# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214510Orig1s000

# MULTI-DISCIPLINE REVIEW

**Summary Review**
**Clinical Review**
**Non-Clinical Review**
**Statistical Review**
**Clinical Pharmacology Review**

# NDA/BLA Multi-Disciplinary Review and Evaluation

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 214510 |
| Priority or Standard | Standard |
| Submit Date(s) | 26-Jun-2020 |
| Received Date(s) | 26-Jun-2020 |
| PDUFA Goal Date | 26-April-2021 |
| Division/Office | Division of Dermatology and Dentistry |
| Review Completion Date | 5-April-2022 |
| Established/Proper Name | Benzoyl peroxide cream, 5% |
| (Proposed) Trade Name | EPSOLAY |
| Pharmacologic Class | Rosacea Agents |
| Code name | S5G4T-1 |
| Applicant | Sol-Gel Technologies Ltd. |
| Dosage form | Cream |
| Applicant proposed Dosing Regimen | Apply a pea-sized amount once daily to each area of the face (forehead, chin, nose, each cheek) on clean and dry skin |
| Applicant Proposed Indication(s)/Population(s) | For the treatment of inflammatory lesions of rosacea in adults 18 years of age and older |
| Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication | 398909004 \|Rosacea (disorder)\| |
| Recommendation on Regulatory Action | Approval pending successful completion of the required pre-approval inspection (manufacturing site) |
| Recommended Indication(s)/Population(s) (if applicable) | indicated for the treatment of inflammatory lesions of rosacea in adult patients |
| Recommended SNOMED CT Indication Disease Term for each Indication (if applicable) | 398909004 \|Rosacea (disorder)\| |
| Recommended Dosing Regimen | Apply a pea-sized amount once daily in a thin layer to each area of the face (forehead, chin, nose, each cheek) on clean and dry skin. |

# Table of Contents

# Table of Tables

# Table of Figures

## Reviewers of Multi-Disciplinary Review and Evaluation

| | |
|---|---|
| Regulatory Project Manager | RPM Needs to be listed |
| Nonclinical Reviewer | Barbara Hill, PhD |
| Nonclinical Supervisor | Barbara Hill, PhD |
| Office of Clinical Pharmacology Reviewer | Luke Oh, PhD |
| Office of Clinical Pharmacology Team Leader | Chinmay Shukla, PhD |
| Clinical Reviewer | Melinda McCord, MD |
| Clinical Team Leader | Gordana Diglisic, MD |
| Statistical Reviewer | Matthew Guerra, PhD |
| Statistical Team Leader | Mohamed Alosh, PhD |
| Cross-Disciplinary Team Leader | Gordana Diglisic, MD |
| Office Director (or designated signatory authority) | Tatiana Oussova, MD, MPH |

## Additional Reviewers of Application

| | |
|---|---|
| OPQ | Application Technical Lead: Hamid Shafiei, PhD<br>Regulatory Business Process Manager: Melinda Bauerlien, MS<br>Drug Substance Reviewers: Zhixing Shan, PhD/Donna Christner, PhD<br>Drug Product Reviewers: Zhengfang Ge, PhD/Wendy Wilson-Lee, PhD<br>Manufacturing Process and Facilities Reviewers: Allison Aldridge, PhD/Rose Xu, PhD<br>Biopharmaceutics Reviewers: Leah Falade, PhD/Tapash Ghosh, PhD<br>Microbiology Reviewers: Alifiya Ghadiali, PhD/Samata Tiwari, PhD<br>Environmental Assessment Reviewers: Zhengfang Ge, PhD/Wendy Wilson-Lee, PhD |
| OPDP | Laurie Buonaccorsi, PharmD/ Matthew Falter, PharmD |
| OSI | Zana H Marks, MD, MPH/Karen Bleich, MD; Phillip Kronstein, MD |
| DMPP | Jessica Chung, PharmD, MS/ LaShawn Griffiths, MSHS-PH, BSN, RN; Barbara Fuller, RN, MSN, CWOCN |
| OSE/DMEPA | Madhuri R. Patel, PharmD/ Sevan Kolejian, PharmD, MBA, BCPPS |
| DPMH | Jane Liedtka MD/ Miriam Dinatale, DO |
| COA | Parima Ghafoori, PharmD/ Selena Daniels, PharmD, MS |
| DPV | Jonn Bailey, PharmD, BCACP; LCDR Melissa Reyes, MD, MPH/ Vicky Chan, PharmD, BCPS |

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DPMH = Division of Pediatrics and Maternal Health
COA= Clinical Outcome Assessment
DPV= Division of Pharmacovigilance
DMPP= Division of Medical Policy Programs

## Signatures

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Nonclinical Reviewer | Barbara Hill, PhD | OII/DPT-II | Sections: 5, 18.3 | Select one:<br>_X_ Authored<br>___ Approved |
| | Signature: Signature in DARRTS | | | |
| Nonclinical Supervisor | Barbara Hill, PhD | OII/DPT-II | Sections: 5, 18.3 | Select one:<br>___ Authored<br>_X_ Approved |
| | Signature: Signature in DARRTS | | | |
| Clinical Pharmacology Reviewer | Luke Oh, Ph.D. | OTS/OCP/DIIP | Section: 6 | Select one:<br>_X_ Authored<br>___ Approved |
| | Signature: Signature in DARRTS | | | |
| Clinical Pharmacology Team Leader | Chinmay Shukla, PhD | OTS/OCP/DIIP | Section: 6 | Select one:<br>___ Authored<br>_X_ Approved |
| | Signature: Signature in DARRTS | | | |

| DISCIPLINE | REVIEWER | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED |
|---|---|---|---|---|
| Clinical Reviewer | Melinda McCord, MD | OII/DDD | Sections: 1, 2, 3, 4.1, 7.8.2, 8.3, 9, 10, 11, 12, 13, 18.1, 18.2 | Select one:<br>_X_ Authored<br>___ Approved |
| | Signature: Signature in DARRTS | | | |
| Clinical Team Leader | Gordana Diglisic, MD | OII/DDD | Sections: all | Select one:<br>_X_ Authored<br>_X_ Approved |
| | Signature: Signature in DARRTS | | | |
| OPQ Team Leader | Hamid Shafiei, PhD | DNDP II, NDPB V | Sections: 4.2 | Select one:<br>_X__ Authored<br>_X_ Approved |
| | Signature: Signature in DARRTS | | | |
| Statistical Reviewer | Matthew Guerra, PhD | OTS/OB/DBIII | Sections: 8.1, 8.3 | Select one:<br>_X_ Authored<br>___ Approved |
| | Signature: Signature in DARRTS | | | |
| Statistical Team Leader | Mohamed Alosh, PhD | OTS/OB/DBIII | Sections: 8.1, 8.3 | Select one:<br>___ Authored<br>_X_ Approved |
| | Signature: Signature in DARRTS | | | |
| Deputy Division Director for Safety (Clinical) | Tatiana Oussova, M.D., M.P.H. | OII/DDD | Sections: | Select one:<br>___ Authored<br>_X_ Approved |
| | Signature: Signature in DARRTS | | | |

## Glossary

| | |
|---|---|
| AC | advisory committee |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BPO | benzoyl peroxide |
| BRF | Benefit Risk Framework |
| 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 |
| 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 |
| DHOT | Division of Hematology Oncology Toxicology |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| 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 |
| GRMP | good review management practice |
| ICH | International Conference on Harmonization |
| IND | Investigational New Drug |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |

| | |
|---|---|
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PAPI | Patient Assessment of Papulopustular Rosacea Impacts |
| PAPSS | Patient Assessment of Papulopustular Rosacea Signs and Symptoms |
| PGI-C | Patient Global Impression of Change |
| PGI-S | Patient Global Impression of Symptom Severity |
| PGI-SE | Patient Global Impression of Treatments Side Effects |
| PGI-TS | Patient Global Impression of Treatments Satisfaction |
| 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 (also known as Patient Information) |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| RosaQoL | Rosacea Quality of Life |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1 Executive Summary

## 1.1. Product Introduction

On June 26, 2020, the Applicant, Sol-Gel Technologies Ltd. (Sol-Gel), submitted an original new drug application (NDA) 214510 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50 for EPSOLAY (benzoyl peroxide) cream, 5%. The proposed indication is the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

The proposed product contains benzoyl peroxide (BPO) which is encapsulated in silicone dioxide microcapsules and then suspended in (b) (4) cream formulation. The intent of the encapsulation is to allow the gradual migration of benzoyl peroxide through the shell, resulting in the continuous release of the active ingredient (AI) to all affected areas of the skin. Various formulations of BPO in concentrations ranging from 2.5% to 10% have been marketed as over- the- counter products (OTC) for the treatment of acne vulgaris for more than 50 years. In addition, BPO is the AI in multiple FDA approved combination products for the treatment of acne vulgaris.

The proposed dosing regimen for benzoyl peroxide (BPO) cream (BPO cream; S5G4T-1) and administration instructions are: " Apply a pea-size amount of EPSOLAY Cream once daily to each area of the face (forehead, chin, nose, each cheek) on clean and dry skin. Spread as a thin layer, covering the entire face. Avoid the eyes, lips and mouth. "

The Food and Drug Administration (FDA) concluded, that the proposed proprietary name, EPSOLAY, was acceptable from both a safety and misbranding perspective under NDA 214510 [Proprietary Name Request Conditionally Acceptable Letter dated 10/1/2020; Proprietary Name Review by Madhuri R. Patel, PharmD dated September 30, 2020].

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials (SGT-54-01 and SGT-54-02) which provided evidence of the effectiveness of BPO cream, 5% for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. Both identically designed trials evaluated subjects with moderate to severe rosacea defined as:

- Investigator Global Assessment (IGA) score of 3 ("moderate") or 4 ("severe"), see section 8.1 for the IGA scale
- 15 to 70 inflammatory lesions (papules and/or pustules) on the face including those present on the nose
- No more than two nodules (papule or pustule greater than 5 mm in diameter) on the face

The protocol specified the following co-primary efficacy endpoints:

- Proportion of subjects achieving IGA success at Week 12, defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline
- Absolute change in inflammatory lesion counts from baseline to Week 12

The protocol specified the following secondary efficacy endpoints:

- Percent change in inflammatory lesion counts from baseline to Week 12
- Absolute change in inflammatory lesion counts from baseline to Week 8
- Proportion of subjects achieving IGA success at Week 8
- Absolute change in inflammatory lesion counts from baseline to Week 4
- Proportion of subjects achieving IGA success at Week 4

For both trials, BPO cream, 5% was statistically superior to vehicle cream on both co-primary efficacy endpoints (p-values $< 0.001$) and all secondary efficacy endpoints (p-values $\leq 0.009$).

The Applicant met the evidentiary standard for adequate and well controlled trials required by 21 CFR 314.126(a)(b) to support approval and has demonstrated that BPO cream, 5% is effective for its intended use in the target population.

## 1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant, Sol-Gel Technologies Ltd. (Sol-Gel), submitted an new drug application (NDA) 214510 for EPSOLAY (benzoyl peroxide) cream, 5% under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relied on published literature data and the OTC monograph for benzoyl peroxide (BPO) to address most of the nonclinical informational needs to support approval. EPSOLAY is a cream formulation of BPO, a moiety with a well-characterized safety profile. The proposed indication is the treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

To establish the safety and efficacy of BPO cream, 5% for the treatment of inflammatory lesions of rosacea, the Applicant submitted data from two identically designed, randomized, multicenter, double-blind, vehicle-controlled, parallel-group phase 3 trials (SGT-54-01 and SGT-54-02). Enrolled subjects were adults with moderate to severe rosacea that was defined as an IGA score of 3 ("moderate") or 4 ("severe"), 15 to 70 inflammatory lesions and no more than 2 nodules. For both trials, BPO cream, 5% was statistically superior to vehicle on both co-primary efficacy endpoints (proportion of subjects achieving IGA success at Week 12 AND an absolute change in inflammatory lesion counts from baseline to Week 12.) In addition, BPO cream, 5% was statistically superior to vehicle on all secondary endpoints.

The primary safety database consisted of data from 722 subjects enrolled in the pooled phase 3 Trials SGT-54-01 and SGT-54-02. The size of the overall safety database was considered adequate to characterize the safety profile of BPO cream, 5% for the treatment of the inflammatory lesions of rosacea and was consistent with ICH E1. A total of 691 adult subjects with rosacea received BPO cream, 5% at the proposed dose and dosing regimen, once daily in the phase 2 and phase 3 trials. In the pooled phase 3 trials, 488 subjects received the to-be-marketed formulation of the proposed product.

Based on the analysis of the submitted data, treatment with BPO cream, 5% was not associated with mortality or drug related serious adverse events (SAEs). In the development program, there were no serious hypersensitivity reactions. Systemic exposure to BPO cream, 5% after topical application was expected to be low due to the rapid conversion of BPO to benzoic acid, an endogenous substance. The most common adverse reactions were application site reactions: pain, erythema, pruritis and edema. Local tolerability evaluations were conducted at baseline and at each study visit in the clinical trials by the assessment of dryness, itching, scaling and stinging/burning. The severity of all signs and symptoms decreased from baseline to Week 12 in both treatment groups. The safety profile during the 52-week, open-label treatment period was comparable to the safety profile during the 12-week, vehicle-controlled period.

Prescription and patient labeling as well as routine pharmacovigilance measures are adequate to manage the risk of EPSOLAY in the postmarketing setting; a Risk Evaluation and Mitigation Strategy (REMS) is not needed. As the benefits and risks are adequately characterized in the target population, postmarketing assessments under 505(o) are not required. Studies in the pediatric population are not required under the Pediatric Research Equity Act 21 U.S.C. 355c since studies are impossible or highly impracticable because the estimated number of pediatric patients with rosacea is small.

In summary, rosacea is a common, chronic cutaneous disease with substantial impacts on quality of life. The available safety and efficacy data support the approval of EPSOLAY for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. None of the FDA-approved pharmacologic therapies for rosacea provides a permanent cure or universal response. Unlike topical and systemic antibiotic therapy, BPO is not associated with bacterial resistance. Because any treatment may be complicated by inadequate response or adverse reactions, there is a need for additional therapeutic options with acceptable benefit-risk profiles. In view of the favorable benefit/risk assessment, the review team recommends approval of this product.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Rosacea is a chronic dermatological condition that predominantly affects the central region of the face (e.g., cheeks, nose, chin, mid forehead).The onset typically occurs at any time after 30 years of age. It may be characterized by flushing (transient erythema), persistent (nontransient) erythema, telangiectasias, and inflammatory acneiform lesions (papules, pustules). Ocular involvement may occur (e.g., blepharitis, conjunctivitis). The pathways that lead to the development of rosacea are not well understood. Proposed contributing factors include abnormalities in innate immunity, inflammatory reactions to cutaneous microorganisms, ultraviolet damage, and vascular dysfunction. Rosacea may be associated with adverse impacts on emotional, social, and occupational well-being. | Rosacea is a common chronic disorder with a range of disease severities which may significantly impact quality of life. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Current Treatment Options | • The currently approved drugs for the treatment of rosacea target the treatment of inflammatory lesions (papules and pustules) of rosacea or the treatment of persistent (nontransient) facial erythema of rosacea. Approved therapies for the treatment of inflammatory lesions (papules and pustules) of rosacea include topical antimicrobials (e.g. metronidazole and minocycline), ivermectin, and azelaic acid. Doxycycline is the only systemic therapy for inflammatory lesions (papules and pustules) of rosacea currently approved in the U.S. | There are a number of FDA-approved products with an acceptable benefit/risk profile for the treatment of inflammatory lesions of rosacea in adults, including doxycycline administered orally. In contrast to topical and oral antibiotics, BPO does not contribute to the development of resistant bacteria.[1] |
| Benefit | • Data from two adequate and well-controlled trials provide substantial evidence of the effectiveness of BPO cream, 5% for the treatment of inflammatory lesions of rosacea. Trial SGT-54-01 enrolled and randomized a total of 361 subjects (243 to BPO and 118 to vehicle) and Trial SGT-54-02 enrolled and randomized a total of 372 subjects (250 to BPO and 122 to vehicle). In both trials, BPO cream, 5% was superior to vehicle on both co-primary endpoints: IGA success at Week 12 (47% vs 21% and 49% vs 28%) and Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12 (mean: -18 vs -10 and -21 vs -12).<br>• Review of the safety data from the clinical trials identified no new or unexpected safety signals with BPO cream which was well tolerated in all evaluated subgroups. | BPO cream, 5% provides an effective and safe treatment option for inflammatory of rosacea in adults. |

[1] Karadag AS et al. Antibiotic resistence in acne: changes, consequences and concerns.JEADV.2021,35: 73-78.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Risk and Risk Management | • The primary safety database from the pooled phase 3 Trials SGT-54-01 and SGT-54-02 included 722 adult subjects with moderate to severe rosacea. There were no deaths or SAEs related to treatment with the study products. The most common ARs in ≥ 1% of subjects and greater than vehicle were application site reactions: pain, erythema, pruritus and edema. Local tolerability evaluations were conducted at baseline and at each study visit by assessment of dryness, itching, scaling and stinging/burning. The severity of all signs and symptoms improved from baseline to Week 12.<br>• Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and those identified during product development.<br>• No issues require further assessment with a postmarketing requirement or postmarketing commitment.<br>• A risk evaluation and mitigation strategy (REMS) is not recommended. | The risks associated with use of BPO cream, 5% are limited to local reactions. Most local reactions were mild or moderate in severity. The benefit risk conclusion appears favorable.<br><br>Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product. |

## 1.4. Patient Experience Data

The protocol captured the patient perception of the status of their disease and response to treatment with the following patient reported outcome instruments: Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS), Patient Assessment of Papulopustular Rosacea Impacts (PAPI), Patient Global Impression of Change (PGI-C), Patient Global Impression of Symptom Severity (PGI-S), Patient Global Impression of Treatments Side Effects (PGI-SE), Patient Global Impression of Treatments Satisfaction (PGI-TS) and Rosacea Quality of Life (RosaQoL .) These measures were pre-specified in the protocol as supportive/exploratory and safety endpoints. As such, the discussion of these findings in this review will be limited. The endpoints based on these instruments included the following:

*Supportive Efficacy Endpoints:*

- Mean change comparison in PAPSS item 1 (burning) between groups from Baseline to Weeks 4, 8, and 12.
- Mean change comparison in PAPSS item 2 (itching) between groups from Baseline to Weeks 4, 8, and 12.
- Mean change comparison in PAPSS item 3 (redness) between groups from Baseline to Weeks 4, 8, and 12.
- Mean change comparison in PAPSS item 4 (bumps) between groups from Baseline to Weeks 4, 8 and 12.
- Mean change in the components of the PAPI score between groups from Baseline to Week 12.
- Proportion of subjects in the E-BPO cream 5% group relative to subjects in the vehicle group achieving a 3-point improvement in the components of the PAPI score from Baseline to Week 12.
- PGI-S at Week 12.
- PGI-TS at Week 12.
- PAPSS within-person absolute change from Baseline to Week 12.

*Exploratory Endpoint:*

- Mean change in RosaQoL subscale scores from Baseline to Week 12.

*Safety Endpoints:*

- PGI-SE.

Table 1: Patient Experience Data Relevant to this Application

| | | | | | Section of review where discussed, if applicable |
|---|---|---|---|---|---|
| □ | **The patient experience data that were submitted as part of the application include:** | | | | |
| | X | Clinical outcome assessment (COA) data, such as | | | |
| | | X | Patient reported outcome (PRO) | | Section 8.2.6 |
| | | □ | Observer reported outcome (ObsRO) | | |
| | | X | Clinician reported outcome (ClinRO) | | Section 8.1.4; 8.1.5 |
| | | □ | Performance outcome (PerfO) | | |
| | X | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | | Section 8.2.6 |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | | |
| | □ | Observational survey studies designed to capture patient experience data | | | |
| | □ | Natural history studies | | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | | |
| | □ | Other: (Please specify): | | | |
| □ | **Patient experience data that were not submitted in the application, but were considered in this review:** | | | | |
| | □ | Input informed from participation in meetings with patient stakeholders | | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | | |
| | □ | Observational survey studies designed to capture patient experience data | | | |
| | □ | Other: (Please specify): | | | |
| □ | **Patient experience data was not submitted as part of this application.** | | | | |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

Rosacea is a chronic dermatological condition that predominantly affects the central region of the face, e.g., cheeks, nose, chin, mid forehead. It may be characterized by flushing (transient erythema), persistent (nontransient) erythema, telangiectasias, and inflammatory acneiform lesions (papules, pustules). Ocular involvement may occur (e.g., blepharitis, conjunctivitis). Rosacea is often characterized by repeated remissions and exacerbations.

