 338 with no erythema/ edema at baseline, 327 (327/338; 96.7%) still had no erythema/edema; 11 (11/338; 3.3%) had developed mild edema/erythema. On Day 7, 327 (327/338; 96.7%) still had no erythema/edema and 3 (3/338; 0.9%) had mild erythema/edema; 8 (8/338; 2.4%) subjects who had no erythema/edema at baseline did not return for evaluation on day 7 and 14 and were lost to follow up. On Day 14, 329 (329/338; 97.3%) had no erythema/edema while 1 (1/338; 0.3%) subject had mild erythema/edema.

Eleven (11/349; 3.2%) subjects treated with Xeglyze had erythema/edema at Baseline visit. Ten (10/349; 2.9%) of these were mild; these were resolved at Day 7 and 14. The 1 (1/349; 0.3%) subject with moderate erythema/edema at baseline showed no change and moderate erythema/edema persisted on Days 1, 7, and 14. No subject had severe erythema/edema at any timepoint during the Phase 3 trials.

An integrated analysis of scalp assessment shifts from baseline for the Xeglyze group in the Phase 3 population is provided in Table 54.

Table 54: **Summary of Scalp Erythema/Edema Shifts from Baseline, Pooled Phase 3 Data, Xeglyze group (N=349)**

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	327/338 (96.7%)	11/338 (3.3%)	0	0	0	338/349 (96.8%)
	1	4/10 (40%)	6/10 (60%)	0	0	0	10/349 (2.9%)
	2	0	0	1/1 (100%)	0	0	1/349 (0.3%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	331/349	17/349	1/349 (0.3%)	0	0	349 (100%)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
		(94.8%)	(4.9%)				
Day 7	0	327/338 (96.7%)	3/338 (0.9%)	0	0	8/338 (2.4%)	338/349 (96.8%)
	1	10/10 (100%)	0	0	0	0	10/349 (2.9%)
	2	0	0	1/1 (100%)	0	0	1/349 (0.3%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	337/349 (96.6%)	3/349 (0.9%)	1/349 (0.3%)	0	8/349 (2.2%)	349 (100%)
Day 14	0	329/338 (97.3%)	1/338 (0.3%)	0	0	8/338 (2.4%)	338/349 (96.8%)
	1	10/10 (100%)	0	0	0	0	10/349 (2.9%)
	2	0	0	1/1 (100%)	0	0	1/349 (0.3%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	339/349 (97.1%)	1/349 (0.3%)	1/349 (0.3%)	0	8/349 (2.2%)	349 (100%)

Source: Adapted from ISS Table 8, Summary of Clinical Safety

A total of 350 subjects comprised the Vehicle group in the pooled Phase 3 safety population. Three hundred thirty eight (338/350; 96.6%) of these had no erythema/edema at baseline, and 12 (12/350; 3.4%) had erythema/edema which was mild. No subjects treated with Vehicle had moderate or severe erythema/edema at any timepoint during the Phase 3 studies.

On Day 1, of the 338 subjects treated with Vehicle with no erythema/edema at Baseline visit, 332 (332/338; 98.2%) still had no erythema/edema, 5 (5/338; 1.5%) subjects had mild erythema/edema, and 1 (1/338; 0.3%) subject did not return for evaluation. On Day 7, 332 (332/338; 98.2%) continued with no erythema/edema, while 2 (2/338; 0.6%) still had mild erythema/edema. On Day 7, 4 (4/338; 1.2%) subjects did not return and were lost to follow up. On Day 14, 329 (329/338; 97.3%) had no erythema/edema, while 4 (4/338; 1.2 %) had mild erythema/edema. On Day 14, 5 (5/338; 1.5%) subjects did not return and were lost to follow up.

Of the 12 subjects with mild erythema/edema at baseline, 5 (5/12; 1.7%) had no erythema/edema on Day 1; 7 (7/12; 58.3%) continued to have mild erythema/edema. On Day 7, 8 (8/12; 66.7%) had no erythema/edema while 4 (4/12; 33.3%) continued with mild erythema/edema. By Day 14, 9 (9/12; 75%) of these subjects had no erythema/edema, while 3 (3/12; 25%) continued with mild erythema/edema.

An integrated analysis of scalp assessment shifts from baseline for the Vehicle group in the Phase 3 population is provided in Table 55.

Table 55: Summary of Scalp Erythema/Edema Shifts from Baseline, Pooled Phase 3 data, Vehicle Group (N=350)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	332/338 (98.2%)	5/338 (1.5%)	0	0	1/338 (0.3%)	338/350 (96.6%)
	1	5/12 (41.7%)	7/12 (58.3%)	0	0	0	12/350 (3.4%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	337/350 (96.3%)	12/350 (3.4%)	0	0	1/350 (0.3%)	350 (100%)
Day 7	0	332/338 (98.2%)	2/338 (0.6%)	0	0	4/338 (1.2%)	338/350 (96.6%)
	1	8/12 (6.67%)	4/12 (33.3%)	0	0	0	12/350 (3.4%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	340/350 (97.1%)	6/350 (1.7%)	0	0	4/350 (1.1%)	350 (100%)
Day 14	0	329/338 (97.3%)	4/338 (1.1%)	0	0	5/338 (1.5%)	338/350 (96.6%)
	1	9/12 (75%)	3/12 (25%)	0	0	0	12/350 (3.4%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	338/350 (96.6%)	7/350 (2.0%)	0	0	5/350 (1.4%)	350 (100%)

Source: Adapted from ISS Table 8, Summary of Clinical Safety

Scalp Erythema/Edema Assessments by Subject Age Group

Six Months to <2 Years

In the 6 months to <2 years age group, a total of 7 subjects were treated with Xeglyze. Investigators noted no scalp erythema/edema in these subjects at the Baseline visit or any timepoint. Eight subjects in this age group were treated with Vehicle; 1 (1/8; 12.5%) subject

from this group had mild erythema/edema at baseline (score =1) which was resolved completely on Trial Day 1, 7, and 14.

Two to <4 Years

In the 2 years to <4 years age group, 14 subjects were treated with Xeglyze. All had no erythema/edema at the Baseline visit. One (1/14; 7.1%) subjects in this age group had mild erythema/edema on Day 1, which was resolved on Days 7 and 14. Of 23 subjects in this age group treated with Vehicle, 1 (1/23; 4.3%) subject had mild erythema/edema at baseline and on Day 1; this was resolved on Day 7 and 14.

Four to <12 Years

In the 4 to <12 years age group, 166 subjects were treated with Xeglyze. One hundred sixty one (161/166; 97%) of these had no erythema/edema at the Baseline visit; 5 (5/166; 3.0%) had erythema/edema which was mild.

Of the 161 subjects with no erythema/edema at baseline, 155 (155/161; 96.3%) had no erythema/edema on Day 1, while 6 (6/161; 3.7%) had mild erythema/edema. On Day 7, 155 (155/161; 96.3%) had no erythema/edema, 2 (2/161; 1.2%) had mild erythema/edema, and 4 (4/161; 2.5%) did not return for assessment on day 7 and were lost to follow-up. On Day 14, 155 (155/161; 96.3%) continued to show no erythema/edema, while 1 (1/161; 0.6%) had mild erythema/edema; 5 (5/161; 3.1%) did not return for the Day 14 evaluation and were lost to follow up.

Five (5/166; 3%) subjects in the 4 to <12 year age group who were treated with Xeglyze had mild erythema/edema at baseline. On Day 1, 3 (3/5; 60%) still had mild erythema/edema, while 2 (2/5; 40%) had no erythema/edema. Erythema/edema was resolved by day 7 and 14 in all 5 of these subjects. No subjects in this age/treatment group had moderate or severe scalp erythema/edema at any timepoint during the Phase 3 studies.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 4 to <12 years, and treated with Xeglyze, is provided in Table 56.

Table 56: Summary of Scalp Erythema/Edema Shifts from Baseline, Subject ages 4 to <12 years, Pooled Phase 3 data, Xeglyze Group (N=166)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	155/161 (96.3%)	6/161 (3.7%)	0	0	0	161/166 (97.0%)
	1	2/5 (40%)	3/5 (60%)	0	0	0	5/166 (3.0%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	157/166 (94.6%)	9/166 (5.4%)	0	0	0	166 (100%)
Day 7	0	155/161 (96.3%)	2/161 (1.2%)	0	0	4/161 (2.5%)	161/166 (97.0%)
	1	5/5 (100%)	0	0	0	0	5/166 (3.0%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	160/166 (96.4%)	2/166 (1.2%)	0	0	4/166 (2.4%)	166 (100%)
Day 14	0	155/161 (96.3%)	1/161 (0.6%)	0	0	5/161 (3.1%)	161/166 (97.0%)
	1	5/5 (10.0%)	0	0	0	0	5/166 (3.0%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	160/166 (96.4%)	1/166 (0.6%)	0	0	5/166 (3.0%)	166 (100%)

Source: Adapted from ISS Table 9

A total of 172 subjects ages 4 to <12 years were treated with Vehicle. A total of 167 (167/172; 97.1%) of these subjects had no scalp erythema/edema at baseline, while 5 (5/172; 2.9%) had mild erythema/edema.

Of the 167 subjects with no erythema/edema at baseline, 165 (165/167; 98.8%) had no erythema/edema on Day 1, while 2 (2/167; 1.2%) subjects showed mild erythema/edema. On Day 7, 164 (164/167; 98.2%) still had no erythema/edema, 2 (2/167; 1.2%) subjects had mild erythema/edema, and 1 (1/167; 0.6%) did not return for evaluation and was lost to follow up. On Day 14, 162 (162/167; 97%) had no erythema/edema, 3 (3/167; 1.8%) had mild erythema/edema, and 2 (2/167; 1.2%) did not return for evaluation on Day 14.

On Days 1 and 7, of the 5 (5/172; 2.9%) with mild erythema/edema at baseline, 2 (2/5; 40%) still showed mild erythema/edema and 3 (3/5; 60%) showed no erythema/edema. By Day 14, only 1 (1/5; 20%) subject still had mild erythema/edema, while 4 (4/5; 80%) had no

erythema/edema. No subjects in this age/treatment group had moderate or severe scalp erythema/edema at any timepoint during the Phase 3 trials.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 4 to <12 years, and treated with Vehicle, is provided in Table 57.

Table 57: **Summary of Scalp Erythema/Edema Shifts from Baseline, Subject ages 4 to <12 years, Pooled Phase 3 data, Vehicle Group (N=172)**

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	165/167 (98.8%)	2/167 (1.2%)	0	0	0	167/172 (97.1%)
	1	3/5 (60%)	2/5 (40%)	0	0	0	5/172 (2.9%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	168/172 (97.7%)	4/172 (2.3%)	0	0	0	172 (100%)
Day 7	0	164/167 (98.2%)	2/167 (1.2%)	0	0	1/167 (0.6%)	167/172 (97.1%)
	1	3/5 (60%)	2/5 (40%)	0	0	0	5/172 (2.9%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	167/172 (97.1%)	4/172 (2.3%)	0	0	1/172 (0.6%)	172 (100%)
Day 14	0	162/167 (97%)	3/167 (1.8%)	0	0	2/167 (1.2%)	167/172 (97.1%)
	1	4/5 (80%)	1/5 (20%)	0	0	0	5/172 (2.9%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	166/172 (96.5%)	4/172 (2.3%)	0	0	2/172 (1.2%)	172 (100%)

Source: Adapted from ISS Table 9.

Twelve to <18 years

In the 12 to <18 year age group, 57 subjects were treated with Xeglyze. Of these subjects, 54 (54/57; 94.7%) had no erythema/edema at baseline, while 3 (3/57; 5.3%) had erythema/edema which was mild. On Day 1, of those with no erythema/edema at baseline, 52 (52/54; 96.3%) still had no erythema/edema while 2 (2/54; 3.7%) had mild erythema/edema. On Day 7 and 14,

53 (53/54; 98.1%) subjects had no erythema/edema while 1 (1/54; 1.9%) did not return for evaluation and was lost to follow up.

On Day 1, of those subjects who had mild erythema/edema at baseline, 1 (1/3; 33.3%) subject had no erythema/edema, while 2 (2/3; 66.7%) subjects still had mild erythema/edema. All 3 subjects showed no scalp erythema/edema at day 7 or 14. No subjects in this age/treatment group had moderate or severe scalp erythema/edema at any timepoint.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 12 to <18 years, and treated with Xeglyze, is provided in Table 58.

Table 58: Summary of Scalp Erythema/Edema Shifts from Baseline, Subject age 12 to <18 years, Pooled Phase 3 Data, Xeglyze Group (N=57)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	52/54 (96.3%)	2/54 (3.7%)	0	0	0	54/57 (94.7%)
	1	1/3 (33.3%)	2/3 (66.7%)	0	0	0	3/57 (5.3%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	53/57 (93.0%)	4/57 (7.0%)	0	0	0	57 (100%)
Day 7	0	53/54 (98.1%)	0	0	0	1/54 (1.9%)	54/57 (94.7%)
	1	3/3 (100%)	0	0	0	0	3/57 (5.3%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	56/57 (98.2%)	0	0	0	1/57 (1.8%)	57 (100%)
Day 14	0	53/54 (98.1%)	0	0	0	1/54 (1.9%)	54/57 (94.7%)
	1	3/3 (100%)	0	0	0	0	3/57 (5.3%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	56/57 (98.2%)	0	0	0	1/57 (1.8%)	57 (100%)

Source: Adapted from ISS, Table 9

In the 12 to <18 year age group, 53 subjects were treated with Vehicle; none showed scalp erythema/edema at Baseline or Day 1 visits. At Day 7, 52 (52/53; 98.1%) had no

erythema/edema, while 1 (1/53; 1.9%) did not return for evaluation and was lost to follow up. At Day 14, 51 (51/53; 96.2%) subjects had no erythema/edema, while 1 (1/53; 1.9%) subject had mild erythema/edema. 1 (1/53; 1.9%) subject did not return for evaluation on Day 7 or 14 and was lost to follow up. No subjects in this age/treatment group had moderate or severe scalp erythema/edema at any timepoint.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 12 to <18 years, and treated with Vehicle, is provided in Table 59.

Table 59: Summary of Scalp Erythema/Edema Shifts from Baseline, Subject age 12 to <18 years, Pooled Phase 3 Data, Vehicle Group (N=53)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	53/53 (100%)	0	0	0	0	53/53 (100%)
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	53/53 (100%)	0	0	0	0	53/53 (100%)
Day 7	0	52/53 (98.1%)	0	0	0	1/53 (1.9%)	53/53 (100%)
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	52/53 (98.1%)	0	0	0	1/53 (1.9%)	53/53 (100%)
Day 14	0	51/53 (96.2%)	1/53 (1.9%)	0	0	1/53 (1.9%)	53/53 (100%)
	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	51/53 (96.2%)	1/53 (1.9%)	0	0	1/53 (1.9%)	53/53 (100%)

Source: Adapted from ISS Table 9

Eighteen Years and Older

In the group of subjects age 18 years or older, 105 were treated with Xeglyze. One hundred two (102/105; 97.1%) had no erythema/edema; three (3/105; 2.9%) had erythema/edema at

baseline. Of the subjects with no erythema/edema at baseline, on Day 1, 100 (100/102; 98%) had no erythema/edema and 2 (2/102; 2%) had mild erythema/edema. On Day 7, 98 (98/102; 96.1%) had no erythema/edema, and 1 (1/102; 1%) had mild erythema/edema. Three (3/102; 2.9%) subjects did not return for the Day 7 visit. On Day 14, 101 (101/102; 99%) showed no erythema/edema, while 1 (1/102; 1%) subject did not return for evaluation on Day 14.

Of the 3 subjects with erythema/edema at baseline, 2 (2/105; 1.9%) subjects age ≥18 and treated with Xeglyze had mild erythema/edema. On Day 1, 1 (1/2; 50%) still had mild erythema/edema while 1 (1/2; 50%) had no erythema/edema. Neither subject had erythema/edema on Day 7 or 14. The other subject in this group with erythema/edema at baseline (1/105; 1%) had moderate erythema/edema. This subject also had moderate erythema/edema on Days 1, 7, and 14. No subject in this age/treatment group had severe erythema/edema at any timepoint.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, age ≥18 years, and treated with Xeglyze, is provided in Table 60.

Table 60: **Summary of Scalp Erythema/Edema Shifts from Baseline, Subject Age ≥18 years, Xeglyze Group (N=105)**

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	100/102 (98%)	2/102 (2%)	0	0	0	102/105 (97.1%)
	1	1/2 (50%)	1/2 (50%)	0	0	0	2/105 (1.9%)
	2	0	0	1/1 (100%)	0	0	1/105 (1.0%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	101/105 (96.2%)	3/105 (2.9%)	1/105 (0.9%)	0	0	105 (100%)
Day 7	0	98/102 (96.1%)	1/102 (1.0%)	0	0	3/102 (2.9%)	102/105 (97.1%)
	1	2/2 (100%)	0	0	0	0	2/105 (1.9%)
	2	0	0	1/1 (100%)	0	0	1/105 (1.0%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	100/105 (95.2%)	1/105 (0.9%)	1/105 (0.9%)	0	3/105 (2.9%)	105 (100%)
Day 14	0	101/102 (99%)	0	0	0	1/102 (1.0%)	102/105 (97.1%)
	1	2/2 (100%)	0	0	0	0	2/105 (1.9%)
	2	0	0	1/1 (1.0%)	0	0	1/105 (1.0%)
	3	0	0	0	0	0	0

	Missing	0	0	0	0	0	0
	Total	103/105 (98%)	0	1/105 (1%)	0	1/105 (1%)	105 (100%)

Source: Adapted from ISS Table 9

In the group of subjects age 18 years or older, 93 subjects were treated with Vehicle. At Baseline visit, 88 (88/93; 94.6%) had no erythema/edema, and 5 (5/93; 5.4%) had mild erythema/edema. On Day 1, of the subjects with no erythema/edema at baseline, 85 (85/88; 96.6%) had no erythema/edema; 3 (3/88; 3.4%) had mild erythema/edema. On Day 7 and 14, 87 (87/88; 98.9%) had no erythema/edema; one (1/88; 1.1%) subject did not return for evaluation on Day 7 or 14 and was lost to follow up.

On Day 1, of the subjects with mild erythema/edema at baseline, 4 (4/5; 80%) still had mild erythema/edema, while 1 (1/5; 20%) had no erythema/edema. On Day 7 and 14, 2 (2/5; 40%) had mild erythema/edema and 3 (3/5; 60%) had no erythema/edema. No subject in this age/treatment group had moderate or severe erythema/edema at any timepoint.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, age ≥18 years, and treated with Vehicle, is provided in Table 61.

Table 61: Summary of Scalp Erythema/Edema Shifts from Baseline, Subject Age ≥18 yr, Vehicle Group (N=93)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	85/88 (96.6%)	3/88 (3.4%)	0	0	0	88/93 (94.6%)
	1	1/5 (20%)	4/5 (80%)	0	0	0	5/93 (5.4%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	86/93 (92.5%)	7/93 (7.5%)	0	0	0	93 (100%)
Day 7	0	87/88 (98.9%)	0	0	0	1/88 (1.1%)	88/93 (94.6%)
	1	3/5 (60%)	2/5 (40%)	0	0	0	5/93 (5.4%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
	Total	90/93 (96.8%)	2/93 (2.2%)	0	0	1/93 (1.1%)	93 (100%)
Day 14	0	87/88 (98.9%)	0	0	0	1/88 (1.1%)	88/93 (94.6%)
	1	3/5 (60%)	2/5 (40%)	0	0	0	5/93 (5.4%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	90/93 (96.8%)	2/93 (2.1%)	0	0	1/93 (1.1%)	93 (100%)

Source: Adapted from ISS Table 9

In conclusion, post- treatment scalp erythema/edema occurred on Day 1 in 3.3% of subjects treated with Xeglyze, compared to 1.5% in those treated with Vehicle. The erythema/edema was mild in severity, and evenly distributed across different age groups. Additionally, subjects who had scalp erythema at baseline tended to improve after treatment with Xeglyze.

Local Safety Evaluation, Erythema and Edema: Phase 2 Trials

All 4 Phase 2 trials included evaluation of local safety by assessment of the scalp for erythema before and after treatment with Xeglyze or Vehicle. **Trial Ha02-002** was a randomized, double-blind, vehicle controlled dose ranging trial in adults with head lice infestation. Subjects were randomized to treatment with Xeglyze 0.37% for 10 minutes, Xeglyze 0.74% for 20 minutes, Vehicle for 10 minutes, or Vehicle for 20 minutes. Investigators did not note scalp erythema at any timepoint during this trial.

Trial Ha02-003 was a Phase 2 trial in adults and children ≥ 2 years of age with head lice infestation. This trial included 3 treatment groups: Xeglyze 0.37%, Xeglyze 0.74%, and Vehicle control groups. Xeglyze was applied for 10 minutes in each group. Erythema assessments for each group were scored as described in Table 62 and are discussed below.

Forty-six subjects were treated with Xeglyze 0.37%. None had scalp erythema at Screening Visit or at 90 minutes post-dose. Forty-two returned for evaluation on Days 1, 7, and 14. None had scalp erythema on day 1 and 7; on Day 14, 3 (3/42; 7.1%) had faint erythema while 39 (39/42; 92.9%) had no erythema. One of the 3 with faint scalp erythema also had unresolved head lice infestation.

Forty-nine subjects were treated with Xeglyze. Forty-eight of these subjects returned for evaluation on Days 1, 7, and 14. Only 1 (1/48; 2.1%) subject with no scalp erythema at baseline developed erythema subsequently; this subject had well defined erythema, first noted on Day 14. Another subject with mild scalp erythema at baseline still had mild erythema on Day 14.

Head lice infestation was resolved in both of these subjects; however, both had significant pruritus with excoriations during their course. Another 3 (3/49; 6.1%) had mild erythema at baseline; erythema resolved in all of these by Day 1 to Day 7.

Forty-seven subjects were treated with Vehicle. Only 1 (1/47; 2.1%) subject with no erythema at baseline subsequently developed scalp erythema. The erythema was mild in intensity, began at 90 minutes post treatment, and persisted through the Day 7 visit; the subject was lost to follow up after Day 7. Head lice infestation was persistent in this subject through day 7, which likely accounts for this subject's scalp findings. Three (3/47; 6.4%) subjects had mild erythema at baseline; all were resolved by Day 1. One (1/47; 2.1%) had severe erythema with excoriation and crusts; this subject gradually improved during subsequent assessments but still had faint erythema on Day 14.

Table 62: Scalp Erythema Evaluation in Trial Ha02-003

Visit	Severity of Erythema	Xeglyze		Vehicle (N=47)
		0.37% (N=46)	0.74% (N=49)	
Screening-Pre-Dose	N	46	49	47
	NONE	0	45/49 (91.8%)	43/47 (91.5%)
	FAINT	0	4/49 (8.2%)	3/47 (6.4%)
	WELL DEFINED	0	0	0
	INTENSE	0	0	0
	ERYTH w/ INDURATION, CRUSTS, VESICLES*	0	0	1/47 (2.1%)
Ninety minutes Post-Dose	N	46	49	47
	NONE	0	46/49 (93.9%)	44/47 (93.6%)
	FAINT	0	3/49 (6.1%)	3/47 (6.4%)
	WELL DEFINED	0	0	0
	INTENSE	0	0	0
Day 1	N	42	48	47
	NONE	42 (100.0%)	46/48 (95.8%)	45/47 (95.7%)
	FAINT	0	1/48 (2.1%)	2/47 (4.3%)
	WELL DEFINED	0	1/48 (2.1%)	0
	INTENSE	0	0	0
.Day 7	N	42	48	47
	NONE	42 (100.0%)	47/48 (97.9%)	45/47 (95.7%)
	FAINT	0	1/48 (2.1%)	2/47 (4.3%)

Visit	Severity of Erythema	Xeglyze		Vehicle (N=47)
		0.37% (N=46)	0.74% (N=49)	
	WELL DEFINED	0	0	0
	INTENSE	0	0	0
Day 14	N	42	48	44
	NONE	39/42 (92.9%)	46/48 (95.8%)	43/44 (97.7%)
	FAINT	3/42 (7.1%)	1/48(2.1%)	1/44 (2.1%)
	WELL DEFINED	0	1/48 (2.1%)	0
	INTENSE	0	0	0

Source: Applicant's submission;Ha02-003 CSR, Table 14.3.5.1
*Erythema of this severity was not noted in any other subjects or visits; for clarity this row is omitted in the remainder of the table

During **Trial Ha03-003** (a pediatric safety and PK trial in children 6 months to <18 years of age), scalp evaluations were assigned scores from 0 to 4, defined as follows:

- 0 indicated no evidence
- 1 was barely perceptible
- 2 was well defined
- 3 was moderate
- 4 was severe evidence of pruritus, erythema, excoriation, edema, or pyoderma

Inclusion criteria for this trial required subjects to have at least Grade 2 erythema or pruritus with evidence of excoriation or inflammation. Nineteen (19) subjects had scalp erythema and/or edema, or irritation at the Screening visit. At the end of trial (follow-up visit 3), only one subject (02-310) had evidence of scalp erythema. This subject had moderate scalp erythema (score 3) at Screening which was improved to mild scalp erythema (score 2) by the end of the trial. No subject experienced worsening of baseline scalp erythema during this trial.

In **Trial Ha03-004** (a pediatric maximal use trial in children 6 months to 17 years of age), only 1 (1/38; 2.6%) subject with no scalp erythema at baseline subsequently developed scalp erythema. Erythema appeared on Day 1 and was resolved before Day 14. Another subject (1/38, 2.6%) had scalp erythema at Baseline visit and Day 1; this also was resolved before Day 14. Table 63 displays scalp erythema evaluations for Studies Ha03-003 and Ha03-004.

Table 63: Scalp Erythema Assessments in Pediatric PK Trials

Treatment Visit	Ha03-003 (N = 22) Erythema and Edema	Ha03-004 (N = 38) Erythema
Screening/Day 0		
No evidence	3 (13.6%)	37 (97.4%)

Treatment Visit	Ha03-003 (N = 22) Erythema and Edema	Ha03-004 (N = 38) Erythema
Evidence	19 (86.4%)	1 (2.6%)
Day 1		
No evidence	14 (63.6%)	36 (94.7%)
Evidence	8 (36.4%)	2 (5.3%)
Day 14		
No evidence	21 (95.5%)	38 (100%)
Evidence	1 (4.5%)	0

Source: Applicant's submission; Ha03-003 CSR Table 14.3.4.7; Ha03-004 CSR Table 14.3.4.8.

In conclusion, in Trial Ha02-003, only 1 (2.1%) of subjects treated with Xeglyze at the to-be-marketed concentration developed scalp erythema post treatment; however, this did not appear until Day 14 and was associated with excoriation. Because of the excoriations, and the delay in appearance of the erythema, it is likely that scalp erythema in this subject was not the result of treatment with Xeglyze. In Ha03-004 only 1 (1/38; 2.6%) subject developed scalp erythema post treatment. The data from the Phase 2 and PK trials are consistent with the data from Phase 3, with development of post treatment scalp erythema in approximately 3% of subjects. Similarly to the Phase 3 trials, scalp erythema present at baseline also tended to improve and resolve post treatment; this is likely attributable to post-treatment resolution of the head lice infestation.

Evaluation of Local Safety: Scalp Pruritus, Phase 3 Trials

Of the 349 subjects treated with Xeglyze in the Pivotal Phase 3 trials, 147 (147/349; 42.1%) had no scalp pruritus at baseline. On Day 1, 2 (2/147, 1.4%) had developed mild pruritus while 145 (145/147; 98.6%) still had no pruritus. Head lice infestation was resolved in both of these subjects. On Days 7 and 14, only 1 (1/147; 0.7%) had mild pruritus; there were 145 (145/147; 98.6%) and 143 (143/147; 97.3%) subjects with no pruritus on Days 7 and 14 respectively. Subjects from this group lost to follow up included 1 (1/147; 0.7%) at Day 7, and 3 (3/147; 2%) at Day 14.

A majority of subjects in this group (202/349; 57.9%) had scalp pruritus at the Baseline visit. Of these subjects (111/349; 31.8%) had mild, 83 (83/349; 23.8%) had moderate, and 8 (8/349; 2.3%) had severe scalp pruritus. As shown in Table 31, subjects with pruritus at baseline tended to improve, regardless of baseline severity. Outcomes for these subjects, stratified by baseline severity, are summarized below.

On Day 1, of the 111 (111/349; 31.8%) subjects treated with Xeglyze who had mild scalp pruritus at baseline, 92 (92/111; 82.9%) had no pruritus and 19 (19/111; 17.1%) still had mild pruritus. On Day 7, 105 (105/111; 94.6%) had no pruritus, 5 (5/111; 4.5%) still had mild

pruritus, and 1 (1/111; 0.9%) did not return for evaluation on the Day 7 or 14 visit. On Day 14, 104 (104/111; 93.7%) had no pruritus, and 6 (6/111; 5.4%) had mild pruritus.

On Day 1, of the 83 (83/349; 23.8%) subjects treated with Xeglyze who had moderate scalp pruritus at baseline, 51 (51/83; 61.4%) had no pruritus, 31 (31/83; 37.3%) had mild pruritus, and 1 (1/83; 1.2%) continued with moderate pruritus. On Day 7, 73 (73/83; 88%) no pruritus, 4 (4/83; 4.8%) had mild pruritus, 1 (1/83; 1.2%) had moderate pruritus, and 5 (5/83; 6%) did not return for evaluation on Day 7. On Day 14, 77 (77/83; 92.8%) had no pruritus, 2 (2/83; 2.4%) had mild pruritus, and 4 (4/83; 4.8%) did not return for evaluation on Day 14.