Rosacea is a common disorder that is most frequently observed in individuals with lightly pigmented skin (skin phototypes I and II). People of Celtic and Northern European origin appear to have the greatest risk for this disorder. Estimates of the prevalence of rosacea in fair-skinned populations range from 1 to 10 percent. Rosacea has also been diagnosed in Asians, Latin Americans, African-Americans, and Africans. Rosacea is seen more often in women than men, and onset typically occurs at any time after age 30. Rosacea is reported to be rare in children.[2,3] The pathways that lead to the development of rosacea are not well understood. Proposed contributing factors include abnormalities in innate immunity, inflammatory reactions to cutaneous microorganisms, ultraviolet damage, and vascular dysfunction. Rosacea patients have an increased expression of a variety of genes with roles in both the innate and adaptive immune systems. Microorganisms, such as Demodex folliculorum, Staphylococcus epidermidis, and others may also contribute to the pathogenesis of rosacea by stimulating the innate immune system. Based on the common triggers for rosacea exacerbations, ultraviolet light radiation and the transient receptor potential family of receptors may also play a role in the pathogenesis of rosacea.[4]

In 2002, the National Rosacea Society assembled an expert committee to develop a standard classification system for rosacea. The committee established four distinct subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous, and ocular rosacea. Since 2002,

---

[2] Gallo RL, RD Granstein, S Kang, M Mannis, M Steinhoff, J Tan, D Thiboutot, Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee, J Am Acad Dermatol. 2018 Jan;78(1):148-155.
[3] Dahl MV, Rosacea: Pathogenesis, clinical features, and diagnosis, UpTo Date, Accessed November 19, 2019, https://www.uptodate.com/contents/rosacea-pathogenesis-clinical-features-and-diagnosis?search=Rosacea:%20Pathogenesis,%20clinical%20features,%20and%20diagnosis&source=search_result&selectedTitle=1~108&usage_type=default&display_rank=1
[4] Two, AM, W Wu, RL Gallo, TR Hata, CME Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors, JAAD 2015;72(5):749-758.

increasing knowledge of the pathophysiology of rosacea has favored the view that rosacea is a multivariate disease process with multiple clinical manifestations rather than distinct subtypes of disease. Following recommendations from an international panel of experts, supporting use of phenotype-based, rather than a subtype-based, approach to the diagnosis and classification of rosacea, the National Rosacea Society Expert Committee released an update supporting a similar approach. The phenotype-based approach describes the individual clinical features of rosacea and divides them into diagnostic, major, and secondary (or minor) features/phenotypes.[2]

Diagnosis of rosacea can be made based upon an assessment for diagnostic, major, and minor phenotypes. At least one diagnostic phenotype or two major phenotypes are required for diagnosis:[2]

- Diagnostic phenotypes
  - Fixed centrofacial erythema in a characteristic pattern that may periodically intensify
  - Phymatous (tissue hypertrophy manifesting as thickened skin with irregular contours) changes
- Major phenotypes
  - Papules and pustules
  - Flushing
  - Telangiectasia
  - Ocular manifestations (e.g., lid margin telangiectases, interpalpebral conjunctival injection, spade-shaped infiltrates in the cornea, scleritis, sclerokeratitis)
- Secondary phenotypes
  - Burning or stinging
  - Edema
  - Dry appearance

Surveys over the last 15 years support the conclusion that patients with rosacea may experience adverse impacts on their emotional, social, and occupational well-being. The seriousness of these impacts is linked to disease severity. The psychological burden encompasses an increased risk of depression, anxiety, and worry.[2] Although the impact of rosacea on physical health is limited, successful treatment may result in improved quality of life.[5]

## 2.2. Analysis of Current Treatment Options

[5] Two, AM, W Wu, RL Gallo, TR Hata, CME Rosacea: part II. Topical and systemic therapies in the treatment of rosacea, JAAD 2015;72(5):761-770.

The approach to the treatment of rosacea includes patient education, skin care, and pharmacologic/procedural interventions.

If specific triggers or exacerbating factors can be identified, avoiding these triggers, if possible, can be beneficial in controlling an individual's symptoms. Common triggers include wind, hot and cold temperatures, exercise, spicy foods, alcohol, hot drinks, and physical or psychological stress. Avoidance of flushing can be important since easy flushing is a common feature of rosacea.

Proper skin care plays a pivotal role in maintaining remission and alleviating the symptoms of rosacea. Rosacea skin has been shown to have increased transepidermal water loss indicative of defective barrier functions, and therefore moisturizers are important to help restore this barrier and facilitate remission of rosacea exacerbations. Daily sun protection is also important in skin care. By blocking ultraviolet light, sunscreens decrease LL-37 production and the subsequent production of reactive oxygen species that can trigger rosacea.
Topical drug products approved by the US Food and Drug Administration for rosacea include azelaic acid gel/foam, 15%, metronidazole cream /gel /lotion 0.75% & gel 1%, ivermectin cream, 1%, oxymetazoline HCl cream, 1%, and brimonidine gel, 0.33%.

Systemic therapies approved by the US Food and Drug Administration for the treatment of inflammatory lesions (papules and pustules) of rosacea include only doxycycline 40 mg capsules.

Table 2: FDA-Approved Products for Rosacea

| NDA Number | Trade Name | Generic Name | Sponsor | Approval Date | Indication |
|---|---|---|---|---|---|
| 020531 | METROCREAM (metronidazole topical cream) | Metronidazole cream, 0.75% | Galderma | 09/20/1995 | Inflammatory papules and pustules of rosacea |
| 020743 | NORITATE (metronidazole cream) Cream, 1% | Metronidazole cream, 1% | Valeant International Bermuda | 09/26/1997 | Inflammatory lesions and erythema of rosacea |
| 019737 | METROGEL (metronidazole) Gel, 0.75% | Metronidazole 0.75% | Galderma | 11/22/1988 | Inflammatory papules and pustules of rosacea |
| 020901 | MetroLotion (metronidazole lotion) Topical Lotion, 0.75% | Metronidazole 0.75% | Galderma | 11/24/1998 | Inflammatory papules and pustules of rosacea |
| 021470 | FINACEA (azaleic acid) Gel, 15% | Azaleic acid gel, 15% | Berlex Laboratories, Inc. | 12/24/2002 | Inflammatory papules and pustules of mild to moderate rosacea |
| 021789 | METROGEL (metronidazole) Gel, 1% | Metronidazole gel, 1% | Galderma | 06/30/2005 | Inflammatory lesions of rosacea |

| NDA Number | Trade Name | Generic Name | Sponsor | Approval Date | Indication |
|---|---|---|---|---|---|
| 050805 | ORACEA (doxycycline) capsules | Doxycycline capsules, 40 mg | Galderma | 05/26/2006 | Inflammatory lesions (papules and pustules) of rosacea |
| 204708 | MIRVASO (brimonidine) topical gel, 0.33% | Brimonidine topical gel, 0.33% | Galderma | 08/23/2013 | Persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older |
| 206255 | SOOLANTRA (ivermectin) cream, 1% | Ivermectin cream, 1.0% | Galderma | 12/19/2014 | Inflammatory lesions of rosacea |
| 207071 | FINACEA (azaleic acid) Foam, 15% | Azaleic acid foam, 15% | Bayer Healthcare Pharmaceuticals, Inc. | 7/29/2015 | Inflammatory papules and pustules of mild to moderate rosacea |
| 208552 | RHOFADE (oxymetazoline HCl) cream, 1% | Oxymetazoline HCl cream, 1% | Allergan | 1/18/2017 | Persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older |

Source: NDA 21369 Multi-Disciplinary Review and Evaluation; data derived from Drugs@FDA, accessed 1/7/2020

Table 3: Additional Information for Representative Examples of FDA-Approved Products for Rosacea

| Product(s) Name/ Year of Approval | Indication | Dosing/ Administration | Efficacy Information From labeling | Important Safety and Tolerability Issues |
|---|---|---|---|---|
| **For treatment of inflammatory lesions of rosacea** | | | | |
| METROGEL (metronidazole) Gel, 1%, NDA 021789 (2005) | Inflammatory lesions of rosacea | Once daily to affected areas | 1, 10-week R, VC trial in 746 subjects<br>Active vs vehicle<br>IGA: 38% vs 27%<br>Inflam: 51% vs 33% | AR: contact dermatitis<br>W&P: Peripheral neuropathy, irritant and allergic contact dermatitis |
| FINACEA (azelaic acid) Foam, 1% NDA 207071 (2015) | Inflammatory papules and pustules of mild to moderate | Twice daily to entire facial area | 2, 12-week R, DB, VC trials in 513 subjects with papulopustular rosacea.<br>Active vs vehicle<br>1) IGA: 32% vs 23<br>Inflam:13% vs 10%<br>2) IGA: 43% vs 33<br>Inflam: 13% vs 10% | AR: application site pain & pruritus,<br>W&P: hypopigmentation, eye irritation, flammable propellant |

| Product(s) Name/ Year of Approval | Indication | Dosing/ Administration | Efficacy Information From labeling | Important Safety and Tolerability Issues |
|---|---|---|---|---|
| SOOLANTRA (ivermectin) cream, 1%<br>NDA 206255 (2014) | Inflammatory lesions of rosacea | Once daily to affected areas | 2, 12-week R, DB, VC trials in 1371 subjects with moderate to severe rosacea<br>Active vs vehicle<br>1) IGA:38% vs 12%<br>Inflam: 65% vs 42%<br>2) IGA:40% vs 19%<br>Inflam:66% vs 43% | AR: skin burning sensation and skin irritation<br>W&P: none |
| **For treatment of persistent (nontransient) facial erythema of rosacea** | | | | |
| MIRVASO (brimonidine) topical gel, 0.33%<br>NDA 204708 (2013) | Persistent (nontransient) facial erythema of rosacea in adults 18 years of age or older | Pea-sized amount once daily to each of the five areas of the face: central forehead, chin, nose, each cheek | 2, 4-week R, DB, VC trials in 553 subjects with moderate to severe, persistent (nontransient) facial erythema of rosacea<br>Active vs vehicle<br>Success<br>1) CEA & PSA:<br>Hour 3: 31% vs 11<br>Hour 6: 30% vs 10<br>Hour 9: 26% vs 10<br>Hour 12: 23% vs 9<br>2) CEA & PSA:<br>Hour 3: 25% vs 9<br>Hour 6: 25% vs 9<br>Hour 9: 18% vs 11<br>Hour 12: 22% vs 10 | AR: erythema, flushing<br>W&P: potentiation of vascular insufficiency, can lower blood pressure – use with caution in patients with severe or unstable or uncontrolled cardiovascular disease |
| RHOFADE (oxymetalozine hydrochloride) cream, 1%<br>NDA 208552 (2017) | Persistent facial erythema associated with rosacea in adults | Pea-sized amount, once daily in a thin layer to cover the entire face (forehead, nose, each cheek, and chin) | 2, 29-day R, DB, VC trials in 885 subjects with moderate to severe persistent erythema of rosacea<br>Active vs vehicle<br>Success:<br>1) CEA & SSA:<br>Hour 3: 12% vs 6<br>Hour 6: 16% vs 8<br>Hour 9: 18% vs 6<br>Hour 12: 15% vs 6<br>2) CEA & SSA:<br>Hour 3: 14% vs 7<br>Hour 6: 13% vs 5<br>Hour 9: 16% vs 9<br>Hour 12: 12% vs 6 | AR: application site dermatitis<br>W&P: may impact blood pressure (use with caution in patients with severe or unstable or uncontrolled cardiovascular disease, orthostatic hypotension, and uncontrolled hypertension or hypotension), used with caution in patients with cerebral or coronary insufficiency, Raynaud's phenomenon, thromboangiitis obliterans, scleroderma, or |

| Product(s) Name/ Year of Approval | Indication | Dosing/ Administration | Efficacy Information From labeling | Important Safety and Tolerability Issues |
|---|---|---|---|---|
| | | | | Sjögren's syndrome, may increase the risk of angle closure glaucoma in patients with narrow-angle glaucoma |
| **Oral product for treatment of inflammatory lesions of rosacea** | | | | |
| ORACEA(doxycycline) capsules<br>NDA 050805 (2006) | treatment of only inflammatory lesions (papules and pustules) of rosacea in adult patients | Capsule (40 mg) once daily | 2, 16-week R, DB, PC trials in 537 subjects with rosacea (10 to 40 papules and pustules and 2 or fewer nodules)<br>Active vs vehicle<br>1) IGA: 31% vs 19<br>Inflam: 12% vs 6%<br>2) IGA: 15% vs 6%<br>Inflam: 10% vs 4% | AR: upper abdominal pain, diarrhea, hypertension, LDH increase<br>W&P: class labeling; teratogenic effects, pseudomonas colitis, may increase BUN, photosensitivity, tissue hyperpigmentation, pseudotumor cerebri |

Abbreviations: AR = adverse reaction; W&P = Warnings and Precautions; R = randomized; DB = double-blind; VC = vehicle controlled; IGA = Investigator Global Assessment; Inflam = inflammatory; CEA = Clinical (or Clinician) Erythema Score; PSA = Patient Self-Assessment Scale; SSA = Subject Self-Assessment scale; BUN = blood urea nitrogen; LDH = lactate dehydrogenase; PC = placebo-controlled
Source: NDA 21369 Multi-Disciplinary Review and Evaluation; data derived from approved labeling for drug products listed

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

This formulation of BPO cream, 5% is not marketed in any jurisdiction. Therefore, the section is not applicable.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed BPO cream under IND 102233. The initial IND submission dated April 17, 2008 included a request for a Pre-IND Meeting. The FDA denied this request (Advice Letter dated May 29, 2008) and addressed these questions during the review of the first phase 2 protocol (SGT-EBPO1-09, submitted July 22, 2009). The FDA provided advice regarding the clinical and nonclinical development plan, Investigator's Global Assessment (IGA) scale (i.e., the category of clear should represent the absence of disease and that the categories should be non-overlapping), the design of this dose ranging trial and the recommended co-primary endpoints for the assessment of the inflammatory papules and pustules of rosacea. The FDA stated that "the recommended co-primary endpoints are a dichotomized Investigator's Global Severity Scale which defines success as a score at Week 12 of clear or almost clear and a two-grade improvement from baseline and an absolute change in inflammatory lesion count." (Advice Letter dated August 1, 2008.)

On December 16, 2011, the Applicant submitted (SDN 9) an amended protocol for their phase 2 trial (SGT-EBPO1-09). An advice letter regarding this submission was sent to the Applicant on May 1, 2012. The FDA reiterated the comments from previous advice letter regarding the recommended co-primary efficacy endpoints and the IGA scale.

Subsequently, the key regulatory interactions included: an End of Phase 2 Meeting [Meeting Minutes dated August 16, 2018], Special Protocol Assessment [Agreement Letter dated April 10, 2018], Initial Pediatric Study Plan (iPSP)[Agreed iPSP dated September 9, 2018], Type C Meetings to discuss CMC issues [Meeting Minutes dated March 22, 2019 and November 5, 2019 (WRO)] and pre-NDA Meetings [Meeting Minutes dated February 21, 2020 and February 24, 2020.

On November 29, 2017, the Applicant met with the FDA for an End-of-Phase 2 (EOP2) meeting to discuss the phase 3 development program for BPO cream and the results of completed phase 2 dose-ranging trial (SGT-EBPO1-09), which investigated two concentrations of their product (i.e., 1% and 5%) The trial enrolled subjects with mild to severe rosacea. The results for IGA success at Week 12 were 20% for vehicle, 37.5% for BPO cream, 1%, and 53.3% for BPO cream, 5%. The results for change in inflammatory lesions at Week 12 were -10.2 for vehicle cream, -19.0 for BPO cream, 1%, and -15.0 for BPO cream, 5%.

In this submission (SDN 20), the Applicant proposed to conduct two identically designed phase 3 trials (SGT-54-01 and SGT-54-02) with the 5% concentration in subjects with moderate to severe rosacea. Regarding the proposed phase 3 trial synopsis, the FDA stated: "your proposed design for two phase 3 trials appear reasonable; however, you have not provided any rationale for your proposed sample size." The Applicant planned to use a different dosage form of the proposed product for the Phase 3 trials. The FDA communicated the following key comments:

- "Clarify whether you intend to manage age group enrollment via stratification and whether your target of 6% of subjects age 65 and older is consistent with the age distribution of your target population. If you intend to use stratified randomization, then we recommend including the stratification factors in your analysis models."
- "You did not include your 5-point IGA scale in your protocol synopsis. The IGA scale should be static, noncomparative with a limited number of categories. Each category should be distinct and non-overlapping and should represent a clinically meaningful gradation of disease."
- (b) (4)
- "We agree that the data accumulated thus far (literature review, expert input, subject input) support the content validity of the Patient Assessment of Papulopustular rosacea

Signs and Symptoms (PAPSS) as a measure of subject reported signs and symptoms of papulopustular rosacea. (b) (4) (b) (4)

- "We recommend you explore multiple anchor scales to provide an accumulation of evidence to help interpret a clinically meaningful within-subject score change in the PAPSS from the subject perspective. (b) (4) (b) (4)
- "You have stated that the change in inflammatory lesions endpoint will be analyzed with an ANCOVA analysis on either the original data or ranked data. The protocol should specify clear guidelines for selecting the primary analysis method to ensure that the statistical methods are adequately prespecified to avoid introducing bias."
- "You have proposed handling missing data using Markov Chain Monte Carlo multiple imputation. Your protocols should include full details of the proposed multiple imputation procedure including such information as the imputation and analysis models, any necessary transformations, the number of imputations, and randomization seeds, etc. In addition to the primary method of handling missing data, you should propose at least two sensitivity analyses that use alternate assumptions to ensure that the method of handling missing data does not impact the results."

On February 20, 2018, the Applicant submitted (SDN 25) the protocol for their identically designed phase 3 trials (SGT-54-01 and SGT-54-02) for Special Protocol Assessment (SPA). The FDA agreed with the overall design, study population, co-primary efficacy endpoints, IGA scale, safety evaluation and analysis methods for change in inflammatory lesions and success on IGA. The FDA provided comments regarding the secondary endpoints, (b) (4) (b) (4) difficulty with interpreting some items on the PAPSS (i.e. bumps), waiver of QT/QTc, handling missing data, unsuitability of supportive efficacy endpoints to support labeling, the proposed interim analysis and the patient global rating scales for use as anchors for determining what constitutes clinically meaningful change in PAPSS (Agreement Letter dated April 5, 2018). Additional comments contained in the Agreement Letter included:

(b) (4)

- (b) (4)

- "You have proposed a multi-step analysis procedure for the absolute change in inflammatory lesions that can follow different paths depending on the skewness of the distribution and the presence of interactions. These determinations also must be handled within the context of multiple imputations. Your protocol should include sufficient detail to explain how the decision paths in the primary analysis will be implemented within the multiple imputation calculations."
- "You have noted that subjects who discontinue due to adverse events related to study treatment or who had a documented lack of treatment effect will be included in the per protocol population. However, you have not specified how missing data will be handled for such subject in the intent-to-treat (ITT) or per protocol (PP) population. We recommend not treating such subjects as missing at random, but rather impute values consistent with their status as treatment failures."
- "You have proposed to conduct a subgroup analyses where age is dichotomized based on the median age as well as at 18 years. Because the minimum age for enrollment in the study is 18 years, dichotomizing the population at age 18 years would not be meaningful. We recommend proposing a subgroup analysis with a more meaningful age cutoff for the study population."