On Day 1, Of the 8 (8/349; 2.3%) with severe scalp pruritus at baseline, 2 (2/8; 25%) had no pruritus, 5 (5/8; 62.5%) had mild, and 1 (1/8; 12.5%) had moderate pruritus. On Day 7, 7 (7/8; 87.5%) had no pruritus, while 1 (1/8; 12.5%) subject did not return for the Day 7 visit. On Day 14, all of the 8 subjects treated with Xeglyze with severe scalp pruritus at baseline reported no pruritus.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, treated with Xeglyze, is provided in Table 64.

Table 64: Summary of Scalp Pruritus Shifts from Baseline, Pooled Phase 3 Data, Xeglyze group (N=349)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	145/147 (98.6%)	2/147(1.4%)	0	0	0	147/349 (42.1%)
	1	92/111 (82.9%)	19/111 (17.1%)	0	0	0	111/349 (31.8%)
	2	51/83 (61.4%)	31/83 (37.3%)	1/83 (1.2%)	0	0	83/349 (23.8%)
	3	2/8 (25%)	5/8 (62.5%)	1/8 (12.5%)	0	0	8/349 (2.3%)
	Missing	0	0	0	0	0	0
	Total	290/349 (83.1%)	57/349 (16.3%)	2/349 (0.6%)	0	0	349 (100%)
Day 7	0	145/147 (98.6%)	1/147 (0.7%)	0	0	1/147 (0.7%)	147/349 (42.1%)
	1	105/111 (94.6%)	5/111 (4.5%)	0	0	1/111 (0.9%)	111/349 (31.8%)
	2	73/83 (88%)	4/83 (4.8%)	1/83 (1.2%)	0	5/83 (6%)	83/349 (23.8%)
	3	7/8 (87.5%)	0	0	0	1/8 (12.5%)	8/349 (2.3%)
	Missing	0	0	0	0	0	0
	Total	330/349 (94.6%)	10/349 (2.9%)	1/349 (0.3%)	0	8/349 (2.3%)	349 (100%)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 14	0	143/147 (97.3%)	1/147 (0.7%)	0	0	3/147 (2%)	147/349 (42.1%)
	1	104/111 (93.7%)	6/111 (5.4%)	0	0	1/111 (0.9%)	111/349 (31.8%)
	2	77/83 (92.8%)	2/83 (2.4%)	0	0	4/83 (4.8%)	83/349 (23.8%)
	3	8/8 (100%)	0	0	0	0	8/349 (2.3%)
	Missing	0	0	0	0	0	0
	Total	332/349 (95.1%)	9/349 (2.6%)	0	0	8/349 (2.3%)	349 (100%)

Source: Adapted from ISS Table 8

Of the 350 subjects treated with Vehicle, 136 (136/350; 38.9%) had no pruritus at baseline. On Day 1, of the 136 with no pruritus at baseline, 134 (134/136; 98.5%) still had no pruritus, 1 (1/136; 0.7%) had mild, and 1 (1/136; 0.7%) did not return for evaluation on Day 1. On Day 7, 134 (134/136; 98.5%) had no pruritus, while 2 (2/136; 1.5%) had mild. On Day 14, 130 (130/136; 95.6%) had no pruritus, 5 (5/136; 3.7%) had mild, and 1 (1/136; 0.7%) did not return for evaluation on Day 14.

A majority of subjects in this group (214/350, 61.1%) had scalp pruritus at baseline. Of these subjects, 113 (113/350; 32.3%) had mild, 94 (94/350; 26.9%) had moderate, and 7 (7/350; 2.0%) had severe scalp pruritus. As shown in Table 31, pruritus also tended to improve after treatment in the Vehicle group, but to a lesser extent than in the Xeglyze group. Outcomes for scalp pruritus in the Vehicle group, stratified by baseline severity, are summarized below.

On Day 1, of the 113 (113/350; 32.3%) subjects treated with Vehicle who had mild pruritus at baseline, 93 (93/113; 82.3%) had no pruritus, while 20 (20/93; 17.7%) continued with mild pruritus. On Day 7, 96 (96/113; 85%) had no pruritus, 14 (14/113; 12.4%) had mild pruritus, and 3 (3/113; 2.6%) did not return for evaluation on day 7. On Day 14, 97 (97/113; 85.8%) had no pruritus, 12 (12/113; 10.6%) had mild, 1 (1/113; 0.9%) had moderate pruritus, and 3 (3/113; 2.7%) did not return for evaluation on Day 14.

On Day 1, of the 94 (94/350; 26.9%) subjects treated with Vehicle with moderate pruritus at baseline, 51 (51/94; 54.3%) had no pruritus, 34 (34/94; 36.2%) had mild pruritus, and 9 (9/94; 9.6%) continued with moderate pruritus. On Day 7, 65 (65/94; 69.1%) had no pruritus, 21 (21/94; 22.3%) had mild pruritus, 7 (7/94; 7.4%) had moderate pruritus, and 1 (1/94; 1.1%) did not return for evaluation on day 7. On Day 14, 68 (68/94; 72.3%) had no pruritus, 21 (21/94; 22.3%) had mild, 4 (4/94; 4.3%) had moderate pruritus, and 1 (1/94; 1.1%) did not return for evaluation on Day 14.

On Day 1, of the 7 (7/350; 2.0%) subjects treated with Vehicle with severe scalp pruritus at baseline, 6 (6/7; 85.7%) had no pruritus and 1 (1/7; 14.3%) had moderate pruritus. On Days 7 and 14, 6 (6/7; 85.7%) had no pruritus and 1 (1/7; 14.3%) had mild pruritus.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, treated with Vehicle, is provided in Table 65.

Table 65: Summary of Scalp Pruritus Shifts from Baseline, Pooled Phase 3 Data, Vehicle group (N=350)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	134/136 (98.5%)	1/136 (0.7%)	0	0	1/136 (0.7%)	136/350 (38.9%)
	1	93/113 (82.3%)	20/113 (17.7%)	0	0	0	113/350 (32.3%)
	2	51/94 (54.3%)	34/94 (36.2%)	9/94 (9.6%)	0	0	94/350 (26.9%)
	3	6/7 (85.7%)	0	1/7 (14.3%)	0	0	7/350 (2.0%)
	Missing	0	0	0	0	0	0
	Total	284/350 (81.1%)	55/350 (15.7%)	10/350 (2.9%)	0	1/350 (0.3%)	350 (100%)
Day 7	0	134/136 (98.5%)	2/136 (1.5%)	0	0	0	136/350 (38.9%)
	1	96/113 (85%)	14/113 (12.4%)	0	0	3/113 (2.6%)	113/350 (32.3%)
	2	65/94 (69.1%)	21/94 (22.3%)	7/94 (7.4%)	0	1/94 (1.1%)	94/350 (26.9%)
	3	6/7 (85.7%)	1/7 (14.3%)	0	0	0	7/350 (2.0%)
	Missing	0	0	0	0	0	0
	Total	301/350 (86.0%)	38/350 (10.9%)	7/350 (2.0%)	0	4/350 (1.1%)	350 (100%)
Day 14	0	130/136 (95.6%)	5/136 (3.7%)	0	0	1/136 (0.7%)	136/350 (38.9%)
	1	97/113 (85.8%)	12/113 (10.6%)	1/113 (0.9%)	0	3/113 (2.7%)	113/350 (32.3%)
	2	68/94 (72.3%)	21/94 (22.3%)	4/94 (4.3%)	0	1/94 (1.1%)	94/350 (26.9%)
	3	6/7 (85.7%)	1/7 (14.3%)	0	0	0	7/350 (2.0%)
	Missing	0	0	0	0	0	0
	Total	301/350 (86.0%)	39/350 (11.1%)	5/350 (1.4%)	0	5/350 (1.4%)	350 (100%)

Source: Adapted from ISS Table 8

Scalp Pruritus Assessments by Subject Age Group: Phase 3 Trials

Age 6 months to <2 years

A total of 7 subjects age 6 months to <2 years were treated with Xeglyze in the Phase 3 trials. At baseline, 1 had no pruritus, 2 had mild, and 4 had moderate scalp pruritus. These remained unchanged on Days 1, 7, and 14.

A total of 8 subjects age 6 months to <2 years were treated with Vehicle in the Phase 3 trials. Three (3/8; 37.5%) subjects had no scalp pruritus at any timepoint during these studies, and 5 (5/8, 62.5%) had pruritus at baseline.

Of the 5 subjects in this age/treatment group with scalp pruritus at baseline, 2 (2/8; 25%) had mild pruritus. On Day 1, 1 (1/2; 50%) had no pruritus while 1 still had mild pruritus. Both of these subjects had no scalp pruritus on Days 7 and 14. Three (3/8; 37.5%) subjects had moderate pruritus at baseline. On Days 1, 7, and 14, 1 (1/3; 33.3%) subject had none, 1 had mild, and 1 still had moderate scalp pruritus.

Age 2 to <4 years

In the 2 to <4 year age group, 14 subjects were treated with Xeglyze. Seven (7/14; 50%) of these subjects had no scalp pruritus at any timepoint during these trials, and 7 had pruritus at baseline. Of the 7 subjects with pruritus at baseline, 2 (2/14; 14.2%) had mild, 3 (3/14; 21.4%) subjects had moderate, and 2 (2/14; 14.2%) subjects had severe scalp pruritus at baseline.

Of the 2 (2/14; 14.2%) subjects with mild pruritus at baseline, on Days 1 and 7, 1 (1/2; 50%) had no pruritus, while 1 still had mild. Both resolved with no pruritus on Day 14. Three (3/14; 21.4%) subjects had moderate pruritus at baseline. On Days 1 and 7, 2 (2/3; 66.7%) of these improved to no pruritus, while 1 (1/3; 33.3%) had mild. On Day 14, 2 (2/3; 66.7%) had no pruritus and 1 did not return for evaluation on Day 14. Two (2/14; 14.2%) subjects had severe scalp pruritus at baseline. On Day 1, 1 (1/2; 50%) had no pruritus and 1 had mild; both resolved to no pruritus on Days 7 and 14.

In the 2 to <4 year age group, 24 subjects were treated with Vehicle. At baseline, 13 (13/24; 54.2%) had no pruritus; 11 (11/24; 45.8%) had scalp pruritus at baseline. Of these 11, 6 (6/24; 25%) had mild, 3 (3/24; 12.5%) had moderate, and 2 (2/24; 8.3%) had severe pruritus.

Of the 13 with no pruritus at baseline, on Day 1, 12 (12/13; 92.3%) still had no pruritus, and 1 (1/13; 7.7%) did not return for evaluation on Day 1. All 13 had no scalp pruritus on Days 7 and 14.

Of the 11 subjects with pruritus at baseline, 6 (6/24; 25%) had mild pruritus at baseline. On Day 1, 5 (5/6; 83.3%) improved to no pruritus while 1 (1/6; 16.7%) still had mild pruritus. On Day 7, 4 (4/6; 66.7%) had no pruritus, while 2 (2/6; 33.3%) had mild pruritus. On Day 14, all 6 subjects with mild pruritus at baseline had no scalp pruritus.

Of the 11 subjects with pruritus at baseline, 3 (3/24; 12.5%) subjects had moderate scalp pruritus at baseline. On Day 1, 1 (1/3; 33.3%) subject had none, 1 had mild, and 1 still had moderate pruritus. On Day 7, 1 (1/3; 33.3%) had none, 1 had moderate pruritus, and 1 subject did not return for evaluation on day 7. On Day 14, 1 (1/3; 33.3%) had none, 1 had mild pruritus, and 1 subject did not return for evaluation on Day 14.

Of the 11 subjects with pruritus at baseline, 2 (2/24; 8.3%) subjects in this age/treatment group had severe pruritus at baseline; pruritus was resolved in both by Days 1, 7, and 14.

Age 4 to < 12 Years

In the 4 to < 12 years age group, 166 subjects were treated with Xeglyze in the Phase 3 trials. Of the 166 subjects, 73 (73/166; 44%) had no scalp pruritus at baseline; 93 (93/166; 56%) had scalp pruritus at baseline. Of the 93 with scalp pruritus at baseline, 50 (50/166; 30.1%) had mild, 40 (40/166; 24.1%) subjects had moderate, and 3 (3/166; 1.8%) had severe pruritus.

Of 73 subjects with no pruritus at baseline, on Day 1, 72 (72/73; 98.6%) of these still had no pruritus, and 1 (1/73; 1.4%) had mild pruritus. On Day 7, 71 (71/73; 97.3%) still had no pruritus, 1 (1/73; 1.4%) had mild pruritus, and 1 did not return for evaluation on Day 7. On Day 14, 70 (70/73; 95.9%) had no scalp pruritus, while 3 (3/73; 4.1%) did not return for evaluation.

Of 93 subjects in this age/treatment group with pruritus at baseline, 50 (50/166; 30.1%) had mild pruritus. On Day 1, 42 (42/50; 84%) of these had improved with no pruritus, while 8 (8/50; 16%) still had mild pruritus. On Day 7, 47 (47/50; 94%) had no pruritus, 2 (2/50; 4%) had mild pruritus, and 1 (1/50; 2%) subject did not return for evaluation. On Day 14, 46 (46/50; 92%) had no pruritus, while 4 (4/50; 8%) had moderate pruritus.

Of 93 subjects in this age/treatment group with pruritus at baseline, 40 (40/166; 24.1%) subjects had moderate pruritus at baseline. On Day 1, 25 (25/40; 62.5%) improved to no pruritus, while 15 (15/40; 37.5%) improved to mild. On Day 7, 37 (37/40; 92.5%) had no pruritus, 1 (1/40; 2.5%) had mild, and 2 (2/40; 5%) did not return for evaluation on Day 7. On Day 14, 36 (36/40; 90%) had no scalp pruritus, 2 (2/40; 5%) had mild pruritus and 2 (2/40; 5%) did not return for evaluation on Day 14.

Of 93 subjects in this age/treatment group with pruritus at baseline, 3 (3/166; 1.8%) had severe pruritus at baseline. On Day 1, 1 (1/3; 33.3%) had no pruritus and 2 (2/3; 66%) had mild pruritus. All 3 subjects had no pruritus on Days 7 and 14.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 4 to <12 years, and treated with Xeglyze, is provided in Table 66.

Table 66: Summary of Scalp Pruritus Shifts from Baseline, Pooled Phase 3 Data, Subject Age 4 to <12 Years, Xeglyze group (N=166)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	72/73 (98.6%)	1/73 (1.4%)	0	0	0	73/166 (44.0%)
	1	42/50 (84%)	8/50 (16%)	0	0	0	50/166 (30.1%)
	2	25/40 (62.5%)	15/40 (37.5%)	0	0	0	40/166 (24.1%)
	3	1/3 (33.3%)	2/3 (66.7%)	0	0	0	3/166 (1.8%)
	Missing	0	0	0	0	0	0
	Total	140/166 (84.3%)	26/166 (15.7%)	0	0	0	166 (100%)
Day 7	0	71/73 (97.3%)	1/73 (1.4%)	0	0	1/73 (1.4%)	73/166 (44.0%)
	1	47/50 (94%)	2/50 (4%)	0	0	1/50 (2%)	50/166 (30.1%)
	2	37/40 (92.5%)	1/40 (2.5%)	0	0	2/40 (5%)	40/166 (24.1%)
	3	3/3 (100%)	0	0	0	0	3/166 (1.8%)
	Missing	0	0	0	0	0	0
	Total	158/166 (95.2%)	4/166 (2.4%)	0	0	4/166 (2.4%)	166 (100%)
Day 14	0	70/73 (95.9%)	0	0	0	3/73 (4.1%)	73/166 (44.0%)
	1	46/50 (92%)	4/50 (8%)	0	0	0	50/166 (30.1%)
	2	36/40 (90%)	2/40 (5%)	0	0	2/40 (5%)	40/166 (24.1%)
	3	3/3 (100%)	0	0	0	0	3/166 (1.8%)
	Missing	0	0	0	0	0	0
	Total	155/166 (93.4%)	6/166 (3.6%)	0	0	5/166 (3.0%)	166 (100%)

Source: Adapted from ISS Table 9

The 4 to <12 years age group, treated with Vehicle, contained 172 subjects. Sixty three (63/172; 36.6%) had no pruritus at baseline and 109 (109/172; 63.4%) had scalp pruritus. Of the 109 subjects with scalp pruritus at baseline, 53 (53/172; 30.8%) had mild, 53 (53/172; 30.8%) had moderate, and 3(3/172; 1.7%) had severe pruritus.

Of the 63 with no pruritus at baseline, all 63 still had no pruritus on Day 1. On Day 7, 61 (61/63; 96.8%) still had no pruritus, while 2 (2/63; 3.2%) had mild pruritus. On Day 14, 58 (58/63; 92.1%) had no pruritus, 4 (4/63; 6.3%) had mild pruritus, and 1 (1/63; 1.6%) did not return for evaluation on Day 14.

Of the 109 subjects in this age/treatment group with pruritus at baseline, 53 (53/172; 30.8%) had mild scalp pruritus. On Day 1, 47 (47/53; 88.7%) of these improved to no pruritus, while 6 (6/53; 11.3%) still had mild pruritus. On Day 7, 46 (46/53; 86.8%) had no pruritus, 6 (6/53; 11.3%) had mild pruritus, and 1 (1/53; 1.9%) subject did not return for evaluation. On Day 14, 44 (44/53; 83%) had no pruritus, 8 (8/53; 15.1%) had mild pruritus, and 1 (1/53; 1.9%) subject did not return for evaluation.

Of the 109 subjects in this age/treatment group with pruritus at baseline, 53 (53/172; 30.8%) subjects had moderate scalp pruritus. On Day 1, 32 (32/53; 60.4%) improved to no pruritus, 17 (17/53; 32.1%) improved to mild pruritus, and 4 (4/53; 7.5%) still had moderate pruritus. On Day 7, 38 (38/53; 71.7%) had no pruritus, 13 (13/53; 24.5%) had mild, and 2 (2/53; 3.8%) had moderate pruritus. On Day 14, 39 (39/53; 73.6%) had no pruritus, 11 (11/53; 20.8%) had mild, and 3 (3/53; 5.7%) still had moderate scalp pruritus.

Of the 109 subjects in this age/treatment group with pruritus at baseline, 3 (3/172; 1.7%) had severe pruritus. On Day 1, 2 (2/3; 66.7%) had no pruritus, and 1 (1/3; 33.3%) had moderate pruritus. On Days 7 and 14, 2 (2/3; 66.7%) had no pruritus and 1 (1/3; 33.3%) had mild pruritus.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 4 to <12 years, and treated with Vehicle, is provided in Table 67.

Table 67: Summary of Scalp Pruritus Shifts from Baseline, Pooled Phase 3 Data, Subject Age 4 to <12 Years, Vehicle group (N=172)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	63/63 (100%)	0	0	0	0	63/172 (36.6%)
	1	47/53 (88.7%)	6/53 (11.3%)	0	0	0	53/172 (30.8%)
	2	32/53	17/53	4/53 (7.5%)	0	0	53/172

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
		(60.4%)	(32.1%)				(30.8%)
	3	2/3 (66.7%)	0	1/3 (33.3%)	0	0	3/172 (1.7%)
	Missing	0	0	0	0	0	0
	Total	144/172 (83.7%)	23/172 (13.4%)	5/172 (2.9%)	0	0	172 (100%)
Day 7	0	61/63 (96.8%)	2/63 (3.2%)	0	0	0	63/172 (36.6%)
	1	46/53 (86.8%)	6/53 (11.3%)	0	0	1/53 (1.9%)	53/172 (30.8%)
	2	38/53 (71.7%)	13/53 (24.5%)	2/53 (3.8%)	0	0	53/172 (30.8%)
	3	2/3 (66.7%)	1/3 (33.3%)	0	0	0	3/172 (1.7%)
	Missing	0	0	0	0	0	0
	Total	147/172 (85.5%)	22/172 (12.8%)	2/172 (1.2%)	0	1/172 (0.6%)	172 (100%)
Day 14	0	58/63 (92.1%)	4/63 (6.3%)	0	0	1/63 (1.6%)	63/172 (36.6%)
	1	44/53 (83%)	8/53 (15.1%)	0	0	1/53 (1.9%)	53/172 (30.8%)
	2	39/53 (73.6%)	11/53 (20.8%)	3/53 (5.7%)	0	0	53/172 (30.8%)
	3	2/3 (66.7%)	1/3 (33.3%)	0	0	0	3/172 (1.7%)
	Missing	0	0	0	0	0	0
	Total	143/172 (83.1%)	24/172 (14.0%)	3/172 (1.7%)	0	2/172 (1.2%)	172 (100%)

Source: Adapted from ISS Table 9

Ages 12 to < 18 Years

In the 12 to <18 years age group, 57 subjects were treated with Xeglyze. Of these 57 subjects, 27 (27/57; 47.4%) had no scalp pruritus at baseline, and did not develop pruritus at other timepoint during these studies. Thirty (30/57; 52.6%) had pruritus at baseline; 20 (20/57; 35.1%) had mild, 9 (9/57; 15.8%) had moderate, and 1 (1/57; 1.8%) had severe scalp pruritus.

Of the 30 subjects in this age/treatment group with pruritus at baseline, 20 (20/57; 35.1%) had mild. Of the 20 (20/57; 35.1%) that had mild pruritus at baseline, 15 (15/20; 75%) had no pruritus on Day 1; five (5/20; 25%) of these subjects still had mild pruritus. On Day 7, 19 (19/20; 95%) had no pruritus, while 1 (1/20; 5%) still had mild pruritus. On Day 14, 18 (18/20; 90%) had no pruritus, 1 (1/20; 5%) still had mild pruritus, and 1 (1/20; 5%) did not return for evaluation on Day 14.

Of the 30 subjects in this age/treatment group with pruritus at baseline, 9 (9/57; 15.8%) had moderate pruritus. On Day 1, 4 (4/9; 44.4%) had no pruritus and 5 (5/9; 55.6%) had mild pruritus. All 9 subjects had no scalp pruritus at Days 7 or 14.

Of the 30 subjects in this age/treatment group with pruritus at baseline, 1(1/57; 1.8%) had severe pruritus. This subject had mild pruritus on Day 1 and no pruritus on Day 14. This subject did not present for assessment on Day 7.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 12 to <18 years, and treated with Xeglyze, is provided in Table 68.

Table 68: Summary of Scalp Pruritus Shifts from Baseline, Pooled Phase 3 Data, Subject Age 12 to <18 Years, Xeglyze group (N=57)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	27/27 (100%)	0	0	0	0	27/57 (47.4%)
	1	15/20 (75%)	5/20 (25%)	0	0	0	20/57 (35.1%)
	2	4/9 (44.4%)	5/9 (55.6%)	0	0	0	9/57 (15.8%)
	3	0	1/1 (100%)	0	0	0	1/57 (1.8%)
	Missing	0	0	0	0	0	0
	Total	46/57 (80.7%)	11/57 (19.3%)	0	0	0	57 (100%)
Day 7	0	27/27 (100%)	0	0	0	0	27/57 (47.4%)
	1	19/20 (95%)	1/20 (5%)	0	0	0	20/57 (35.1%)
	2	9/9 (100%)	0	0	0	0	9/57 (15.8%)
	3	0	0	0	0	1/1 (100%)	1/57 (1.8%)
	Missing	0	0	0	0	0	0
	Total	55/57 (96.5%)	1/57 (1.8%)	0	0	1/57 (1.8%)	57 (100%)
Day 14	0	27/27 (100%)	0	0	0	0	27/57 (47.4%)
	1	18/20 (90%)	1/20 (5%)	0	0	1/20 (5%)	20/57 (35.1%)
	2	9/9 (100%)	0	0	0	0	9/57 (15.8%)
	3	1/1 (100%)	0	0	0	0	1/57 (1.8%)
	Missing	0	0	0	0	0	0
	Total	55/57 (96.5%)	1/57 (1.8%)	0	0	1/57 (1.8%)	57 (100%)

Source: Adapted from ISS Table 9

In the 12 to <18 years age group, 53 subjects were treated with Vehicle. Twenty one (21/53; 39.6%) had no pruritus at the Baseline, Day 1, or Day 7 visits. On Day 14, 20 (20/21; 95.2%) had no pruritus, while 1 (1/21; 4.8%) had mild pruritus. At baseline, 32 (32/53; 60.4%) had scalp pruritus; 15 (15/53; 28.3%) had mild, 15 (15/53; 28.3%) had moderate, and 2 (2/53; 3.8%) had severe pruritus.

Of the 30 subjects in this age/treatment group with pruritus at baseline, 15 (15/53; 28.3%) had mild scalp pruritus. Of these 15, on Day 1, 13 (13/15; 86.7%) had no pruritus, and 2 (2/15; 13.3%) had mild pruritus. On Day 7, 13 (13/15; 86.7%) had no pruritus, 1 (1/15; 6.7%) had mild pruritus, and 1 (1/15; 6.7%) did not return for evaluation on Day 7. On Day 14, 14 (14/15; 93.3%) had no pruritus, and 1 (1/15; 6.7%) did not return for evaluation on Day 14.

Of the 30 subjects in this age/treatment group with pruritus at baseline, 15 (15/53; 28.3%) had moderate scalp pruritus. Of these 15, on Day 1, 8 (8/15; 53.3%) had no pruritus, 4 (4/15; 26.7%) had mild pruritus, and 3 (3/15; 20%) still had moderate scalp pruritus. On Day 7, 10 (10/15; 66.7%) had no pruritus, 2 (2/15; 13.3%) had mild pruritus, and 3 (5.7%) still had moderate scalp pruritus. On Day 14, 11 (11/15; 73.3%) had no pruritus and 4 (4/15; 26.7%) had mild pruritus.

Of the 30 subjects in this age/treatment group with pruritus at baseline, 2 (2/53; 3.8%) subjects had severe pruritus; both reported no pruritus on Days 1, 7, and 14.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 12 to <18 years, and treated with Vehicle, is provided in Table 69.

Table 69: Summary of Scalp Pruritus Shifts from Baseline, Pooled Phase 3 Data, Subject Age 12 to <18 Years, Vehicle group (N=53)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	21/21 (100%)	0	0	0	0	21/53 (39.6%)
	1	13/15 (86.7%)	2/15 (13.3%)	0	0	0	15/53 (28.3%)
	2	8/15 (53.3%)	4/15 (26.7%)	3/15 (20%)	0	0	15/53 (28.3%)
	3	2/2 (100%)	0	0	0	0	2/53 (3.8%)
	Missing	0	0	0	0	0	0
	Total	44/53 (83.0%)	6/53 (11.3%)	3/53 (5.7%)	0	0	53 (100%)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 7	0	21/21 (39.6%)	0	0	0	0	21/53 (39.6%)
	1	13/15 (86.7%)	1/15 (6.7%)	0	0	1/15 (6.7%)	15/53 (28.3%)
	2	10/15 (66.7%)	2/15 (13.3%)	3/15 (20%)	0	0	15/53 (28.3%)
	3	2/2 (100%)	0	0	0	0	2/53 (3.8%)
	Missing	0	0	0	0	0	0
	Total	46/53 (86.8%)	3/53 (5.7%)	3/53 (5.7%)	0	1/53 (1.9%)	53 (100%)
Day 14	0	20/21 (95.2%)	1/21 (4.8%)	0	0	0	21/53 (39.6%)
	1	14/15 (93.3%)	0	0	0	1/15 (6.7%)	15/53 (28.3%)
	2	11/15 (73.3%)	4/15 (26.7%)	0	0	0	15/53 (28.3%)
	3	2/2 (100%)	0	0	0	0	2/53(3.8%)
	Missing	0	0	0	0	0	0
	Total	47/53 (88.7%)	5/53 (9.4%)	0	0	1/53 (1.9%)	53 (100%)

Source: Adapted from ISS Table 9

Ages 18 Years and Older

A total of 105 subjects ages 18 and older were treated with Xeglyze. Of these subjects, 39 (39/105; 37.1%) had no pruritus at baseline, and 66 (66/105; 62.9%) had scalp pruritus at baseline. Of these 66, 37 (37/105; 35.2%) had mild, 27 (27/105; 25.7%) had moderate, and (2/105; 1.9%) had severe pruritus.

Of the 39 subjects in this age/treatment with no pruritus at baseline, on Day 1, 38 (38/39; 97.4%) had no pruritus and 1 (1/39; 2.6%) had mild pruritus. On Day 7, all 39 (39/39; 100%) had no pruritus. On Day 14, 38 (38/39; 97.4%) had no pruritus and 1 (1/39; 2.6%) had mild pruritus.

Of the 66 subjects in this age/treatment group with pruritus at baseline, 37 (37/105; 35.2%) had mild pruritus. Of these 37, on Day 1, 32 (32/37; 86.5%) had no pruritus and 5 (5/37; 13.5%) had mild pruritus. On Days 7 and 14, 36 (36/37; 97.3%) had no pruritus, and 1 (1/37; 2.7%) still had mild pruritus.

Of the 66 subjects in this age/treatment group with pruritus at baseline, 27 (27/105; 25.7%) had moderate pruritus. Of these 27, on Day 1, 16 (16/27; 59.3%) had no pruritus, 10 (10/27; 37%) had mild, and 1 (1/27; 3.7%) still had moderate pruritus. On Day 7, 21 (21/27; 77.8%) had no

pruritus, 2 (2/27; 7.4%) had mild, 1 (1/27; 3.7%) had moderate pruritus, and 3 (3/27; 11.1%) did not return for evaluation. On Day 14, 26 (26/27; 96.3%) had no pruritus, and 1 (1/27; 3.7%) did not return for evaluation.

Of the 66 subjects in this age/treatment group with pruritus at baseline, 2 (2/105; 1.9%) subjects had severe pruritus. Of these 2, on Day 1, 1 (1/2; 50%) had mild and 1 (1/2; 50%) had moderate pruritus. On Days 7 and 14, both subjects had no pruritus.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, age >18 years, and treated with Xeglyze, is provided in Table 70.

Table 70: Summary of Scalp Pruritus Shifts from Baseline, Pooled Phase 3 Data, Subject Age >18 Years, Xeglyze group (N=105)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	38/39 (97.4%)	1/39 (2.6%)	0	0	0	39/105 (37.1%)
	1	32/37 (86.5%)	5/37 (13.5%)	0	0	0	37/105 (35.2%)
	2	16/27 (59.3%)	10/27 (37%)	1/27 (3.7%)	0	0	27/105 (25.7%)
	3	0	1/2 (50%)	1/2 (50%)	0	0	2/105 (1.9%)
	Missing	0	0	0	0	0	0
	Total	86/105 (81.9%)	17/105 (16.2%)	2/105 (1.9%)	0	0	105 (100%)
Day 7	0	39/39 (100%)	0	0	0	0	39/105 (37.1%)
	1	36/37 (97.3%)	1/37 (2.7%)	0	0	0	37/105 (35.2%)
	2	21/27 (77.8%)	2/27 (7.4%)	1/27 (3.7%)	0	3/27 (11.1%)	27/105 (25.7%)
	3	2/2 (100%)	0	0	0	0	2/105 (1.9%)
	Missing	0	0	0	0	0	0
	Total	98/105 (93.3%)	3/105 (2.9%)	1/105 (0.9%)	0	3/105 (2.9%)	105 (100%)
Day 14	0	38/39 (97.4%)	1/39 (2.6%)	0	0	0	39/105 (37.1%)
	1	36/37 (97.3%)	1/37 (2.7%)	0	0	0	37/105 (35.2%)
	2	26/27 (96.3%)	0	0	0	1/27 (3.7%)	27/105 (25.7%)
	3	2/2 (100%)	0	0	0	0	2/105 (1.9%)
	Missing	0	0	0	0	0	0
	Total	102/105 (97.1%)	2/105 (1.9%)	0	0	1/105 (0.9%)	105 (100%)

Source: Adapted from ISS Table 9

A total of 93 subjects age >18 years were treated with Vehicle. At baseline, 36 (36/93; 38.7%) had no scalp pruritus, and 57 (57/93; 61.3%) had scalp pruritus. Of these 57, 37 (37/93; 39.8%) had mild and 20 (20/93; 21.5%) had moderate scalp pruritus.

On Day 1, of the 36 (36/93; 38.7%) with no scalp pruritus at baseline, 35 (35/36; 97.2%) still had no pruritus while 1 (1/36; 2.8%) had mild pruritus. All 36 with no pruritus at baseline had no pruritus on Day 7 and 14.

Of the 57 subjects in this age/treatment group with pruritus at baseline, 37 (37/93; 39.8%) had mild pruritus. Of these 37, on Day 1, 27 (27/37; 73%) had no pruritus, while 10 (10/37; 27%) still had mild pruritus. On Day 7, 31 (31/37; 83.8%) had no pruritus, 5 (5/37; 13.5%) had mild pruritus, and 1 (1/37; 2.7%) did not return for evaluation. On Day 14, 31 (31/37; 83.8%) had no pruritus, 4 (4/37; 10.8%) had mild pruritus, 1 (1/37; 2.7%) had moderate pruritus, and 1 (1/37; 2.7%) did not return for evaluation on Day 14.

Of the 57 subjects in this age/treatment group with pruritus at baseline, 20 (20/93; 21.5%) had moderate pruritus. Of these 20, on Day 1, 9 (9/20; 45%) had no pruritus and 11 (11/20; 55%) had mild pruritus. On Day 7, 15 (15/20; 75%) had no pruritus, while 5 (5/20; 25%) had mild pruritus. On Day 14, 16 (16/20; 80%) had no pruritus, and 4 (4/20; 20%) had mild scalp pruritus.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages >18 years, and treated with Vehicle, is provided in Table 71.

Table 71: Summary of Scalp Pruritus Shifts from Baseline, Pooled Phase 3 Data, Subject Age >18 Years, Vehicle group (N=93)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	35/36 (97.2%)	1/36 (2.8%)	0	0	0	36/93 (38.7%)
	1	27/37 (73%)	10/37 (27%)	0	0	0	37/93 (39.8%)
	2	9/20 (45%)	11/20 (55%)	0	0	0	20/93 (21.5%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	71/93 (76.3%)	22/93 (23.7%)	0	0	0	93 (100%)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 7	0	36/36 (100%)	0	0	0	0	36/93 (38.7%)
	1	31/37 (83.8%)	5/37 (13.5%)	0	0	1/37 (2.7%)	37/93 (39.8%)
	2	15/20 (75%)	5/20 (25%)	0	0	0	20/93 (21.5%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	82/93 (88.2%)	10/93 (10.8%)	0	0	1/93 (1.1%)	93 (100%)
Day 14	0	36/36 (100%)	0	0	0	0	36/93 (38.7%)
	1	31/37 (83.8%)	4/37 (10.8%)	1/37 (2.7%)	0	1/37 (2.7%)	37/93 (39.8%)
	2	16/20 (80%)	4/20 (20%)	0	0	0	20/93 (21.5%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	83/93 (89.2%)	8/93 (8.6%)	1/93 (1.1%)	0	1/93 (1.1%)	93 (100%)

Source: Adapted from ISS Table 9

In conclusion, during the Phase 3 trials, post treatment scalp pruritus (i.e. scalp pruritus on Day 1 in subjects with no pruritus at Baseline visit) occurred in 1.4% of subjects treated with Xeglyze for head lice infestation; this was also seen in 0.7% of subjects in the Vehicle group. Head lice infestation was resolved in subjects in the Xeglyze group who experienced post-treatment scalp pruritus. Subjects who had scalp pruritus at baseline tended to improve after treatment with Xeglyze. New-onset or worsening scalp pruritus after treatment with Xeglyze was not reported in subjects less than 4 years of age in the Phase 3 trials.

Local Safety Evaluation, Pruritus: Phase 2 Trials

All 4 Phase 2 trials included evaluation of local safety by assessment of the scalp before and after treatment with Xeglyze or Vehicle. **Trial Ha02-002** was a randomized, double-blind, vehicle controlled dose ranging trial in adults with head lice infestation. Subjects were randomized to treatment with Xeglyze 0.37% for 10 minutes, Xeglyze 0.74% for 20 minutes, Vehicle for 10 minutes, or Vehicle for 20 minutes. Investigators did not note any local scalp reactions at any timepoint during this trial; however, pruritus is not mentioned specifically in the CSR.

Trial Ha02-003 was a Phase 2 trial in adults and children ≥ 2 years of age with head lice infestation. This trial included 3 treatment groups: Xeglyze 0.37%, Xeglyze 0.74%, and Vehicle.

Xeglyze was applied for 10 minutes in each group. Scalp pruritus assessments for each group were scored as described in Table 43 and are discussed below.

A total of 46 subjects were treated with Xeglyze 0.37%. On Day 1, 42 subjects returned for evaluation. New onset, post-treatment scalp pruritus on Day 1 occurred in 3 (3/42; 7.1%) subjects. Two (2/3; 66.7%) of these subjects ultimately had persistent head lice infestation, which likely contributed to the persistence of pruritus. Scalp pruritus was resolved in all of these subjects by Day 14.

A total of 49 subjects were treated with Xeglyze 0.74% lotion. On Day 1, 48 subjects returned for evaluation. New onset post-treatment scalp pruritus on Day 1 occurred in 2 (2/48; 4.2%) subjects. Head lice infestation was resolved in both of these subjects. Scalp pruritus was resolved in 1 (1/2; 50%) subject by Day 14.

A total of 47 subjects were treated with Vehicle, and returned for evaluation on Day 1. New onset post-treatment scalp pruritus on Day 1 occurred in 8 (8/47; 17%) of these subjects. Each of these subjects experienced treatment failure, with persistence of head lice infestation requiring rescue therapy. The persistence of head lice infestation in these subjects likely played a more significant role in the onset of scalp pruritus than did treatment with the Vehicle.

Table 72 describes overall shifts in scalp pruritus from Screening Visit through Day 14. Although overall improvement in pruritus is seen in all groups, the improvement is most pronounced in subjects treated with Xeglyze 0.74%.

Table 72: Scalp Pruritus Evaluation in Trial Ha02-003

Visit	Severity of Pruritus	Xeglyze		Vehicle (N=47)
		0.37% (N=46)	0.74% (N=49)	
Screening-Pre-Dose	N	46	49	47
	NONE	9 (19.6%)	8 (16.3%)	7 (14.9%)
	MILD	20 (43.5%)	18 (36.7%)	23 (48.9%)
	MODERATE	12 (26.1%)	16 (32.7%)	14 (29.8%)
	SEVERE	5 (10.9%)	7 (14.3%)	3 (6.4%)
Screening-90 minutes Post-Dose	N	46	49	47
	NONE	29 (63.0%)	33 (67.3%)	28 (59.6%)
	MILD	16 (34.8%)	12 (24.5%)	19 (40.4%)
	MODERATE	1 (2.2%)	4 (8.2%)	0
	SEVERE	0	0	0

Day 1	N	42	48	47
	NONE	26 (61.9%)	35 (72.9%)	25 (53.2%)
	MILD	14 (33.3%)	13 (27.1%)	21 (44.7%)
	MODERATE	1 (2.4%)	0	1 (2.4%)
	SEVERE	1 (2.4%)	0	0
Day 7	N	42	48	47
	NONE	34 (81.0%)	47 (97.9%)	35 (74.5%)
	MILD	8 (19.0%)	1 (2.1%)	11 (23.4%)
	MODERATE	0	0	1 (2.1%)
	SEVERE	0	0	0
Day 14	N	42	48	44
	NONE	37 (88.1%)	46 (95.8%)	36 (81.8%)
	MILD	5 (11.9%)	2 (4.2%)	8 (18.2%)
	MODERATE	0	0	0
	SEVERE	0	0	0

Source: Applicant's submission; Table 14.3.5.1, Ha02-003 CSR

During **Trial Ha03-003**, a pediatric safety and PK trial in children 6 months to <18 years of age, scalp evaluations were assigned scores from 0 to 4, defined as follows:

- 0 indicated no evidence
- 1 was barely perceptible
- 2 was well defined
- 3 was moderate
- 4 was severe evidence of pruritus, erythema, excoriation, edema, or pyoderma

Inclusion criteria for this trial required subjects to have at least Grade 2 erythema or pruritus with evidence of excoriation or inflammation. As shown in Table 33, 21 (21/22; 95.5%) subjects in this trial had scalp pruritus at screening; on Day 1, 7 (7/22; 31.8%) had scalp pruritus. On Day 14, only 1 (1/22; 4.5%) subject still had scalp pruritus. This subject had a pruritus score of 4 at screening, which improved to 1 at Day 14.

In **Ha03-004** (pediatric maximal use trial in children 6 months to 17 years of age), 15 of 38 (39.5%) had scalp pruritus at screening. On Day 1, only 1 (2.6%) had pruritus. No subjects had scalp pruritus on Day 14. For all subjects who had pruritus, the severity was mild.

Table 73 displays scalp pruritus evaluations for Studies Ha03-003 and Ha03-004.

Table 73: Scalp Pruritus Assessments in Pediatric PK Trials

Treatment Visit	Ha03-003 (N=22)	Ha03-004 (N=38)
Screening/Day 0		
No evidence	1 (4.5%)	23 (60.5%)
Evidence	21 (95.5%)	15 (38.5%)
Day 1		
No evidence	15 (68.2%)	37 (97.4%)
Evidence	7 (31.8%)	1 (2.6%)
Day 14		
No evidence	21 (95.5%)	38 (100%)
Evidence	1 (4.5%)	0

Source: Applicant's submission; Ha03-003 CSR Table 14.3.4.7; Ha03-004 CSR Table 14.3.4.8.

In Trial Ha02-003, 2 (2/48; 4.2%) of subjects treated with Xeglyze 0.74% developed post treatment scalp pruritus on Day 1; head lice infestation was resolved in both. In contrast, 8 (8/47; 17%) of those treated with Vehicle developed post treatment scalp pruritus on Day 1; all of these subjects had treatment failure with persistence of head lice infestation. It is likely that ongoing head lice infestation (rather than Vehicle itself) accounts for the pruritus seen in the Vehicle group in Ha02-003. In Ha03-003 and Ha03-004, as in the Phase 3 trials, those subjects with scalp pruritus at baseline tended to show improvement in both the Xeglyze and Vehicle groups, regardless of baseline severity.

Evaluation of Local Safety, Scalp Excoriation and Pyoderma; Pivotal Trials

As with erythema and edema, investigators performed assessments of the scalp for excoriation and pyoderma and scored them together during the Phase 3 trials. Of the 349 subjects treated with Xeglyze in the Phase 3 trials, 322 (322/349; 92.3%) had no excoriation/pyoderma at baseline. None of these developed excoriation/pyoderma at any timepoint during the trial; however, 8 (8/322; 2.5%) subjects did not return for evaluation on Day 7 or 14 and were lost to follow-up. A total of 27 subjects had excoriation/pyoderma at Baseline visit; 18 (18/349; 5.2%) of these had mild and 9 (9/349; 2.6%) had moderate excoriation/pyoderma.

At baseline, 18 (18/349; 5.2%) subjects had mild excoriation/pyoderma. At Day 1, 6 (6/18; 33.3%) had no excoriation/pyoderma, while 12 (12/18; 66.7%) continued with mild. At Day 7, 17 (17/18; 94.4%) had no excoriation/pyoderma and 1 (1/18; 5.6%) still had mild. At Day 14, all 18 subjects had no excoriation/pyoderma.

Nine (9/349; 2.6%) subjects had moderate excoriation/pyoderma at baseline. At Day 1, 4 (4/9; 44.4%) improved to mild, while 5 (5/9; 55.6%) still had moderate. At Day 7, 8 (8/9; 88.9%) had mild, while 1 (1/9; 11.1%) still had moderate. On Day 14, 4 (4/9; 44.4%) had none, 4 (4/9; 44.4%) had mild, and 1 (1/9; 11.1%) subject still had moderate excoriation/pyoderma. No subject in this group had severe excoriation/pyoderma at any timepoint during these studies.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, treated with Xeglyze, is provided in Table 74.

Table 74: Summary of Scalp Excoriation/Pyoderma Shifts from Baseline, Pooled Phase 3 Data, Xeglyze group (N=349)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	322/322 (100%)	0	0	0	0	322/349 (92.3%)
	1	6/18 (33.3%)	12/18 (66.7%)	0	0	0	18/349 (5.2%)
	2	0	4/9 (44.4%)	5/9 (55.6%)	0	0	9/349 (2.6%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	328/349 (94.0%)	16/349 (4.6%)	5/349 (1.4%)	0	0	349 (100%)
Day 7	0	314/322 (97.5%)	0	0	0	8/322 (2.5%)	322/349 (92.3%)
	1	17/18 (94.4%)	1/18 (5.6%)	0	0	0	18/349 (5.2%)
	2	0	8/9 (88.9%)	1/9 (11.1%)	0	0	9/349 (2.6%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	331/349 (94.8%)	9/349 (2.6%)	1/349 (0.3%)	0	8/349 (2.3%)	349 (100%)
Day 14	0	314/322 (97.5%)	0	0	0	8/322 (2.5%)	322/349 (92.3%)
	1	18/18 (100%)	0	0	0	0	18/349 (5.2%)
	2	4/9 (44.4%)	4/9 (44.4%)	1/9 (11.1%)	0	0	9/349 (2.6%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	336/349 (96.3%)	4/349 (1.1%)	1/349 (0.3%)	0	8/349 (2.3%)	349 (100%)

Source: Adapted from ISS Table 8

Of 350 subjects treated with Vehicle, 309 (309/350; 88.3%) had no scalp excoriation/pyoderma at the Baseline visit. A total of 41 (41/350; 11.7%) had excoriation/pyoderma at the Baseline visit; 31 (31/350; 8.9%) of these had mild and 10 (10/350; 2.9%) had moderate excoriation/pyoderma.

On Day 1, of the 309 subjects with no excoriation/pyoderma at the Baseline visit, 307 (307/309; 99.3%) still had none, and 1 (1/309; 0.3%) had mild excoriation/pyoderma. 1 (1/309; 0.3%) subject did not return for evaluation on Day 1. At Day 7, 304 (304/309; 98.4%) had none, and 2 (2/309; 0.6%) had mild; 3 (3/309; 1%) did not return for evaluation on Day 7. At Day 14, 302 (302/309; 97.7%) had none, and 3 (3/309; 1%) had mild scalp excoriation/pyoderma. Four (4/309; 1.3%) subjects did not return for evaluation on Day 14.

On Day 1, of 31 (31/350; 8.9%) subjects with mild excoriation/pyoderma at baseline, 7 (7/31; 22.6%) had none, while 24 (24/31; 77.4%) still had mild excoriation/pyoderma. On Day 7, 18 (18/31; 58.1%) had none, 12 (12/31; 38.7%) had mild, and 1 (1/31; 0.3%) did not return for evaluation. On Day 14, 21 (21/31; 67.7%) had none and 9 (9/31; 29%) had mild scalp excoriation/pyoderma; 1 (1/31; 3.2%) did not return for evaluation on Day 14.

Ten (10/350; 2.9%) subjects in the Vehicle group had moderate excoriation/pyoderma at baseline. On Day 1, 1 (1/10; 10%) had improved with no excoriation/pyoderma, 6 (6/10; 60%) had improved to mild, and 3 (3/10; 30%) continued with moderate excoriation/pyoderma. On Day 7, 4 (4/10; 40%) had none, 5 (5/10; 50%) had mild, and 1 (1/10; 10%) continued with moderate excoriation/pyoderma. On Day 14, 5 (5/10; 50%) had none, while 5 had mild excoriation/pyoderma. No subjects in the Vehicle group had severe excoriation/pyoderma at any timepoint during these trials.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, treated with Vehicle, is provided in Table 75.

Table 75: Summary of Scalp Excoriation/Pyoderma Shifts from Baseline, Pooled Phase 3 Data, Vehicle group (N=350)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	307/309 (99.3%)	1/309 (0.3%)	0	0	1/309 (0.3%)	309/350 (88.3%)
	1	7/31 (22.6%)	24/31 (77.4%)	0	0	0	31/350 (8.9%)
	2	1/10 (10%)	6/10 (60%)	3/10 (30%)	0	0	10/350 (2.9%)
	3	0	0	0	0	0	0

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
	Missing	0	0	0	0	0	0
	Total	315/350 (90.0%)	31/350 (8.9%)	3/350 (0.9%)	0	1/350 (0.3%)	350 (100%)
Day 7	0	304/309 (98.4%)	2/309 (0.6%)	0	0	3/309 (1%)	309/350 (88.3%)
	1	18/31 (58.1%)	12/31 (38.7%)	0	0	1/31 (3.2%)	31/350 (8.9%)
	2	4/10 (40%)	5/10 (50)	1/10 (10%)	0	0	10/350 (2.9%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	326/350 (93.1%)	19/350 (5.4%)	1/350 (0.3%)	0	4/350 (1.1%)	350 (100%)
Day 14	0	302/309 (97.7%)	3/309 (1%)	0	0	4/309 (1.3%)	309/350 (88.3%)
	1	21/31 (67.7%)	9/31 (29%)	0	0	1/31 (3.2%)	31/350 (8.9%)
	2	5/10 (50%)	5/10 (50%)	0	0	0	10/350 (2.9%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	328/350 (93.7%)	17/350 (4.9%)	0	0	5/350 (1.4%)	350 (100%)

Source: Adapted from ISS Table 8

Scalp Excoriation/Pyoderma Assessments by Subject Age Group: Pivotal Trials

Ages 6 months to <2 years

In the 6 month to <2 years age group, 7 subjects were treated with Xeglyze. Four (4/7; 57.1%) had no excoriation/pyoderma at baseline or at Days 1, 7, and 14. Three subjects had excoriation/pyoderma at baseline; 2 (2/7; 28.6%) were mild and 1 (1/7; 14.3%) was moderate. Of the 2 (2/7; 28.6%) who had mild excoriation and pyoderma at baseline; on Days 1 and 7, 1 (1/7; 14.3%) had none and 1 had mild excoriation/pyoderma. Both subjects had no excoriation/pyoderma at Day 14. One (1/7; 14.3%) subject had moderate excoriation/pyoderma at baseline and at Day 1; this improved to mild on Day 7 and resolved to none by Day 14. None of the 8 subjects in this age group who were treated with Vehicle had excoriation/pyoderma at any timepoint during these studies.

Ages 2 to <4 years

None of the 14 subjects age 2 to <4 years who were treated with Xeglyze experienced any scalp excoriation/pyoderma at any timepoint during these studies; however, 1 (1/14; 7.1%) did not return for evaluation on Day 14.

Of 24 subjects age 2 to <4 years treated with Vehicle, 22 (22/24; 91.7%) had no excoriation/pyoderma at baseline, and 2 (2/24; 8.3%) had excoriation/pyoderma which was mild. On Day 1, of the 22 with no excoriation/pyoderma at baseline, 21 (21/22; 95.5%) still had none; 1 (1/22; 4.5%) did not return for evaluation on Days 1, 7, or 14. On Day 7, 20 (20/22; 90.9%) had none, while 1 (1/22; 4.5%) had mild. On Day 14, 21 (21/22; 95.5%) had no scalp excoriation/pyoderma.

At baseline, 2 (2/24; 8.3%) had mild excoriation/pyoderma. At day 1, 1 (1/2; 50%) each had none and mild excoriation/pyoderma, respectively. Both subjects had no scalp excoriation/pyoderma at Days 7 and 14. No subjects in this age group had moderate or severe excoriation/pyoderma at any timepoint during these studies.

Ages 4 to <12 years

In the cohort of subjects ages 4 to <12 years, 166 were treated with Xeglyze. At baseline, 157 (157/166; 94.6%) had no excoriation/pyoderma. Investigators did not observe excoriation/pyoderma in any of these 157 subjects at any timepoint during this trial. However, 4 (4/157; 2.5%) did not return for evaluation on Day 7, and 5 (5/157; 3.2%) did not return on Day 14. A total of 9 (9/166; 5.4%) had excoriation/pyoderma at the Baseline visit; 7 (7/166; 4.2%) of these subjects had mild and 2 (2/166; 1.2%) had moderate scalp excoriation/pyoderma.

Seven (7/166; 4.2%) subjects in this age/treatment cohort had mild excoriation/pyoderma at baseline. On Day 1, 3 (3/7; 42.9%) had none and 4 (4/7; 57.1%) still had mild excoriation and pyoderma; this was resolved in all 7 subjects at Day 7 and 14 with no excoriation/pyoderma at these timepoints.

Two (2/166; 1.2%) subjects ages 4 to <12 years had moderate excoriation/pyoderma at baseline. Both improved to mild at Days 1 and 7; at Day 14, 1 (1/2; 50%) had mild and 1 had no scalp excoriation/pyoderma. An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 4 to <12 years, treated with Xeglyze, is provided in Table 76.

Table 76: Summary of Scalp Excoriation/Pyoderma Shifts from Baseline, Subject Ages 4 to <12 Years, Pooled Phase 3 Data, Xeglyze group (N=166)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	157/157 (100%)	0	0	0	0	157/166 (94.6%)
	1	3/7 (42.9%)	4/7 (57.1%)	0	0	0	7/166 (4.2%)
	2	0	2/2 (100%)	0	0	0	2/166 (1.2%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	160/166 (96.4%)	6/166 (3.6%)	0	0	0	166 (100%)
Day 7	0	153/157 (97.5%)	0	0	0	4/157 (2.5%)	157/166 (94.6%)
	1	7/7 (100%)	0	0	0	0	7/166 (4.2%)
	2	0	2/2 (100%)	0	0	0	2/166 (1.2%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	160/166 (96.4%)	2/166 (1.2%)	0	0	4/166 (2.4%)	166 (100%)
Day 14	0	152/157 (96.8%)	0	0	0	5/157 (3.2%)	157/166 (94.6%)
	1	7/7 (100%)	0	0	0	0	7/166 (4.2%)
	2	1/2 (50%)	1/2 (50%)	0	0	0	2/166 (1.2%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	160/166 (96.4%)	1/166 (0.6%)	0	0	5/166 (3.0%)	166 (100%)

Source: Adapted from ISS Table 9

A total of 172 subjects age 4 to <12 years were treated with Vehicle. A total of 153 (153/172; 89.0%) had no excoriation/pyoderma, and 19 (19/172; 11%) had scalp excoriation/pyoderma at baseline. Of these 19, 16 (16/172; 9.3%) had mild excoriation/pyoderma and 3 (3/172; 1.7%) had moderate excoriation/pyoderma at baseline.

Of the 153 (153/172; 89.0%) with no excoriation/pyoderma at baseline, none had excoriation/pyoderma at the Day 1 visit. At day 7, 151 (151/153; 98.7%) had none and 1 (1/153; 0.6%) had mild excoriation/pyoderma; 1 did not return for evaluation on Day 7. On Day 14, 149 (149/153; 97.4%) had none and 2 (2/153; 1.3%) had mild excoriation/pyoderma. Two subjects did not return for evaluation on Day 14.

On Day 1, of 16 (16/172; 9.3%) with mild excoriation/pyoderma at baseline, 3 (3/16; 18.8%) had none and 13 (13/16; 81.2 %) still had mild excoriation/pyoderma. On Day 7, 10 (10/16; 62.5%)

had none and 6 (6/16; 37.5%) had mild; on Day 14, 11 (11/16; 68.8%) had none and 5 (5/16; 31.2%) had mild scalp excoriation/pyoderma.

Three (3/172; 1.7%) had moderate excoriation/pyoderma at baseline; on Day 1, 2 (2/3; 66.7%) had improved to mild while 1 (1/3; 33.3%) still had moderate excoriation/pyoderma. On Day 7, 2 (2/3; 66.7%) had none and 1 (1/3; 33.3%) had mild; On Day 14 all 3 (3/3; 100%) had resolved with no excoriation/pyoderma.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 4 to <12 years, treated with Vehicle, is provided in Table 77.

Table 77: Summary of Scalp Excoriation/Pyoderma Shifts from Baseline, Subject Ages 4 to <12 Years, Pooled Phase 3 Data, Vehicle Group (N=172)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	153/153 (100%)	0	0	0	0	153/172 (89.0%)
	1	3/16 (18.8%)	13/16 (81.2%)	0	0	0	16/172 (9.3%)
	2	0	2/3 (66.7%)	1/3 (33.3%)	0	0	3/172 (1.7%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	156/172 (90.7%)	15/172 (8.7%)	1/172 (0.6%)	0	0	172 (100%)
Day 7	0	151/153 (98.7%)	1/153 (0.6%)	0	0	1/153 (0.6%)	153/172 (89.0%)
	1	10/16 (62.5%)	6/16 (37.5%)	0	0	0	16/172 (9.3%)
	2	2/3 (66.7%)	1/3 (33.3%)	0	0	0	3/172 (1.7%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	163/172 (94.8%)	8/172 (4.7%)	0	0	1/172 (0.6%)	172 (100%)
Day 14	0	149/153 (97.4%)	2/153 (1.3%)	0	0	2/153 (1.3%)	153/172 (89.0%)
	1	11/16 (68.8%)	5/16 (31.2%)	0	0	0	16/172 (9.3%)
	2	3/3 (100%)	0	0	0	0	3/172 (1.7%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	163/172 (94.8%)	7/172 (4.1%)	0	0	2/172 (1.2%)	172 (100%)

Source: Adapted from ISS Table 9

Ages 12 to <18 years

In the 12 to <18 years age group, 57 subjects were treated with Xeglyze. Fifty-three (53/57; 93%) had no excoriation/pyoderma at baseline or Day 1. On Days 7 and 14, 52 (52/53; 98.1%) had no excoriation/pyoderma; 1 (1/53; 1.9%) subject did not return for evaluation on Days 7 and 14. Four (4/57; 7%) subjects had excoriation/pyoderma at baseline; 2 (2/57; 3.5%) had mild and 2 (2/57; 3.5%) subjects had moderate excoriation/pyoderma.

Two subjects (2/57; 3.5%) had mild excoriation/pyoderma at baseline. On Day 1, 1 (1/2; 50%) improved to no excoriation/pyoderma, while 1 still had mild. Both had no excoriation/pyoderma on Days 7 and 14.

Two (2/57; 3.5%) subjects had moderate excoriation/pyoderma at baseline. On Day 1, 1 (1/2; 50%) improved to mild and 1 still had moderate. On Day 7, both had mild; on Day 14, 1 had none and 1 had mild excoriation/pyoderma.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 12 to <18 years, treated with Xeglyze, is provided in Table 78.