On April 20, 2018, the Applicant submitted (SDN 27) an amended protocol for their phase 3 trials (SGT-54-01 and SGT-54-02). The Applicant modified the list of key secondary efficacy endpoints. (b) (4) . The Applicant also modified the significance level for the skewness test for the analysis of the co-primary endpoint of absolute change in inflammatory lesions from baseline to Week 12. A Special Protocol – No Agreement to Modification letter was sent to the Applicant on March 5, 2019. The letter contained the following comments:

- No Agreement to Modification(s):
  - "Agreement #4 of the SPA Agreement Letter dated 4/5/2018 stated 'Your proposal to analyze the change in inflammatory lesions with analysis of covariance (ANCOVA) is acceptable. In your analysis, the ANCOVA analysis will include terms for treatment, analysis center, and baseline count, (and treatment-by-center interaction if the term is

significant at 0.10). If the two-sided p-value for the skewness test is significant at 0.01 then rank-transformed data will be used in the analysis instead of the nominal values.' As we reached agreement on your original proposal to conduct the skewness test at a significance level of 0.01, we recommend that you conduct the test at 0.01 rather than changing the significance level (b) (4)."

- Additional Comments:
  - "You have proposed to analyze a subset of the supportive efficacy endpoints (mean change in PAPSS items 1-4 from baseline to Week 12) using the Benjamini-Hochberg method. Supportive endpoints are not suitable for establishing claims or for inclusion in labeling, and thus do not need to be adjusted for multiplicity."
  - "One of your supportive efficacy endpoints is listed as 'Mean change comparison in PAPPS item 4 (bumps) between groups from Baseline to Weeks 4, 8 and 12 Rosacea erythema assessment at Week 12' throughout the protocol. It appears that this bullet point is intended to be two separate bullet points rather than one. Clarify your list of supportive efficacy endpoints."
  - "Your protocol now states that subjects who discontinue from the study due to an adverse event related to treatment or documented lack of treatment effect will be imputed with values consistent with their status as treatment failures and will not be included in the multiple imputation. While such imputation is straightforward for binary success/failure endpoints, how this would be implemented for the change in lesion count endpoints is less clear. Clarify in your protocol how you will implement this strategy for the change in inflammatory lesion count endpoint."

The Applicant requested a full waiver from conducting pediatric studies in children from birth (0) to less than 17 years of age, as necessary studies are impossible or highly impracticable because the number of patients is small and those that may be diagnosed with rosacea are geographically dispersed (Agreed initial Pediatric Study Plan dated September 9, 2018). See Section 8.2.9 Pediatrics and Assessment of Growth.

The CMC issues discussed at multiple meetings (March 5, 2019 and February 5, 2020), including the Pre-NDA meeting (b) (4)

On February 5, 2020, the Applicant met with the FDA for a Pre-NDA meeting. The key discussion comments included:

- "We agree that the proposed nonclinical data from published literature and the nonclinical data package available for your topical drug product are adequate to support submission of a 505(b)(2) NDA application."
- "…your protocols did not prespecify efficacy endpoints (b) (4). In general, only endpoints that are pre-specified, clinically meaningful, and adjusted for multiplicity are eligible for consideration for labeling."

(b) (4)

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

## 4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. Initially, the Division requested that the Office of Scientific Investigations conduct clinical inspections of 2 domestic sites. The criteria used to select these sites were high enrollment, high efficacy, disparity of results on IGA and lesion counts (Site 202), large amounts of missing data (Site 109) and inspection history.

Table 4: Planned Clinical Site Inspections

| Site Number, Name, and Address | Site Number | Number of Subjects | Inspection dates | Classification |
|---|---|---|---|---|
| | | **SGT-54-01** | | |
| Jackson, Sarah<br>3525 Prytania St.<br>Suite 308, 321 & 501<br>New Orleans, LA 70115 | 109 | 21 | Cancelled inspection due to the COVID 19 pandemic | |
| | | **SGT-54-02** | | |
| Badar, Francisco<br>19123 Bloomfield Avenue<br>Cerritos, CA 90703 | 202 | 30 | Cancelled inspection due to the COVID 19 pandemic | |

Source: Reviewer's Table with data from CDER's Clinical Investigator Site Selection Tool Generated July 29, 2020 Key to Compliance Classifications -Abbreviations: NAI = No Action Indicated, VAI = Voluntary Action Indicated, OAI = Official Action Indicated

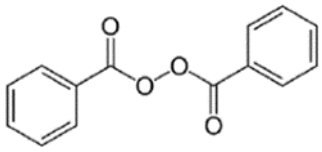
The statistical reviewer, Matthew Guerra, PhD, performed multiple analyses of the efficacy data which excluded data from the specified sites above. Efficacy was not driven by any one site and overall conclusions regarding efficacy were not impacted by exclusion of data from these sites. Therefore, the review team concluded that conduct of clinical sites inspection is not necessary. The review team communicated this decision to the OSI reviewer, Zana H Marks, MD, MPH.

## 4.2. Product Quality

1) Drug Substance

The active ingredient, benzoyl peroxide (BPO), is a compendial drug substance and has been classified as an oxidizing agent. Benzoyl peroxide has been marketed for more than 50 years as the active ingredient of topical over-the-counter products for the treatment of acne vulgaris. It has also been used as the active ingredient of multiple approved combination drug products for topical use.

Benzoyl peroxide is a white granular powder with a melting range of 103°C to 106°C and no observed polymorphic forms. It is sparingly soluble in water or alcohol and soluble in benzene, chloroform, and ether. The chemical name for BPO is benzoyl benzenecarboperoxoate. It has a molecular formula of $C_{14}H_{10}O_4$, a molecular weight of 242.23g/mol, and the chemical structure provided below:



Benzoyl peroxide, USP for this application is manufactured in accordance current Good Manufacturing Practices (cGMP) requirements (b) (4) It is tested, released, and accepted according to the USP compliant specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its currently assigned retest date of (b) (4). The detailed manufacturing process for BPO produced (b) (4) have been provided in DMF (b) (4) which has been reviewed and found to be adequate to support this new drug application.

2) Drug Product

The drug product, EPSOLAY® (benzoyl peroxide) cream, 5% is a white to off white cream containing 50mg of BPO per each gram. It will be packaged as 50g in 50-mL (commercial drug product) and as (b) (4)g in 30-mL (physician sample) high-density polyethylene (HDPE) bottles with (b) (4) airless pumps and (b) (4) caps. This drug product is intended for topical administration as a thin layer to the affected skin area and it is indicated for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

Each gram of EPSOLAY contains 50mg of (b) (4) BPO as the active ingredient and silicone dioxide, cetrimonium chloride, polyquaternium-7, lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, glycerin, mono and di-glycerides, macrogol stearate type 1 (b) (4), edetate disodium, cyclomethicone, cetyl alcohol, phenoxyethanol, and purified water as the inactive ingredients.

The active ingredient, BPO in this drug product (b) (4) (b) (4). The encapsulation is intended to allow slow migration of the BPO through the microcapsule

shells leading to continuous release of this active ingredient over time and delivery to the affected skin area. (b) (4)

EPOSLAY is manufactured for Sol-Gel (b) (4) in accordance with cGMP requirements.. It is tested and released against a drug product specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. The proposed expiration dating period of 24 months is supported by the stability data submitted in the application and is granted. This drug product should be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30ºC (59°F to 86ºF). The unused drug product should be discarded 30 days after opening. It will also be labeled with "keep away from heat" and "do not freeze".

3) The OPQ Recommendation

- The Applicant of this 505(b)(2) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, benzoyl peroxide, and the drug product, EPSOLAY (benzoyl peroxide ) Cream, 5% for topical use.
- The Office Pharmaceutical Manufacturing Assessment has made an overall recommendation of adequate for the facilities involved in this application.
- The CMC issues on labels/labeling have been satisfactorily resolved
- The Applicant's request for categorical exclusion from the environmental assessment has been granted.

Therefore, from the OPQ perspective, this application is recommended for approval with an expiration dating period of 24 months.

## 4.3. Microbiology

The Division of Microbiology Assessment identified no deficiencies. Refer to the Microbiology Chapter of the Integrated Quality assessment (IQA) by the Office of Pharmaceutical Quality dated April 7, 2021.

## 4.4. Devices and Companion Diagnostic Issues

The Applicant packaged the drug product in a (b) (4) pump as described above, Section 4.2. Product Quality. The review team identified no issues related to device. Refer to the Drug Product Chapter of the IQA Review by the Office of Pharmaceutical Quality dated April 7, 2021.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

The Applicant submitted a 505(b)(2) application for BPO cream, 5% for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. The Applicant is relying on literature data available for benzoyl peroxide, the OTC monograph for benzoyl peroxide (2.5 – 10%) for the treatment of acne and two nonclinical studies conducted with the benzoyl peroxide cream formulation.

The Applicant submitted two pivotal GLP nonclinical studies conducted with BPO cream. The Applicant conducted a 13-week dermal toxicity study in minipigs and a phototoxicity study in rabbits. The results from these two nonclinical studies do not raise any safety concerns for the applicant's BPO cream formulation.

Cetrimonium chloride (CTAC) and polyquaternium-7 (PDAC) are two noncompendial excipients used (b) (4). The concentrations of CTAC and PDAC in the BPO cream formulation are (b) (4)% and (b) (4)%, respectively. These two excipients were originally in the FDA Inactive Ingredient Database but have been removed, not for reasons of safety, at the time of this review. The concentrations of these two excipients in this topical drug product are acceptable from a Pharmacology/Toxicology perspective. The specifications for CTAC and PDAC provided in the NDA submission are acceptable from a Pharmacology/Toxicology perspective. There are no safety issues associated with the use of the CTAC and PDAC excipients in this topical drug product.

This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA.

## 5.2. Referenced NDAs, BLAs, DMFs

None

## 5.3. Pharmacology

Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects. However, the mechanism of action for the treatment of rosacea is unknown. This information supports information contained in Section 12.1 of labeling.

## 5.4. ADME/PK

Benzoyl peroxide is converted in the skin to benzoic acid and hydrogen peroxide. Therefore, BPO cannot be directly measured due to its rapid conversion to benzoic acid. The

toxicokinectics of BPO cream, 5% and 10% was evaluated in the 13-week dermal toxicity study in minipigs. Plasma concentrations of benzoic acid from samples collected at multiple timepoints on Days 1 and 90 were determined using a validated high pressure liquid chromatography method with ultraviolet detection. Analysis of the data indicated that repeated daily applications of BPO cream, 5% and 10% to minipig skin did not demonstrate systemic exposure to benzoic acid above endogenous levels.

## 5.5. Toxicology

### 5.5.1. General Toxicology

Study title/ number: Encapsulated Benzoyl Peroxide Gel: A 13-Week Dermal Toxicity Study in Gottingen Minipigs

- The nomenclature for BPO gel was subsequently changed to BPO cream.
- No systemic exposure to benzoic acid was noted after 13-weeks of daily topical application of BPO cream, 5% or 10% to minipig skin.
- BPO cream, 5% or 10% only caused minimal hyperkeratosis at the treatment site.
- The no-observed-adverse-effect-level (NOAEL) was 10% BPO cream, the highest concentration evaluated in this study.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

| | |
|---|---|
| Dose and frequency of dosing: | 0 (vehicle control), 0 (untreated control), 5% and 10% BPO cream, once daily |
| Route of administration: | Topical |
| Formulation/Vehicle: | Clinical vehicle |
| Species/Strain: | Minipig/Gottingen |
| Number/Sex/Group: | 4 |
| Age: | Not specified; males weighed 9.2 to 12.2 kg, females weighed 9.2 to 13.2 kg |
| Satellite groups/ unique design: | Topically applied test article to a 10 x 20 cm treatment site at a rate of 2 mg/cm$^2$ (400 mg of formulation per application) |
| Deviation from study protocol affecting interpretation of results: | No |

Observations and Results: changes from control

| Parameters | Major findings |
|---|---|
| **Mortality** | No treatment related effects. |

| Parameters | Major findings |
|---|---|
| **Clinical Signs** | No treatment related effects for clinical signs. Very slight erythema was observed for both benzoyl peroxide cream treatment groups. |
| **Body Weights** | No treatment related effects. |
| **Ophthalmoscopy** | No treatment related effects. |
| **ECG** | No treatment related effects. |
| **Hematology** | No treatment related effects. |
| **Clinical Chemistry** | No treatment related effects. |
| **Gross Pathology** | No treatment related effects. |
| **Organ Weights** | No treatment related effects. |
| **Histopathology**<br>Adequate battery: Yes | Minimal hyperkeratosis was noted at the treatment site for both benzoyl peroxide cream treatment groups. |

### 5.5.2. Genetic Toxicology

A review of literature information available for the genetic toxicity of BPO indicates that a variety of genetic toxicity studies have been conducted with BPO. The results of these studies have sometimes been positive and sometimes been negative.

Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in *Salmonella typhimurium* tests (i.e., Ames assay) by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. This genetic toxicity information supports nonclinical information contained in Section 13.1 of labeling.

### 5.5.3. Carcinogenicity

The Applicant references the OTC monograph for BPO (2.5 – 10%) for the treatment of acne (21 CFR 333.310; 56 FR 37622, August 7, 1991; 21 CFR 201.66) for BPO safety information. The Consumer Health Products Association conducted topical carcinogenicity studies in rodents with an aqueous carbopol gel formulation of BPO. The results from these topical carcinogenicity studies in rodents is contained in the final rule for the OTC monograph for BPO posted on March 4, 2010 with an effective date of March 4, 2011 (75 FR 9767). The Applicant references these topical carcinogenicity studies in Section 13.1 of the submitted labeling for BPO cream.

No significant increase in tumor formation was observed in rats treated topically with a 15 to 25% BPO carbopol gel for two years. Similar results were obtained in mice topically treated with 25% BPO gel for 56 weeks followed by intermittent treatment with 15% BPO gel for rest of the 2 years study period and in mice topically treated with 5% BPO gel for two years.

The carcinogenicity of BPO has been investigated in a number of literature studies. However, most of the studies have not been of two years duration and have not used daily application. In most studies, BPO applied alone did not produce skin tumors. In a study conducted by the

National Toxicology Program, BPO was shown to promote tumor formation in the skin initiated by dimethylbenzathracene or methylnitro-nitrosoguanidine in B6C3F1, Swiss CD-1 and SENCAR mice (NTP TR 441, 1996). In this study the initiator was administered once and BPO was administered weekly for 52 weeks. The results from these literature studies clearly show that BPO is a tumor promoter and tumor progression agent in the skin in several animal models.

This carcinogenicity information supports nonclinical information contained in Section 13.1 of labeling.

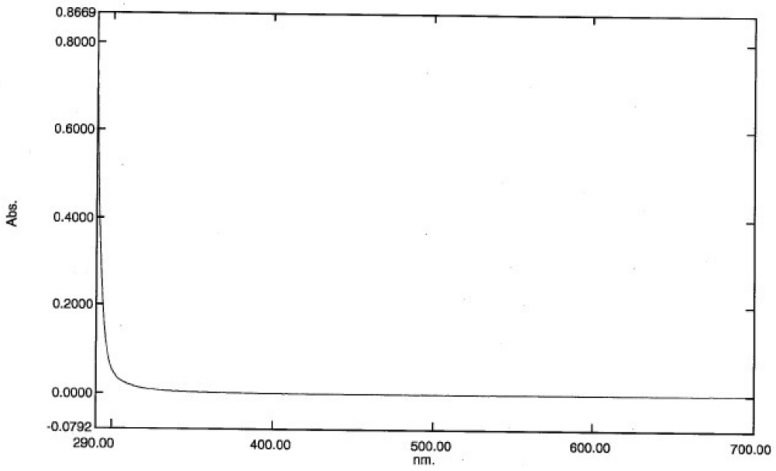
### 5.5.4. Reproductive and Developmental Toxicology

The Applicant submitted literature data that describes reproductive and developmental toxicology studies conducted with BPO that were basically negative. However, the validity of these studies is questionable due to the rapid breakdown of BPO to benzoic acid. It is not clear if the fetus would ever be exposed to BPO in a reproductive and developmental toxicology study due to the short half-life of BPO. Therefore, reproductive and developmental toxicology information for BPO is not included in the ESPOLAY Cream, 5% labeling.

### 5.5.5. Other Toxicology Studies

In vitro UV/Vis spectrum

Study title / number: E-BPO cream, 5% UV/VIS spectrum by Spectophotometic Method – Photosafety Evaluation
The maximum absorbance between 290 – 700 nm was determined at a concentration of 0.5 mg/ml BPO in methanol and the extinction coefficient was calculated for any absorption peaks. The absorption spectrum is provided below.




The molar extinction coefficient calculated for the absorption peak shoulder at 290 nm was 368 L $mol^{-1}cm^{-1}$ which indicates that there is no phototoxicity concern for BPO.

In vivo phototoxicity:

Study title / number: Phototoxicity Test in Rabbits / 043LS89.001
Aliquots (0.1 ml) of BPO cream, 5%, vehicle control or positive control (1% methoxypsoralen in ethanol) were topically administered to rabbits on duplicate symmetrical intact skin sites (to the left and right of the midline) on six rabbits (3/sex). One additional site on each side of all rabbits remained untreated. One set of treated sites was exposed to UV light (>320 nm) for 60 minutes (approximately 197 J/cm$^2$) and the other set of treated sites were non-irradiated. Vehicle and positive control treated sites produced expected results. Benzoyl peroxide cream, 5% did not display evidence of phototoxicity potential under the conditions of this study.

# 6 Clinical Pharmacology

## 6.1. Executive Summary

Benzoyl peroxide is an oxidizing agent and has been marketed for over 50 years as an active ingredient in the treatment of acne vulgaris. A number of over-the-counter (OTC) formulations contain BPO at concentrations ranging from 2.5 to 10 % are marketed in the U.S. The Applicant has developed microencapsulated BPO as a 5% cream to treat inflammatory lesions of rosacea in adults.

When topically applied, BPO is absorbed by the skin and it is converted into benzoic acid, which is an endogenous substance and is eliminated in urine. This NDA was submitted with a waiver request for the pharmacokinetic (PK) assessment of BPO as it is nearly impossible to measure systemic level of BPO.

### 6.1.1. Recommendations

From clinical pharmacology perspective, the overall information provided in this NDA supports the approval.

Post-marketing requirement/post-marketing commitment: None

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Due to a current impracticality of PK assessment of BPO, the Applicant has not conducted any PK assessment of the product. The Applicant provided scientific literature information to support that systemic levels of BPO following topical application is likely to be very low.

### 6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed a dosing regimen that a pea-sized amount of BPO cream, 5% be topically applied as a thin layer to each area of the face (forehead, chin, nose, each cheek) once daily. The Applicant's proposed dosing regimen appears to be consistent with the dosing regimens used in phase 3 trials. Thus, the efficacy and safety results in phase 3 trials should support the proposed dosing regimen. For efficacy and safety findings, refer to Clinical and Biostatistical reviews in Sections 7 and 8.

Therapeutic Individualization

Therapeutic individualization is not applicable. No studies were conducted for assessment of the effects of intrinsic and extrinsic factors on the PK of the BPO cream, 5 %, and this is not deemed necessary as the FDA waived the PK study.

Outstanding Issues

There are no outstanding issues that would preclude the approval of BPO cream, 5% from the Clinical Pharmacology perspective.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Benzoyl peroxide is an oxidizing agent with bactericidal and keratolytic effects but the precise mechanism of action is unknown. The Applicant has developed a micro-encapsulated benzoyl peroxide 5% in a cream formulation. Benzoyl peroxide is absorbed by the skin and it is converted to benzoic acid which is an endogenous substance which is excreted in the urine. The Applicant has not conducted PK assessment during the development of BPO cream, 5% and they have submitted a waiver request along with some literature. The waiver request for PK assessment is deemed acceptable.