Table 78: Summary of Scalp Excoriation/Pyoderma Shifts from Baseline, Subject Ages 12 to <18 Years, Pooled Phase 3 Data, Xeglyze group (N=57)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	53/53 (100%)	0	0	0	0	53/57 (93.0%)
	1	1/2 (50%)	1/2 (50%)	0	0	0	2/57 (3.5%)
	2	0	1/2 (50%)	1/2 (50%)	0	0	2/57 (3.5%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	54/57 (94.7%)	2/57 (3.5%)	1/57 (1.8%)	0	0	57 (100%)
Day 7	0	52/53 (98.1%)	0	0	0	1/53 (1.9%)	53/57 (93.0%)
	1	2/2 (100%)	0	0	0	0	2/57 (3.5%)
	2	0	2/2 (100%)	0	0	0	2/57 (3.5%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	54/57 (94.7%)	2/57 (3.5%)	0	0	1/57 (1.8%)	57 (100%)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 14	0	52/53 (98.1%)	0	0	0	1/53 (1.9%)	53/57 (93.0%)
	1	2/2 (100%)	0	0	0	0	2/57 (3.5%)
	2	1/2 (50%)	1/2 (50%)	0	0	0	2/57 (3.5%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	55/57 (96.5%)	1/57 (1.8%)	0	0	1/57 (1.8%)	57 (100%)

Source: Adapted from ISS Table 9

In the 12 to <18 years age group, 53 subjects were treated with Vehicle. Of these, 47 (47/53; 88.7%) of these had no excoriation/pyoderma at the Baseline or Day 1 visit. Six (6/53; 11.3%) had scalp excoriation/pyoderma at baseline; 4 (4/53; 7.5%) subjects had mild and 2 (2/53; 3.8%) had moderate excoriation/pyoderma.

On Day 7, of the 47 with no excoriation/pyoderma at the Baseline or Day 1 visit, 46 (46/47; 97.9%) still had no excoriation/pyoderma; 1 (1/47; 2.1%) did not return for evaluation on Day 7. On Day 14, 45 (45/47; 95.7%) had no excoriation/pyoderma, 1 (1/47; 2.1%) had mild, and 1 did not return for evaluation on Day 14.

Four (4/53; 7.5%) subjects had mild excoriation/pyoderma at baseline. On Days 1 and 7, 2 (2/4; 50%) had no excoriation/pyoderma, while 2 still had mild. On Day 14, 3 (3/4; 75%) had none, and 1 (1/4; 25%) had mild scalp excoriation/pyoderma.

Two (2/53; 3.8%) had moderate excoriation/pyoderma at baseline. On Days 1 and 7, 1 (1/2; 50%) subject had mild and 1 still had moderate excoriation/pyoderma. On Day 14, both (2/2; 100%) had mild scalp excoriation/pyoderma.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages 12 to <18 years, treated with Vehicle, is provided in Table 79.

Table 79: Summary of Scalp Excoriation/Pyoderma Shifts from Baseline, Subject Ages 12 to <18 Years, Pooled Phase 3 Data, Vehicle Group (N=53)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	47/47 (100%)	0	0	0	0	47/53 (88.7%)
	1	2/4 (50%)	2/4 (50%)	0	0	0	4/53 (7.5%)
	2	0	1/2 (50%)	1/2 (50%)	0	0	2/53 (3.8%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	49/53 (92.5%)	3/53 (5.7%)	1/53 (1.9%)	0	0	53 (100%)
Day 7	0	46/47 (97.9%)	0	0	0	1/47 (2.1%)	47/53 (88.7%)
	1	2/4 (50%)	2/4 (40%)	0	0	0	4/53 (7.5%)
	2	0	1/2 (50%)	1/2 (50%)	0	0	2/53 (3.8%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	48/53 (90.6%)	3/53 (5.7%)	1/53 (1.9%)	0	1/53 (1.9%)	53 (100%)
Day 14	0	45/47 (95.7%)	1/47 (2.1%)	0	0	1/47 (2.1%)	47/53 (88.7%)
	1	3/4 (75%)	1/4 (25%)	0	0	0	4/53 (7.5%)
	2	0	2/2 (100%)	0	0	0	2/53 (3.8%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	48/53 (90.6%)	4/53 (7.5%)	0	0	1/53 (1.9%)	53 (100%)

Source: Adapted from ISS Table 9

Ages 18 and older

In the 18 years and older age group, 105 subjects were treated with Xeglyze. At baseline, 94 (94/105; 89.5%) had no excoriation/pyoderma. Eleven (11/105; 10.5%) had excoriation/pyoderma at baseline; 7 (7/105; 6.7%) of these had mild and 4 (4/405; 3.8%) had moderate excoriation/pyoderma.

None of the 94 subjects with no excoriation/pyoderma at baseline developed excoriation/pyoderma during this trial; however, 3 (3/94; 3.2%) did not return on Day 7 and 1 (1/94; 1.1%) did not return on Day 14.

Seven (7/105; 6.7%) had mild excoriation/pyoderma at baseline. On Day 1, 1 (1/7; 14.3%) had none and 6 (6/7; 85.7%) still had mild excoriation/pyoderma. All 7 had no excoriation/pyoderma at Day 7 or 14.

Four (4/405; 3.8%) had moderate excoriation/pyoderma at baseline. On Day 1, 1 (1/4; 25%) had mild and 3 (3/4; 75%) had moderate. On Day 7, 3 (3/4; 75%) had mild and 1 (1/4; 25%) had moderate. On Day 14, 1 (1/4; 25%) had none, 2 (2/4; 50%) had mild, and 1 (1/4; 25%) still had moderate scalp excoriation/pyoderma.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages ≥18 years, treated with Xeglyze, is provided in Table 80.

Table 80: Summary of Scalp Excoriation/Pyoderma Shifts from Baseline, Subject Ages ≥18 Years, Pooled Phase 3 Data, Xeglyze group (N=105)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	94/94 (100%)	0	0	0	0	94/105 (89.5%)
	1	1/7 (14.3%)	6/7 (85.7%)	0	0	0	7/105 (6.7%)
	2	0	1/4 (25%)	3/4 (75%)	0	0	4/105 (3.8%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	95/105 (90.5%)	7/105 (6.7%)	3/105 (2.9%)	0	0	105 (100%)
Day 7	0	91/94 (96.8%)	0	0	0	3/94 (3.2%)	94/105 (89.5%)
	1	7/7 (100%)	0	0	0	0	7/105 (6.7%)
	2	0	3/4 (75%)	1/4 (25%)	0	0	4/105 (3.8%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	98/105 (93.3%)	3/105 (2.9%)	1/105 (1.0%)	0	3/105 (2.9%)	105 (100%)
Day 14	0	93/94 (98.9%)	0	0	0	1/94 (1.1%)	94/105 (89.5%)
	1	7/7 (100%)	0	0	0	0	7/105 (6.7%)
	2	1/4 (25%)	2/4 (50%)	1/4 (25%)	0	0	4/105 (3.8%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	101/105 (96.2%)	2/105 (1.9%)	1/105 (1.0%)	0	1/105 (1.0%)	105 (100%)

Source: Adapted from ISS Table 9

In the 18 years and older age group, 93 subjects were treated with Vehicle. Of these subjects, 79 (79/93; 84.9%) had no excoriation/pyoderma at baseline. Fourteen subjects (14/93; 15.1%)

had excoriation/pyoderma at baseline; 9 (9/93; 9.7%) of these had mild and 5 (5/93; 5.4%) had moderate.

Of the 79 subjects with no excoriation/pyoderma at baseline, on Day 1, 1 (1/79; 1.3%) subject had mild excoriation/pyoderma which was resolved at Day 7 and 14; the remaining 78 had no scalp excoriation/pyoderma at any timepoint during this trial.

Nine (9/93; 9.7%) subjects had mild excoriation/pyoderma at baseline. On Day 1, 1 (1/9; 11.1%) had no excoriation/pyoderma, while 8 (8/9; 88.9%) still had mild. On Day 7, 4 (4/9; 44.4%) had none and 4 had mild excoriation/pyoderma; 1 (1/9; 11.1%) subject did not return for evaluation on Day 7. On Day 14, 5 (5/9; 55.6%) had none and 3 (3/9; 33.3%) had mild excoriation/pyoderma; 1 (1/9; 11.1%) subject did not return for evaluation on Day 14.

Five (5/93; 5.4%) had moderate scalp excoriation/pyoderma at baseline. On Day 1, 1 (1/5; 20%) had none, 3 (3/5; 60%) had mild, and 1 (1/5; 20%) still had moderate excoriation/pyoderma. On Day 7 and 14, 2 (2/5; 40%) had none and 3 (3/5; 60%) had mild scalp excoriation/pyoderma.

An integrated analysis of scalp assessment shifts from baseline for the pooled Phase 3 population, ages ≥18 years, treated with Vehicle, is provided in Table 81.

Table 81: Summary of Scalp Excoriation/Pyoderma Shifts from Baseline, Subject Ages ≥18 Years, Pooled Phase 3 Data, Vehicle Group (N=93)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	78/79 (98.7%)	1/79 (1.3%)	0	0	0	79/93 (84.9%)
	1	1/9 (11.1%)	8/9 (88.9%)	0	0	0	9/93 (9.7%)
	2	1/5 (20%)	3/5 (60%)	1/5 (20%)	0	0	5/93 (5.4%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	80/93 (86.0%)	12/93 (12.9%)	1/93 (1.1%)	0	0	93 (100%)
Day 7	0	79/79 (100%)	0	0	0	0	79/93 (84.9%)
	1	4/9 (44.4%)	4/9 (44.4%)	0	0	1/9 (11.1%)	9/93 (9.7%)
	2	2/5 (40%)	3/5 (60%)	0	0	0	5 (5.4%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
	Total	85/93 (91.4%)	7/93 (7.5%)	0	0	1/93 (1.1%)	93 (100%)
Day 14	0	79/79 (100%)	0	0	0	0	79/93 (84.9%)
	1	5/9 (55.6%)	3/9 (33.3%)	0	0	1/9 (11.1%)	9/93 (9.7%)
	2	2/5 (40%)	3/5 (60%)	0	0	0	5/93 (5.4%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	86/93 (92.5%)	6/93 (6.5%)	0	0	1/93 (1.1%)	93 (100%)

Source: Adapted from ISS Table 9

In conclusion, in the Phase 3 trials, subjects treated with Xeglyze who had no excoriation/pyoderma at baseline did not develop these at any timepoint during the studies. Subjects who had excoriation and pyoderma at baseline tended to improve or resolve after treatment; this was true for both the Xeglyze and Vehicle Groups.

Local Safety Evaluation, Excoriation/Pyoderma: Phase 2 Trials

All 4 Phase 2 trials included evaluation of local safety by assessment of the scalp before and after treatment with Xeglyze or Vehicle. **Trial Ha02-002** was a randomized, double-blind, vehicle controlled dose ranging trial in adults with head lice infestation. Subjects were randomized to treatment with Xeglyze 0.37% for 10 minutes, Xeglyze 0.74% for 20 minutes, Vehicle for 10 minutes, or Vehicle for 20 minutes. Investigators did not note any local scalp reactions at any timepoint during this trial.

Trial Ha02-003 was a Phase 2 trial in adults and children ≥ 2 years of age with head lice infestation. This trial included 3 treatment groups: Xeglyze 0.37%, Xeglyze 0.74%, and Vehicle groups. Xeglyze was applied for 10 minutes in each group. Investigators scored scalp excoriation assessments for each group as described in Table 82; these are discussed below.

A total of 46 subjects were treated with Xeglyze at 0.37% concentration. At Screening and 90 minutes post dose, only 1 (1/46; 2.2%) had scalp excoriation while 45 (46/46; 97.8%) had none. Forty-two subjects returned for evaluation on Days 1, 7, and 14. All subjects had no excoriation on Days 1 and 7, while 1 (1/42; 2.4%) had excoriation on Day 14.

Forty-nine subjects were treated with Xeglyze 0.74%. At Screening and 90 minutes post dose, 4 (4/49; 8.2%) had excoriation while 45 (45/49; 91.8%) did not. On Day 1, 7, and 14, 48 subjects returned for evaluation. On Day 1, 2 (2/48; 4.2%) had excoriation while 46 (46/48; 95.8%) did

not. However, no subjects who had no excoriation at screening developed new-onset scalp excoriation on Day 1. On Day 7, all 48 subjects had no excoriation. On Day 14, once again 2 (2/48; 4.2%) had excoriation while 46 (46/48; 95.8%) did not.

Forty-seven subjects were treated with Vehicle, and returned for the Day 1 and Day 7 Visits. At Screening, 3 (3/47; 6.4%) had excoriation while 44 (44/47; 93.6%) did not. At 90 minutes post dose, 2 (2/47; 4.3%) had excoriation while 45 (95.7%) did not. At Day 1, 1 (1/47; 2.1%) had excoriation while 46 (46/47; 97.9%) did not; at Day 7, none of the 47 subjects had excoriation. On Day 14, none of the 44 subjects who returned for evaluation had excoriation.

Table 82: Scalp Excoriation Evaluation in Trial Ha02-003

Visit	Scalp Excoriation Present?	Xeglyze		Vehicle (N=47)
		0.37% (N=46)	0.74% (N=49)	
Screening-Pre-Dose	N	46	49	47
	YES	1/46 (2.2%)	4/49 (8.2%)	3/47 (6.4%)
	NO	45/46 (97.8%)	45/49 (91.8%)	44/47 (93.6%)
Screening-90 minutes Post-Dose	N	46	49	47
	YES	1/46 (2.2%)	4/49 (8.2%)	2/47 (4.3%)
	NO	45/46 (97.8%)	45/49 (91.8%)	45/47 (95.7%)
Day 1	N	42	48	47
	YES	0 (0.0%)	2/48 (4.2%)	1/47 (2.1%)
	NO	42/42 (100.0%)	46/48 (95.8%)	46/47 (97.9%)
Day 7	N	42	48	47
	YES	0 (0.0%)	0 (0.0%)	0 (0.0%))
	NO	42/42 (100.0%)	48/48 (100.0%)	47/47 (100.0%)
Day 14	N	42	48	44
	YES	1/42 (2.4%)	2/48 (4.2%)	0 (0.0%)
	NO	41/42 (97.6%)	46/48 (95.8%)	44/44 (100.0%)

Source: Applicant's submission; Adapted from Table 14.3.5.1, Ha02-003 CSR

During **Trial Ha03-003**, a pediatric safety and PK trial in children 6 months to <18 years of age, scalp evaluations were assigned scores from 0 to 4, defined as follows:

- 0 indicated no evidence

- 1 was barely perceptible
- 2 was well defined
- 3 was moderate
- 4 was severe evidence of pruritus, erythema, excoriation, edema, or pyoderma

Inclusion criteria for this trial required subjects to have at least Grade 2 erythema or pruritus with evidence of excoriation or inflammation. At screening, 18 (18/22; 81.8%) of subjects had excoriation/pyoderma; 4 (4/22; 18.2%) did not. On Day 1, 6 (6/22; 27.3%) had excoriation/pyoderma, 16 (16/22; 72.7%) did not. On Day 14, only 1 (1/22; 4.5%) had evidence of excoriation/pyoderma; 21 (21/22; 95.5%) did not. These findings are summarized in Table 83.

Table 83: Scalp Excoriation/Pyoderma in Ha 03-003

Excoriation/Pyoderma	Screening/Day 0	Day 1	Day 14
Evidence	18 (81.8)	6 (27.3)	1 (4.5)
No Evidence	4 (18.2)	16 (72.7)	21 (95.5)

Source: Applicant's submission; Data from Table 14.3.4.7, Ha03-003 CSR

In **Trial Ha03-004** (a pediatric maximal use trial in children 6 months to 17 years of age), investigators did not note scalp excoriation in any subjects at any timepoint.

Analysis of scalp excoriation/pyoderma in the Phase 2 trials revealed results similar to those seen in the Phase 3 trials. Subjects who lacked scalp excoriation/pyoderma at baseline did not tend to develop these signs after treatment with Xeglyze. Furthermore, subjects who had excoriation/pyoderma at baseline tended to improve after treatment.

Evaluation of Local Safety, Eye Irritation: Pivotal Trials

In the pooled Phase 3 population, a total of 349 subjects were treated with Xeglyze. 343 (343/349; 98.3%) of these had no eye irritation at baseline. Six (6/349; 1.7%) had eye irritation at baseline; 4 (4/349; 1.1%) subjects had mild and 2 (2/349; 0.6%) subjects had moderate eye irritation.

On Day 1, 6 (6/343; 1.7%) with no eye irritation at baseline had developed mild post-treatment eye irritation, and 337 (337/343; 98.3%) still had none. On Days 7 and 14, 335 (335/343; 97.7%) had no eye irritation, while 8 (8/343; 2.3%) did not return for evaluation on these days.

Four (4/349; 1.1%) subjects had mild eye irritation at baseline. On Days 1 and 7, 2 (2/4; 50%) had resolved with no eye irritation, while 2 (2/4; 50%) still had mild eye irritation. On Day 14, 3 (3/4; 75%) had none and 1 (1/4; 25%) still had mild eye irritation.

Two (2/349; 0.6%) subjects had moderate eye irritation at baseline and on Day 1. This resolved by Day 7; both subjects had no eye irritation on Days 7 and 14.

An integrated analysis of eye irritation shifts from baseline for the pooled Phase 3 population, treated with Xeglyze, is provided in Table 84.

Table 84: Summary of Eye Irritation Shifts from Baseline, Pooled Phase 3 Data, Xeglyze group (N=349)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	337/343 (98.3%)	6/343 (1.7%)	0	0	0	343/349 (98.3%)
	1	2/4 (50%)	2/4 (50%)	0	0	0	4/349 (1.1%)
	2	0	0	2/2 (100%)	0	0	2/349 (0.6%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	339/349 (97.1%)	8/349 (2.3%)	2/349 (0.6%)	0	0	349 (100%)
Day 7	0	335/343 (97.7%)	0	0	0	8/343 (2.3%)	343/349 (98.3%)
	1	2/4 (50%)	2/4 (50%)	0	0	0	4/349 (1.1%)
	2	2/2 (100%)	0	0	0	0	2/349 (0.6%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	339/349 (97.1%)	2/349 (0.6%)	0	0	8/349 (2.3%)	349 (100%)
Day 14	0	335/343 (98.3%)	0	0	0	8/343 (2.3%)	343 (98.3%)
	1	3/4 (75%)	1/4 (25%)	0	0	0	4/349 (1.1%)
	2	2/2 (100%)	0	0	0	0	2/349 (0.6%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	340/349 (97.4%)	1/349 (0.3%)	0	0	8/349 (2.3%)	349 (100%)

Source: Adapted from ISS Table 10

The Vehicle group included 350 subjects. At baseline, 345 (345/350; 98.6%) had no eye irritation and 5 (5/345; 1.4%) had eye irritation. Of the 5 with eye irritation at baseline, 4 (4/350; 1.1%) had mild and 1 (1/350; 0.3%) subject had moderate eye irritation.

Of the 345 subjects with no eye irritation at baseline, on Day 1, 339 (339/345; 98.3%) still had none. Five (5/345; 1.4%) had developed mild eye irritation post treatment, and 1 (1/345; 0.3%) did not return for evaluation on Day 1. On Day 7, 338 (338/345; 98%) had none, 3 (3/345; 0.9%) had mild, 1 (1/345; 0.3%) had moderate eye irritation, and 3 (3/345; 0.9%) subjects did not return for evaluation on Day 7. On Day 14, 338 (338/345; 98%) still had none, 3 (3/345; 0.9%) had mild eye irritation, and 4 (4/345; 1.1%) did not return for evaluation on Day 14.

Four (4/350; 1.1%) subjects treated with Vehicle had mild eye irritation at baseline. On Day 1, 2 (2/4; 50%) had none, while 2 still had mild eye irritation. On Day 7, 3 (3/4%) had mild and 1 (1/4; 25%) had no eye irritation. On Day 14, all 4 subjects had no eye irritation.

One (1/350; 0.3%) subject had moderate eye irritation at baseline and on Day 1. This subject did not return for evaluation on Days 7 and 14.

An integrated analysis of eye irritation shifts from baseline for the pooled Phase 3 population, treated with Vehicle, is provided in Table 85.

Table 85: Summary of Eye Irritation Shifts from Baseline, Pooled Phase 3 Data, Vehicle Group (N=350)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	339/345 (98.3%)	5/345 (1.4%)	0	0	1/345 (0.3%)	345/350 (98.6%)
	1	2/4 (50%)	2/4 (50%)	0	0	0	4/350 (1.1%)
	2	0	0	1/1 (100%)	0	0	1/350 (0.3%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	341/350 (97.4%)	7/350 (2.0%)	1/350 (0.3%)	0	1/350 (0.3%)	350 (100%)
Day 7	0	338/345 (98%)	3/345 (0.9%)	1/345 (0.3%)	0	3/345 (0.9%)	345/350 (98.6%)
	1	3/4 (75%)	1/4 (25%)	0	0	0	4/350 (1.1%)
	2	0	0	0	0	1/1 (100%)	1/350 (0.3%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	341/350 (97.4%)	4/350 (1.1%)	1/350 (0.3%)	0	4/350 (1.1%)	350 (100%)
Day 14	0	338/345 (98%)	3/345 (0.9%)	0	0	4/345 (1.1%)	345/350 (98.6%)
	1	4/4 (100%)	0	0	0	0	4/350 (1.1%)
	2	0	0	0	0	1/1 (100%)	1/350 (0.3%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	342/350 (97.7%)	3/350 (0.9%)	0	0	5/350 (1.4%)	350 (100%)

Source: Adapted from ISS Table 10

Eye Irritation Assessments by Subject Age Group: Pivotal Trials

Ages 6 Months to <2 Years
During the Phase 3 trials, there were 7 subjects aged 6 months to <2 years who were treated with Xeglyze; 8 were treated with Vehicle. Investigators noted no eye irritation in any of these subjects at any timepoint during these studies.

Ages 2 to <4 Years

In the 2 to <4 years age group, 14 subjects were treated with Xeglyze. None of these subjects had eye irritation at any timepoint, although 1 subject did not return for evaluation on Day 14. 24 subjects in this age group were treated with Vehicle. At baseline, 23 had no eye irritation. These subjects did not have eye irritation at any timepoint, although 1 (4.2%) did not return for evaluation on Day 1. One (1/24; 4.2%) subject had moderate eye irritation at baseline and on Day 1; this subject did not return for evaluation on Days 7 or 14.

Ages 4 to <12 Years

In the 4 to <12 years age group, 166 subjects were treated with Xeglyze. At baseline, 163 (163/166; 98.2%) had no eye irritation and 3 (3/166; 1.8%) had eye irritation at baseline. Of the 3 with eye irritation at baseline, 1 (1/166; 0.6%) subject had mild and (2/166; 1.2%) subjects had moderate eye irritation.

Of the 163 subjects with no eye irritation at baseline, on Day 1, 159 (159/163; 97.5%) still had no eye irritation, while 4/163 (2.5%) had mild. On Day 7, 159 (159/163; 97.5%) had no eye irritation; 4 (4/163; 2.5%) did not return for evaluation on Day 7. On Day 14, 158 (158/163; 96.9%) had no eye irritation, and 5 (5/163; 3.1%) did not return for evaluation on Day 14.

One (1/166; 0.6%) subject had mild eye irritation at baseline, as well as the Day 1 and Day 7 visits. This subject had no eye irritation at Day 14. Two (2/166; 1.2%) subjects had moderate eye irritation at baseline and Day 1. Both subjects had no eye irritation on Days 7 or 14.

An integrated analysis of eye irritation shifts from baseline for the pooled Phase 3 population, ages 4 to <12 years, and treated with Xeglyze, is provided in Table 86.

Table 86: Summary of Eye Irritation Shifts from Baseline, Subject Age 4 to <12 Years, Pooled Phase 3 Data, Xeglyze group (N=166)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	159/163 (97.5%)	4/163 (2.5%)	0	0	0	163/166 (98.2%)
	1	0	1/1 (100%)	0	0	0	1/166 (0.6%)
	2	0	0	2/2 (100%)	0	0	2/166 (1.2%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	159/166 (95.8%)	5/166 (3.0%)	2/166 (1.2%)	0	0	166 (100%)
Day 7	0	159/163 (97.5%)	0	0	0	4/163 (2.5%)	163/166 (98.2%)
	1	0	1/1 (100%)	0	0	0	1/166 (0.6%)
	2	2/2 (100%)	0	0	0	0	2/166 (1.2%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	161/166 (97.0%)	1/166 (0.6%)	0	0	4/166 (2.4%)	166 (100%)
Day 14	0	158/163 (96.9%)	0	0	0	5/163 (3.1%)	163/166 (98.2%)
	1	1/1 (100%)	0	0	0	0	1/166 (0.6%)
	2	2/2 (100%)	0	0	0	0	2/166 (1.2%)
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	161/166 (97.0%)	0	0	0	5 (3.0%)	166 (100%)

Source: Adapted from ISS Table 11

In the 4 to <12 years age group, 172 subjects were treated with Vehicle. Of these, 171 (171/172; 99.4%) had no eye irritation at baseline and 1 (1/172; 0.6%) subject had mild eye irritation at baseline.

Of the 171 subjects with no eye irritation at baseline, on Day 1, 167 (167/171; 97.7%) still had no eye irritation, while 4 (/171; 2.3%) had mild. On Day 7, 169 (169/171; 98.8%) had none, 1 (1/171; 0.6%) had moderate eye irritation, and 1 subject did not return for evaluation. On Day 14, 169 (169/171; 98.8%) had no eye irritation; 2 (1.2%) subjects did not return for evaluation.

One (1/172; 0.6%) subject had mild eye irritation at baseline and Day 1; which resolved to no eye irritation on Days 7 and 14.

An integrated analysis of eye irritation shifts from baseline for the pooled Phase 3 population, ages 4 to <12 years, and treated with Vehicle, is provided in Table 87.

Table 87: Summary of Eye Irritation Shifts from Baseline, Subject Age 4 to <12 Years, Pooled Phase 3 Data, Vehicle group (N=172)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	167/171 (97.7%)	4/171 (2.3%)	0	0	0	171/172 (99.4%)
	1	0	1/1 (100%)	0	0	0	1/172 (0.6%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	167/172 (97.1%)	5/172 (2.9%)	0	0	0	172 (100%)
Day 7	0	169/171 (98.8%)	0	1/171 (0.6%)	0	1/171 (0.6%)	171/172 (99.4%)
	1	1/1 (100%)	0	0	0	0	1/172 (0.6%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	170/172 (98.8%)	0	1/172 (0.6%)	0	1/172 (0.6%)	172 (100%)
Day 14	0	169/171 (98.8%)	0	0	0	2/171 (1.2%)	171/172 (99.4%)
	1	1/1 (100%)	0	0	0	0	1/172 (0.6%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	170/172 (98.8%)	0	0	0	2/172 (1.2%)	172 (100%)

Source: Adapted from ISS Table 11

Ages 12 to <18 Years

In the 12 to <18 years age group, none of the 57 subjects treated with Xeglyze had eye irritation at baseline. At Day 1, 56 (56/57; 98.2%) had no eye irritation, while 1 (1/57; 1.8%) had mild. On Days 7 and 14, 56 (56/57; 98.2%) had no eye irritation; 1 (1/57; 1.8%) did not return for evaluation on Day 7 or 14.

In the 12 to <18 years age group, none of the 53 subjects treated with Vehicle had eye irritation at baseline or Day 1. 52 (52/53; 98.1%) had no eye irritation at Days 7 and 14; 1 (1/53; 1.9%) subject did not return for evaluation for these visits.

Age 18 Years and Older

In the ≥18 years age group, 105 subjects were treated with Xeglyze. Of these subjects, (102/105; 97.1%) had no eye irritation at baseline. Three (3/105; 2.9%) subjects in this age group had eye irritation at baseline which was mild.

Of the 102 subjects with no eye irritation at baseline, on Day 1, 101 (101/102; 99%) had no eye irritation; 1 (1/102; 1%) had mild eye irritation. On Day 7, 99 (99/102; 97.1%) had no eye irritation, while 3 (3/102; 2.9%) did not return for evaluation. On Day 14, 101 (707/102; 99%) had no eye irritation; 1 (1/102; 1.0%) did not return for evaluation.

Three (3/105; 2.9%) subjects in this age group had mild eye irritation at baseline. On Days 1, 7, and 14, 2 (2/3; 66.7%) had no eye irritation, while 1 (1/3; 33.3%) had mild eye irritation.

An integrated analysis of eye irritation shifts from baseline for the pooled Phase 3 population, age ≥18 years, and treated with Xeglyze, is provided in Table 88.

Table 88: Summary of Eye Irritation Shifts from Baseline, Subject Age ≥18 Years, Pooled Phase 3 Data, Xeglyze group (N=105)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	101/102 (99%)	1/102 (1.0%)	0	0	0	102/105 (97.1%)
	1	2/3 (66.7%)	1/3 (33.3%)	0	0	0	3/105 (2.9%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	103/105 (98.1%)	2/105 (1.9%)	0	0	0	105 (100%)
Day 7	0	99/102 (97.1%)	0	0	0	3/102 (2.9%)	102/105 (97.1%)
	1	2/3 (66.7%)	1/3 (33.3%)	0	0	0	3/105 (2.9%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	101/105 (96.2%)	1/105 (1.0%)	0	0	3 (2.9%)	105 (100%)

Day 14	0	101/102 (99%)	0	0	0	1/102 (1.0%)	102/105 (97.1%)
	1	2/3 (66.7%)	1/3 (33.3%)	0	0	0	3/105 (2.9%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	103/105 (98.1%)	1/105 (1.0%)	0	0	1/105 (1.0%)	105 (100%)

Source: Adapted from ISS Table 11

A total of 93 subjects age ≥18 years were treated with Vehicle. Ninety (90/93; 96.8%) of these subjects had no eye irritation at baseline, and 3 (3/93; 3.2%) subjects in this age/treatment group had mild eye irritation.

Of the 90 subjects with no eye irritation at baseline, on Day 1, 89 (89/90; 98.9%) still had no eye irritation, while 1 (1/90; 1.1%) had mild eye irritation. On Days 7 and 14, 86 (86/90; 95.6%) had no eye irritation, 3 (3/90; 3.3%) had mild, and 1 (1/90; 1.1%) did not return for evaluation.

Three subjects in this age/treatment group had mild eye irritation at baseline. At Days 1 and 7, 2 (2/3; 66.7%) had none and 1 (1/3; 33.3%) had mild eye irritation. All 3 had no eye irritation at Day 14.

An integrated analysis of eye irritation shifts from baseline for the pooled Phase 3 population, age ≥18 years, and treated with Vehicle, is provided in Table 89.

Table 89: Summary of Eye Irritation Shifts from Baseline, Subject Age ≥18 Years, Pooled Phase 3 Data, Vehicle group (N=93)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 1	0	89/90 (98.9%)	1/90 (1.1%)	0	0	0	90/93 (96.8%)
	1	2/3 (66.7%)	1/3 (33.3%)	0	0	0	3/93 (3.2%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	91/93 (97.8%)	2/93 (2.2%)	0	0	0	93 (100%)
Day 7	0	86/90 (95.6%)	3/90 (3.3%)	0	0	1/90 (1.1%)	90/93 (96.8%)
	1	2/3 (66.7%)	1 (33.3%)	0	0	0	3/93 (3.2%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	88/93 (94.6%)	4/93 (4.3%)	0	0	1/93 (1.1%)	93 (100%)

Visit	Baseline Severity	Post-Baseline Severity					
		0	1	2	3	Missing	Total
Day 14	0	86/90 (95.6%)	3/90 (3.3%)	0	0	1/90 (1.1%)	90/93 (96.8%)
	1	3/3 (100%)	0	0	0	0	3/93 (3.2%)
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	Missing	0	0	0	0	0	0
	Total	89/93 (95.7%)	3/93 (3.2%)	0	0	1/93 (1.1%)	93 (100%)

Source: Adapted from ISS Table 11

In conclusion, in the Phase 3 trials, post treatment eye irritation was slightly more common in the Xeglyze group (1.7%) than the Vehicle group (1.4%). Children under age 4 years were not at increased risk for eye irritation after treatment with Xeglyze. Subjects with eye irritation at baseline tended to improve after treatment.

Local Safety Evaluation, Eye Irritation: Phase 2 Trials

All 4 Phase 2 PK studies evaluated eye irritation (lids, sclera and conjunctiva) pre- and post-dose. **Trial Ha02-002** was a randomized, double-blind, vehicle controlled dose ranging trial in adults with head lice infestation. Subjects were randomized to treatment with Xeglyze 0.37% for 10 minutes, Xeglyze 0.74% for 20 minutes, Vehicle for 10 minutes, or Vehicle for 20 minutes. Investigators noted no eye irritation in any subject at any timepoint during this trial.

Trial Ha02-003 was a Phase 2 trial in adults and children ≥ 2 years of age with head lice infestation. This trial included 3 treatment groups: Xeglyze 0.37%, Xeglyze 0.74%, and Vehicle control groups. Xeglyze was applied for 10 minutes in each group. Investigators scored eye irritation assessments for each group as described in Table 90; these are discussed below.

A total of 46 subjects were treated with Xeglyze at 0.37% concentration. At Screening, 41 (41/46; 89.1%) had no eye irritation; 5 (10.9%) had slight eye irritation. At 90 minutes post dose, 44 (44/46; 95.7%) had none, while 2 (4.3%) still had slight eye irritation. On Days 1, 7, and 14, 42 subjects from this treatment group returned for evaluation. On Days 1 and 7, 41 (41/42; 97.6%) had none, and 1 (1/42; 2.4%) had slight eye irritation. On Day 14, 39 (39/42; 92.9%) had none, while 3 (3/42; 78.1%) had slight eye irritation. No subject in this group who had no eye irritation at baseline had eye irritation at the 90 minute or Day 1 visit.

A total of 49 subjects were treated with Xeglyze 0.74%. At Screening, 40 (40/49; 81.6%) had no eye irritation, while 9 (9/49; 18.4%) had slight. At 90 minutes post dose, 46 (46/49; 93.9%) had none, and 3 (3/49; 6.1%) had slight eye irritation. 48 subjects returned for evaluation on Days 1, 7, and 14. On Day 1, 46 (46/48; 95.8%) had none, while 2 (4.2%) had slight eye irritation. On

Day 7, all 48 subjects had no eye irritation. On Day 14, 47 (97.9%) had none, while 1 (2.1%) had slight eye irritation. One (1/48; 2.1%) had mild eye irritation at Day 14; this subject also had persistent head lice infestation. No subject who did not have eye irritation at baseline had eye irritation at the 90 minute or Day 1 visit.

The Vehicle control group was comprised of 47 subjects. At Screening, 37 (37/47; 78.7%) had no eye irritation, while 10 (10/47; 21.3%) had slight eye irritation. At 90 minutes post dose, 38 (38/47; 80.9%) had none, and 9 (9/47; 19.1%) had slight eye irritation. Forty-seven subjects from this group returned for assessment on Days 1 and 7. On Day 1, 45 (45/47; 95.7%) had none, while 2 (2/47; 4.3%) had slight eye irritation; both of these had no eye irritation at the 90 minute timepoint. On Day 7, 46 (46/47; 97.9%) had none, while 1 (1/47; 2.1%) had severe eye irritation; this subject was noted to have "allergic or viral" then "bacterial conjunctivitis". On Day 14, 44 returned for evaluation; 43 (43/44; 97.7%) had none, while 1 (1/43; 2.3%) had slight eye irritation.

Table 90: Eye Irritation Evaluation in Trial Ha02-003

Visit	Severity of Eye Irritation	Xeglyze		Vehicle (N=47)
		0.37% (N=46)	0.74% (N=49)	
Screening-Pre-Dose	N	46	49	47
	NONE	41/46 (89.1%)	40/49 (81.6%)	37/47 (78.7%)
	SLIGHT	5/46 (10.9%)	9/49 (18.4%)	10/47 (21.3%)
	MODERATE	0	0	0
	SEVERE	0	0	0
Screening-90 minutes Post-Dose	N	46	49	47
	NONE	44/46 (95.7%)	46/49 (93.9%)	38/47 (80.9%)
	SLIGHT	2/46 (4.3%)	3/49 (6.1%)	9/47 (19.1%)
	MODERATE	0	0	0
	SEVERE	0	0	0
Day 1	N	42	48	47
	NONE	41/42 (97.6%)	46/48 (95.8%)	45/47 (95.7%)
	SLIGHT	1/42 (2.4%)	2/48 (4.2%)	2/47 (4.3%)
	MODERATE	0	0	0
	SEVERE	0	0	0
Day 7	N	42	48	47
	NONE	41/42 (97.6%)	48/48 (100.0%)	46/47 (97.9%)
	SLIGHT	1/42 (2.4%)	0	0
	MODERATE	0	0	0
	SEVERE	0	0	1/47 (2.1%)

Visit	Severity of Eye Irritation	Xeglyze		Vehicle (N=47)
		0.37% (N=46)	0.74% (N=49)	
Day 14	N	42	48	44
	NONE	39/42 (92.9%)	47/48 (97.9%)	43/44 (97.7%)
	SLIGHT	3/42 (7.1%)	1/48 (2.1%)	1/44 (2.3%)
	MODERATE	0	0	0
	SEVERE	0	0	0

Source: Applicant's submission; Adapted from Table 14.3.5.1, Ha02-003 CSR

In **Trial Ha03-003**, a pediatric safety and PK trial in children 6 months to <18 years of age, 19 (19/22; 86.4%) had no eye irritation at screening; 3 (3/22; 13.6%) had mild eye irritation. At Day 1, 20 (20/22; 90.9%) had none, while 2 (2/22; 9.1%) had mild eye irritation. No subjects had eye irritation at the Day 7 or 14 visits.

In **Trial Ha03-004**, a pediatric maximal use trial in children 6 months to 17 years of age, evaluated 38 subjects. From the CSR: "One subject (b) (6) had slight irritation of the lids, sclera and conjunctiva at Day 1 and one subject (b) (6) had slight irritation of the lids, sclera and conjunctiva at the Screening and Days 1, 7 and 14 visits."

In the Phase 2 trials, new-onset eye irritation after treatment with Xeglyze was observed less commonly than in the Phase 3 trials. However, as seen in the Phase 3 trials, subjects with eye irritation at baseline tended to improve after treatment. This occurred in both Xeglyze and Vehicle groups.

Local Safety: Conclusions and Implications for Product Labeling

In conclusion, the most clinically relevant aspect of the active assessment of local safety are those exam findings that were absent at the Baseline visit, but present at the Day 1 visit. Table 91 displays results of the active assessment of local safety in the pooled Phase 3 population. Events described during the active assessment of local safety which occurred at a frequency of >1%, and more frequently with Xeglyze than Vehicle, will be included in a separate table in Section 6.1 in the Adverse Reactions section of Xeglyze labeling.

Table 91: Results of Active Assessment of Local Safety: Signs/Symptoms Absent at Baseline but Present on Day 1

Signs/Symptoms	Xeglyze (N=349)	Vehicle (N=350)
Erythema/Edema	11 (3.2%)	5 (1.4%)

Signs/Symptoms	Xeglyze (N=349)	Vehicle (N=350)
Pruritus	2 (1.4%)	1 (0.7%)
Excoriation/Pyoderma	0	3 (0.9%)
Ocular Irritation	6 (1.7%)	5 (1.4%)

Source: Reviewer's Table

Treatment Emergent Adverse Events (TEAE) in the Phase 3 Trials

The Phase 3 protocols defined TEAE as any new-onset untoward medical occurrence, or worsening of a pre-existing medical condition, temporally associated with treatment with Xeglyze or Vehicle. Investigators asked subjects or caregivers about AE at the Baseline, Day 1, Day 7, and Day 14 Visits, using non-leading questions. In general, investigators identified more subjects Treatment-Emergent Adverse Events (TEAE) in the Xeglyze group than in the Vehicle group. Investigators reported TEAE most frequently in the system organ classes of Skin and Subcutaneous Disorders, and Respiratory and Mediastinal Disorders. Table 92 displays a listing of TEAE (System Organ Class (SOC) and Dictionary-Defined Term) for the pooled Phase 3 population, sorted by treatment arm.

Table 92: TEAE by SOC/Preferred Term and Treatment Arm, Pooled Phase 3 Population

Body System or Organ Class	Preferred Term	Xeglyze (N=349)	Vehicle (N=350)
Blood and lymphatic system disorders	Anemia	0 (0.0%)	1 (0.3%)
Ear and labyrinth disorders	Ear pain	0 (0.0%)	1 (0.3%)
Eye disorders	Conjunctival hyperemia	1 (0.3%)	0 (0.0%)
	Conjunctivitis	1 (0.3%)	2 (0.6%)
	Conjunctivitis allergic	0 (0.0%)	1 (0.3%)
	Eye irritation	4 (1.1%)	2 (0.6%)
	Eye pruritus	0 (0.0%)	1 (0.3%)
	Scleral disorder	0 (0.0%)	2 (0.6%)
Gastrointestinal disorders	Chapped lips	0 (0.0%)	1 (0.3%)
	Diarrhea	2 (0.6%)	1 (0.3%)
	Gastritis	0 (0.0%)	1 (0.3%)
	Nausea	3 (0.9%)	0 (0.0%)
	Vomiting	6 (1.7%)	2 (0.6%)
General disorders and administration site conditions	Application site pain	2 (0.6%)	0 (0.0%)
	Local swelling	0 (0.0%)	1 (0.3%)
	Edema	0 (0.0%)	1 (0.3%)

Body System or Organ Class	Preferred Term	Xeglyze (N=349)	Vehicle (N=350)
	Pain	1 (0.3%)	0 (0.0%)
	Pyrexia	1 (0.3%)	4 (1.1%)
	Vessel puncture site hemorrhage	1 (0.3%)	0 (0.0%)
Infections and infestations	Bronchitis	0 (0.0%)	1 (0.3%)
	Gastroenteritis	1 (0.3%)	0 (0.0%)
	Nasopharyngitis	0 (0.0%)	1 (0.3%)
	Otitis media	0 (0.0%)	1 (0.3%)
	Pharyngitis	3 (0.9%)	1 (0.3%)
	Pharyngitis streptococcal	4 (1.1%)	1 (0.3%)
	Pyoderma	0 (0.0%)	1 (0.3%)
	Sinusitis	0 (0.0%)	1 (0.3%)
	Urinary tract infection	1 (0.3%)	1 (0.3%)
Injury, poisoning and procedural complications	Animal bite	0 (0.0%)	1 (0.3%)
	Arthropod bite	1 (0.3%)	3 (0.9%)
	Excoriation	0 (0.0%)	1 (0.3%)
Investigations	Alanine aminotransferase increased	0 (0.0%)	2 (0.6%)
	Blood alkaline phosphatase increased	1 (0.3%)	0 (0.0%)
	Blood chloride increased	1 (0.3%)	0 (0.0%)
	Blood lactate dehydrogenase increased	1 (0.3%)	0 (0.0%)
	Blood potassium increased	1 (0.3%)	1 (0.3%)
	Blood urea increased	0 (0.0%)	1 (0.3%)
	Cardiac murmur	1 (0.3%)	0 (0.0%)
	Hepatic enzyme increased	0 (0.0%)	1 (0.3%)
	Neutrophil count decreased	1 (0.3%)	0 (0.0%)
	Protein total decreased	1 (0.3%)	0 (0.0%)
	White blood cell count decreased	1 (0.3%)	0 (0.0%)
Metabolism and nutrition disorders	Diabetes mellitus	1 (0.3%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Arthralgia	1 (0.3%)	0 (0.0%)
	Back pain	1 (0.3%)	1 (0.3%)
Nervous system disorders	Burning sensation	0 (0.0%)	1 (0.3%)
	Dizziness	1 (0.3%)	0 (0.0%)
	Headache	2 (0.6%)	5 (1.4%)
	Paresthesia	1 (0.3%)	0 (0.0%)
Psychiatric disorders	Sleep disorder	0 (0.0%)	1 (0.3%)
Renal and urinary disorders	Renal impairment	0 (0.0%)	1 (0.3%)
	Renal pain	1 (0.3%)	0 (0.0%)

Body System or Organ Class	Preferred Term	Xeglyze (N=349)	Vehicle (N=350)
Respiratory, thoracic and mediastinal disorders	Asthma	1 (0.3%)	0 (0.0%)
	Cough	3 (0.9%)	3 (0.9%)
	Nasal mucosal disorder	1 (0.3%)	0 (0.0%)
	Oropharyngeal pain	1 (0.3%)	0 (0.0%)
	Pharyngeal erythema	2 (0.6%)	0 (0.0%)
	Productive cough	0 (0.0%)	1 (0.3%)
	Respiratory disorder	0 (0.0%)	1 (0.3%)
	Rhinitis allergic	1 (0.3%)	0 (0.0%)
	Rhinorrhea	5 (1.4%)	1 (0.3%)
	Tonsillar hypertrophy	2 (0.6%)	0 (0.0%)
	Wheezing	1 (0.3%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Dermatitis	0 (0.0%)	3 (0.9%)
	Dermatitis contact	6 (1.7%)	4 (1.1%)
	Dry skin	0 (0.0%)	3 (0.9%)
	Erythema	14 (4.0%)	6 (1.7%)
	Hair color changes	3 (0.9%)	0 (0.0%)
	Pruritus	3 (0.9%)	10 (2.9%)
	Rash	11 (3.2%)	8 (2.3%)
	Rash erythematous	0 (0.0%)	1 (0.3%)
	Rash pruritic	0 (0.0%)	1 (0.3%)
	Skin burning sensation	9 (2.6%)	0 (0.0%)
	Skin disorder	2 (0.6%)	0 (0.0%)
	Skin exfoliation	3 (0.9%)	8 (2.3%)
	Skin irritation	2 (0.6%)	0 (0.0%)
	Skin plaque	0 (0.0%)	2 (0.6%)
	Swelling face	0 (0.0%)	1 (0.3%)
	Urticaria	0 (0.0%)	2 (0.6%)
Vascular disorders	Hypotension	0 (0.0%)	1 (0.3%)
	Lymphedema	1 (0.3%)	0 (0.0%)

Source: Reviewer's Table; created in JReview using applicant's datasets

Table 93 displays common adverse events, i.e. adverse events occurring in >1% of the safety population and at a greater frequency in Xeglyze than Vehicle. Erythema and eye irritation reported below are AE reports elicited by investigators from subjects, as opposed to erythema and eye irritation documented by investigators during the active assessment of local safety.

Table 93: Common TEAE and AE of Interest, Pooled Phase 3 population

	Xeglyze (N=349) Subjects (%)	Vehicle (N=350) Subjects (%)	Adverse Event vs Adverse Reaction*
Erythema	14 (4.0)	6 (1.7)	AR
Rash	11 (3.2)	8 (2.3)	AR
Skin burning sensation	9 (2.6)	0 (0.0)	AR
Contact dermatitis	6 (1.7)	4 (1.1)	AR
Vomiting	6 (1.7)	2 (0.6)	AR
Rhinorrhea	5 (1.3)	1 (0.3)	AE
Eye Irritation	4 (1.2)	2 (0.6)	AE
Pharyngitis streptococcal	4 (1.2)	1 (0.3)	AE
Hair color changes	3 (0.9)	0 (0.0)	AR

Source: Reviewer's Table; * AR to be included in product labelling

Erythema, Rash and Skin Burning Sensation

The applicant reported a total of 14 (14/349; 4.0%) subjects who had erythema, 11 (11/349, 3.2%) subjects who developed rash, and 9 (9/349, 2.6%) who complained of skin burning sensation after treatment with Xeglyze. Again, erythema discussed here is an AE report elicited by investigators from subjects, as opposed to erythema documented by investigators during the active assessment of local safety. Independent analysis of the applicant's datasets revealed the same results. I concur with the applicant's decision to include these in the proposed labeling.

Contact Dermatitis

Six subjects (6/349; 1.7%) in the Phase 3 population treated with Xeglyze had contact dermatitis as reported by investigators, compared to 4 (4/350; 1.1%) in the Vehicle group. In Trial Ha03-006, a dermal safety trial to evaluate the potential of Xeglyze to induce contact sensitization, 2 (2/206; 0.97%) subjects showed evidence suggestive of sensitization. The Phase 3 trials were conducted in subjects with head lice infestation; in contrast, the dermal safety trials were conducted in healthy subjects.

The applicant has reported contact dermatitis as an AR in the proposed labeling; I agree that it should be included. Table 94 graphically displays characteristics of the 6 subjects treated with Xeglyze who experienced the AR of contact dermatitis.

Table 94: Subjects with AE of Contact Dermatitis, treated with Xeglyze, Pooled Phase 3 Safety Population

Subject ID	Age	Onset/Resolution (Study Day)	Severity	Outcome	Relation to Xeglyze treatment[1]	Notes
(b) (6)	7 years	2/15	Moderate	Recovered	Possibly Related	"Contact dermatitis over ear lobes, back of neck"2
	9 years	2/15	Mild	Recovered	Probably Related	"Contact dermatitis of neck and cheeks"[2]
	5 years	6/10	Mild	Recovered	Probably Related	"Irritant Dermatitis"[2]
	8 years	9/10	Mild	Recovered	Probably Related	"Irritant Dermatitis", "Scalp Discomfort"[2] on day 1
	10 years	6/10	Mild	Recovered	Probably Related	"Irritant Dermatitis"[2]
	11 years	6/ongoing	Mild	Ongoing	Probably Related	"Irritant Dermatitis"[2]

Source: Reviewer's Table, 1- Relationship to study drug as judged by investigator, 2- From Listing 16.2.7.1.2, Ha03-001 CSR

Vomiting

In the pooled Phase 3 population (Trials Ha03-001 and Ha03-002), vomiting occurred in 6 (6/349; 1.7%) subjects in the Xeglyze group and 2 (2/350; 0.6%) in the Vehicle group. In Trial Ha03-001, 2 subjects, a 5 year old female (Subject (b) (6)) and 16 year old female (Subject (b) (6) are siblings who experienced nausea and vomiting; Subject (b) (6) experienced diarrhea also. Subject (b) (6) experienced nausea and vomiting which began on Day 1 and resolved on Day 2, followed by the sibling (b) (6) whose symptoms began on Day 3 and resolved on Day 4. Laboratory studies (including hematology, electrolytes, and liver and renal function studies) for both subjects were unremarkable; vital signs and physical exam findings were normal. The severity was mild, and both subjects recovered. Investigators judged the relationship of the vomiting to Xeglyze as "unlikely", which the applicant defines as "Onset of the AE had a reasonable temporal relationship to study product administration and although a causal relationship was unlikely, it was biologically plausible."

Four subjects in Trial Ha03-002 experienced vomiting. An 11 month old female, (Subject (b) (6) experienced "vomiting during treatment of hair"; vomiting began and resolved on Day 1. The vomiting was mild in intensity and the subject recovered. Vital signs and physical examination were normal; laboratory studies were not performed because investigators were unable to obtain blood samples. Investigators judged the vomiting to be "possibly" related to Xeglyze, which the applicant defines as "Onset of the AE had a strong temporal relationship to administration of the IP, could not be explained by the subject's clinical state or other factors, and a causal relationship was biologically plausible".

A 9 year old female subject (Subject (b) (6) experienced "vomiting a few hours after treatment", which began and resolved on Day 1. The vomiting was moderate in intensity and the subject recovered. Vital signs and physical examination were normal; laboratory studies were not performed because investigators were unable to obtain blood samples. Investigators judged the vomiting to be "possibly" related to Xeglyze.

A 3 year old female (Subject (b) (6) experienced vomiting which began on Day 5 and resolved on Day 6. The vomiting was mild in intensity and the subject recovered. Vital signs were normal and laboratory results (including hematology, electrolytes, and liver and renal function studies) were unremarkable; other than "redness of the ears and scalp" on Day 1, the physical exam was normal also. Investigators judged the vomiting to be "unlikely" to be related to Xeglyze.

A 4 year old female (Subject (b) (6) developed vomiting on Day 10, and diarrhea on Day 13, and also fever. The vomiting and diarrhea were moderate in intensity and were marked "ongoing" at the end of the study. Vital signs were normal and baseline lab results including hematology, electrolytes, and liver and renal function studies) were unremarkable; investigators were unable to obtain blood for Day 14 laboratory studies. A full physical examination on Day 14 noted the subject "appeared ill" but no other abnormal physical findings were noted. The Day 14 examination included a normal gastrointestinal examination. Investigators judged the vomiting, fever, and diarrhea to be "unlikely" to be related to Xeglyze.

Although pediatric PK data were insufficient to calculate the half-life of Xeglyze in children, the half- life in adults was approximately 21 hours. The applicant did not provide the half-life of the carboxyl metabolite due to limited available data; however, using data from 6 adult subjects in Ha02-003 a rough estimate of the mean half-life of the carboxyl metabolite was 71 ± 40 hours (per Dr. Doanh Tran, Clinical Pharmacologist). In those subjects where the relationship between Xeglyze and vomiting is judged by the investigator to be unlikely, such a relationship cannot be excluded based on available data. Therefore, I concur with applicant's inclusion of vomiting in Section 6 of the proposed product labeling. Table 95 provides a graphic display of Phase 3 subjects, treated with Xeglyze, who experienced vomiting.

Table 95: Subjects with AE of vomiting, treated with Xeglyze, Pooled Phase 3 Safety Population

Subject ID	Age	Onset/Resolution (Study Day)	Severity	Outcome	Relation to Xeglyze Treatment*	Notes
(b) (6)	5 years	3/4	Mild	Recovered	Unlikely	N/V/D; sib (b) (6) also affected
	16 years	1/2	Mild	Recovered	Unlikely	N/V; sib (b) (6) also affected
	4 years	10/ongoing	Moderate	Ongoing	Unlikely	Fever, Diarrhea also
	3 years	5/6	Mild	Recovered	Unlikely	N/V
	11 months	1/1	Mild	Recovered	Possibly	Vomiting during Tx of hair
	9 years	1/1	Moderate	Recovered	Possibly	Vomiting a few hours after Tx

Source: Reviewer's Table; *in the judgment of the investigator

Hair Color Changes

During Trial Ha03-002 (Phase 3), investigators reported hair discoloration (pink/red) in a total of 3 (3/349; 1%) subjects treated with Xeglyze (Subjects (b) (6) from the same trial site in Mississippi. One subject had blond hair and the other 2 had brown hair. Xeglyze was applied to and left on their hair for 10 minutes as per application instructions. These events all resolved within 7 days. The applicant has included this AE in the proposed labeling. No hair discoloration was seen in the Vehicle Group.

Hair discoloration also occurred during one of the Phase1 trials. During Trial Ha02-005, investigators reported hair discoloration (pink) in 1 subject (Subject (b) (6)). The subject had chemically-treated blond hair. Xeglyze was applied to and left on the hair for 60 minutes during Part 1 of the trial. The investigator judged the event to be not serious, moderate in intensity, and probably related to the trial drug. This event resolved within approximately 2.5 months. It is possible that the longer persistence of discoloration than occurred in Phase 3 is a result of the much longer application time in the Phase 1 trial.

The mechanism of action of Xeglyze is chelation of metal cations such as iron and zinc. In the presence of the ferrous (Fe^{+2}) ion, Xeglyze forms a water-soluble pink/red colored complex at

iron concentrations as low as 1 ppm. Iron is commonly found in both well and tap water at varying concentrations.

Rhinorrhea

Five subjects (5/349; 1.4%) in the Phase 3 population treated with Xeglyze had rhinorrhea, compared to 1 (1/350; 0.3%) in the Vehicle group. The investigators concluded that the rhinorrhea was unrelated to treatment with Xeglyze. In all 5 cases, the onset and duration of rhinorrhea did not temporally correlate with treatment. Additionally, all cases of rhinorrhea occurred in pediatric subjects, in whom viral URI occur more commonly. Therefore, I concur with the conclusion of the investigators that rhinorrhea, although it occurred more commonly than in the Vehicle group, is not related to treatment with Xeglyze and therefore does not need to be included in labeling. The applicant did not include rhinorrhea in the AE section of the proposed Labeling. Table 96 graphically displays subjects in the Xeglyze group who experienced rhinorrhea, along with information about associated symptoms.

Table 96: Subjects with AE of Rhinorrhea, treated with Xeglyze, Pooled Phase 3 Safety Population

Subject ID	Age/Sex	Onset/Resolution (Study Day)	Severity	Outcome	Relation to Xeglyze treatment*	Notes (from Applicant's AE Listings)
(b) (6)	6 years/F	2/9 16/ongoing	Mild (all Sx)	Ongoing	Not related	Rhinorrhea d2-9, 16-on; Lt AC nodes swell and turbinate edema d10-on; cough and eryth nasal mucosa d16-on
	4 years/F	15/ongoing	Mild	Ongoing	Not related	Rhinorrhea d15-on
	3 years/F	12/ongoing	Mild	Ongoing	Not related	Rhinorrhea & Pharyngeal erythema d12-on
	7 years/F	12/ongoing	Mild	Ongoing	Not related	Rhinorrhea & Pharyngeal erythema d12-on; elev. ALT (BL) and AST (BL,d14)

Subject ID	Age/Sex	Onset/Resolution (Study Day)	Severity	Outcome	Relation to Xeglyze treatment*	Notes (from Applicant's AE Listings)
(b) (4)	15 years/F	2/ongoing	Mild	Ongoing	Not related	Rhinorrhea d2-on

Source: Reviewer's Table; *in the judgment of the investigator

Analysis by Subgroup

The frequency of TEAE was analyzed by subgroups including gender and stratification by age group. Appendix 13.3 contains tables which display AE rates by subgroup. The rates of occurrence of TEAE were evenly distributed across subgroups. The number of subjects of non-White race was insufficient to conduct meaningful racial subgroup analysis.

Adverse Reactions

Adverse events classified as probably, possibly, or unlikely related to treatment with Xeglyze are classified as adverse reactions (AR). Adverse reactions occurring in >1% of subjects, and with a greater frequency in the Xeglyze group than the Vehicle group are displayed in Table 97 and will be included in product labeling. AE derived from active assessment of local safety (scalp erythema and pruritus, eye irritation) will be presented in a separate table in the labeling for Xeglyze.