### 6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Given the characteristic of BPO, the clinical pharmacology study was waived. The data from phase 3 trials support the effectiveness of the BPO cream, 5% (See Sections 7 and 8 for details).

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

Yes. The proposed topical application as a thin layer to affected lesions once daily is acceptable for the treatment of rosacea in adults.

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

Alternative dosing regimen for subpopulation for example in pediatric population is not necessary as the proposed target population is adult subjects 18 years and older with rosacea.

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

Given the topical product, food-drug interaction is not applicable in this scenario. The drug-drug interaction studies were not conducted because of the characteristics of BPO rapidly converting to benzoic acid following topical application and PK assessment is waived.

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

To support the safety and efficacy of BPO cream, 5% for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older, the Applicant conducted 4 clinical trials: one phase 2 dose- finding trial (SGT-EBPO1-09) and three phase 3 trials. The phase 3 development program included two identically designed 12- week trials (SGT-54-01 and SGT-54-02) and one open- label, long- term, safety trial (SGT-54-07) with dosing for up to 52 weeks. The Applicant conducted all of the clinical trials in the United States. The phase 3 trials evaluated the to-be-marketed formulation of BPO cream, 5%, while the phase 2 trial (SGT-EBPO1-09) evaluated BPO gel. The differences in the formulations included changes in the composition, manufacturing process, scale and dosage form classification. However, evaluation by the product quality team suggests that these differences were minor and would not be expected to impact safety or efficacy.

Phase 3 Trials:

- SGT-54-01: Randomized, double-blind, vehicle-controlled, trial to evaluate the efficacy and safety of BPO cream, 5% once daily for 12 weeks
- SGT-54-02 Randomized, double-blind, vehicle-controlled, trial to evaluate the efficacy and safety of BPO cream, 5% once daily for 12 weeks
- SGT-54-07: Open-label, long-term extension trial enrolling subjects who completed SGT-54-01/ SGT-54-02 and demonstrated compliance (not missed more than one visit of Visits 3, 4 or 5). (The Applicant discontinued the trial once the target number of completers was reached.)

Phase 2 Trial:

- SGT-EBPO1-09: Randomized, double-blind, vehicle -controlled, dose ranging trial evaluating 2 doses of BPO gel (1% or 5%) applied once daily for 12 weeks.

Table 5: Listing of Clinical Trials Relevant to NDA 214510

| Trial Identity | NCT no. | Trial Design | Regimen/ schedule/ route (# subjects enrolled) | Study Endpoints | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|
| | | | | | | |
| SGT-54-01 | 03448939 | Multicenter, double-blind, randomized, parallel-group, vehicle-controlled, phase 3 trial | BPO cream, 5% (243)<br>Vehicle cream (118)<br><br>Topical application once daily for 12 weeks (no follow-up) | Coprimary efficacy<br>•Proportion of subjects achieving IGA success at Week 12, defined as an IGA score of 0 ("clear") or 1 ("almost clear") with ≥ 2 grade reduction from baseline<br>•Absolute change in inflammatory lesion counts from baseline to Week 12<br>Safety:<br>cutaneous safety (dryness, and scaling) and local tolerability (itching and burning/stinging), AE, physical examinations, vital signs, and PGI-SE. | Subjects with moderate or severe rosacea with ≥ 15 and ≤ 70 inflammatory lesions and ≤ 2 nodules (361)<br>95M/266F<br>19 to 85 years | 27 sites in the US |
| SGT-54-02 | 03564119 | Multicenter, double-blind, randomized, parallel-group, vehicle-controlled, phase 3 trial | BPO cream, 5% (250)<br>Vehicle cream (122)<br><br>Topical application once daily for 12 weeks (no follow-up) | Coprimary efficacy endpoints:<br>•Proportion of subjects achieving IGA success at Week 12, defined as an IGA score of 0 ("clear") or 1 ("almost clear") with ≥ 2 grade reduction from baseline<br>•Absolute change in inflammatory lesion counts from baseline to Week 12<br>Safety:<br>cutaneous safety (dryness, and scaling) and local tolerability (itching and burning/stinging), AE, physical examinations, vital signs, and PGI-SE. | Subjects with moderate or severe rosacea with ≥ 15 and ≤ 70 inflammatory lesions and ≤ 2 nodules (372)<br>104M/268F<br>18 to 84 years | 27 sites in the US |
| SGT-EBPO1-09 | | Multicenter, double-blind, | BPO gel, 5% (30)<br>BPO gel, 1% (32)<br>Vehicle gel (30) | 2-grade improvement in the IGA at Week 12 relative to baseline | Subjects with mild, moderate, or | 10 sites in the US |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | randomized, vehicle-controlled, parallel-group, dose-ranging phase 2 trial | (Total enrolled: 92)<br><br>Topical application once daily for 12 weeks | Safety<br>Tolerability, AEs, pregnancy testing | severe rosacea with ≥ 12 inflammatory lesions<br>25M/67F<br>23 to 82 years | |
| | | | | | | |
| SGT-54-07 | 03564145 | Multicenter, open-label, long-term, phase 3 safety trial | BPO cream, 5% (535)<br><br>Once daily for up to 52 weeks<br>Prior treatment in blinded trials:<br>BPO cream, 5% (336)<br>Vehicle cream (172) | Not intended to evaluate efficacy<br>Safety<br>AEs, cutaneous safety (dryness and scaling) and local tolerability (itching and burning/stinging) physical examinations, and vital signs. | Subjects with rosacea who completed SGT-54-01 or SGT-54-02 (535)<br>153M/382F<br>19 to 81 years | 50 sites in the US |

PGI-SE :Patient Global Impression of Treatments Side Effects questionnaire
M: Male; F: Female; BPO: benzoyl peroxide; AE: adverse events; US: United States; IGA: Investigator Global Assessment Scale

## 7.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety of BPO cream for the proposed indication included final trial reports submitted by the Applicant, and datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)]. This application was submitted in electronic common technical document format and entirely electronic. The electronic submission included protocols, statistical analysis plans (SAPs), clinical trial reports, SAS transport datasets in Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) format. The datasets were in the following network path:

Original submission: \\cdsesub1\evsprod\nda214510\0001\m5\datasets

### Compliance with Good Clinical Practices

The Applicant stated that the trials in the development program were conducted in compliance with the ethical principles of Good Clinical Practice (GCP). The Institutional Review Board (IRB), reviewed and approved the protocol, any amendments, advertising materials, written instructions to subjects, all questionnaires / diaries and the informed consent form (ICF). The entry criteria ensured that subject at increased risk of adverse events from the study product were excluded. All subjects received information regarding the nature and risks of participation in the trial and provided written informed consent prior to participation.

### Data Quality and Integrity

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of BPO cream, 5% for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy

### 8.1.1. Study Design and Endpoints

The Applicant conducted two identically designed phase 3 trials (SGT-54-01 and SGT-54-02). Both were randomized, multicenter, double-blind, vehicle-controlled, parallel-group trials to investigate the safety and efficacy of BPO cream, 5% for the treatment of inflammatory lesions of moderate to severe rosacea. For enrollment, the protocol specified the following key inclusion criteria:

- Male and female subjects, 18 years of age and older
- Investigator Global Assessment (IGA) score of 3 ("moderate") or 4 ("severe"), see Table 6 for details on the IGA scale
- A total of 15 to 70 inflammatory lesions (papules and/or pustules) on the face including those present on the nose
- No more than two nodules (papule or pustule greater than 5 mm in diameter) on the face

The entry criteria excluded the enrollment of subjects using important concomitant medications such as topical and systemic antibiotics, retinoids and other products indicated for the treatment of rosacea that could have confounded the assessments of safety and efficacy.

Each trial was designed to enroll and randomize approximately 350 subjects from up to 28 centers in a 2:1 ratio to receive either BPO cream, 5% (N=200) or Vehicle cream (N=150). Subjects applied study product once daily for 12 weeks. The protocol specified subjects to use a "peas-size" amount for each area of the face (chin, left cheek, right cheek, nose, left forehead and right forehead). Subjects were specified to be evaluated at the following 6 study visits: screening (Day -35 to -1), baseline (Day 1), and Weeks 2, 4, 8, and 12 (end of treatment / end of study).

The protocol specified the following co-primary efficacy endpoints:

- Proportion of subjects achieving IGA success at Week 12, defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline
- Absolute change in inflammatory lesion counts from baseline to Week 12

The protocol specified the following secondary efficacy endpoints:

- Percent change in inflammatory lesion counts from baseline to Week 12
- Absolute change in inflammatory lesion counts from baseline to Week 8
- Proportion of subjects achieving IGA success at Week 8
- Absolute change in inflammatory lesion counts from baseline to Week 4
- Proportion of subjects achieving IGA success at Week 4

The protocol specified several "supportive" efficacy endpoints; however, as these endpoints were not included in the multiplicity testing procedure, the results of these endpoints are considered exploratory and are not included in this review.

Table 6: Investigator Global Assessment (IGA) Scale

| Grade | Description |
|---|---|
| 0 – Clear | Skin clear of inflammatory papules or pustules |
| 1 – Almost Clear | Very few small papules or pustules and very mild dull erythema is present |
| 2 – Mild | Few small papules or pustules and mild dull or light pink erythema is present |
| 3 – Moderate | Several to many small or larger papules or pustules and moderate light to bright red erythema is present |
| 4 – Severe | Numerous small and/or larger papules or pustules and severe erythema that is bright red to deep red is present |

Source: page 46 of the protocol for Trials SGT-54-01 and SGT-54-02

The protocols for each trial was entitled, "A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S5G4T-1 in the Treatment of Papulopustular Rosacea". There were 4 versions of the protocols:

- Original Protocol 06 March 2018
- Version 2.0 26 April 2018
- Version 3.0 06 June 2018
- Version 4.0 24 October 2018

Subjects enrolled in versions 2.0, 3.0 and 4.0 of the protocols. Version 2.0 excluded the assessment of perilesional erythema. The protocols redefined the secondary objectives and endpoints, relegating the patient reported outcomes (i.e. PAPPS, PAPI, PGI-S, PGI-TS) to supportive endpoints in the hierarchy . In addition, the protocol specified a different imputation method. Version 3.0 had minor changes in language and limited the primary objective to "assess the efficacy and safety of S5G4T-1 compared to S5G4T-1 Vehicle when applied once daily for 12 weeks in patients with papulopustular rosacea." Version 4.0 included the addition of the RosaQoL tool.

The Applicant submitted the required certification and disclosure information for participating investigators (Form 3454). Refer to section 18.2 Financial Disclosure of this review for additional information.

### 8.1.2. Statistical Methodologies

The protocol-specified primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all subjects who are randomized and dispensed study drug. The protocol also specified conducting supportive analyses using the per-protocol (PP) population. The PP population was defined as all subjects in the ITT population without noteworthy study protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the

therapeutic administration of the treatment or the precise evaluation of treatment efficacy). The PP population includes subjects in the ITT population who do not meet any of the following criteria:

- Failed any of the inclusion/exclusion criteria
- Have taken any interfering concomitant medications
- Did not attend the Week 12 visit
- Missed more than 1 post baseline study visit prior to Week 12
- Have not been compliant with the dosing regimen (i.e., subjects may not miss more than five consecutive days of dosing and must take 80 to 120% of expected doses. The number of expected doses will be determined for each subject based on the length of their participation in the study)
- Out of visit window (± 4 days) at the Week 12 visit

The protocol specified that the trials were to be conducted in a manner such that a minimum of 5 subjects per treatment arm per center. Centers that do not enroll a minimum of 15 subjects were specified in the SAP to be pooled by ordering these centers and combining the smallest with the largest, second smallest with second largest, and so on. After pooling, the centers (pooled and unpooled) are termed "analysis centers."

For the analysis of binary efficacy endpoints, the protocol and SAP specified using logistic regression with treatment group and analysis center as factors in the model. The protocol and SAP specified analyzing the continuous efficacy endpoints using analysis of covariance (ANCOVA) with treatment group and analysis center as factors, and baseline value as a covariate. The treatment-by-analysis center interaction was specified to be included in the ANCOVA model if it is significant at the 0.10 level. The protocol and SAP specified conducting a skewness test, based on the methods presented in Zar 1984. The protocol specified conducting the ANCOVA using the rank-transformed data if the two-sided p-value for the skewness test is significant at the 0.05 level. However, the SAP specified using a significance level of 0.01, which is consistent with the SPA agreement letter. The Applicant's clinical study reports followed the SAP.

To control the Type I error rate for testing multiple secondary efficacy endpoints, the protocol and SAP specified analyzing the secondary efficacy endpoints using a sequential gatekeeping approach. The secondary endpoints were specified to be analyzed in the order listed in Section 8.1.1 and the testing will stop once a non-statistically significant value is observed (i.e., p-value ≥ 0.05).

The protocol and SAP specified that the consistency of treatment response across analysis centers for the co-primary efficacy endpoints will be investigated using the treatment-by-analysis center interaction in the logistic regression model and the ANCOVA model. If the p-value for the interaction is significant at the 0.10 level, then the protocol specified that a sensitivity analysis will be conducted where analysis centers with "extreme" efficacy results will be excluded. Extreme analysis centers will be identified by analyzing all the possible subsets

that can be created by excluding one analysis center. Each data subset will be analyzed to see if the interaction between treatment and analysis center remains significant at the 0.10 level. If one or more of the subsets result in an interaction p-value greater than or equal to 0.10, then the analysis center excluded that resulted in the largest interaction p-value is deemed to be the extreme analysis center. If all subset interaction p-values are less than 0.10, then the process will continue with all subsets that can be created by excluding two analysis centers. The process of identifying the extreme analysis centers will continue in stepwise manner (excluding one, two, three, etc.) until the p-value of the interaction exceeds 0.10.

The protocol and SAP also specified investigating the center-to-center variability prior to pooling. Specifically, the SAP specified:

> "Prior to investigating the treatment effect within the analysis centers, the treatment effect within investigational site will be investigated to determine if the site-to-site variability is such that it could mask the analysis center effects. Thus, prior to pooling, change from Baseline in inflammatory lesions will be analyzed with an ANCOVA (unranked or ranked) with factors of treatment group, investigational site, and treatment group by investigational site interaction, and the Baseline lesion count variable as a covariate. The dichotomized primary endpoint will be analyzed with a logistic regression with factors of treatment group, investigational site, and the interaction term of treatment group by investigational site. If any of the analyses are not computationally feasible due to some investigational sites having very few subjects enrolled, the low-enrolling investigational sites will be excluded from the analysis."

The protocol-specified primary method for handling missing data is the multiple imputation (MI) approach. The protocol specified that missing data will be imputed 5 times within each treatment arm independently using the Markov Chain Monte Carlo method. The protocol specified the following two sensitivity analyses for the handling of missing data for the coprimary efficacy endpoints:

- Observed Data: observed data will be analyzed using repeated measures approaches. Absolute change in inflammatory lesion counts from baseline to Week 12 will be analyzed using a repeated measures ANCOVA with treatment group, analysis center, visit, and treatment-by-visit interaction as factors, and baseline value as a covariate. IGA success at Week 12 will be analyzed using a repeated measures logistic regression (i.e., generalized estimating equations [GEE]) with treatment group, analysis center, visit, treatment-by-visit interaction as factors in the model.
- Model-Based Multiple Imputation: missing data will be imputed 5 times using the model-based MI approach. For absolute change in inflammatory lesion counts from baseline to Week 12, the imputation model will include treatment group, analysis center, and baseline lesion count. For IGA success at Week 12, the imputation model will include treatment group and analysis center.

### 8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial SGT-54-01 enrolled and randomized a total of 361 subjects (243 to BPO cream and 118 to vehicle) from 26 centers in the United States. Trial SGT-54-02 enrolled and randomized a total of 372 subjects (250 to BPO cream and 122 to vehicle) from 26 centers in the United States. Table 7 presents the disposition of subjects for Trials SGT-54-01 and SGT-54-02. The discontinuation rate was slightly higher in Trial SGT-54-01 compared to Trial SGT-54-02.

Table 7: Disposition of Subjects

| | Trial SGT-54-01 | | Trial SGT-54-02 | |
|---|---|---|---|---|
| | BPO Cream (N=243) | Vehicle Cream (N=118) | BPO Cream (N=250) | Vehicle Cream (N=122) |
| **Discontinued, n (%)** | 21 (9) | 11 (9) | 15 (6) | 9 (7) |
| Adverse events | 5 (2) | 1 (1) | 4 (2) | 0 |
| Lost to follow-up | 6 (2) | 6 (5) | 1 (<1) | 4 (3) |
| Pregnancy | 1 (<1) | 1 (1) | 0 | 0 |
| Protocol violation | 0 | 0 | 1 (<1) | 0 |
| Withdrawal by subject | 9 (4) | 3 (3) | 9 (4) | 4 (3) |
| Other | 0 | 0 | 0 | 1 (1) |

Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

The demographics and baseline disease characteristics for Trials SGT-54-01 and SGT-54-02 are presented in Table 8. The demographics were generally balanced across the treatment groups within each trial and were similar in terms of age and sex between the two trials. Trial SGT-54-01 had a higher proportion of subjects identify as White compared to Trial SGT-54-02. The baseline disease characteristics were generally balanced across the treatment groups within each trial and were similar between the two trials.

Table 8: Demographics and Baseline Disease Characteristics

| | Trial SGT-54-01 | | Trial SGT-54-02 | |
|---|---|---|---|---|
| | BPO Cream (N=243) | Vehicle Cream (N=118) | BPO Cream (N=250) | Vehicle Cream (N=122) |
| **Age (years)** | | | | |
| Mean (SD) | 52.8 (13.2) | 52.4 (13.3) | 49.5 (14.0) | 51.5 (12.6) |
| Median | 54.0 | 52.5 | 50.0 | 53.0 |
| Min, Max | 19, 81 | 24, 85 | 18, 79 | 22, 84 |
| Categories, n (%) | | | | |
| < 65 | 204 (84) | 97 (82) | 212 (85) | 108 (89) |
| ≥ 65 | 39 (16) | 21 (18) | 38 (15) | 14 (11) |
| **Sex, n (%)** | | | | |
| Female | 183 (75) | 83 (70) | 181 (72) | 87 (71) |
| Male | 60 (25) | 35 (30) | 69 (28) | 35 (29) |
| **Race, n (%)** | | | | |
| White | 233 (96) | 116 (98) | 220 (88) | 110 (90) |
| Asian | 9 (4) | 2 (2) | 20 (8) | 8 (7) |
| Black / African American | 0 | 0 | 2 (1) | 0 |
| Other | 1 (<1) | 0 | 8 (3) | 4 (3) |

| | Trial SGT-54-01 | | Trial SGT-54-02 | |
|---|---|---|---|---|
| | BPO Cream (N=243) | Vehicle Cream (N=118) | BPO Cream (N=250) | Vehicle Cream (N=122) |
| **IGA Score, n (%)** | | | | |
| 3 – Moderate | 210 (86) | 104 (88) | 227 (91) | 112 (92) |
| 4 – Severe | 33 (14) | 14 (12) | 23 (9) | 10 (8) |
| **Inflammatory Lesion Counts** | | | | |
| Mean (SD) | 25.7 (11.1) | 26.3 (12.5) | 29.8 (14.0) | 27.5 (13.0) |
| Median | 22.0 | 21.0 | 25.0 | 22.5 |
| Min, Max | 15, 69 | 15, 70 | 15, 70 | 15, 70 |

Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

### 8.1.4. Results of the Co-primary Efficacy Endpoints

Table 9 presents the results of the co-primary efficacy endpoints for the ITT population. For both trials, BPO cream, 5% was statistically superior to vehicle cream on both coprimary efficacy endpoints (p-values < 0.001). The results in the PP population (not shown) were similar to those in the ITT population.