Table 97: Treatment-Related Adverse Reactions, Pooled Phase 3 Population

	Xeglyze (N=349) Subjects (%)	Vehicle (N=350) Subjects (%)
Erythema	14 (4.0)	6 (1.7)
Rash	11 (3.2)	8 (2.3)
Skin burning sensation	9 (2.6)	0 (0.0)
Contact dermatitis	6 (1.7)	4 (1.1)
Vomiting	6 (1.7)	2 (0.6)
Eye Irritation	4 (1.2)	2 (0.6)
Hair color changes	3 (0.9)	0 (0.0)

Source: Reviewer's Table

Phase 2 Trials

The applicant reported no treatment-related AE for Studies Ha02-002, Ha03-003, or Ha03-004. In Trial Ha02-003 (in which subjects 2 years of age and older with head lice infestation were treated with Xeglyze 0.37%, Xeglyze 0.74%, or Vehicle), a total of 26 subjects experienced treatment-related AE. Treatment related AE were more common in the Vehicle group (13/47, 27.7%) than in the Xeglyze 0.74% (8/49, 16.3%) or Xeglyze 0.37% (5/46, 10.9%). Table 98 displays treatment related AE observed in Trial Ha02-003, grouped by system organ class (SOC) and preferred term. Monitored adverse events recorded during the active assessment of local safety are considered separately and discussed in Evaluation of Local Safety section of this review.

Table 98: Treatment Related AE in Trial Ha02-003

SOC/Preferred Term[a]	**Trial Ha02-003**		
	Xeglyze 0.37% n= 46	**Xeglyze 0.74% n = 49**	**Vehicle n = 47**
Overall Incidence[b]	**5 (10.9)**	**8 (16.3)**	**13 (27.7)**
Skin and Subcutaneous Tissue Disorders	**5 (10.9)**	**6 (12.2)**	**12 (25.5)**
Pruritus	4 (8.7)	2 (4.1)	12 (25.5)
Dermatitis allergic	0	2 (4.1)	0
Dermatitis contact	0	2 (4.1)	0
Dry skin	0	0	1 (2.1)
Exfoliative rash	0	1 (2.0)	0
Rash	1 (2.2)	0	0
Nervous System Disorders	0	1 (2.0)	0
Headache	0	1 (2.0)	0
Hyperesthesia	0	1 (2.0)	0
Eye Disorders	0	1 (2.0)	1 (2.1)
Ocular hyperemia	0	1 (2.0)	0
Conjunctival hyperemia	0	0	1 (2.1)
Infections and infestations	0	1 (2.0)	0
Cellulitis	0	1 (2.0)	0

Source: Applicant's submission; Table 9, Summary of Clinical Safety

a Values for SOC and preferred term are given as the number of events reported.

b Values for Overall Incidence are given as the number of subjects that reported an AE during trial execution. If an event was reported more than once by a subject, it was only counted once for the Overall Incidence.

8.4.6 **Laboratory Findings**

Assessment of systemic safety of Xeglyze, applied topically for the treatment of head lice infestation, included monitoring of clinical laboratory parameters. Investigators performed clinical laboratory testing at baseline and at various points after application of Xeglyze. We will discuss the tests performed as well as the timing of the tests for the Pivotal Phase 3 and the Phase 2/PK trials.

Laboratory Assessments: Phase 3 Trials

Investigators conducted hematology and blood chemistry measurements at baseline and Day 14 in each of the Phase 3 trials. Hematology parameters included hemoglobin, red blood cell (RBC) count, hematocrit, mean cell volume, white blood cell (WBC) count, WBC differential count, and platelet count; blood chemistry parameters included sodium, potassium, bicarbonate, chloride, calcium, phosphate, blood urea nitrogen (BUN), creatinine, glucose, aspartate aminotransferase (AST),alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transferase (GGT), lactate dehydrogenase, total bilirubin, total protein, and albumin. No significant treatment-related changes occurred in either hematology or blood chemistry results during the Phase 3 trials.

A comparison between the hemoglobin, hematocrit, leukocytes, and platelets at Visit Number 0 (Screening) and Visit 3 (Day 14) for Xeglyze abametapir lotion, 0.74% and Vehicle are diagrammed in Figures 4-7.

Figure 4: Pre- and Post-Treatment (Day 14) Hematocrit by Treatment Arm

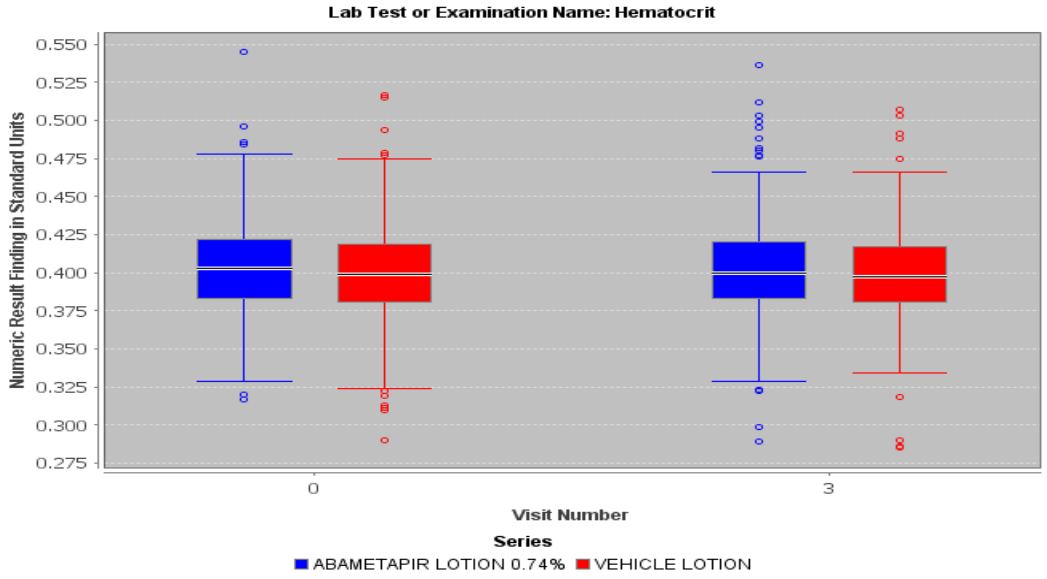


Figure 5: Pre- and Post-treatment (Day 14) Hemoglobin by Treatment Arm

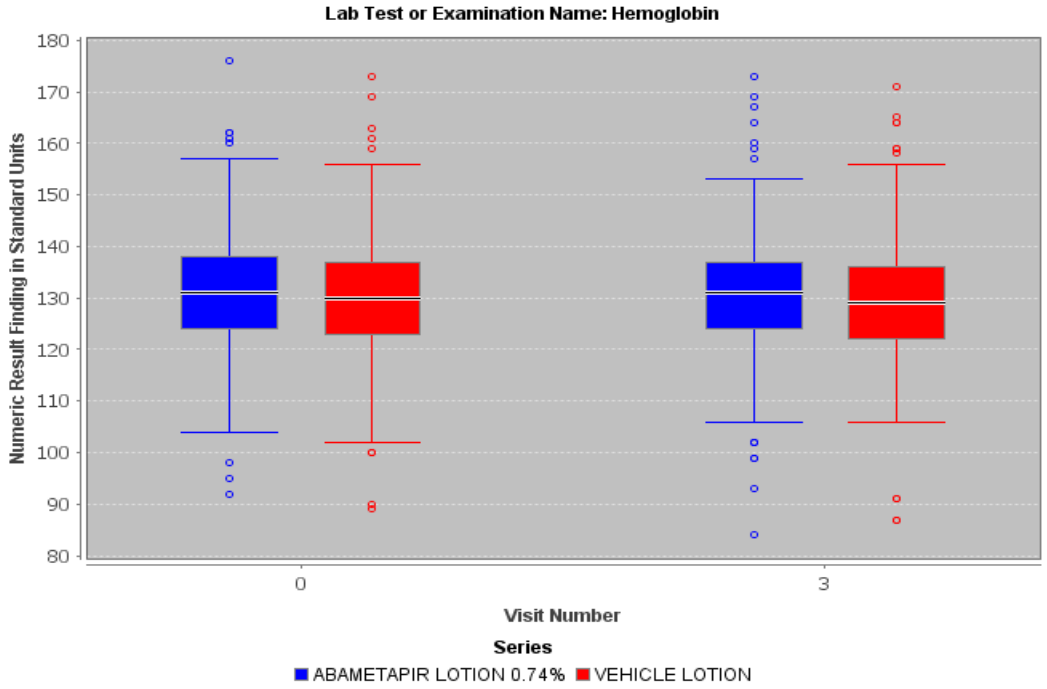


Figure 6: Pre- and Post-treatment (Day 14) Leukocyte count by Treatment Arm

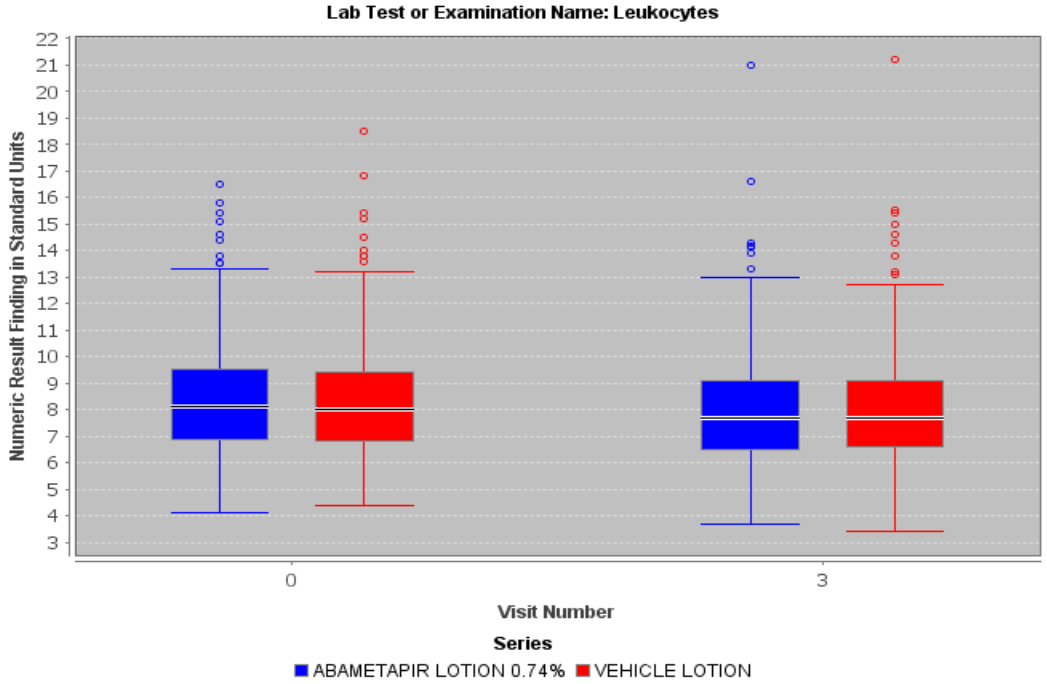
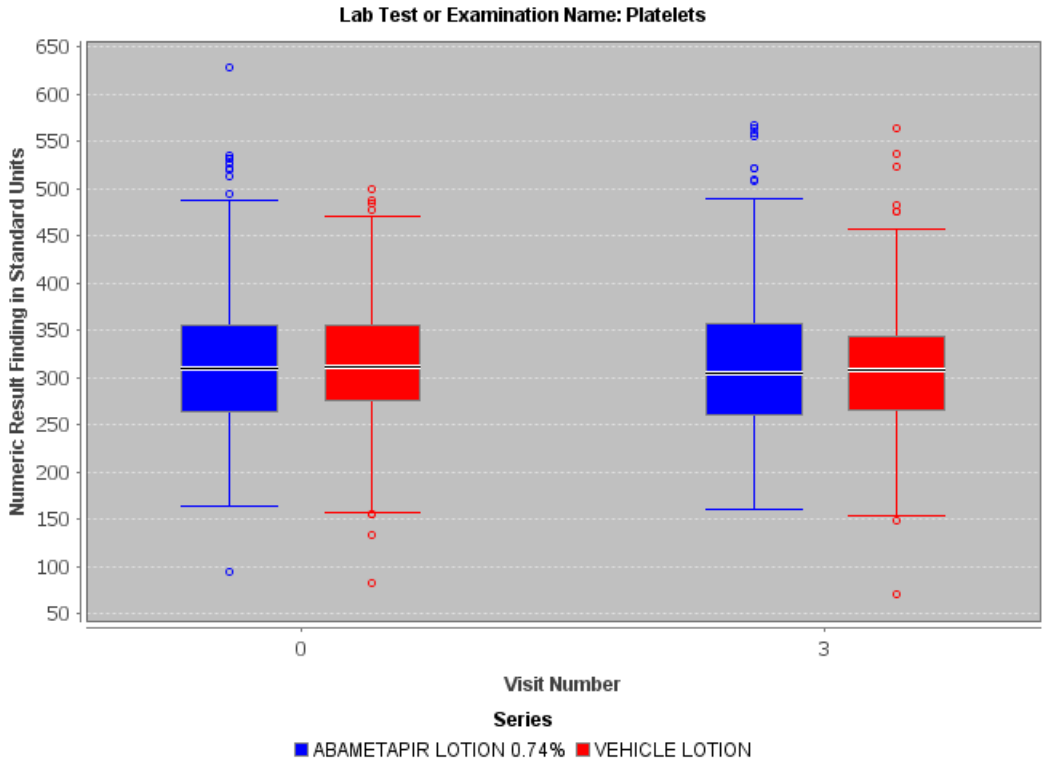


Figure 7: Pre- and Post-treatment (Day 14) Platelet count by Treatment Arm



A comparison between the ALT, AST, Alkaline Phosphatase, and Bilirubin at Visit Number 0 (Screening) and Visit 3 (Day 14) for Xeglyze (Abametapir) lotion, 0.74% and Vehicle are diagrammed in Figures 8-11.

Figure 8: Pre- and Post-treatment (Day 14) ALT by Treatment Arm

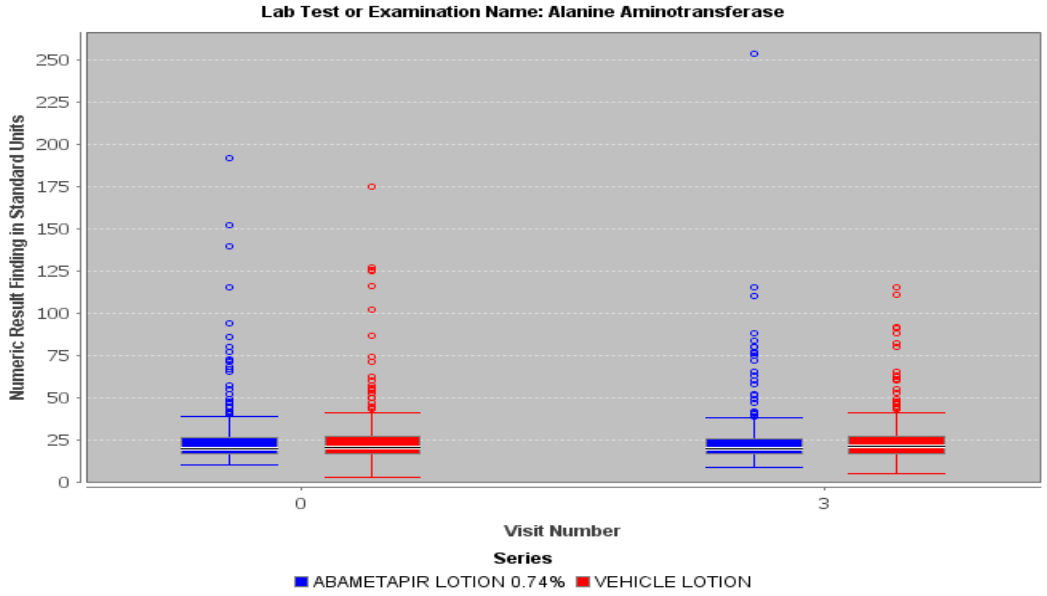


Figure 9: Pre- and Post-treatment (Day 14) AST by Treatment Arm

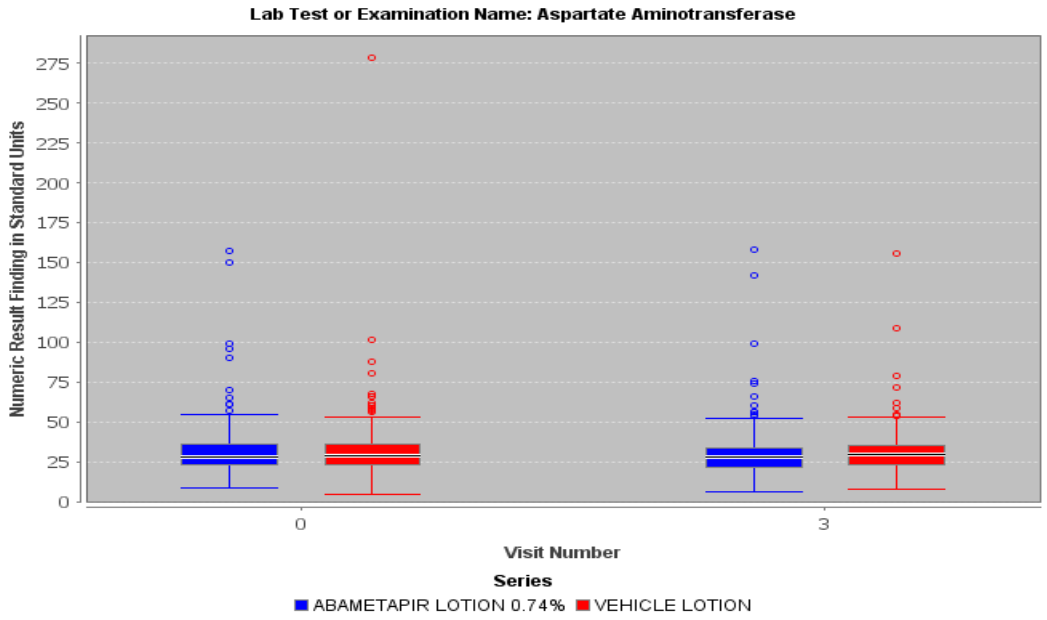


Figure 10: Pre- and Post-treatment (Day 14) Alkaline Phosphatase by Treatment Arm

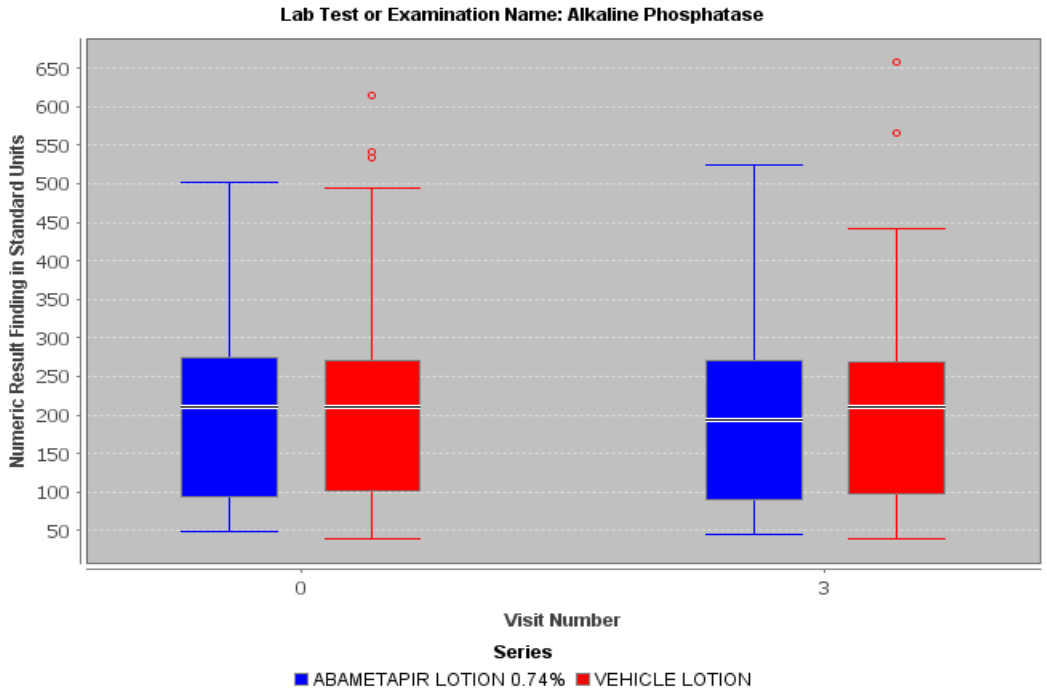
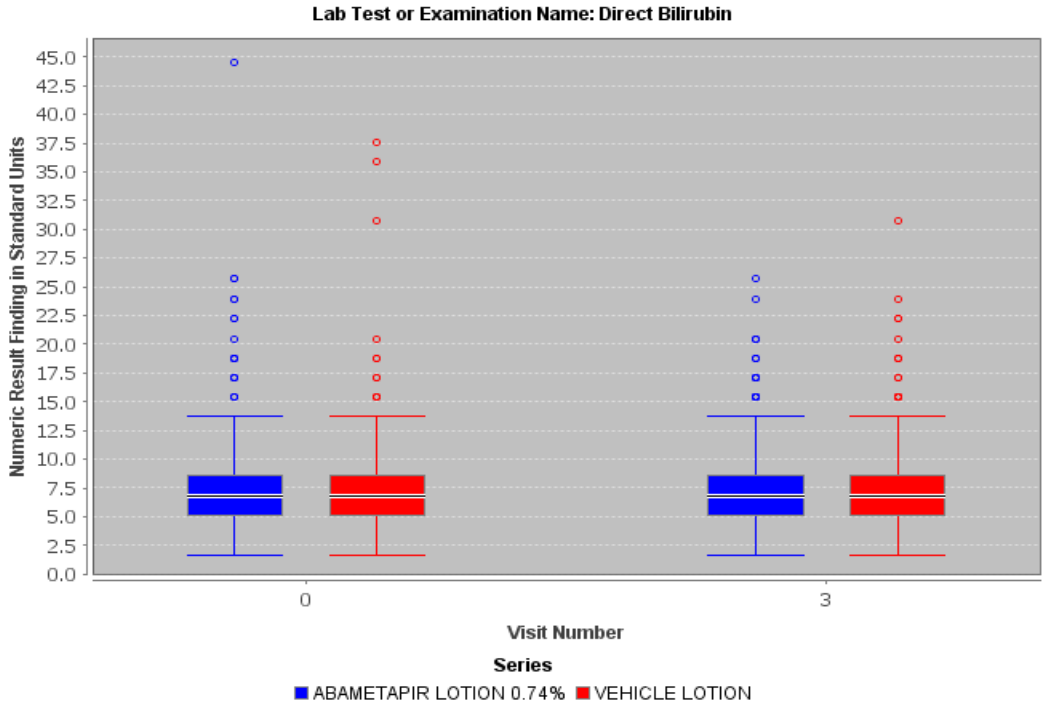


Figure 11: Pre- and Post-treatment (Day 14) Bilirubin by Treatment Arm



Overall, there were no abnormal laboratory values reported as AR related to treatment with Xeglyze in the Phase 3 studies. Table 75 displays a summary of the clinically significant laboratory changes that occurred during the Phase 3 studies.

Table 99: Summary of Laboratory Changes during the Phase 3 Trials

Trial / Treatment Group	Adverse Event	Trial Day	Causality	Severity
Ha03-001 / Vehicle	Elevated potassium	Day 14 Visit	Possibly Related	Mild
Ha03-001 / Vehicle	Increased ALT	Day 14 Visit	Unlikely Related	Mild
Ha03-001 / Vehicle	Worsening serum ALT	Day 14 Visit	Possibly Related	Mild
Ha03-001 / Vehicle	Increased liver enzymes	Day 14 Visit	Possibly Related	Mild
Ha03-002 / Vehicle	Elevated blood urea nitrogen	Day 14 Visit	Not Related	Mild
Ha03-002/Xeglyze	Elevated LDH	Day 14 Visit	Not Related	Mild
Ha03-002/Xeglyze	Low absolute neutrophil count	Day 14 Visit	Not Related	Mild
Ha03-002/Xeglyze	Low WBC	Day 14 Visit	Not Related	Mild
Ha03-002/Xeglyze	Elevated chloride	Day 14 Visit	Not Related	Mild
Ha03-002/Xeglyze	Elevated potassium	Day 14 Visit	Not Related	Mild
Ha03-002/Xeglyze	Elevated alkaline phosphatase	Day 14 Visit	Not Related	Mild
Ha03-002/Xeglyze	Low protein	Day 14 Visit	Not Related	Mild

Source: Applicant's submission; Trial Ha03-001 CSR Table 35 and Trial Ha03-002 CSR Table 40.

Laboratory Assessments: Phase 2 Trials

In all 4 Phase 2 PK studies, investigators collected hematology measurements, including hemoglobin, RBC, hematocrit, mean cell volume, WBC, WBC differential count, and platelet count. Investigators also collected clinical chemistry measurements, including sodium, potassium, bicarbonate, chloride, calcium, phosphate, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, gamma glutamyl transferase, lactate dehydrogenase, total bilirubin, total protein, and albumin. In Trial Ha02-002, investigators collected blood for these tests at Screening (pre-dose), 24 hours post-dose, Day 7, Day 14, and Day 28. In Trial Ha02-003, investigators collected blood for these measurements at Day 0 (pre-dose), Day 1 and Day 7. In Trial Ha03-003 and Trial Ha03-004, investigators collected blood for hematology and chemistry testing on Day 0 (pre-dose) and Day 14.

The applicant reports that for all 4 studies, there was no evidence of a treatment-related effect on any clinical chemistry measurements and no clinically meaningful trends were observed across the treatment groups.

Vital Signs

Phase 3 Trials

During the Phase 3 trials (Ha03-001 and Ha03-002), investigators performed vital sign assessments at the Screening, Day 1, Day 7, and Day 14 visits. The applicant reported no treatment-related effect on any vital sign measurement during these studies. Investigators observed no clinically meaningful trends across the treatment groups. Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, and temperature) by treatment arm and visit day are graphically displayed in Figures 12-15(Abametapir Lotion 0.74%=Xeglyze).

Figure 12: Systolic Blood Pressure by Treatment Arm and Visit Day

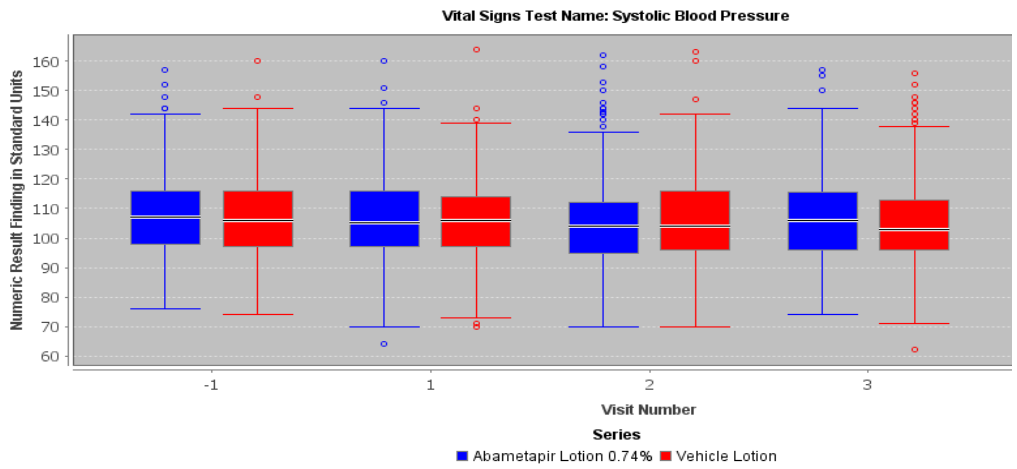


Figure 13: Diastolic BP by Treatment Arm and Visit Day

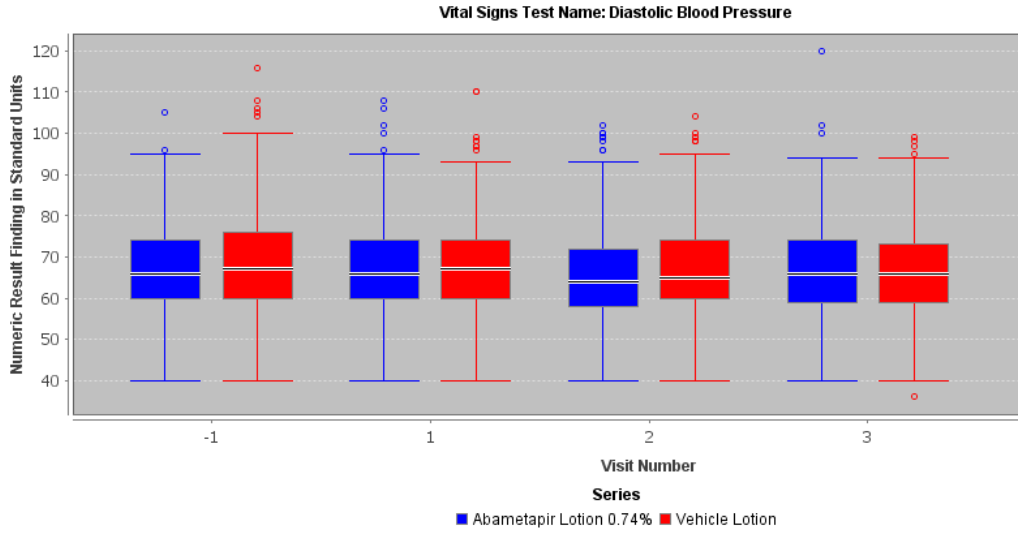


Figure 14: Pulse Rate by Treatment Arm and Visit Day

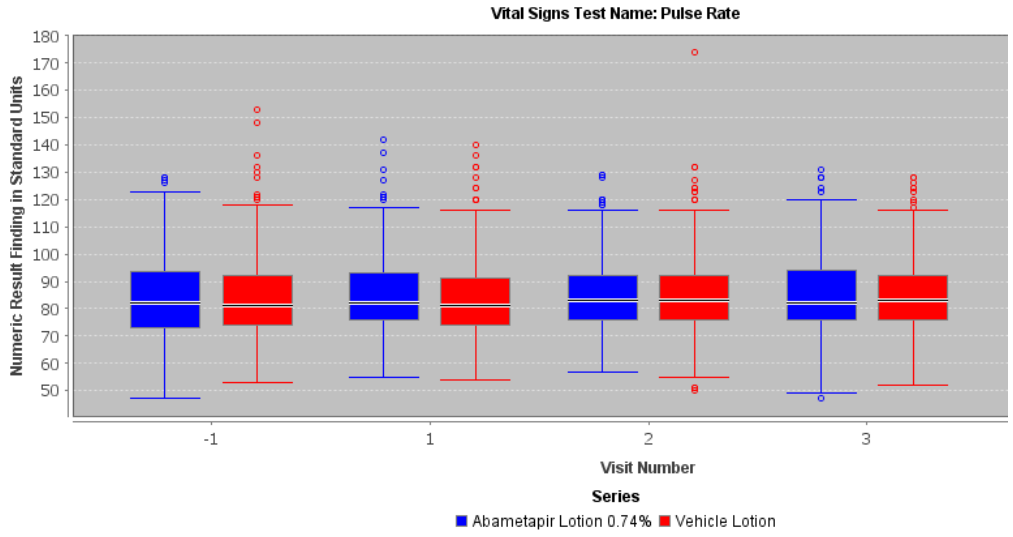
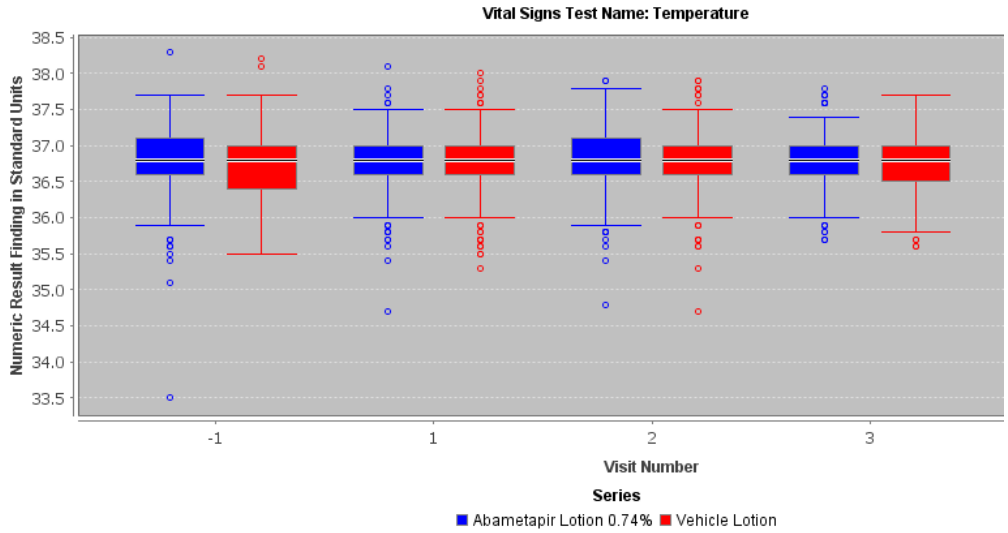


Figure 15: Temperature by Treatment Arm and Visit Day



Phase 2 PK Trials

Investigators recorded vital signs during all 4 Phase 2 trials. For Trial Ha02-002, investigators recorded vital signs at Screening, Pre-Dose, 1, 2, 4, 8, 10 and 24 hours post-dose, Day 7, Day 14 and Day 28. For Trial Ha02-003, investigators recorded vital signs at Screening, 30, 60 and 90 minutes post dose, Day 7 and Day 14. For Trial Ha03-003 and Trial Ha03-004, investigators recorded vital signs at Screening, Day 1, Day 7, and Day 14. As in the Phase 3 trials, the applicant reported no treatment-related effect on any vital sign measurement during these studies; furthermore, no clinically meaningful trends were observed across the treatment groups.

8.4.8. Electrocardiograms (ECGs)

A total of 5 trials in the development program of Xeglyze included cardiac safety monitoring. These were trials Ha01-001, Ha02-002, Ha02-003, Ha02-005, and Ha03-003. Ha02-005 was the Thorough QT trial and is discussed in section 8.4.9. A summary of cardiac safety monitoring is presented in Table 100.

Table 100: Cardiac Safety monitoring by ECG during the development program for Xeglyze

Trial Number	Subject Population	Dosage strength; Duration of application	Timing of ECG recording
Ha02-005	Healthy adults (TQT Trial)	0.74%; 60 minutes to scalp and back	10 min pretreatment; 20 min, 40 min, 1, 2, 3, 6, 12, 24, and 36 hr post dose
Ha01-001	Healthy adults	0.37%, 0.74%; 10 and 20 minutes to hair and scalp	Screening; 24h and Day 28 post dose
Ha02-002	Adults with head lice infestation	0.37%; 10 min or 0.74%; 20 min to hair and scalp	screening, pre-dose; 30 min, 1, 2, 4 and 8 hr, then 1, 7, 14 and 28 days post dose
Ha02-003	Head lice Infestation, Adults, Pediatrics (age 2 years and older)	0.37% or 0.74%; 10 min to hair and scalp	predose, 0.5 and 1 hr, 8 hr and 24 hours post dose
Ha03-003	Head lice infestation, Pediatrics (0.9 to < 18 years of age)	0.74%; 10 min to hair and scalp	pre-dose, 45 minutes and 7.5 hours post dose

Source: Table designed by reviewer with data from CSR

Ha01-001

This Phase 1 trial was conducted in healthy adults to assess the safety, tolerability and absorption of Xeglyze (then referred to as Ha44 Lotion) following topical administration to the hair and scalp. A total of 32 subjects were divided into 4 groups and treated with study product at concentrations of 0.37% and the to-be-marketed strength of 0.74% at durations of 10 and 20 minutes.

ECG was recorded at Screening, 24h after dose and Day 28 (End of Trial). Clinically significant abnormal findings were to be flagged as Adverse Events (AE). All ECGs were reviewed by Investigator and cardiologist (b) (4) Quantitative measurements made on each ECG included heart rate, PR interval, QRS duration, and QT interval.

There were no significant changes in heart rate, PR interval, QRS duration, or QT interval in either the treatment group as a whole, or within the placebo group. Apart from a slightly longer pre-treatment QRS duration in the active treatment groups, there were no differences between the treatment groups and placebo group at any time point. The minor prolongation in QRS duration seen at the one month time point in Cohort 4 is most likely a chance finding and is not statistically significant when corrected for multiple comparisons.

Overall the findings did not suggest any electrocardiographic change as a result of exposure to Ha44.

Ha02-002

This Phase 2a trial enrolled adult subjects with head lice infestation. Thirty (30) eligible subjects were randomized to receive either Xeglyze 0.37% or Vehicle for 10 minutes, or Xeglyze 0.74% or

Vehicle for 20 minutes.

12-lead ECGs were performed in triplicate at screening, pre-dose, 30 minutes, 1, 2, 4 and 8 hours, and then 1, 7, 14 and 28 days post Investigational Product application. The primary ECG endpoint was the QTcF interval. Differences from the respective placebo treatment group in changes from the pre dose baseline were calculated for both doses of Xeglyze at all post dose time points.

Although slight variations in the QTcF were noted, they were not felt to be clinically significant by the applicant nor by the QT-IRT and did not correlate with plasma concentration profiles. While the applicant concluded that the study product at either 0.37% for 10 minutes or 0.74% for 20 minutes had no apparent adverse effect on the QTcF interval, the QT-IRT stated that "small changes in QTc interval (< 10 ms), defined by ICH E14 guidance, cannot be ruled out from the current trial." The QT-IRT also recommended a Thorough QT trial, and that cardiac safety monitoring be included in Trial Ha02-003, which contained pediatric subjects.

Ha02-003

This Phase 2b trial evaluated Xeglyze at 2 different dose levels (0.37% w/v and 0.74% w/v) compared to Vehicle in adults and children (ages 2 and older). ECGs were recorded in triplicate at predose, 0.5 and 1 hr ± 10 minutes, 8 hr ± 10 minutes and 24 hours ± 1 hour. The ECG recordings were then sent to a central laboratory for final interpretation and reporting.

Changes in all ECG numerical data (HR, PR, QRS, QT, and QTc) were small and were similar in all three treatment groups. The changes that were observed were consistent with expected spontaneous variability and circadian change, and therefore not clinically significant. Most ECGs were interpreted as normal, and the applicant concluded that the distribution of the few ECGs with abnormalities was not consistent with a drug effect. These data indicate that the two doses of Ha44 Gel that were tested did not have an effect on the electrocardiogram after single application to the scalp.

Ha03-003

This was a Phase 2, open-label safety and pharmacokinetic (PK) trial of a single application of Xeglyze in a pediatric population 6 months to <18 years of age. All participants had to have an active head lice infestation (at least 3 live lice) and scalp erythema with evidence of excoriation or inflammation. Electrocardiograms (ECGs) were obtained at pre-dose (prior to PK sampling), 45 minutes and 7.5 hours on Day 0.

The majority of the subjects had normal ECG overall assessments throughout the trial. Five (5)

subjects had abnormal ECG overall assessments at Pre-dose (b) (6) 45 minutes (b) (6) and 7.5 hours (b) (6) with the average values of QTcB or QTcF > 450 msec. Highest abnormal values for QTcB (474.3 msec) and QTcF (453.7 msec) that were observed in one subject (b) (6) at 45 min post-dose showed very minor difference (<30 msec) from the standard limit. Three subjects (b) (6) who did have abnormal average ECG finding at their 45 m in post dose values demonstrated no change from baseline in HR, PR, QRS or QTcF duration or any new morphological changes and hence there is no evidence of any drug effect on the ECG. The ECG findings were confirmed by the Division of Cardiovascular and Renal Products. Although the sample size was small, the findings confirm that Xeglyze does not affect cardiac electrical activity in pediatric patients.

In conclusion, none of these trials demonstrated a clinically significant effect of Xeglyze on cardiac electrical activity. A Thorough QT trial was also performed and is discussed in section 8.4.9.

8.4.9. **QT**

A Thorough QT trial was conducted was conducted under Protocol Number Ha02-005. Part 1 of the trial was designed to determine the maximum well-tolerated exposure to Xeglyze (then referred to as Ha44 gel). Investigators applied Xeglyze to the scalp and back of healthy adults for treatment periods of 20, 40, and 60 minutes. Application for 60 minutes proved to be well tolerated, and C_{max} values were 6 times higher than C_{max} seen in trial Ha02-003 (10 minute application, adults and children >2 years of age with head lice infestation). Therefore, investigators chose the 60 minute exposure as the supratherapeutic exposure for Part 2, the TQT evaluation.

Part 2 of trial Ha02-005 was a randomized, double-blind, placebo- and active-controlled, crossover design. There were three treatment periods, and subjects were allocated to one of six treatment sequences. Consecutive treatment periods were separated by a washout period of at least 4 days. The investigator used both placebo and positive (Moxifloxacin) controls. There were 3 treatment arms, defined as follows:

- Treatment A (Ha44 (Xeglyze)): Ha44 0.74% Gel applied to the scalp and back for 60 minutes + moxifloxacin placebo.
- Treatment B (placebo): Placebo Gel applied to the scalp and back for 60 minutes + moxifloxacin placebo.

- Treatment C (moxifloxacin): Placebo Gel applied to the scalp and back for 60 minutes + moxifloxacin 400 mg.

Continuous 12-lead ECGs were extracted in triplicate approximately 1 minute apart at the following timepoints during all confinement periods: within 10 minutes prior to dosing (time 0), and at the following postdose timepoints (±5 minutes):40 minutes, and 1, 1.25, 2, 3, 6, 12, 24, and 36 hours postdose. ECGs were collected before the blood sample collection. Blood samples were collected for pharmacokinetic analysis at predose, and 5 minutes after the following timepoints: 40 minutes, and 1, 1.25, 2, 3, 6, 12, 24, and 36 hours postdose. The QT-IRT deemed the timing of ECG recordings and PK measurement to be acceptable. The QT-IRT conducted its own review and analysis of the ECGs and data from the TQT trial.

Results of Analysis by QT-IRT

Table 101 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 101: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms		Value>480	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
0.74% Ha44 Gel	57	513	57 (100%)	513 (100%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)
Baseline	57	57	57 (100%)	57 (100%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)
Moxifloxacin 400 mg	53	477	51 (96.2%)	474 (99.4%)	2 (3.8%)	3 (0.6%)	0 (.%)	0 (0.0%)
Placebo	54	485	54 (100%)	485 (100%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)

Source: QT-IRT Thorough QT Trial Review

Table 102 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 102: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
0.74% Ha44 Gel	57	513	57 (100%)	513 (100%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)
Moxifloxacin 400	53	477	52	475	1 (1.9%)	2 (0.4%)	0 (.%)	0 (0.0%)
Placebo	54	485	54 (100%)	485 (100%)	0 (0.0%)	0 (0.0%)	0 (.%)	0 (0.0%)

Source: QT-IRT Thorough QT Trial Review

Based on their analysis, the QT-IRT concluded that "No significant QTc prolongation effect of 0.74% Ha44 Gel was detected in this TQT trial. The largest upper bounds of the 2-sided 90% CI for the mean difference between 0.74% Ha44 Gel and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established." (From QT-IRT review of Thorough QT trial, Dr. Qianyu Dang, 14June2013)

Based on these results, as well as the other 4 trials where cardiac safety was monitored, Xeglyze applied topically for the treatment of head lice does not impact cardiac electrical activity, even at supratherapeutic doses. Because the mean C_{max} in this trial was greater than that seen in earlier pediatric PK trials, as well as that expected in subsequent maximal use pediatric studies, cardiac safety monitoring by ECG was not required for the Phase 3 trials.

8.4.10. Immunogenicity

This section is not applicable to this NDA.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hair Discoloration

Three subjects in Trial Ha03-002 and one subject in Trial Ha02-005 experienced red or pink hair discoloration after treatment with Xeglyze. No subjects in the Vehicle group experienced this AE. This AE is discussed in detail in "Evaluation of Local Safety" section of this review.

8.6. Specific Safety Studies/Clinical Trials

Investigators conducted 2 dermal safety studies as part of the development program for Xeglyze. Trial Ha03-006 evaluated the potential of dermal sensitization, and Trial Ha03-007 evaluated potential of dermal irritation from exposure to Xeglyze. These protocols were reviewed under IND 77510 by the Division on December 12, 2013 and found to be acceptable. The Division granted waivers for photoallergy and phototoxicity studies because Xeglyze does not absorb light in the visible wavelengths.

Trial Ha03-006: A Randomized, Controlled Study to Evaluate the Sensitizing Potential of Abametapir Lotion in Healthy Volunteers Using a Repeat Insult Patch Test Design

Objective: To determine the potential of Xeglyze to induce contact sensitization on healthy skin.

Trial Design: Ha03-006 was a single-center, randomized, controlled, within-subject comparison study of the investigational products (Xeglyze and Vehicle), and positive and negative controls, under occlusive conditions, in healthy volunteers.

Number of healthy volunteers: Investigators enrolled 238 subjects, with 206 completing the trial.

Key Inclusion Criteria:

- Healthy adults, male or female, age 18 or older
- Women of childbearing potential willing and able to use an acceptable form of birth control, and have a negative urine pregnancy test at Day 1
- Were of any skin type or race, providing the skin pigmentation allowed discernment of erythema
- Were willing to avoid using topical/systemic analgesics such as aspirin (daily use of 81 mg aspirin was acceptable), Ibuprofen, or systemic/topical antihistamines for 72 hours prior to and during the trial

Key Exclusion Criteria:

- Had any visible skin disease at the application site
- Use of inhaled/systemic/topical corticosteroids in the 3 weeks prior to and during the trial
- Were unwilling or unable to refrain from the use of sunscreens, cosmetics, creams, ointments, lotions, or similar products on the back during the trial

- Presence of psoriasis and/or active atopic dermatitis/eczema
- Had damaged skin in or around the test sites, including sunburn, excessively deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfigurations of the test site
- Had a known sensitivity to adhesives or constituents present in the material being evaluated
- Had a history of, or were currently being treated for skin cancer, or any type of internal cancer within 5 years prior to the trial

Trial Methodology:

Induction Phase:

During the Induction Phase, investigators applied Xeglyze, Vehicle, positive control (sodium lauryl sulfate (SLS) in 1% aqueous solution), and negative control (0.9% saline solution) topically under occlusive conditions. Each application consisted of 0.2 ml of Xeglyze, Vehicle, and controls; each 0.2 ml application was made to a 2 cm x 2 cm area of skin at each site. Investigators performed the applications 3 times weekly for 3 consecutive weeks. Investigators assessed each application site for local irritation after each patch removal during the Induction Phase and scored the assessments using the scales displayed in Tables 103, 104, and 105. Each subject in this trial served as his or her own control. All subjects received the study products and control products at adjacent application sites. Subjects received 9 total applications during the Induction Phase. A 10-14 day rest period separated the Induction and Challenge Phases.

Challenge Phase:

After the 10-14 day rest period, subjects entered the Challenge Phase. The Challenge Phase consisted of a single application of Xeglyze, Vehicle, SLS, and saline, applied under occlusion to a naïve area of the back for 48 hours. Investigators evaluated these application sites at 30 minutes and then 24, 48, and 72 hours after patch removal. If a dermal response indicated possible sensitization, investigators performed a rechallenge. A Rechallenge patch containing the 4 products was to be applied as soon as initial challenge reactions had resolved. Investigators planned to leave the rechallenge patch in place for 48 hours, then reevaluate the subject 30 minutes, then 24, 48, and 120 hours after removal; investigators then compared responses observed in the Challenge and Rechallenge phases to determine whether contact sensitization had taken place.

Table 103: Response symbols and numerical equivalents

Score	Definition
0	No evidence of irritation
1	Minimal erythema; barely perceptible
2	Definite erythema, readily visible; or minimal edema; or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Source: Applicant's submission; Table 9-2, Ha03-006 CSR

Table 104: Effects on Superficial Layers of the Skin

Symbol	Grade	Response
A	0	Slight glazed appearance
C	1	Marked glazing
E	2	Glazing with peeling and cracking
F	3	Glazing with fissures
G	3	Film of dried serous exudate covering all or portion of the patch
H	3	Small petechial erosions and/or scabs

Source: Applicant's submission; Table 9-3, Ha03-006 CSR

Notations (see Table 65) may have been made in addition to a score to designate particular circumstances preventing the assignment of a score or to provide extra information in addition to a score to identify damage to the epidermis and/or spreading of a reaction beyond the patch site.

Table 105: Response Notations

Notation	Response/Comment
S	Spreading of reaction beyond patch study site
B	Burning or stinging sensation
p	Papular response >50%
pv	Papulovesicular response >50%
D	Damage to epidermis: oozing, crusting and/or superficial erosions
I	Itching
X	Subject absent
PD	Patch dislodged
NA	Not applied due to reasons other than dermal reaction
NP	Not patched (due to reaction achieved)
N9G	No ninth grading

Source: Applicant's submission; Table 9-4, Ha03-006 CSR

Results

Disposition of Subjects:

A total of 238 subjects were enrolled and randomized and comprised the safety population. A total of 206 (86.6%) completed the trial and comprised the sensitization population. The trial design also permitted an evaluation of cumulative irritancy; 211 subjects were included in the cumulative irritancy population. Thirty-two (13.4%) subjects discontinued from the trial for reasons described below:

- 13 (13/238; 5.5%) were lost to follow-up
- 6 (6/238; 2.5%) missed more than one induction evaluation visit or any challenge visit
- 5 (5/238; 2.1%) withdrew consent
- 4 (4/238; 1.7%) were subject's request
- 2 (2/238; 0.8%) were or became pregnant
- 1 (1/238; 0.4%) withdrew because of an AE/SAE
- 1 (1/238; 0.4%) was Investigator's judgment

Demographics:

The safety population included 238 subjects, of whom 169 (71.0%) were females and 69 (29.0%) were males. Overall, 211 subjects (88.7%) were White, 26 subjects (10.9%) were Black

or African American, and 1 subject (0.4%) was Asian. One hundred sixty-six subjects (73.8%) were not Hispanic or Latino, and 72 subjects (30.3%) were Hispanic or Latino. Subjects ranged in age from 19 to 75 years with a mean age of 48.4 years. Fitzpatrick skin types of subjects were distributed as follows: 44.1% type III, 22.7% type II, 17.6% type IV, 8.8% type V, and the remaining 6.7% of the subjects had Fitzpatrick skin type I.

Results:

Of the 206 subjects who completed the Challenge Phase of the trial, one subject exhibited sensitivity reactions during induction; two subjects had reactions suggestive of contact sensitization. Subject (b) (6) showed sensitization during the challenge Phase for both Xeglyze and Vehicle. During Rechallenge, the subject again reacted to both Xeglyze and Vehicle. The reactions for each at Rechallenge were less intense than at Challenge; the reaction to Vehicle was more intense than the reaction to Xeglyze at both Challenge and Rechallenge. Subject (b) (6) showed sensitization to Xeglyze during the Challenge and Rechallenge Phase. At Rechallenge, the reaction was less intense and was judged by investigators to represent irritation rather than sensitization.

During the Induction Phase of Trial Ha03-006, investigators also analyzed cumulative irritancy; this analysis included 211 subjects. The mean cumulative irritation score for the Xeglyze site was 0.35, Vehicle site 0.23, SLS 0.1% site 1.03, and saline 0.9% site was 0.12. SLS 0.1% was statistically significantly more irritating than the other sites ($p<0.0001$). The Xeglyze site was statistically significantly more irritating when compared to the Vehicle site ($p=0.003$) and saline 0.9% site ($p<0.0001$), respectively. The Vehicle site was statistically significantly more irritating when compared to the saline 0.9% site ($p=0.008$). Table 106 graphically displays results of the cumulative irritation assessment in Trial Ha03-006.

Table 106: Summary of Mean Irritation Score, Cumulative Irritancy Population, Trial Ha03-006

	Mean Irritation Score (SD)	Treatment Comparison p Values		
		Vehicle	SLS 0.1%	Saline 0.9%
Xeglyze	0.35 (0.55)	0.003	<.0001	<.0001
Vehicle	0.23 (0.50)		<.0001	0.008
SLS 0.1%	1.03 (0.65)			<.0001
Saline 0.9%	0.12 (0.33)			

Source: Applicant's submission; Table 12-2, Ha03-006 CSR

Adverse Events:

During Trial Ha03-006, investigators reported revealed 3 severe AE and 1 serious AE. Subject (b) (6) (who experienced a miscarriage) and Subject (b) (6) (fluid sac on left testicle) are discussed in

more detail in Sections 8.4.2 (Serious Adverse Events) and 8.4.3 (Dropouts and/or Discontinuations due to Adverse Events), respectively. Investigators also reported AE in Subject (b) (6) who experienced a severe headache from trial days 8-11. The headache was severe in intensity. The headache resolved; although investigators ultimately judged the AE to be possibly related to study product, the subject completed the trial. Subject (b) (6) experienced shortness of breath and light headedness from trial days 15-18. Both symptoms were mild in nature, resolved, and investigators judged these symptoms unlikely related to the study treatment.

Conclusions:

Only 2 (2/206; 0.97%) subjects, showed any evidence suggestive of sensitization in Trial Ha03-006. One of these subjects reacted to both Xeglyze and Vehicle during the Challenge Phase; the reaction to Vehicle was more intense. This suggests that Vehicle was the more likely trigger of this subject's reactions. The other subject (1/206; 0.5%) showed a pattern of reaction consistent with sensitization, although investigators judged the reaction to be more consistent with irritation at Rechallenge. These results are not suggestive of a clinically significant contact sensitization risk in a product intended for a single, 10 minute application.

In contrast, investigators reported contact dermatitis in 6 (6/349; 1.7%) subjects in the Phase 3 population, treated with Xeglyze. This is more than would be predicted based on results of Trial Ha03-006. As was discussed in section 8.4.5.2, the Phase 3 subjects had head lice infestation, while the dermal sensitization trial enrolled healthy subjects; this is likely the reason contact dermatitis was reported more frequently in the Phase 3 trials. Contact dermatitis will be included in the Adverse Reactions section of Xeglyze labeling.

Analysis of cumulative irritancy in Trial Ha03-006 revealed that Xeglyze was more irritating than Vehicle and saline control, and that the difference in irritation was statistically significant. Both Xeglyze and Vehicle were less irritating than SLS 0.1% control; this difference was also statistically significant. Trial Ha03-007 was conducted to evaluate the cumulative irritancy potential of Xeglyze; if findings of cumulative irritancy potential are replicated, Xeglyze labeling will need to reflect this.

Trial Ha03-007: "A 21-Day, Randomized, Controlled Study to Evaluate the Irritation Potential of Abametapir Lotion in Healthy Volunteers, Using a Cumulative Irritant Patch Test Design"

Objective: The primary objective of this study was to determine the potential of abametapir lotion to cause irritation after repeated topical application to the healthy skin of humans under controlled conditions.

Trial Design: This was a randomized, evaluator-blind, single-center, controlled, within-subject comparison study of Xeglyze and Vehicle, along with positive and negative controls under occlusive conditions in healthy volunteers.

Number of healthy volunteers: A total of 40 subjects were enrolled, and 37 subjects completed the study.

Key Inclusion Criteria:

- Healthy adults, male or female, age 18 or older
- Women of childbearing potential willing and able to use an acceptable form of birth control, and have a negative urine pregnancy test at Day 1, and were willing to submit to a pregnancy test at the end of study.
- Were of any skin type or race, providing the skin pigmentation allowed discernment of erythema
- Were willing to avoid using topical/systemic analgesics such as aspirin (daily use of 81 mg aspirin was acceptable), Ibuprofen, or systemic/topical antihistamines for 72 hours prior to and during the trial

Key Exclusion Criteria:

- Had any visible skin disease at the application site
- Use of inhaled/systemic/topical corticosteroids in the 3 weeks prior to and during the trial
- Were unwilling or unable to refrain from the use of sunscreens, cosmetics, creams, ointments, lotions, or similar products on the back during the trial
- Presence of psoriasis and/or active atopic dermatitis/eczema
- Had damaged skin in or around the test sites, including sunburn, excessively deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfigurations of the test site
- Had a known sensitivity to adhesives or constituents present in the material being evaluated
- Had a history of, or were currently being treated for skin cancer

Trial Methodology:

This study design is based on the Modified Berger procedure, and is the accepted standard methodology used for assessment of cumulative irritation potential. Investigators applied Xeglyze, Vehicle, Positive control (Sodium Lauryl sulfate (SLS) 0.2%) and negative control (saline solution 0.9%) daily for 21 consecutive days. Investigators applied 0.2 ml of study products and controls under occlusion to a 2cm x 2 cm area of skin. Investigators assessed patch sites at the Baseline visit, then daily for 21 days post-baseline, and scored the assessments using the scales displayed in Tables 103-105.

Results

Disposition of Subjects:

Investigators enrolled 40 subjects; 37 completed the trial. Investigators discontinued 3 subjects: 1 subject for "withdrawal of informed consent", and 2 subjects for "Subject misses any evaluation visits". Investigators recorded no protocol deviations during this trial.

Demographics:

The study population included 12 (30.0%) males and 28 (70.0%) females; 37 (92.5%) were White, 1 (2.5%) was Black or African American, and 2 (5.0%) were Asian. Subjects ranged in age from 18 to 72 years with a mean age of 46.95 years. Fitzpatrick skin types of subjects were distributed as follows: 37.5% type II, 30% type IV, 27.5% Type III and 2.5% each were type I and type V.

Results:

The results of the mean cumulative irritation scores were as follows: Xeglyze 0.05, Vehicle 0.03, saline 0.9% 0.05, and SLS 0.2% 2.34. There were no statistically significant differences between Xeglyze and Vehicle, Xeglyze and saline, or Vehicle and saline. The positive control, SLS 0.2%, was statistically significantly more irritating than Xeglyze, Vehicle, or saline ($p<0.0001$). Table 107 displays a summary of mean cumulative irritation scores.

Table 107: Summary of Mean Irritation Scores (n=40)

	Mean Irritation Score (SD)	Treatment Comparison p Values		
		Vehicle	Saline 0.9%	SLS 0.2%
Xeglyze	0.05 (0.15)	0.752	1.000	<.0001
Vehicle	0.03 (0.14)		0.752	<.0001
Saline 0.9%	0.05 (0.31)			<.0001
SLS 0.2%	2.34 (0.42)			

Source: Applicant submission, Table 14.2.3 Ha03-007 CSR

The results of the total cumulative irritation scores were as follows: Xeglyze 1.10, Vehicle 0.07, saline 0.9% 1.10, and SLS 0.2% 49.15. There were no statistically significant differences between Xeglyze and Vehicle, Xeglyze and saline, or Vehicle and saline. The positive control, SLS 0.2%, was statistically significantly more irritating than Xeglyze, Vehicle, or saline ($p<0.0001$). Table 108 displays a summary of total cumulative irritation scores.