Table 9: Results of the Co-primary Efficacy Endpoints (ITT[1])

| | Trial SGT-54-01 | | Trial SGT-54-02 | |
|---|---|---|---|---|
| | BPO Cream (N=243) | Vehicle Cream (N=118) | BPO Cream (N=250) | Vehicle Cream (N=122) |
| **IGA Success[2] at Week 12** | | | | |
| Proportion[3] | 47.4% | 20.7% | 49.2% | 28.2% |
| Difference (95% CI) | 26.7% (16.7%, 36.8%) | | 21.0% (10.7%, 31.3%) | |
| Adjusted Proportion[4] | 43.5% | 16.1% | 50.1% | 25.9% |
| Difference (95% CI)[4] | 27.4% (16.4%, 38.5%) | | 24.3% (12.9%, 35.6%) | |
| P-Value[4] | <0.001 | | <0.001 | |
| **Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12** | | | | |
| Mean[3] | -17.7 | -9.7 | -20.7 | -12.3 |
| LS Mean[5] | -17.4 | -9.5 | -20.3 | -13.3 |
| Difference (95% CI)[5] | -7.9 (-10.0, -5.9) | | -6.9 (-9.0, -4.9) | |
| P-Value (unranked data)[5] | <0.001 | | <0.001 | |
| P-Value (ranked data)[6] | <0.001 | | <0.001 | |

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline.
[3] Average over the five imputed datasets.
[4] Adjusted proportions, difference (95% CI), and p-value are based on logistic regression with factors of treatment group and analysis center. For Trial SGT-54-01, the logistic regression used the Firth's penalized likelihood due to quasi-complete separation of the data.
[5] Least square (LS) means, difference (95% CI) and p-value are based on ANCOVA with factors of treatment group, analysis center and treatment-by-analysis center interaction, and baseline value as a covariate.
[6] P-value is based on a ranked ANCOVA with factors of treatment group, analysis center and treatment-by-analysis center interaction, and baseline value as a covariate. For both trials, the p-value for the skewness test was <0.001.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADEFF.xpt

For Trial SGT-54-01, standard logistic regression did not converge due to quasi-complete separation of the data; therefore, the Applicant used the Firth's penalized likelihood for this trial. As a sensitivity analysis, the statistical reviewer analyzed the coprimary efficacy endpoint of IGA success at Week 12 using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis centers. For both trials, the CMH test produced statistically significant results (i.e., p-values < 0.001). Table 10 presents the estimated treatment effect (i.e., difference [95% CI]) by the various analysis approaches.

Table 10: Treatment Effect on IGA Success[1] at Week 12 by Analysis Approach (ITT[2])

| | Trial SGT-54-01 | Trial SGT-54-02 |
|---|---|---|
| **Unadjusted[3]** | | |
| Difference from Vehicle (95% CI) | 26.7% (16.7%, 36.8%) | 21.0% (10.7%, 31.3%) |
| **Logistic Regression – Standard[4]** | | |
| Difference from Vehicle (95% CI) | NA | 24.3% (12.9%, 35.6%) |
| **Logistic Regression – Firth's[5]** | | |
| Difference from Vehicle (95% CI) | 27.4% (16.4%, 38.5%) | 23.0% (11.7%, 34.3%) |
| **CMH (Sensitivity Analysis)[6]** | | |
| Difference from Vehicle (95% CI) | 26.8% (17.1%, 36.5%) | 20.4% (10.7%, 30.1%) |

[1] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[3] Average over the five imputed datasets.
[4] Adjusted difference in proportions is based on logistic regression with factors of treatment group and analysis center. For Trial SGT-54-01, the logistic regression did not converge due to quasi-complete separation of the data.
[5] Adjusted difference in proportions is based on logistic regression using the Firth's penalized likelihood with factors of treatment group and analysis center.
[6] Adjusted difference in proportions is the weighted average of the treatment differences across analysis center with the Cochran-Mantel-Haenszel (CMH) weights.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Table 11 presents the number of subjects with missing data for the co-primary efficacy endpoints along with the results of the co-primary efficacy endpoints across the various prespecified imputation methods. The proportion of subjects with missing data was slightly higher in Trial SGT-54-01 compared to Trial SGT-54-02. The results were generally similar across the various prespecified methods. For IGA success at Week 12, the statistical reviewer conducted an additional sensitivity analysis where missing data was imputed under the worst-case scenario (i.e., missing data for BPO cream were imputed as nonresponders and missing data for vehicle were imputed as responders). In this extreme case, BPO cream, 5% remained statistically superior to vehicle cream in both trials (p-values ≤ 0.017).

Table 11: Results for the Co-primary Efficacy Endpoints with Different Approaches for Handling Missing Data

| | Trial SGT-54-01 | | | Trial SGT-54-02 | | |
|---|---|---|---|---|---|---|
| | BPO Cream (N=243) | Vehicle Cream (N=118) | Difference (P-Value) | BPO Cream (N=250) | Vehicle Cream (N=122) | Difference (P-Value) |
| **Subject with Missing Data** | 22 (9%) | 11 (9%) | | 15 (6%) | 9 (7%) | |
| **IGA Success[1] at Week 12** | | | | | | |
| MI-MCMC (primary)[2] | 43.5% | 16.1% | 27.4% (<0.001) | 50.1% | 25.9% | 24.3% (<0.001) |
| MI-Model[2] | 44.7% | 17.1% | 27.6% (<0.001) | 51.0% | 25.6% | 25.4% (<0.001) |
| Observed[3] | 49.1% | 21.1% | 28.0% (<0.001) | 50.2% | 27.8% | 22.4% (<0.001) |
| Worst-Case[2] | 41.7% | 23.6% | 18.1% ( 0.001) | 47.5% | 33.3% | 14.2% ( 0.017) |
| **Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12** | | | | | | |
| MI-MCMC (primary)[4] | -17.4 | -9.5 | -7.9 (<0.001) | -20.3 | -13.3 | -6.9 (<0.001) |
| MI-Model[5] | -17.9 | -9.9 | -8.1 (<0.001) | -20.5 | -14.1 | -6.4 (<0.001) |
| Observed[6] | -18.2 | -9.9 | -8.3 (<0.001) | -21.2 | -13.6 | -7.5 (<0.001) |

[1] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline.
[2] Proportions and p-values are based on a logistic regression with factors of treatment group and analysis center.
[3] Proportions and p-value are based on a repeated measures logistic regression (i.e., generalized estimating equations) with factors of treatment group, analysis center, visit, and treatment-by-visit interaction.
[4] Least square (LS) means and p-value are based on ANCOVA with factors of treatment group, analysis center and treatment-by-analysis center interaction, and baseline value as a covariate.
[5] Least square (LS) means and p-value are based on ANCOVA with factors of treatment group and analysis center, and baseline value as a covariate.
[6] Least square (LS) means and p-value are based on a repeated measures ANCOVA with factors of treatment group, analysis center, visit, and treatment-by-visit interaction, and baseline value as a covariate.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis except for additional worst-case analysis); ADEFF.xpt

### 8.1.5. Results of the Secondary Efficacy Endpoints

Table 12 presents the results for the secondary efficacy endpoints for the ITT population. For both trials, BPO cream, 5% was statistically superior to vehicle cream on all secondary efficacy endpoints (p-values ≤ 0.009). The results in the PP population (not shown) were similar to those in the ITT population.

Table 12: Results of the Secondary Efficacy Endpoints for Trials SGT-54-01 and SGT-54-02 (ITT[1])

| | Trial SGT-54-01 | | Trial SGT-54-02 | |
|---|---|---|---|---|
| | BPO Cream (N=243) | Vehicle Cream (N=118) | BPO Cream (N=250) | Vehicle Cream (N=122) |
| **Percent Change in Inflammatory Lesion Counts from Baseline to Week 12** | | | | |
| Mean[2] | -69.5% | -38.8% | -69.3% | -46.3% |
| LS Mean[3] | -68.2% | -38.3% | -69.4% | -46.0% |
| Difference (95% CI)[3] | -29.9% (-37.8%, -22.0%) | | -23.4% (-30.5%, -16.3%) | |
| P-Value (unranked data)[3] | <0.001 | | <0.001 | |
| P-Value (ranked data)[4] | <0.001 | | <0.001 | |

| | Trial SGT-54-01 | | Trial SGT-54-02 | |
|---|---|---|---|---|
| | **BPO Cream (N=243)** | **Vehicle Cream (N=118)** | **BPO Cream (N=250)** | **Vehicle Cream (N=122)** |
| **Absolute Change in Inflammatory Lesion Counts from Baseline to Week 8** | | | | |
| Mean[2] | -17.0 | -10.4 | -20.3 | -11.2 |
| LS Mean[3] | -16.8 | -10.6 | -20.0 | -12.4 |
| Difference (95% CI)[3] | -6.2 (-7.9, -4.5) | | -7.5 (-9.5, -5.6) | |
| P-Value (unranked data)[3] | <0.001 | | <0.001 | |
| P-Value (ranked data)[4] | <0.001 | | <0.001 | |
| **IGA Success[5] at Week 8** | | | | |
| Proportion[2] | 43.8% | 21.2% | 44.8% | 28.7% |
| Difference (95% CI) | 22.6% (12.5%, 32.7%) | | 16.1% (5.0%, 27.2%) | |
| Adjusted Proportion[6] | 39.6% | 15.8% | 44.0% | 26.0% |
| Difference (95% CI)[6] | 23.8% (12.6%, 34.9%) | | 18.1% (5.8%, 30.3%) | |
| P-Value[5] | <0.001 | | 0.006 | |
| **Absolute Change in Inflammatory Lesion Counts from Baseline to Week 4** | | | | |
| Mean[2] | -14.9 | -8.9 | -16.9 | -9.4 |
| LS Mean[3] | -14.6 | -8.7 | -16.7 | -10.5 |
| Difference (95% CI)[3] | -5.9 (-7.5, -4.3) | | -6.3 (-8.6, -4.1) | |
| P-Value (unranked data)[3] | <0.001 | | <0.001 | |
| P-Value (ranked data)[4] | <0.001 | | <0.001 | |
| **IGA Success[5] at Week 4** | | | | |
| Proportion[2] | 32.2% | 10.5% | 29.4% | 16.7% |
| Difference (95% CI) | 21.7% (13.5%, 29.9%) | | 12.7% (3.9%, 21.5%) | |
| Adjusted Proportion[6] | 25.4% | 6.6% | 26.1% | 14.1% |
| Difference (95% CI)[6] | 18.8% (10.0%, 27.6%) | | 12.1% (2.4%, 21.7%) | |
| P-Value[6] | <0.001 | | 0.009 | |

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Average over the five imputed datasets.
[3] Least square (LS) mean and p-value are based on ANCOVA with factors of treatment group and analysis center, and baseline value as a covariate. The treatment-by-analysis center interaction was included if significant at the 0.10 level.
[4] P-value are based on a ranked ANCOVA with factors of treatment group and analysis center, and baseline value as a covariate. The treatment-by-analysis center interaction was included if significant at the 0.10 level. For both trials, the p-value for the skewness test was <0.001.
[5] Success is defined as an IGA score of 0 ("clear") or 1 ("almost clear") with at a least a two-grade reduction from baseline.
[6] Adjusted proportion and p-value are based on a logistic regression with factors of treatment group and analysis center. The Firth's penalized likelihood was used when there was quasi-complete separation of the data.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

### 8.1.6. Findings in Special/Subgroup Populations

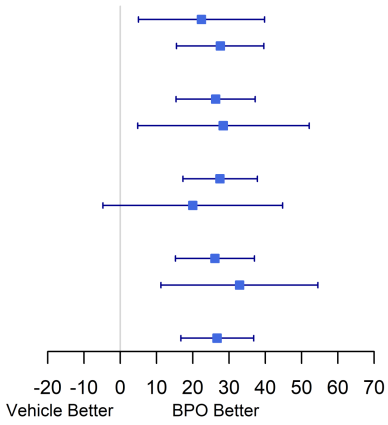
#### 8.1.6.1. Sex, Age, Race, and Baseline IGA Score

The results for IGA success at Week 12 by sex, age (<65 and ≥65 years), race (white and non-white), and baseline IGA score for Trials SGT-54-01 and SGT-54-02 are presented in Figure 1 and

Figure 2, respectively. The results for absolute change in inflammatory lesion counts from baseline to Week 12 by sex, age (<65 and ≥65 years), race (white and non-white), and baseline IGA score for Trials SGT-54-01 and SGT-54-02 are presented in Figure 3 and Figure 4, respectively. Treatment effects were generally consistent across the subgroups, with some variability from the smaller subgroups (e.g., race).

Figure 1: IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA Score for Trial SGT-54-01 (ITT[1])

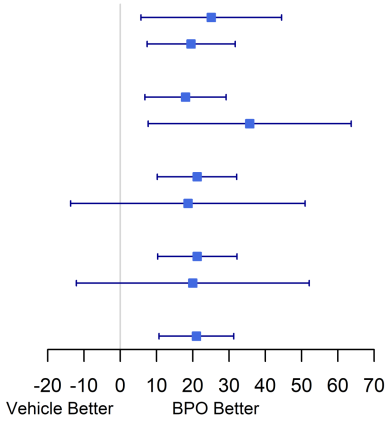
| Subgroups (n[E], n[V]) | BPO Cream (N=243) | Vehicle Cream (N=118) | Difference |
|---|---|---|---|
| Sex | | | |
| Males (60, 35) | 36.7% | 14.3% | 22.4% |
| Females (183, 83) | 50.9% | 23.4% | 27.6% |
| Age (years) | | | |
| 18-64 (204, 97) | 45.2% | 18.9% | 26.3% |
| 65+ (39, 21) | 56.3% | 27.8% | 28.4% |
| Race | | | |
| White (233, 116) | 48.6% | 21.0% | 27.5% |
| Non-White (10, 2) | 20.0% | 0% | 20.0% |
| Baseline IGA | | | |
| 3 - Moderate (210, 104) | 48.6% | 22.5% | 26.1% |
| 4 - Severe (33, 14) | 40.0% | 7.1% | 32.8% |
| Overall | 47.4% | 20.7% | 26.7% |




[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Figure 2: IGA Success at Week 12 by Sex, Age, Race, and Baseline IGA Score for Trial SGT-54-02 (ITT[1])

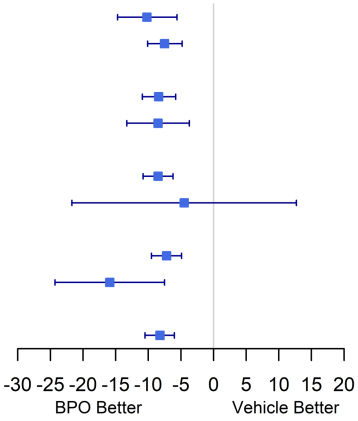
| Subgroups (n[E], n[V]) | BPO Cream (N=250) | Vehicle Cream (N=122) | Difference |
|---|---|---|---|
| Sex | | | |
| Males (69, 35) | 57.1% | 32.0% | 25.1% |
| Females (181, 87) | 46.2% | 26.7% | 19.5% |
| Age (years) | | | |
| 18-64 (212, 108) | 46.2% | 28.1% | 18.0% |
| 65+ (38, 14) | 64.3% | 28.6% | 35.7% |
| Race | | | |
| White (220, 110) | 48.8% | 27.6% | 21.2% |
| Non-White (30, 12) | 52.0% | 33.3% | 18.7% |
| Baseline IGA | | | |
| 3 - Moderate (227, 112) | 50.1% | 28.9% | 21.2% |
| 4 - Severe (23, 10) | 40.0% | 20.0% | 20.0% |
| Overall | 49.2% | 28.2% | 21.0% |




[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Figure 3: Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12 by Sex, Age, Race, and Baseline IGA Score for Trial SGT-54-01 (ITT[1])

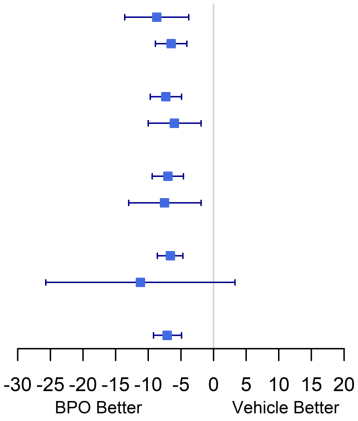
| Subgroups (n[E], n[V]) | BPO Cream (N=243) | Vehicle Cream (N=118) | Difference |
|---|---|---|---|
| Sex | | | |
| Males (60, 35) | -17.5 | -7.4 | -10.2 |
| Females (183, 83) | -17.9 | -10.4 | -7.5 |
| Age (years) | | | |
| 18-64 (204, 97) | -18.2 | -9.8 | -8.4 |
| 65+ (39, 21) | -16.4 | -7.9 | -8.5 |
| Race | | | |
| White (233, 116) | -18.0 | -9.5 | -8.5 |
| Non-White (10, 2) | -13.7 | -9.2 | -4.5 |
| Baseline IGA | | | |
| 3 - Moderate (210, 104) | -16.0 | -8.7 | -7.2 |
| 4 - Severe (33, 14) | -30.0 | -14.1 | -15.9 |
| Overall | -17.8 | -9.5 | -8.2 |




[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Values displayed are the least square (LS) means based on analysis of covariance (ANCOVA) with treatment group as a factor and baseline value as a covariate.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Figure 4: Absolute Change in Inflammatory Lesion Counts from Baseline to Week 12 by Sex, Age, Race, and Baseline IGA Score for Trial SGT-54-02 (ITT[1])

| Subgroups (n[E], n[V]) | BPO Cream (N=250) | Vehicle Cream (N=122) | Difference |
|---|---|---|---|
| Sex | | | |
| Males (69, 35) | -22.3 | -13.7 | -8.7 |
| Females (181, 87) | -19.5 | -13.0 | -6.5 |
| Age (years) | | | |
| 18-64 (212, 108) | -20.5 | -13.2 | -7.3 |
| 65+ (38, 14) | -19.2 | -13.2 | -6.0 |
| Race | | | |
| White (220, 110) | -19.6 | -12.6 | -7.0 |
| Non-White (30, 12) | -25.9 | -18.4 | -7.5 |
| Baseline IGA | | | |
| 3 - Moderate (227, 112) | -19.3 | -12.6 | -6.6 |
| 4 - Severe (23, 10) | -30.6 | -19.4 | -11.2 |
| Overall | -20.3 | -13.2 | -7.1 |




[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Values displayed are the least square (LS) means based on analysis of covariance (ANCOVA) with treatment group as a factor and baseline value as a covariate.
Source: Statistical Reviewer's Analysis; ADEFF.xpt

#### 8.1.6.2. Center

Trial SGT-54-01 randomized a total of 361 subjects (243 to BPO cream and 118 to vehicle) from 26 centers in the United States. Trial SGT-54-02 randomized a total of 372 subjects (250 to BPO cream and 122 to vehicle) from 26 centers in the United States. The SAP specified a pooling strategy for centers that enrolled less than 15 subjects. These centers were pooled by ordering and combining the smallest with the largest. The process repeated until all centers had at least 15 subjects. For Trial SGT-54-01, 11 out of the 26 centers enrolled less than 15 subjects and the pooling process yielded 19 analysis centers (15 unpooled and 4 pooled). For Trial SGT-54-02, 10 out of the 26 centers enrolled less than 15 subjects and the pooling process yielded 20 analysis centers (16 unpooled and 4 pooled).

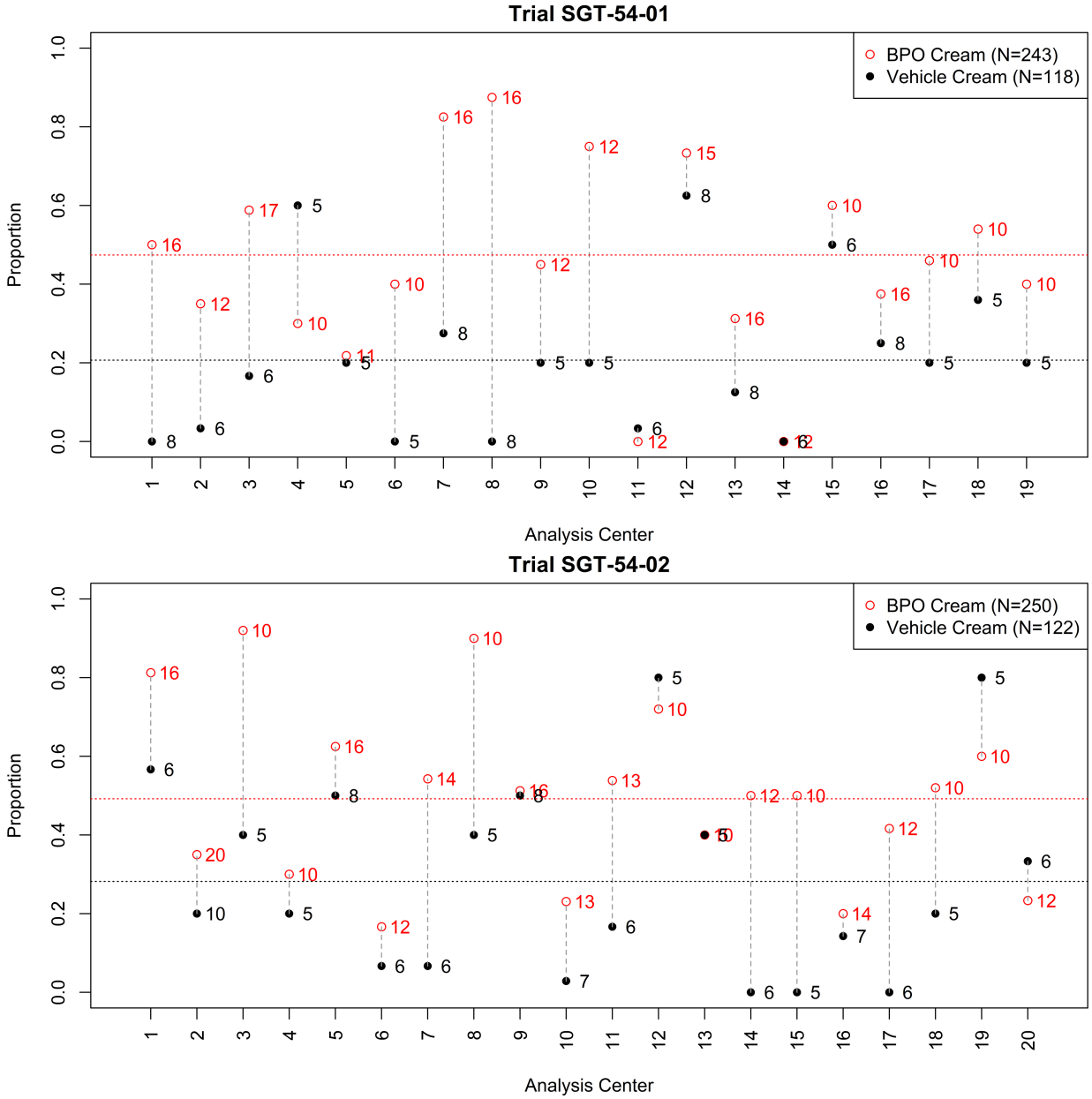
Figure 5 presents the results for IGA success at Week 12 by analysis centers for Trials SGT-54-01 and SGT-54-02. Figure 6 presents the results for absolute change in inflammatory lesion counts from baseline to Week 12 for Trials SGT-54-01 and SGT-54-02. In both trials, most analysis centers had higher efficacy with BPO cream, 5% than vehicle cream for both coprimary efficacy endpoints.

The Applicant investigated the consistency of results across analysis centers by testing the treatment-by-analysis center interaction in the logistic regression model for IGA success and in the ANCOVA model for change in inflammatory lesion counts. The Applicant also evaluated the interactions prior to pooling (i.e., treatment-by-center interaction). If the interaction was significant at the 0.10 level, the protocol specified a sensitivity analysis where the data were to be analyzed excluding one analysis center (or center) at a time to identify the impact of each analysis center (or center) on the overall results.

For IGA success, the p-values for the treatment-by-analysis center interaction were 0.566 and 0.841 for Trials SGT-54-01 and SGT-54-02, respectively. The p-values for the treatment-by-center interaction were 0.575 and 0.880 for Trials SGT-54-01 and SGT-54-02, respectively.

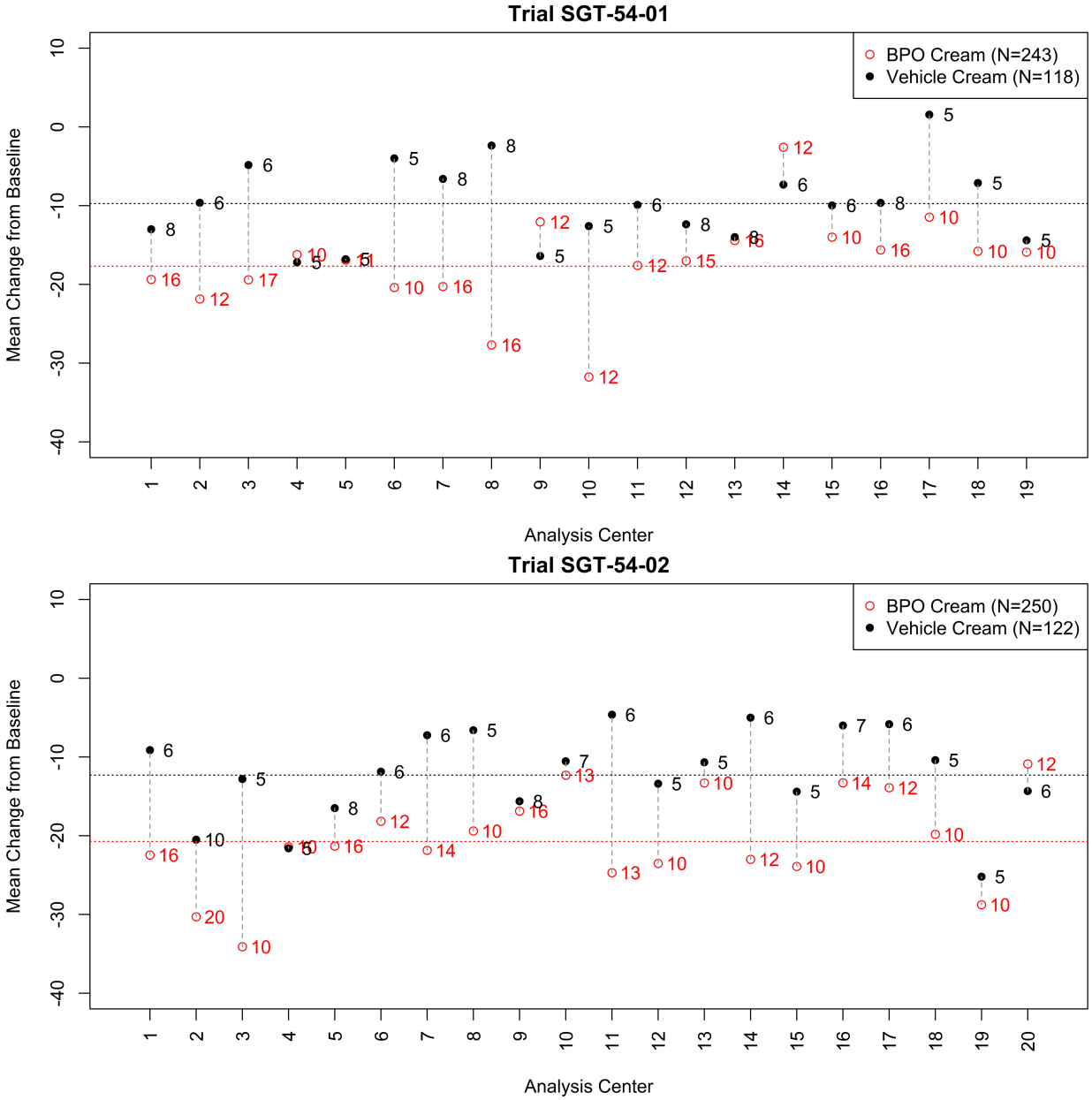
For absolute change in inflammatory lesion counts, the p-values for the treatment-by-analysis center interaction and the treatment-by-center interaction in both trials were significant at the 0.10 level (i.e., p-values ≤ 0.001). For Trial SGT-54-01, the Applicant's sensitivity analysis identified analysis center #8 (site #110) as an extreme analysis center. The removal of this analysis center did not affect the overall conclusions for both coprimary efficacy endpoints (i.e., p-values remained < 0.001). For Trial SGT-54-02, the Applicant's sensitivity analysis identified analysis center #14 (site #216) and analysis center #19 (site #225) as extreme analysis centers. The removal of both these analysis centers did not affect the overall conclusions for both coprimary efficacy endpoints (i.e., p-values remained < 0.001).

Figure 5: IGA Success at Week 12 by Analysis Centers (ITT[1])




[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] The dotted horizontal line denotes the overall result for each treatment group (red for BPO and black for vehicle).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

Figure 6: Absolute Change from Baseline in Inflammatory Lesion Counts by Center (ITT[1])




[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] The dotted horizontal line denotes the overall result for each treatment group (red for BPO and black for vehicle).
Source: Statistical Reviewer's Analysis; ADEFF.xpt

### 8.1.7. Protocol Violations/Deviations

Major protocol deviations were defined as protocol deviations with the potential to influence the evaluation of the primary efficacy endpoint. Subjects with major protocol deviations were excluded from the per protocol (PP) population. The frequency of protocol deviations by treatment arm were similar.

Trial SGT-54-01
In Trial SGT-54-01, the most common protocol deviations that resulted in exclusion from the PP population included: Week 12/ET Visit Out of Window (+/-4 days)(7.5%), Used Interfering Concomitant Medication (6.1%), Did not Attend Week 12 Visit (5.3%), Not Compliant with Dosing Regimen (1.1%),and Missed More Than 1 Post-Baseline Visit Prior to Week 12 (1.1%). The most frequent protocol deviations in the BPO group were: Week 12/ET Visit Out of Window (+/-4 days)(8.6%), Used Interfering Concomitant Medication (5.3%), and Did not Attend Week 12 Visit (4.9%); the most frequent protocol deviations in the vehicle group were: Used Interfering Concomitant Medication (7.6%), Did not Attend Week 12 Visit (5.9%) and Week 12/ET Visit Out of Window (+/-4 days)(5.1%).

Trial SGT-54-02
In Trial SGT-54-02, the most common protocol deviations that resulted in exclusion from the PP population included: Used Interfering Concomitant Medication (6.5%), Week 12/ET Visit Out of Window (+/-4 days) (4.8%), Not Compliant with Dosing Regimen (3.8%), Did not Attend Week 12 Visit (2.7%), and Missed More Than 1 Post-Baseline Visit Prior to Week 12 (1.3%). The most frequent protocol deviations in the BPO group were: Used Interfering Concomitant Medication (7.6%); the most frequent protocol deviations in the vehicle group were: Did not Attend Week 12/ET Visit and Week 12/ET Visit Out of Window (+/-4 days)(both 5.7%.)

### 8.1.8. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Investigators captured subject compliance with treatment instructions using a diary and by assessing the weight of the study product containers when dispensed and returned. Most subjects in both treatment groups (>97%) were compliant with study drug administration. See section 8.2.2 under *Compliance* in this review for the specific findings on each measure by treatment group.

The Applicant documented concomitant medications using the WHO Drug Global Dictionary (Format B3, Version March 1, 2018. ) All subjects participating in the pooled phase 3 trials reported at least one concomitant medication. In both treatment groups, common concomitant medications included: agents acting on the renin-angiotensin system (20% in the BPO group and 21% in the vehicle group), analgesics (11% in the BPO group and 14% in the vehicle group), emollients and protectives (99% in both groups), lipid modifying agents (17% in the BPO group and 15% in the vehicle group), psychanaleptics (11% in the BPO group and 12% in the vehicle

group), and vitamins (12% in both groups.)

Investigators offered no rescue medications to non-responders during the pooled phase 3 trials (SGT-54-01 /SGT-54-02) or long term safety trial (SGT-54-07). The investigator could withdraw subjects for lack of efficacy or worsening of their condition. During the long term safety trial, investigators instructed subjects with rosacea of "mild", "moderate" or "severe" (IGA 2, 3 or 4, respectively) severity to apply BPO cream while subjects with rosacea that was "clear" or "almost clear" did not apply the study product.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

The primary review of safety of BPO cream, 5% for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older focused on the evaluation of pooled data from two randomized, double-blind, vehicle-controlled, phase 3 Trials SGT-54-01 and SGT-54-02. Both phase 3 trials were similar with regard to design, trial population, dosing regimen and key primary and secondary endpoints. Eligible subjects were randomized in a 2:1 ratio to receive either BPO cream, 5% or vehicle once daily for 12 weeks. Subjects who completed Trials SGT-54-01 and SGT-54-02, were compliant and did miss more than one of the 3 final visits were eligible to participate in Trial SGT-54-07. Trial SGT-54-07 was a long -term extension trial which was intended to provide safety information of intermittent dosing of BPO cream for an additional 40 weeks (up to 52 weeks total exposure).

The study populations for the three trials included adult male and female subjects age 18 years and older with a clinical diagnosis of moderate to severe rosacea defined as:

- Investigator Global Assessment (IGA) score of 3 ("moderate") or 4 ("severe")
- 15 to 70 inflammatory lesions (papules and/or pustules) on the face including those present on the nose
- No more than two nodules (papule or pustule greater than 5 mm in diameter) on the face

The Applicant provided additional safety data from a phase 2 dose- finding Trial SGT-EPO1-09. This trial evaluated two concentrations of the study product compared with vehicle in a 1:1:1 ratio and enrolled a study population with mild to severe rosacea. However, due to differences in the trial populations, trial designs, randomization ratios and/or trial product formulation, data from the phase 2 Trial SGT-EPO1-09 and the phase 3 extension Trial SGT-54-07 were reviewed separately.

The Applicant provided additional safety data in the 120-Day safety update report (SUR).

The review team analyzed following types of pooled data: exposure, demographics and baseline characteristics, treatment-emergent adverse events (TEAEs), serious AEs (SAEs), AEs

leading to discontinuation, and other abnormal findings observed on physical examination including vital signs, ECGs and laboratory monitoring.

### 8.2.2. Review of the Safety Database

#### Overall Exposure

The size of the overall safety database is tabulated below. A total of 814 subjects in the development program provided safety information. Of these, 723 subjects received one of two concentrations of BPO cream (1% or 5%) and 691 subjects received 5% BPO cream. The number of subjects exposed to the study products is summarized below by trial.

Table 13: Exposure-Safety Population (Actual Treatment Received)

| | BPO Cream 1% | BPO Cream 5% | Vehicle Cream | Total |
|---|---|---|---|---|
| Phase 2: EBP01-09, N | 32 | 30 | 30 | 92 |
| Phase 3-pooled, N | | 488 | 234 | 722 |
| SGT-54-01 | | 239 | 113 | 352 |
| SGT-54-02 | | 250 | 120 | 370 |
| Long Term Safety: SGT-54-07 | | 535 | - | 535 |
| Received BPO in Phase 3 Trials | | 362 | - | 363 |
| Received vehicle in Phase 3 Trials | | 173 | - | 172 |
| Overall totals * | 32 | 691 | 263 | 814 |
| Total BPO exposure (any conc) | 723 | | - | |

Reviewer's Table *Note: overall totals include all subjects who received BPO cream in the phase 3 and phase 2 trials plus the subjects who initially received vehicle in the phase 3 trials and then received BPO cream in the long term safety extension trial

#### Compliance

Investigators evaluated compliance with trial requirements by reviewing the subject diary and documenting the results in the electronic case report form (eCRF). Investigators recorded exposure to the study product by documenting the total number of days of exposure, the total number of applications and number of missed doses. The compliance data is summarized below.

Table 14: Compliance with Treatment

| | BPO 5% Cream n=488 | Vehicle Cream n=234 | Totals n=722 |
|---|---|---|---|
| Treatment Compliance | | | |
| subjects with data | 474 | 227 | 701 |
| mean and std.dev. | 97% [10.0] | 98% [4.9] | 97.% [8.7] |
| Median | 100 | 100 | 100 |
| Range | 7-151 | 68.- 112 | 7. -151 |
| Treatment Compliance: subjects (%) | | | |
| COMPLIANT | 457 (94%) | 223 (95%) | 680 (94%) |
| (missing) | 14 (2.9%) | 7 (3.0%) | 21 (2.9%) |
| NOT COMPLIANT | 17 (3.5%) | 4 (1.7%) | 21 (2.9%) |

| | BPO 5% Cream n=488 | Vehicle Cream n=234 | Totals n=722 |
|---|---|---|---|
| Total Treatment Duration Days | | | |
| subjects with data | 474 | 227 | 701 |
| mean and std.dev. | 81.88 [12.91] | 83.43 [7.78] | 82.38 [11.52] |
| Median | 84 | 84 | 84 |
| Range | 5-89 | 16-89 | 5-89 |
| Total Number of Applications | | | |
| subjects with data | 474 | 227 | 701 |
| mean and std.dev. | 80. [14.69] | 82 [8.85] | 81 [13.11] |
| Median | 84 | 84 | 84 |
| Range | 1-133 | 15-95 | 1-133 |
| Total Number of Missed Applications | | | |
| subjects with data | 474 | 227 | 701 |
| mean and std.dev. | 2.05 [4.08] | 1.72 [3.66] | 1.94 [3.95] |
| Median | 0 | 0 | 0 |
| Range | 0-31 | 0-26 | 0-31 |
| Max Number of Missed Consecutive Doses | | | |
| subjects with data | 474 | 227 | 701 |
| mean and std.dev. | 1 [2.67] | 1 [1.88] | 1 [2.44] |
| Median | 0 | 0 | 0 |
| Range | 0-31 | 0-23 | 0-31 |
| Amount of Study Drug Used | | | |
| subjects with data | 462 | 225 | 687 |
| mean and std.dev. | 66.5 [33.97] | 71.1 [35.35] | 68.0 [34.47] |
| Median | 59.6 | 65.4 | 60.9 |
| Range | 1.4-162.2 | 4-172.1 | 1.4-172.1 |
| End of Study Status - count subjects and % | | | |
| COMPLETED | 456 (93%) | 221 (94%) | 677 (94%) |
| DISCONTINUED | 32 (7%) | 13 (6%) | 45 (6%) |

Source: Reviewer's table JReview

Relevant Characteristics of the Safety Population

The baseline demographics of the safety population are similar to the baseline demographics of the intent to treat (ITT) population. The majority of the subjects were female (72.9%), not Hispanic/Latino (71.1%) and White (92.5%). The mean age was 51.4 years (range: 18-85 years) and mean BMI of 31.2 kg/m2 (range: 18.4-56.6). Most subjects had rosacea of moderate severity (89.2%) with a mean inflammatory lesion count of 27.5 (range: 15-70). These characteristics were balanced across treatment groups. However, the BPO group had a greater percentage of subjects with severe rosacea (11.5% ) compared with the vehicle group (9.4%).

One potential limitation of the data is that neither treatment group included an adequate number of African American subjects: two subjects received BPO cream (0.4%) and no subjects received vehicle (0.0%). Because the diagnosis of rosacea in patients with darker skin types may be missed, the incidence of rosacea in the United States is not well documented. One author (Alexis, 2019) indicated that in the National Ambulatory Medical Care Survey (1993-2010) an estimated 2% of patients with rosacea in the United States identified as African American.

Based on the portion of African Americans who are affected worldwide, the authors conclude that this likely represents an underestimation of the prevalence of the disorder in this population.

Demographic characteristics of the ITT population in the phase 3 Trials SGT-54-01 / SGT-54-02 are similar and presented in greater detail in Section 8.1.2

Adequacy of the safety database:

The total exposure to BPO cream which was administered once daily for 12 weeks, provides adequate data for the evaluation of safety. The Applicant submitted additional long-term safety data. The demographics of the trial population are sufficiently representative of the target population. Therefore, the safety database presented by the Applicant is sufficient to characterize the safety profile of BPO cream for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of BPO cream. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

The phase 3 protocols defined an adverse event (AE) as "any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product."