Table 108: Summary of Total Irritation Scores (n=40)

	Total Irritation Score (SD)	Treatment Comparison p Values		
		Vehicle	Saline 0.9%	SLS 0.2%
Xeglyze	1.10 (3.11)	0.752	1.000	<.0001
Vehicle	0.70 (2.89)		0.752	<.0001
Saline 0.9%	1.10 (6.48)			<.0001
SLS 0.2%	49.15 (8.87)			

Source: Applicant submission, Table 14.2.3 Ha03-007 CSR

Adverse Events:

Investigators recorded no adverse events during this trial.

Conclusions:

Analysis of cumulative irritation in Trial Ha03-007 revealed that under exaggerated conditions of use, with continuous application under occlusion for 21 days, Xeglyze showed no evidence suggestive of irritation or cumulative irritation potential. Therefore, cumulative irritation will not be included in Xeglyze labeling.

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

During the drug development program for Xeglyze, the design of the clinical trials did not include assessment of carcinogenicity or screening for signals of malignancy. However, nonclinical studies showed that neither the active ingredient abametapir, nor the carboxyl metabolite, were clastogenic or mutagenic. This is discussed in Section 4.4 Nonclinical Pharmacology/Toxicology.

From applicant's proposed labeling: (b) (4) No effects on fertility have been observed in rats following repeated doses of up to 75 mg/kg/day."

8.7.2. Human Reproduction and Pregnancy

Pregnancy was an exclusion criterion for the Phase 1 and Phase 2 trials, and regular pregnancy testing was performed. However, 1 subject did become pregnant during the dermal sensitization trial Ha03-006, and was discontinued from the protocol. This subject experienced a miscarriage 12 days after her last study treatment which was felt to be unrelated to the study drug. This subject is discussed in more detail in Section 8.4.2.

Pregnancy was not an exclusion criterion for the Phase 3 trials. One subject in Ha03-001 was 6 months pregnant at enrollment, was treated with Xeglyze, and experienced no adverse events. The other subject, in Trial Ha03-002, was in her late 3rd trimester. This subject experienced elevated alkaline phosphatase and low protein, which were both mild and not related to study drug. Pregnancy was ongoing at the end of the trial.

8.7.3. Pediatrics and Assessment of Effects on Growth

The applicant formally requested a pediatric waiver to the NDA for Xeglyze for the pediatric study requirement for ages birth through 6 months of age because necessary studies are impossible or highly impracticable as limited data is publically available to demonstrate the prevalence of head lice infestation in infants less than 6 months of age. In addition, the applicant is requesting a pediatric waiver for Xeglyze for subjects aged 0 – 6 months because there is evidence to suggest that, as with other topical pediculicides, there is the potential of increased systemic absorption due to a high ratio of skin surface to body mass and the potential for an immature skin barrier in pediatric subjects from birth to 6 months. The Agency's Pediatric Review Committee concurred with the Pediatric Study Plan on April 30, 2014.

Because Xeglyze is administered as a single dose treatment for head lice infestation, the clinical trials were not of sufficient duration to permit evaluation of growth.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose is unlikely with Xeglyze when used as directed: a single application of sufficient product to saturate the scalp and hair, with rinsing after 10 minutes. The development program for Xeglyze included studies in which the drug was applied to larger areas (scalp and back) for up to 60 minutes with no change in the AE profile. However, the product contains benzyl alcohol (b) (4) w/w, or a total of (b) (4) of benzyl alcohol per bottle. In the event of accidental ingestion, particularly by a small child, this poses a substantial threat of systemic toxicity. Xeglyze will be packaged with a child-resistant container closure, and proposed labeling includes warnings regarding the danger with accidental ingestion with advice to seek immediate medical attention.

Investigators reported no instances of drug abuse or drug-seeking behavior by subjects during the development program for Xeglyze. Investigators did not evaluate withdrawal and rebound; however, both would be unlikely in a product intended for a single dose treatment course. The proposed labeling does not contain references to these phenomena; I concur with the applicant that drug abuse, withdrawal, and rebound are unlikely with Xeglyze.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Xeglyze is not yet a marketed product, therefore this section is not applicable.

8.8.2. Expectations on Safety in the Postmarket Setting

This section is not applicable to this NDA.

8.9. Additional Safety Issues From Other Disciplines

Clinical Pharmacology

As discussed in Section 4.5.3 of this review, the carboxyl metabolite of the active ingredient abametapir is cleared slowly from the systemic circulation and results in plasma concentration significantly higher than that of abametapir. Based on data in adults in Trial Ha02-003, where

samplings was carried out to 72 hours, the ratios of Cmax and AUC0-72h between abametapir carboxyl and abametapir were about 30 and 250, respectively. The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be approximately (mean ± SD) 71 ± 40 hours or higher. Pediatric PK sampling was only carried out for 8 hours. Because concentrations of abametapir carboxyl were continuing to rise at that time, C_{max} and T_{max} could not be characterized in pediatric subjects. Furthermore, studies using hepatocytes showed concentration dependent inhibition by abametapir carboxyl of CYP3A4 and to a lesser extent CYP2B6 and CYP1A2. Therefore, the clinical pharmacology team recommends the following post-marketing requirements:

- Conduct a maximal use pharmacokinetic trial of Xeglyze lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age to fully characterize the concentration time profile of abametapir and metabolite abametapir carboxyl.
- Conduct a clinical trial to evaluate the potential for Xeglyze lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatrics. Additional drug interaction trials may be needed depending on the results of this trial.

8.10. Integrated Assessment of Safety

The safety profile for Xeglyze was adequately characterized during the drug development program. No deaths occurred and no serious adverse events were attributed to Xeglyze during the development program. Dermal safety studies demonstrated that contact sensitization and cumulative irritation are uncommon. Cardiac safety monitoring, including a thorough QT trial, demonstrated that Xeglyze does not affect cardiac electrical activity.

The most common adverse reactions (AR) in the Phase 3 trials were application site erythema (4%), rash (3.2%), skin burning sensation (2.6%), contact dermatitis (1.7%), vomiting (1.7%), eye irritation (1.2%), and hair color changes (0.9%). Investigators also performed active assessments of local safety at the Baseline visit and post-treatment; monitored local safety adverse events with onset after treatment in the Phase 3 trials included scalp erythema (3.2%), eye irritation (1.7%), and scalp pruritus (1.4%). The frequency of AR was similar across all age groups. Labeling for Xeglyze in the Adverse Reactions subsection will include both subject-reported AR as well as monitored AR from the active assessment of local safety.

Xeglyze contains benzyl alcohol (b) (4) as an excipient. The potential for toxicity of benzyl alcohol was addressed by the Department of Pediatric and Maternal Health in their consult (for the comprehensive review, please refer to consult report from DPMH):

> "Each bottle (200 g) of abametapir lotion contains (b) (4) of benzyl alcohol as a (b) (4). Benzyl alcohol 0.9% when used in flush solutions has been shown to cause severe metabolic acidosis, encephalopathy and respiratory depression with gasping leading to death in infants at doses of 99 to 234 mg/kg/day.[5] Benzyl alcohol toxicity has been particularly associated with low birth-weight infants, because of the greater dose of benzyl alcohol relative to body weight, and because the metabolic and excretory pathways for benzyl alcohol are still immature.[6] Additionally, infants in hospital settings may be exposed to benzyl alcohol through routine administration of multiple medications and may be at increased risk of toxicity.[7]
>
> In May, 1982, FDA in conjunction with the American Academy of Pediatrics (AAP) and CDC issued a Drug Bulletin[8] containing strong recommendations to warn pediatricians and hospital personnel against using fluids and diluents preserved with benzyl alcohol in newborn infants. In addition, the AAP recommended that medications containing benzyl alcohol also be avoided in newborn infants when possible.[9] In 1997, the AAP Committee on Drugs published a review of the available published literature on neonatal benzyl alcohol toxicity and reported that most therapeutic agents, other than large-volume fluids, contain amounts of benzyl alcohol smaller than those associated with neonatal death; however, the effects of lower amounts of benzyl alcohol have not been adequately studied.[10]"

The potential toxicity posed by benzyl alcohol if infants under 6 months of age were treated with Xeglyze, or in case of accidental ingestion, will be addressed in the Warnings and Precautions and Pediatric Use subsections of product labeling using language recommended by DPMH. Furthermore, Xeglyze will be packaged with a childproof container/closure system, and printed warnings will be included on both the carton and container.

As discussed in Sections 4.5.3, 8.9, and 12 of this review, the major metabolite of the active ingredient, abametapir carboxyl, is cleared slowly from systemic circulation. Although pediatric PK data on this metabolite are incomplete, available data indicate that exposure to abametapir carboxyl is greater in pediatric subjects and inversely proportional to weight. Furthermore, studies in hepatocytes have demonstrated possible concentration-dependent inhibition of

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[5] Gershanik, J et al. The Gasping Syndrome and Benzyl Alcohol Poisoning. *NEJM.* 1982; 307:1384-1388.
[6] Hiller J, Benda G, Rahatzad M, et al. Benzyl alcohol Toxicity: Impact on mortality and intraventricular hemorrhage among very low birth-weight infants. *Pediatrics.* 1986; 77(4):500-6.
[7] Anderson C, Ng J, et al. Benzyl alcohol poisoning in a premature newborn infant. *Am J Obstet Gynecol.* 1984;148:344-346.
[8] 4 FDA Drug Bulletin, August 1982.
[9] American Academy of Pediatrics, Committee on Fetus and Newborn, Committee on Drugs. Benzyl Alcohol: Toxic Agent in Neonatal Units. *Pediatrics.* 1983;72(3):356-8.
[10] AAP Committee on Drugs. Inactive ingredients in pharmaceutical products: update. Pediatrics. 1997;99

CYP3A4 by abametapir carboxyl. Post-marketing requirements will be recommended to address these concerns; those are discussed in Section 12 of this review.

The safety data demonstrate that Xeglyze is safe for the treatment of head lice infestation in patients 6 months of age and older. Therefore, post-marketing risk management beyond professional labeling, prescription status and routine pharmacovigilance is not needed for Xeglyze.

9 Advisory Committee Meeting and Other External Consultations

This section is not applicable to this NDA because no Advisory Committee meeting was held for Xeglyze.

10 Labeling Recommendations

10.1. Prescribing Information

Recommendations for specific sections of labeling are contained within the body of this review. Labeling has not been finalized at the time of this review; however, major modifications on which the review team has agreed will be discussed.

- **1 Indications and Usage**

  The review team deleted language regarding (b) (4) Xeglyze. As discussed in section 6.2.2 of this review, the Agency informed the applicant during the drug development program that in vitro trials would not support a labeling claim for (b) (4)

- **5 Warnings and Precautions**

  Because Xeglyze contains benzyl alcohol (b) (4) as an excipient, Section 5 is revised to include warnings regarding the potential toxicity of benzyl alcohol (see section 4.2 of this review for further discussion):

  - "(b) (4) XEGLYZE (b) (4) contains (b) (4) of benzyl alcohol. Systemic exposure to benzyl alcohol has been associated with serious and fatal adverse reactions including "gasping syndrome" in neonates and low birth weight infants. The "gasping syndrome" is characterized by central nervous system

depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birthweight infants may be more likely to develop toxicity. [see Use in Specific Populations (8.4)]. The safety and effectiveness of XEGLYZE Lotion have not been established in pediatric patients below the age of 6 months. Not recommended in pediatric patients under 6 months of age; potential for increased systemic absorption."

(b) (4)

- **6 Adverse Reactions**

As proposed by the applicant, Table 1, which listed the adverse reactions, included adverse reactions observed in Trials 1 and 2 in (b) (4) This table was modified to include adverse reactions occurring in 1 percent or greater in the Xeglyze group, and at a greater frequency than in the Vehicle group. This resulted in the addition of eye irritation and hair color changes to the table of adverse events. Adverse reactions are discussed in detail in Section 8.4.5.2 of this review.

Because investigators actively assessed and scored local safety adverse reactions, Table 2 was added to the labeling. Table 2 displays monitored local adverse reactions with new onset on Day 1 post treatment. The listed reactions occurred in 1 percent or greater of the Xeglyze group, and at a greater frequency than in the Vehicle group. Adverse reactions discovered during the active assessment of local safety are discussed in Section 8.4.5.1 in this review.

- **8 Use in Specific Populations**
  - 8.1 Pregnancy

    There are no available data on Xeglyze use during pregnancy to inform a drug associated risk. Relevant animal data were added to the labeling by the Pharmacology/Toxicology reviewer, Dr. Jill Merrill. Language regarding the background rate of major birth defects and miscarriage was added in compliance with current guidances and regulations.

  - 8.2 Lactation

    No data are available regarding the presence of abametapir (b) (4)

[redacted] in human milk, or the effects of abametapir on the breastfed infant or on milk production. Standard language was included as follows: "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XEGLYZE [redacted] and any potential adverse effects on the breastfed child from XEGLYZE [redacted] or from the underlying maternal condition."

- 8.4 Pediatric Use

  The review team inserted language regarding benzyl alcohol toxicity and the "gasping syndrome". The primary purpose of the inclusion of information regarding benzyl alcohol toxicity in this section and Section 5 Warnings and Precautions is to ensure that product labeling accurately conveys to prescribers the potential risk associated with off-label use in infants less than 6 months of age.

- **12 Clinical Pharmacology**

  - 12.1 Mechanism of Action

    The review team deleted [redacted] As discussed in Section 6.2.2 of this review, the Agency informed the applicant during the development program that [redacted]

  - 12.3 Pharmacokinetics

    Clinical Pharmacology reviewer Dr. Doanh Tran added pharmacokinetic (PK) information about absorption of both the active moiety in Xeglyze, abametapir, and the excipient benzyl alcohol to this section of product labeling. Dr. Tran discussed the metabolism of abametapir to abametapir carboxyl, as well as providing estimated PK parameters for abametapir carboxyl that could be calculated using available data.

    Dr. Tran also comments on *in vitro* studies that suggest a "potential for inhibition of cytochrome P450 enzymes following application of XEGLYZE Lotion due to high and prolonged systemic exposure of the metabolite abametapir carboxyl." Review of this potential inhibition is still ongoing at the time of this review; however, if inhibition of cytochrome P450 enzymes by abametapir carboxyl is confirmed, Section 7 Drug Interactions will be added to Xeglyze labeling.

- **13 Nonclinical Toxicology**

    - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

      Dr. Jill Merrill, Pharmacology/Toxicology reviewer, incorporated results of *in vitro* and *in vivo* tests that demonstrate that Xeglyze was not clastogenic or mutagenic, and that "No effects on fertility have been observed in rats following repeated oral doses of up to 75 mg/kg/day abametapir (50 times the MRHD based on Cmax comparisons)."

- **14 Clinical Studies**

  In the paragraphs describing the two Phase 3 trials, the review team made minor modifications to the language and added demographic information regarding age, gender, and race of the index subjects. The review team deleted (b) (4) As discussed in section 6.3.2 of this review, the Agency informed the applicant during the drug development program that in vitro trials would not support a labeling (b) (4)

- **17 Patient Counseling Information**

  The review team added a warning regarding potential benzyl alcohol toxicity. The benzyl alcohol warning in this section includes cross-references to sections 5 and 8.4 of the labeling where the potential for toxicity is discussed in more detail.

10.2. Patient Labeling

The applicant included Patient Information in the proposed labeling. Review of this section by staff of the Office of Medical Policy (OMP), and suggested modifications were made to the applicant's proposed patient labeling.

10.3. Nonprescription Labeling

This section is not applicable to this NDA.

11 Risk Evaluation and Mitigation Strategies (REMS)

11.1. Safety Issue(s) that Warrant Consideration of a REMS

12 Postmarketing Requirements and Commitments

As discussed in Sections 4.5.3 and 8.9 of this review, the primary metabolite of the active ingredient abametapir is abametapir carboxyl. Abametapir carboxyl is cleared slowly from the systemic circulation and results in plasma concentration significantly higher than that of abametapir. However, studies using hepatocytes showed concentration dependent inhibition by abametapir carboxyl of CYP3A4 and to a lesser extent CYP2B6 and CYP1A2. Furthermore, pediatric PK sampling was only carried out for 8 hours. Because concentrations of abametapir carboxyl were continuing to rise at that time, C_{max} and T_{max} could not be characterized in pediatric subjects, but were greater than adult exposures and increased with decreasing body mass. Because of the potential inhibition on CYP3A4 by abametapir carboxyl, the exposure to abametapir carboxyl needs to be further characterized. Therefore, the following Postmarketing Requirements are recommended:

1. Conduct a maximal use pharmacokinetic trial of Xeglyze lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age to fully characterize the concentration time profile of abametapir and metabolite abametapir carboxyl.
2. Conduct a clinical trial to evaluate the potential for Xeglyze lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatrics. Additional drug interaction trials may be needed depending on the results of this trial.

Additionally, during the drug development program for Xeglyze, assays of abametapir carboxyl were performed on samples that had been stored at-80 ºC for duration of 1251 days. To ensure validity of this data, the clinical pharmacology team recommends the following Postmarketing Commitment (PMC):

1. Conduct a study to evaluate the long-term storage stability of abametapir carboxyl in plasma stored at -80 ºC for duration of at least 1251 days.

13 Appendices

13.1. References

Literature references are cited in the body of the review.

13.2. Financial Disclosure

[Insert text here.]

Covered Clinical Study (Name and/or Number): Ha03-001, Ha03-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _____Ha03-001: 25 investigators; Ha03-002: 38 investigators		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) **N/A**
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) **N/A**
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)

13.3 Adverse Events by Subgroup Tables

Adverse events occurring at a frequency of 1% or greater in subjects treated with Xeglyze are presented by subgroups in the tables below:

Table 109: AE by SOC and Dictionary Derived Term, Pooled Phase 3 Safety Population, Females

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n=298)	Vehicle (n=286)
Eye disorders	Conjunctival hyperemia	1 (0.3%)	0 (0%)
	Conjunctivitis	1 (0.3%)	1 (0.4%)
	Eye irritation	4 (1.3%)	2 (0.7%)
Gastrointestinal disorders	Diarrhea	2 (0.7%)	1 (0.4%)
	Nausea	3 (1.0%)	0 (0%)
	Vomiting	5 (1.7%)	2 (0.7%)
General disorders and administration site conditions	Application site pain	1 (0.3%)	0 (0%)
	Pain	1 (0.3%)	0 (0%)
	Pyrexia	1 (0.3%)	3 (1.1%)
	Vessel puncture site hemorrhage	1 (0.3%)	0 (0%)
Infections and infestations	Gastroenteritis	1 (0.3%)	0 (0%)
	Pharyngitis	2 (0.7%)	1 (0.4%)
	Pharyngitis streptococcal	2 (0.7%)	1 (0.4%)
	Urinary tract infection	1 (0.3%)	1 (0.4%)
Injury, poisoning and procedural complications	Excoriation	0 (0%)	1 (0.4%)
Investigations	Blood alkaline phosphatase increased	1 (0.3%)	0 (0%)
	Blood chloride increased	1 (0.3%)	0 (0%)
	Blood lactate dehydrogenase increased	1 (0.3%)	0 (0%)
	Blood potassium increased	1 (0.3%)	0 (0%)
	Protein total decreased	1 (0.3%)	0 (0%)
Metabolism and nutrition disorders	Diabetes mellitus	1 (0.3%)	0 (0%)
Musculoskeletal and connective tissue disorders	Arthralgia	1 (0.3%)	0 (0%)
	Back pain	1 (0.3%)	1 (0.4%)
Nervous system disorders	Dizziness	1 (0.3%)	0 (0%)

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n=298)	Vehicle (n=286)
	Headache	2 (0.7%)	5 (1.8%)
	Paresthesia	1 (0.3%)	0 (0%)
Renal and urinary disorders	Renal pain	1 (0.3%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	Asthma	1 (0.3%)	0 (0%)
	Cough	3 (1.0%)	1 (0.4%)
	Nasal mucosal disorder	1 (0.3%)	0 (0%)
	Oropharyngeal pain	1 (0.3%)	0 (0%)
	Pharyngeal erythema	2 (0.7%)	0 (0%)
	Rhinorrhea	5 (1.7%)	0 (0%)
	Tonsillar hypertrophy	1 (0.3%)	0 (0%)
Skin and subcutaneous tissue disorders	Dermatitis contact	6 (2.0%)	4 (1.4%)
Skin and subcutaneous tissue disorders	Erythema	11 (3.7%)	5 (1.8%)
	Hair color changes	3 (1.0%)	0 (0%)
	Pruritus	3 (1.0%)	8 (2.8%)
	Rash	11 (3.7%)	7 (2.5%)
	Skin burning sensation	5 (1.7%)	0 (0%)
	Skin disorder	2 (0.7%)	0 (0%)
	Skin exfoliation	3 (1.0%)	7 (2.5%)
	Skin irritation	2 (0.7%)	0 (0%)
Vascular disorders	Lymphedema	1 (0.3%)	0 (0%)

Source: Reviewer's Table; Created in JReview using Applicant's datasets

Table 110: AE by SOC and Dictionary Derived Term, Pooled Phase 3 Safety Population, Males

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n= 51)	Vehicle (n=64)
Eye disorders	Conjunctivitis	0 (0%)	1 (1.6%)
	Conjunctivitis allergic	0 (0%)	1 (1.6%)
Gastrointestinal disorders	Gastritis	0 (0%)	1 (1.6%)
	Vomiting	1 (2.0%)	0 (0%)
General disorders and administration site conditions	Application site pain	1 (2.0%)	0 (0%)
	Pyrexia	0 (0%)	1 (1.6%)
Infections and infestations	Pharyngitis	1 (2.0%)	0 (0%)
	Pharyngitis streptococcal	2 (3.9%)	0 (0%)
Investigations	Alanine aminotransferase increased	0 (0%)	1 (1.6%)
	Blood potassium increased	0 (0%)	1 (1.6%)
	Cardiac murmur	1 (2.0%)	0 (0%)
	Neutrophil count decreased	1 (2.0%)	0 (0%)
	White blood cell count decreased	1 (2.0%)	0 (0%)
Nervous system disorders	Burning sensation	0 (0%)	1 (1.6%)
Respiratory, thoracic and mediastinal disorders	Cough	0 (0%)	2 (3.1%)
	Rhinitis allergic	1 (2.0%)	0 (0%)
	Rhinorrhea	0 (0%)	1 (1.6%)
	Tonsillar hypertrophy	1 (2.0%)	0 (0%)
	Wheezing	1 (2.0%)	0 (0%)
Skin and subcutaneous tissue disorders	Erythema	3 (5.9%)	1 (1.6%)
	Pruritus	0 (0%)	2 (3.1%)
	Rash	0 (0%)	1 (1.6%)
	Skin burning sensation	4 (7.8%)	0 (0%)
	Skin exfoliation	0 (0%)	1 (1.6%)

Source: Reviewer's Table; Created in JReview using Applicant's datasets

Table 111: AE by SOC and Dictionary Derived Term, Pooled Phase 3 Safety Population, Ages 6 Months to <2 Years

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n=7)	Vehicle (n=8)
Gastrointestinal disorders	Vomiting	1 (14.3%)	0 (0%)
Infections and infestations	Pharyngitis streptococcal	1 (14.3%)	0 (0%)

Source: Reviewer's Table; Created in JReview using Applicant's datasets

Table 112: AE by SOC and Dictionary Derived Term, Pooled Phase 3 Safety Population, Age 2 to <4 Years

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n=15)	Vehicle (n=24)
Gastrointestinal disorders	Diarrhea	0 (0%)	1 (4.2%)
	Nausea	1 (6.7%)	0 (0%)
	Vomiting	1 (6.7%)	1 (4.2%)
General disorders and administration site conditions	Pyrexia	0 (0%)	1 (4.2%)
Musculoskeletal and connective tissue disorders	Back pain	0 (0%)	1 (4.2%)
Respiratory, thoracic and mediastinal disorders	Pharyngeal erythema	1 (6.7%)	0 (0%)
	Rhinorrhea	1 (6.7%)	0 (0%)
Skin and subcutaneous tissue disorders	Dermatitis	0 (0%)	1 (4.2%)
	Dermatitis contact	0 (0%)	1 (4.2%)
	Erythema	1 (6.7%)	0 (0%)
	Rash	1 (6.7%)	0 (0%)
	Skin exfoliation	1 (6.7%)	0 (0%)

Source: Reviewer's Table; Created in JReview using Applicant's datasets

Table 113: AE by SOC and Dictionary Derived Term, Pooled Phase 3 Safety Population, Age 4 to <12 Years

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n=166)	Vehicle (n=174)
Eye disorders	Eye irritation	3 (1.8%)	2 (1.2%)
Gastrointestinal disorders	Diarrhea	2 (1.2%)	0 (0%)
	Vomiting	3 (1.8%)	0 (0%)
General disorders and administration site conditions	Application site pain	1 (0.6%)	0 (0%)
	Pain	1 (0.6%)	0 (0%)
	Pyrexia	1 (0.6%)	3 (1.7%)
Infections and infestations	Gastroenteritis	1 (0.6%)	0 (0%)
	Pharyngitis	2 (1.2%)	1 (0.6%)
	Urinary tract infection	1 (0.6%)	1 (0.6%)
Investigations	Cardiac murmur	1 (0.6%)	0 (0%)
	Neutrophil count decreased	1 (0.6%)	0 (0%)
	White blood cell count decreased	1 (0.6%)	0 (0%)
Nervous system disorders	Headache	1 (0.6%)	2 (1.2%)
	Paresthesia	1 (0.6%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	Asthma	1 (0.6%)	0 (0%)
	Cough	3 (1.8%)	3 (1.7%)
	Nasal mucosal disorder	1 (0.6%)	0 (0%)
	Oropharyngeal pain	1 (0.6%)	0 (0%)
	Pharyngeal erythema	1 (0.6%)	0 (0%)
	Rhinorrhea	3 (1.8%)	1 (0.6%)
	Tonsillar hypertrophy	2 (1.2%)	0 (0%)
Skin and subcutaneous tissue disorders	Dermatitis contact	6 (3.6%)	2 (1.2%)
	Erythema	8 (4.8%)	4 (2.3%)
	Hair color changes	3 (1.8%)	0 (0%)
	Pruritus	1 (0.6%)	6 (3.5%)
	Rash	6 (3.6%)	7 (4.0%)
	Skin burning sensation	7 (4.2%)	0 (0%)
	Skin disorder	2 (1.2%)	0 (0%)
	Skin exfoliation	2 (1.2%)	7 (4.0%)
Vascular disorders	Lymphedema	1 (0.6%)	0 (0%)

Source: Reviewer's Table; Created in JReview using Applicant's datasets

Table 114: AE by SOC and Dictionary Derived Term, Pooled Phase 3 Safety Population, Age 12 to <18 Years

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n=56)	Vehicle (n=52)
Eye disorders	Eye irritation	1 (1.8%)	0 (0%)
Gastrointestinal disorders	Nausea	1 (1.8%)	0 (0%)
	Vomiting	1 (1.8%)	0 (0%)
General disorders and administration site conditions	Application site pain	1 (1.8%)	0 (0%)
	Vessel puncture site hemorrhage	1 (1.8%)	0 (0%)
Infections and infestations	Pharyngitis streptococcal	1 (1.8%)	0 (0%)
Renal and urinary disorders	Renal pain	1 (1.8%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	1 (1.8%)	0 (0%)
	Rhinorrhea	1 (1.8%)	0 (0%)
	Wheezing	1 (1.8%)	0 (0%)
Skin and subcutaneous tissue disorders	Erythema	2 (3.6%)	1 (1.9%)
	Rash	1 (1.8%)	0 (0%)
	Skin burning sensation	1 (1.8%)	0 (0%)

Source: Reviewer's Table; Created in JReview using Applicant's datasets

Table 115: AE by SOC and Dictionary Derived Term, Pooled Phase 3 Safety Population, Age ≥18 Years

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n=105)	Vehicle (n=92)
Eye disorders	Conjunctival hyperemia	1 (1.0%)	0 (0%)
	Conjunctivitis	1 (1.0%)	0 (0%)
Infections and infestations	Pharyngitis	1 (1.0%)	0 (0%)
	Pharyngitis streptococcal	2 (1.9%)	0 (0%)
Investigations	Blood alkaline phosphatase increased	1 (1.0%)	0 (0%)
	Blood chloride increased	1 (1.0%)	0 (0%)
	Blood lactate dehydrogenase increased	1 (1.0%)	0 (0%)
	Blood potassium increased	1 (1.0%)	0 (0%)
	Protein total decreased	1 (1.0%)	0 (0%)
Metabolism and nutrition disorders	Diabetes mellitus	1 (1.0%)	0 (0%)
Musculoskeletal and connective tissue	Arthralgia	1 (1.0%)	0 (0%)

Body System or Organ Class	Dictionary Derived Term	Xeglyze (n=105)	Vehicle (n=92)
disorders			
	Back pain	1 (1.0%)	0 (0%)
Nervous system disorders	Dizziness	1 (1.0%)	0 (0%)
	Headache	1 (1.0%)	1 (1.1%)
Skin and subcutaneous tissue disorders	Erythema	3 (2.9%)	1 (1.1%)
	Pruritus	2 (1.9%)	3 (3.3%)
	Rash	3 (2.9%)	1 (1.1%)
	Skin burning sensation	1 (1.0%)	0 (0%)
	Skin irritation	2 (1.9%)	0 (0%)

Source: Reviewer's Table; Created in JReview using Applicant's datasets

Clinical Review
Kevin L. Clark, MD
NDA 209966
Xeglyze (abametapir) Lotion,0.74%

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/s/

KEVIN L CLARK
04/28/2016

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04/29/2016