A serious adverse event (SAE) was defined as an adverse event that resulted in any of the following outcomes:

- Death
- Life-threatening event (i.e., the patient was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires in-patient hospitalization or prolongs hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to

conduct normal life functions
- Congenital anomaly/birth defect
- Other adverse events that may be considered serious based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Immediately Reportable Adverse Events (IRAE) was defined as "any serious AE or any AE that necessitates discontinuation of study product, including pregnancy." An Unexpected Adverse Event was defined as "any adverse drug experience, the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the study product, the Investigator's Brochure, or as described in the clinical protocol and consent materials."

At each study visit, the investigator evaluated subjects for AEs by asking a non-specific question to avoid bias (e.g., "How have you been feeling since your last visit?"), by observation or by documenting spontaneous or directly elicited responses. Investigators recorded the seriousness, expectedness, intensity/severity, and relatedness of the event to the study product or procedure in the case report form (eCRF.)

Investigators categorized the severity of the AE according to the following criteria:
- Mild - AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.
- Moderate - AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Severe - AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Investigators also assessed the relationship of the AE to treatment with study drug using the following criteria:

Definitely - The AE:
- follows a reasonable temporal sequence from study product administration
- abates upon discontinuation of the study product (de-challenge)
- is confirmed by reappearance of the reaction on repeat exposure

Probably - The AE:
- follows a reasonable temporal sequence from study product administration
- abates upon discontinuation of the study product (de-challenge).
- cannot be reasonably explained by the known characteristics of the patient's state.

Possible - The AE:
- follows a reasonable temporal sequence from study product administration
- but that could readily be produced by a number of other factors.

Unlikely - The AE:
- follows a reasonable temporal sequence from study product administration.

- could have been produced by either the patient's clinical state or by study product administration.

Not related - The AE:

- does not have a reasonable temporal association with the administration of study product
- has some other obvious explanation for the event.

Routine Clinical Tests

Investigators monitored the safety of BPO cream by documenting AEs, cutaneous safety assessments (application site dryness and scaling) and local tolerability (application site itching and burning/stinging) at Baseline, Weeks 2, 4, 8 and 12. In addition, investigators recorded findings from brief physical examinations (heart, lung, abdomen) with vital signs (blood pressure, oral temperature, heart rate and respiratory rate) at Baseline and Week 12 and concomitant medications at all visits. In view of the limited systemic absorption and known safety profile, routine laboratory testing was not included in the protocol. However, investigators performed urine pregnancy testing at Screening, Baseline, Weeks 2, 4, 8 and 12. Systemic adverse events were not anticipated with topical application of BPO cream.

### 8.2.4. Safety Results

Deaths

There were no deaths in the development program.

Serious Adverse Events

In the pooled phase 3 Trials SGT-54-01 and SGT-54-02, two subjects (0.3%) experienced nonfatal serious adverse events (SAEs), one subject in each treatment group. In the BPO cream group, one subject reported spinal compression fracture (severe); in the vehicle group, one subject reported femur fracture (moderate). There was no mechanistically plausible relationship of these events to the study product. Both SAEs were considered to be unrelated to the study product and resulted in study discontinuation. See tabulation below.

Table 15: Serious Adverse Events in Trials SGT-54-01 and SGT-54-02

| Body System or Organ Class | Dictionary-Derived Term | BPO 5% Cream | Vehicle Cream |
|---|---|---|---|
| **Subject totals** | | 488 | 234 |
| Injury, poisoning and procedural complications | Femur fracture | 1 ( 0.2%) | 0 ( 0.0%) |
| | Spinal compression fracture | 0 ( 0.0%) | 1 ( 0.4%) |

Source: Reviewer's table JReview

No subjects reported SAEs in the phase 2 trial and ten subjects (10/535; 1.9%) reported SAEs in the long- term safety Trial SGT-54-07. In Trial SGT-54-07, all SAEs occurred in single subjects.

There was no mechanistically plausible relationship of these events to the study product. None of the SAEs were considered to be related to the study product or resulted in study discontinuation. However, one SAE (1/535; 0.2%) resulted in study product discontinuation (tonsil cancer.)

Table 16: Serious Adverse Events in Trial SGT-54-07

| Unique Subject ID | Start Day | End Day | Preferred Term | Action Taken | Outcome | Body System or Organ Class |
|---|---|---|---|---|---|---|
| SGT-54-(b) (6) | 84 | 86 | Arrhythmia | DOSE NOT CHANGED | RESOLVED (SEQUELAE) | Cardiac disorders |
| SGT-54-(b) (6) | 237 | 243 | Mastectomy | NA | RESOLVED | Surgical & medical procedures |
| SGT-54-(b) (6) | 253 | 262 | Squamous cell carcinoma | DOSE NOT CHANGED | RESOLVED | Neoplasms benign, malignant & unspecified |
| SGT-54-(b) (6) | 25 | 76 | Rib fracture | DOSE NOT CHANGED | RESOLVED | Injury, poisoning and procedural complications |
| SGT-54-(b) (6) | 148 | 150 | Migraine | NA | RESOLVED (SEQUELAE) | Nervous system disorders |
| SGT-54-(b) (6) | 245 | 246 | Atrial fibrillation | DOSE NOT CHANGED | RESOLVED | Cardiac disorders |
| SGT-54-(b) (6) | 85 | 86 | Nephrolithiasis | NA | RESOLVED | Renal and urinary disorders |
| SGT-54-(b) (6) | 32 | 37 | Embolic stroke | NA | RESOLVED | Nervous system disorders |
| SGT-54-(b) (6) | 141 | 144 | Pulmonary embolism | NA | RESOLVED | Respiratory, thoracic and mediastinal disorders |
| SGT-54-(b) (6) | 30 | -- | Tonsil cancer | DRUG WITHDRAWN | NOT RESOLVED | Neoplasms benign, malignant & unspecified |

Source: Reviewer's Table JReview

Selected narratives

- A 66-year-old white, male (b) (6) with no relevant medical history experienced symptomatic premature ventricular contractions on Day 84 of treatment with BPO cream. The subject received a single dose of aspirin and began daily dosing of metoprolol.
- A 42-year-old white female (b) (6) with a history of BRCA 1 gene mutation underwent a bilateral mastectomy on Day 321 of treatment with BPO cream. The subject completed the trial.
- A 71-year-old white male (b) (6) who provided no relevant history experienced a squamous cell carcinoma on his right ear after approximately 8 months of treatment with BPO cream. The subject completed the trial.
- A 67-year-old white male (b) (6) with a history of metabolic syndrome sustained multiple rib fractures during a motor vehicle accident on Day 25 of treatment with BPO cream The subject completed the trial.
- A 63-year-old white female (b) (6) with a history of mitral valve prolapse, hypertension, and atrial fibrillation experienced a recurrence of atrial fibrillation on Day 329 of treatment with BPO cream. During hospitalization, the subject received intravenous diltiazem hydrochloride and underwent cardiac ablation for exacerbation of atrial fibrillation.

- A 73-year-old white, male (b) (6) with a history of atrial fibrillation, blood cholesterol increased, and hypertension experienced an embolic stroke on Day 116. The subject received treatment with anticoagulants and completed the trial.
- A 73-year-old white, male (b) (6) with a history of hypercholesterolemia and hypertension experienced a right upper lobe pulmonary embolism on Day 141 of treatment with BPO cream. The subject completed the trial.
- A 67-year-old white male (b) (6) who provided no relevant medical history was diagnosed with stage II squamous cell carcinoma of his right tonsil on Day 111 of treatment with BPO cream. After tonsillectomy and radiotherapy, the subject decided not to continue participation in the trial. The subject withdrew from the trial on Day 2.

Dropouts and/or Discontinuations Due to Adverse Effects

The disposition of the subjects in the pooled phase 3 trials (Trial SGT-54-01/ Trial SGT-54-02) is summarized below.

Table 17: Disposition: Pooled Phase 3 Trials (Safety Population)

| Reason for Discontinuation from Trial: # subjects (%) | BPO 5% Cream n=488 | Vehicle Cream n=234 | Totals n=722 |
|---|---|---|---|
| WITHDRAWAL BY SUBJECT | 16 (3.3%) | 6 (2.6%) | 22 (3.0%) |
| ADVERSE EVENT | 9 (1.8%) | 1 (0.4%) | 10 (1.4%) |
| LOST TO FOLLOW-UP | 5 (1.0%) | 4 (1.7%) | 9 (1.2%) |
| PREGNANCY | 1 (0.2%) | 1 (0.4%) | 2 (0.3%) |
| OTHER | 0 (0.0%) | 1 (0.4%) | 1 (0.1%) |
| PROTOCOL VIOLATION | 1 (0.2%) | 0 (0.0%) | 1 (0.1%) |

Source: Reviewer's table JReview

A greater proportion of subjects withdrew from the trial due to TEAEs in the BPO group compared with the vehicle group. All of the subjects who withdrew from the trials due to treatment emergent adverse events (TEAEs) experienced local reactions; none of the subjects provided relevant historical information that would account for those reactions apart from study drug exposure. All of these reactions occurred early in the course of treatment (i.e. within the first 30 days.) Two subjects reported TEAE that were assessed as severe [Subjects (b) (6) )

Brief narratives are below.

A) BPO cream, 5% group

- A 49-year-old White female (Subject (b) (6)) experienced TEAEs of severe application site pain and application site pruritus on Day 26. These TEAEs were both considered probably related to study drug, which was withdrawn. The subject discontinued the trial on Day 29.
- A 41-year-old White female (Subject (b) (6)) experienced a TEAE of moderate application site dermatitis on Day 5. The TEAE was considered probably related to study drug, which was withdrawn. The moderate application site dermatitis had not resolved when the

subject discontinued the trial on Day 6.

- A 47-year-old White female (Subject (b) (6)) experienced a TEAE of moderate application site swelling on Day 3. The TEAE was considered probably related to study drug, which was withdrawn. The moderate application site swelling resolved on Day 5. The subject discontinued the trial on Day 26.
- A 70-year-old White female (Subject (b) (6)) experienced TEAEs of mild application site pain and application site erythema on Day 3. TEAE of application site pain was considered possibly and the TEAE of application site erythema was considered probably related to study drug, which was withdrawn. The TEAEs had resolved when the subject withdrew from the trial on Day 10.
- A 50-year-old White male (Subject (b) (6)) experienced TEAEs of moderate application site edema, severe application site erythema, and moderate application site discharge on Day 17. All TEAEs were considered definitely related to the study product, which was withdrawn. The TEAEs had not resolved when the subject withdrew from the trial on Day 19.

B) Vehicle cream group

- A 46-year-old White female experienced TEAEs of mild application site papules and application site erythema on Day 25. Both TEAEs were considered possibly related to the study drug, which was withdrawn. The subject withdrew consent on Day 30 stating that her condition had worsened. At the time that the subject withdrew the TEAEs had resolved.

Brief narratives:

C) BPO cream, 5% group

- A 67-year-old White female (Subject (b) (6)) experienced TEAEs of mild application site exfoliation, swelling, pruritus, and erythema on Day 4 of the trial. All of these TEAEs were considered to be definitely related to BPO cream and resulted in discontinuation of the product and withdrawal from the trial (Day 7).
- A 43-year-old White female (Subject (b) (6)) experienced TEAEs of moderate application site pain, irritation, and pruritus on Day 15. All of these TEAEs were considered to be definitely related to BPO cream and resulted in discontinuation of the study product and withdrawal from the trial (Day 21).
- A 56-year-old White female (Subject (b) (6)) experienced a TEAE of moderate application site dermatitis on Day 2. In addition, the subject experienced TEAEs of mild mouth injury on Day 4 and mild nausea on Day 6. The TEAE of application site dermatitis was considered to be definitely related to BPO cream and resulted in discontinuation of the product and withdrawal from the trial (Day 9). The outcome of the TEAE of application site dermatitis is unknown. The TEAE of mild mouth injury and mild nausea were both considered not related to study drug.
- A 33-year-old Native Hawaiian or other Pacific Islander female (Subject (b) (6)) experienced a TEAE of mild application site rash on Day 2. The application site rash was considered to be definitely related to BPO cream and resulted in discontinuation of the study product. The TEAE resolved on Day 4. As the TEAE occurred after the first application of the study product, the subject withdrew her consent on Day 15 and withdrew from the

trial.

- A 42-year-old White female (Subject (b) (6)) experienced TEAEs of mild application site pruritus and application site pain on Day 24. These TEAE were considered possibly related to study drug and BPO cream was withdrawn due to the TEAEs. The outcomes of the TEAEs are unknown. The subject withdrew her consent on Day 31.

D) Vehicle cream group

- A 59-year-old White female (Subject (b) (6)) experienced a TEAE of mild urinary tract infection (UTI) on Day 23. The TEAE of UTI was considered not related but the study drug was withdrawn. The subject withdrew from the trial on Day 36.

Significant Adverse Events

For a topical product with limited systemic absorption, local safety findings are significant. See section 8.2.5 Analysis of Submission-Specific Safety Issues of this review.

Treatment Emergent Adverse Events and Adverse Reactions

In the phase 3 Trials SGT-54-01/ SGT-54-02, a greater proportion of subjects experienced TEAEs in the BPO cream group compared with the vehicle group. The most common TEAEs after pooling of related terms include upper respiratory tract infection, application site pain, application site pain erythema, application site pruritus and application site edema.

Table 18: Treatment emergent adverse events (TEAEs) which occurred in >2 subjects in the BPO group with greater frequency than the vehicle group (Pooled Trials SGT-54-01 and SGT-54-02)

| | **BPO 5% Cream n=488** | **Vehicle Cream n=234** | **Totals n=722** |
|---|---|---|---|
| Subjects with at least 1 TEAE : # subjects (% ) | **99 (20.3%)** | **39 (16.7%)** | **138 (19.1%)** |
| **Pooled URI** | 20 (4.1%) | 9 (3.8%) | 29 (4.0%) |
| **Application site pain** | 11 (2.3%) | 2 (0.9%) | 13 (1.8%) |
| **Application site erythema** | 11 (2.3%) | 2 (0.9%) | 13 (1.8%) |
| **Application site pruritus** | 6 (1.2%) | 1 (0.4%) | 7 (1.0%) |
| **Pooled application site edema** | 4 (0.8%) | 0 (0.0%) | 4 (0.6%) |
| **Muscle strain** | 3 (0.6%) | 1 (0.4%) | 4 (0.6%) |
| **Application site dermatitis** | 3 (0.6%) | 1 (0.4%) | 4 (0.6%) |

Source: Reviewer's table JReview

Upper respiratory tract infection (URI) includes the pooled terms: nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection, and sinusitis. Application site edema includes the pooled terms: application site swelling and application site edema.

After pooling related terms for URI and rounding to the nearest digit, there was no difference between treatment arms in incidence of URI. Similarly, the difference in the incidences of

muscle strain and application site dermatitis in the treatment arms was not meaningful. Therefore, the adverse reactions that were included in labeling are tabulated below.

Table 19: Treatment Emergent Adverse Reaction which occurred in **≥** 1% of subjects in the BPO cream group and with greater frequency than the vehicle group Pooled Trials SGT-54-01 and SGT-54-02)

| | **BPO 5% Cream n=488** | **Vehicle Cream n=234** |
|---|---|---|
| Subjects with at least 1 TEAE : (%) | **20** | **17** |
| **Application site pain** | 2 | 1 |
| **Application site erythema** | 2 | 1 |
| **Application site pruritus** | 1 | 0 |
| **Pooled application site edema** | 1 | 0 |

Source: Reviewer's table JReview

Labeling Recommendations

The FDA proposed labeling for Section 6.1 Adverse Reactions is below.

6 Adverse Reactions

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two randomized, double-blind, vehicle-controlled trials, adult subjects with rosacea applied EPSOLAY (N = 488) or vehicle (N = 234) once daily for 12 weeks. The majority of subjects were Caucasian (93%), female (73%) and had a mean age of 51 years.

Table 1 presents the most common adverse reactions occurring in ≥ 1% of subjects treated with EPSOLAY and more frequently than in subjects treated with vehicle.

Adverse Reactions Occurring in **≥** 1% of Subjects Treated with EPSOLAY and with Greater Frequency than Subjects Treated with Vehicle

| | **EPSOLAY N=488 N** | **Vehicle N=234 N** |
|---|---|---|
| **Application site pain** | 11 (2%) | 2 (1%) |
| **Application site erythema** | 11 (2%) | 2 (1%) |
| **Application site pruritus** | 6 (1%) | 1 (<1%) |
| **Pooled application site edema[1]** | 4 (1) | 0 (0%) |

[1] Application site edema includes: application site swelling and application site edema

During the clinical trials, local tolerability evaluations were conducted at baseline and at each study visit by assessment of dryness, itching, scaling and stinging/burning. Table 2 presents the local tolerability assessments by severity grade at Week 12.

Facial Cutaneous Tolerability Assessment

| | EPSOLAY, (%) (N=455*) | | |
|---|---|---|---|
| | Severity at Week 12 | | |
| **Sign/Symptom** | Mild | Moderate | Severe |
| **Dryness** | 25 % | 7 % | 0 % |
| **Itching** | 24 % | 6 % | 0 % |
| **Scaling** | 13 % | 4 % | 0 % |
| **Stinging/ Burning** | 20 % | 3 % | 1 % |

* Of the 488 subjects treated with EPSOLAY, 455 subjects had local tolerability assessments at Week 12.

In a 40-week open-label extension safety study (for a total of up to 52 weeks of treatment) the frequency and severity of local tolerability signs and symptoms at Week 52 were comparable to those reported at Week 12.

Laboratory Findings

In the absence of systemic exposure, the Applicant did not conduct clinical laboratory evaluations in any of the 4 clinical trials in the BPO cream development program. Laboratory assessments included urine pregnancy testing at Screening, Baseline, Week 2, Week 4, Week 8 and Week 12. There were no positive pregnancy tests among subjects participating in the phase 2 trial (SGT-EBPO1-09), two positive pregnancy tests among subjects participating in the phase 3 trials and one positive pregnancy test in the long-term safety trial (SGT-54-07.) See section 8.2.9 Additional Safety Explorations of this review for a discussion of the results of the pregnancy testing.

Vital Signs

The assessment of vital signs and physical examinations varied by trial. Investigators did not measure vital signs or perform physical examinations in the phase 2 trial (SGT-EBPO1-09.) Investigators measured vital signs (blood pressure, pulse rate, respiration rate, and oral temperature) at Baseline and Week 12 in the phase 3 trials and Weeks 12, 24, 36 and 48 in the long term safety trial (SGT-54-07).

Most subjects had normal vital sign measurements throughout the trial. There were no significant changes in vital signs or findings on brief physical examinations except one subject who received vehicle had abnormal cardiovascular findings at Week 12.

Electrocardiograms (ECGs) and QT

Benzoyl peroxide is rapidly converted to benzoic acid, an endogenous metabolic product found in the plasma of animals and plants. Plasma samples from a 13-week dermal toxicity study of BPO cream, 5% and 10%, in minipigs revealed no increase in the plasma levels of benzoic acid above endogenous levels and no changes qualitative or quantitative changes in ECG parameters, or heart rate. (See review by Daivender Mainigi dated March 2, 2010). Concentrations of topical BPO ranging from 2.5 to 10% are generally recognized as safe and effective (GRASE) for the treatment of acne by the FDA. After decades of use as an active ingredient for the topical treatment of acne, investigators have not identified a safety signal related to any cardiovascular adverse events, including QT prolongation per Applicant.

In view of the systemic exposure and safety information from the literature, the proposed product is not expected to prolong the QT interval or cause arrhythmias. Therefore, the Applicant did not conduct a thorough QT/QTc studies or perform cardiac safety monitoring. The Applicant submitted a request for a waiver from conducting a thorough QT/QTc study based on systemic exposure and safety information (Module 1.12.5) which is considered acceptable.

Immunogenicity

As the proposed product is not a therapeutic protein, the applicant did not assess the potential immunogenicity.

### 8.2.5. Analysis of Submission-Specific Safety Issues

#### 8.2.5.2 Hypersensitivity

In the literature, there are rare reports of the use of BPO associated with serious hypersensitivity reactions (FDA Safety Announcement dated 6/25/2014.) Therefore, this review evaluated subjects who reported TEAEs associated with potential allergic reactions (Preferred terms [PTs]: anaphylaxis, hypersensitivity, angioedema, urticaria, rash, facial swelling).

In the pooled phase 3 trials, there was one case of an application site "hypersensitivity" reaction and one case of urticaria in the BPO group. Both subjects completed the trial with no additional reactions.

- A 40- year- old white female (SGT-54-(b) (6)) with a history of allergy to cephazolin, multiple sclerosis and stem cell transplantation developed an "application site hypersensitivity eruption" on Day 2 of BPO cream which was attributed to the use of a moisturizer with sunscreen. The AE of application site hypersensitivity eruption resolved on Day 4 with discontinuation of the suspect product and use of an emollient. The TEAE was moderate in severity, assessed as

not related and resulted in drug interruption. The subject completed the trial and enrolled in the extension trial until it was terminated.

- A 40- year- old Hispanic female (SGT-54-(b) (6)) with a history of intolerance to shellfish and anxiety experienced mild "urticaria" on forearm of unknown etiology on Day 29 of BPO cream which resolved on the following day with hydrocortisone. The TEAE did not result in discontinuation of BPO cream and was assessed as unlikely to be related to BPO cream.

In the pooled phase 3 trials, there was one case of an application site "rash" and 2 cases of rash on the chest in subjects who received BPO cream. No subjects in the vehicle group experienced TEAE of rash

- A 33- year- old Native Hawaiian/Pacific Islander female (SGT-54-(b) (6)) with no relevant history developed a rash on her face on Day 2 of administration of BPO cream. The rash was assessed as mild in severity, definitely related and resulted in discontinuation of the study product.
- Two female subjects aged 65 years and 39 years respectively (SGT-54-(b) (6) and SGT-54-(b) (6)) developed a "rash" on Days 51 and 15 of treatment with BPO cream. These events were localized to the chest, assessed as mild in severity and did not result in discontinuation from the trial. Both subjects continued BPO cream and received treatment with hydrocortisone with resolution of the rash in 6 to 8 days.
  - A 62- year- old White male (SGT-54-(b) (6)) with a history of contact dermatitis to nickel experienced 2 TEAEs of contact dermatitis during treatment with BPO cream. The first episode of contact dermatitis occurred on Day 2 and represented a worsening of an eruption on the left forearm which was first observed 2 days prior to Baseline. The subject treated the eruption with calamine lotion with improvement by Day 8. On Day 14, the subject was diagnosed with poison ivy (site not indicated) which was treated with cortisone (dosage form not indicated.) The TEAE resolved on Day 43. Both TEAEs were assessed as mild and not related to the study product. The subject completed the trial.

In Trial SGT-54-07, there were 2 additional TEAEs of urticaria and contact dermatitis.

- A 56 year old White female (SGT-54-(b) (6)) with a history of drug hypersensitivity and food allergies experienced urticaria on her neck and chest from Day 111 to 141 of treatment with BPO cream. The subject also experienced eye swelling from Day 129 to 136 and allergic contact dermatitis from Day 342 to 256. All TEAE were assessed as moderate in severity and unlikely or not related to BPO cream. The subject received concomitant medication for the TEAEs of urticaria and contact dermatitis. The subject did not change the dosing regimen of BPO cream; allergic contact dermatitis was reported at the end of the trial.
- A 41 year old White Latino female (SGT-54-(b) (6)) with a history of seasonal

allergies experienced urticaria (location not provided) on Day 42 and contact dermatitis of the eyelids on Day 216 to 221. Both TEAEs were assessed as mild in severity, not related to BPO cream and did not result in discontinuation of BPO cream.

There was an imbalance in events related to contact dermatitis and hypersensitivity in the BPO group compared with the vehicle group. In the absence of an etiologic agent, a plausible explanation is the secondary transfer of BPO cream to the thin/sensitive skin of the eyelids, neck and chest with resultant irritant contact dermatitis.

Jonn Bailey, PharmD, BCACP, Division of Pharmacovigilance I (DPV) evaluated the FDA Adverse Event Reporting System (FAERS) reports and the literature for an association between benzoyl peroxide (BPO) only products, excluding Proactiv products, and severe hypersensitivity to include anaphylaxis, angioedema, and urticaria. The FAERS case series included strong temporal associations between BPO product application and the development of anaphylaxis with positive dechallenge and rechallenge as well as angioedema with positive dechallenge. Dr. Baily acknowledged the limitations of spontaneous reports and medical literature cases in determining if the BPO moiety versus an excipient is the trigger for anaphylaxis, angioedema, or urticaria. However, DPV supports inclusion of appropriate language into labeling to adequately inform the public of the potential for the development of severe hypersensitivity reactions including anaphylaxis, angioedema, and urticaria with BPO product use (DPV Review dated 2/5/2021.)

Selected FAERS cases which were summarized by Dr. Bailey are below:

- FAERS Case #9165308, Version 1, Expedited (15-Day), USA, Initial FDA Received date March 14, 2013, Hospitalization, UMC Report ID #A1013063A. A 54-year-old female reported that she used a single application of Panoxyl Soap with BPO and immediately experienced facial edema and difficulty breathing. She immediately discontinued use of the soap and was treated at the emergency room with an unspecified shot for an allergic reaction to BPO after which symptoms resolved. The patient stated that the physician performed a “test” and notified her that she was allergic to BPO. Many years later, while cleaning up some of her husband’s unspecified BPO wash from a counter with a wipe, she experienced anaphylactic shock for which treatment was not reported. The patient’s symptoms have since resolved.

- FAERS Case #10174269, Version 5, Expedited (15-Day), USA, Initial FDA Received date May 15, 2014, Other Serious, UMC Report ID #US-RB-065691-14. A 19-year-old female with no known allergies and no reported concomitant medications applied Clearasil Daily Clear Vanishing Cream with BPO and an unknown soap to her face for the first time and woke up the next day with difficulty breathing and periorbital edema. Her eyes being “swollen shut.” The patient was treated with

oral and injectable steroids and was discharged. She immediately discontinued use of the BPO product but resumed use of the soap with no further issues. Approximately 5 months later, the patient applied the same BPO cream to her face for the second time and woke up the next day with periorbital edema and facial hives. The patient immediately discontinued use of the benzoyl peroxide product. Due to a lack of insurance, the patient treated herself with diphenhydramine every 4 hours until the adverse events resolved.

- FAERS Case #10422679, Version 1, Expedited (15-Day), USA, Initial FDA Received date September 02, 2014, Other Serious, UMC Report ID #US-JNJCP-30000237713. A 16-year-old female with no known medical history and no concomitant medications applied Neutrogena Clear Pore Cleanser/Mask with BPO to her face for the first time. A few hours later the patient experienced facial and periorbital edema, "hot" skin, erythema with a blistery rash, and difficulty breathing. She immediately discontinued use of the cleanser/mask. The patient received medical care with steroids and other unspecified medications at the emergency room where she later recovered.

- FAERS Case #10040010, Version 2, Expedited (15-Day), USA, Initial FDA Received date March 26, 2014, Other Serious, UMC Report ID #US-JNJCP-30000211498. A 22-year-old female with unknown medical history applied Neutrogena On-the-Spot Acne Treatment with BPO to her skin on five to seven small spots. Fifteen minutes after the first application of the BPO product, she experienced a severe hypersensitivity reaction including pharyngeal and tongue edema requiring treatment with unspecified allergy medications. She discontinued use of the product with no further information provided.

Dr. Baily provided the following labeling recommendations. Proposed additions are underlined, and deletions are indicated by a ~~strikethrough.~~

(b) (4)


8.2.5.3 Local Safety

The use of benzoyl peroxide is known to be associated with local reactions including irritation and contact dermatitis. Per protocol, the investigator evaluated the application site for dryness and scaling using a 4 -point scale at Baseline and all follow-up visits.

Table 20: Cutaneous Safety Assessment Scale

| Grade | Description |
|---|---|
| *Dryness* | |
| 0 – None | No dryness |
| 1 – Mild | Slight but definite dryness |
| 2 – Moderate | Moderate dryness |
| 3 – Severe | Marked dryness and/or cracking |
| *Scaling* | |
| 0 – None | No scaling |
| 1 – Mild | Barely perceptible scaling |
| 2 – Moderate | Obvious but not profuse scaling |
| 3 – Severe | Heavy scale production and/or peeling |

Source: Table 4 Protocol SGT-54-02, Version 4.0

In addition, at Baseline and Weeks 2, 4, 8 and 12, investigators asked subjects to grade the severity stinging and burning at the application site during the last 24 hours on 4- point local tolerability assessment scales.

Table 21: Local Tolerability Assessment Scale

| Grade | Description |
|---|---|
| *Itching* | |
| 0 – None | No itching |
| 1 – Mild | Slight itching, not really bothersome |
| 2 – Moderate | Definite itching that is somewhat bothersome |
| 3 – Severe | Intense itching that may interrupt daily activities and/or sleep |
| *Burning/Stinging* | |
| 0 – None | No burning/stinging |
| 1 – Mild | Slight burning/stinging sensation; not really bothersome |
| 2 – Moderate | Definite warm, burning/stinging sensation that is somewhat bothersome |
| 3 – Severe | Hot burning sensation that causes definite discomfort and may interrupt daily activities or sleep |

Source: Table 5 Protocol SGT-54-02, Version 4.0

The protocol did not categorize these results as adverse events unless the findings resulted in the temporary discontinuation of the study product, discontinuation of the subject from the trial or required treatment with a new concomitant medication. Investigators recorded other application site reactions (e.g. pain) as adverse events.

Most assessments of local tolerability were mild or moderate in severity and improved from Baseline to Week 12. Signs and symptoms occurred at a similar frequency and severity in both treatment groups, BPO cream and vehicle. Refer to Section 8.2.4 of this review for the findings and proposed language for inclusion in labeling in section 6.1.

See section 8.2.5.2 of this review for brief narratives regarding TEAEs of "rash" and "contact dermatitis."

Photosensitivity reactions

The Applicant coded photosensitivity reactions using the preferred terms of "application site photosensitivity" and "sunburn." Although all TEAEs were assessed as unrelated, there was an imbalance of photosensitivity reactions in the active arm compared with the placebo arm. All photosensitivity reactions were associated with the use of BPO cream. Most of these subjects used sunscreen.

During the phase 3 trials and extension trial one subject, a 42 year-old White female (SGT-54-(b) (6)), with no relevant medical history experienced a "photosensitivity reaction" on her face on Day 76. The reaction resolved on the following day without treatment. The subject was using sunscreen. The causality of the TEAE was assessed as unlikely. The TEAE did not result in trial discontinuation. This subject also experienced periorbital irritation (Day 170) which was assessed as possibly related and 2 episodes of "facial flushing" coded as "application site reaction." A 46- year- old White female (SGT-54-(b) (6)) and 55- year- old White female (SGT-54-(b) (6)) who used sunscreen experienced mild photosensitivity reactions on Day 53 and 252 respectively. The TEAEs were assessed as mild in severity and unrelated to the study product. The subjects completed the trial. Two additional subjects (SGT-54-(b) (6) and SGT-54-(b) (6)) reported "sunburn" on their nose which was assessed as mild and not related to BPO cream.

Section 5 Warnings and Precautions and Section 17 includes language regarding photosensitivity as indicated below:

> 5.3 Photosensitivity
> Benzoyl peroxide may increase sensitivity to sunlight. Minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while using EPSOLAY. Instruct the patient to implement sun protection measures (e.g., sunscreen and loose-fitting clothes) when sun exposure cannot be avoided. Discontinue EPSOLAY at the first evidence of sunburn.
>
> 17 Patient Counseling Information
> (b) (4)

### 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The phase 3 protocol included a patient reported outcome (PRO) measure of the tolerability of treatment with BPO cream, 5%. The Patient Global Impression of Treatments Side Effects (PGI-SE) which was administered at Weeks 2, 4, 8 and 12, was utilized to assess the impact of the side effects of treatment (how bothersome). The protocol specified this measure as a supportive endpoint. Per the Special Protocol (SPA) Agreement Letter (dated 4/5/2018), the FDA informed the Applicant, "You may conduct hypothesis tests on supportive efficacy endpoints for descriptive purposes. (b) (4)

(b) (4)


### 8.2.7. Safety Analyses by Demographic Subgroups

The review team conducted additional analyses to evaluate the safety profile of BPO cream in different demographic subgroups. Because the trials were not powered for these analyses, the data must be interpreted with caution. Additionally, most of the subjects in the safety population of the pooled Phase 3 trials were White (93%). This precluded a meaningful subgroup safety analyses based on race. Furthermore, the number of subjects age 65 years and older (126/722; 17%) and 75 years and older (28/722; 4%) was also limited. The Applicant conducted a subgroup analysis comparing the populations who were older and younger than the median age of 52 years. Overall, there were no differences in the preferred terms or general frequencies of the adverse events. With regard to gender, female subjects experienced TEAE with greater frequency than male subjects (21% versus 17%.) These TEAEs included both application site TEAEs and systemic TEAEs. However, number of female subjects who participated in the trial was far greater than male subjects (526 versus 196) which limits definitive conclusions.

Reviewer analyses are below. These comparisons included no pooling of related terms.

Table 22: Treatment Emergent Adverse Events by Age

| | **BPO 5% Cream** | | **Vehicle Cream** | |
|---|---|---|---|---|
| | **Age ≥ 18 & < 65 n=398** | **Age ≥ 65 n=90** | **Age ≥ 18 & < 65 n=198** | **Age ≥65 n=36** |
| Treatment Emergent Adverse Events - subjects ( % ) | **77 (19.3%)** | **22 (24.4%)** | **35 (17.7%)** | **4 (11.1%)** |
| Nasopharyngitis | 9 (2.3%) | 3 (3.3%) | 4 (2.0%) | 0 (0.0%) |
| Application site pain | 9 (2.3%) | 2 (2.2%) | 2 (1.0%) | 0 (0.0%) |
| Application site erythema | 7 (1.8%) | 4 (4.4%) | 2 (1.0%) | 0 (0.0%) |
| Application site pruritus | 4 (1.0%) | 2 (2.2%) | 1 (0.5%) | 0 (0.0%) |
| Sinusitis | 3 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Application site dermatitis | 3 (0.8%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) |
| Urinary tract infection | 3 (0.8%) | 0 (0.0%) | 2 (1.0%) | 1 (2.8%) |
| Influenza | 3 (0.8%) | 0 (0.0%) | 3 (1.5%) | 0 (0.0%) |
| Seasonal allergy | 2 (0.5%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) |
| Tooth infection | 2 (0.5%) | 0 (0.0%) | 1 (0.5%) | 0 (0.0%) |
| Muscle strain | 2 (0.5%) | 1 (1.1%) | 1 (0.5%) | 0 (0.0%) |
| Ligament sprain | 2 (0.5%) | 1 (1.1%) | 0 (0.0%) | 0 (0.0%) |
| Application site edema | 2 (0.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Application site irritation | 2 (0.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| URI | 2 (0.5%) | 3 (3.3%) | 4 (2.0%) | 0 (0.0%) |

Upper respiratory tract infection=URI
Source: Reviewer's table; JReview

Table 23: Treatment Emergent Adverse Events by Sex

| | BPO 5% Cream | | Vehicle Cream | |
|---|---|---|---|---|
| | F n=361 | M n=127 | F n=165 | M n=69 |
| **Treatment Emergent Adverse Events - subjects ( % )** | **77 (21.3%)** | **22 (17.3%)** | **32 (19.4%)** | **7 (10.1%)** |
| Application site pain | 11 (3.0%) | 0 (0.0%) | 2 (1.2%) | 0 (0.0%) |
| Application site erythema | 9 (2.5%) | 2 (1.6%) | 2 (1.2%) | 0 (0.0%) |
| Nasopharyngitis | 8 (2.2%) | 4 (3.1%) | 3 (1.8%) | 1 (1.4%) |
| Application site pruritus | 6 (1.7%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) |
| URI | 4 (1.1%) | 1 (0.8%) | 4 (2.4%) | 0 (0.0%) |
| Urinary tract infection | 3 (0.8%) | 0 (0.0%) | 3 (1.8%) | 0 (0.0%) |
| Application site dermatitis | 3 (0.8%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) |
| Ligament sprain | 3 (0.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Influenza | 3 (0.8%) | 0 (0.0%) | 3 (1.8%) | 0 (0.0%) |
| Sinusitis | 2 (0.6%) | 1 (0.8%) | 0 (0.0%) | 0 (0.0%) |
| Musculoskeletal pain | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Application site irritation | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pruritus | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Rash | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Application site swelling | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Wrist fracture | 2 (0.6%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) |
| Dermatitis | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Back pain | 2 (0.6%) | 0 (0.0%) | 0 (0.0%) | 1 (1.4%) |

Upper respiratory tract infection=URI
Source: Reviewer's table; JReview

The review team proposed the following for section 8.5 Geriatric Use of labeling:

8.5 Geriatric Use

> Of the 733 subjects in the clinical trials of EPSOLAY, 127 (17%) subjects were 65 and over, while 37 (3%) subjects were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

### 8.2.8. Specific Safety Studies/Clinical Trials

The Applicant submitted supportive safety Information from two additional trials: long-term safety Trial SGT-54-07 and dose-ranging Trial SGT-BPO1-09.

Phase 3 Trial SGT-54-07

This was a multi-center, open-label, phase 3 trial which evaluated the safety of BPO cream, 5% (S5G4T-1) for the treatment of adult subjects with moderate to severe rosacea for up to 52 weeks. Subjects who completed one of the vehicle controlled phase 3 trials (SGT-54-01/ SGT-54-02) were eligible to enroll in Trial SGT-54-07. In Trial SGT-54-07, subjects could receive up to 40 weeks of open-label, once daily treatment with BPO cream. For subjects who received 12

weeks of BPO cream in Trials SGT-54-01/ SGT-54-02, the total exposure was up to 52 weeks.

At each visit, investigators/staff evaluated subjects on the 5-point IGA scale and dispensed BPO cream to subjects who had experienced a loss of treatment success, a score of "mild" (2), "moderate" (3) or "severe" (4). Investigators/staff instructed subjects who remained "clear" (0) or "almost clear" (1) not to apply the study product. As in previous trials, investigators directed subjects to apply a "pea-size" amount of BPO cream to each treatment area (chin, left cheek, right cheek, nose, left forehead and right forehead) and gently rub the cream into the skin.

Disposition, Demographics, and Baseline Disease Characteristics

A total of 547 subjects enrolled in Trial SGT-54-07 from Trials SGT-54-01/ SGT-54-02. The safety population included 535 (98%) of these subjects; the remaining 12 subjects who were previously randomized to vehicle were excluded from the safety population because they had no documented use of the study product. Of the 535 subjects, 172 subjects previously received vehicle and 363 subjects previously received BPO cream. The demographic characteristics were similar to Trials SGT-54-01/ SGT-54-02. The majority were female (71%), White (92%), not Hispanic or Latino (71.0%) with a mean age of 52 years (range 19 to 81 years.) Subjects had a baseline mean inflammatory lesion count of 28.4. Most subjects had rosacea of moderate severity on IGA (89.2% .)

Table 24: Disposition-Trial SGT-54-07

| | **BPO Cream,5% n=535** |
|---|---|
| **DISPOSITION EVENT** | **216 (40.4%)** |
| STUDY TERMINATED BY SPONSOR | 141 (26.4%) |
| WITHDRAWAL BY SUBJECT | 46 (8.6%) |
| LOST TO FOLLOW-UP | 20 (3.7%) |
| ADVERSE EVENT | 4 (0.7%) |
| PROTOCOL VIOLATION | 2 (0.4%) |
| PREGNANCY | 1 (0.2%) |
| PHYSICIAN DECISION | 1 (0.2%) |
| OTHER | 1 (0.2%) |

Reviewer's Table JReview

Safety

The most frequently reported TEAEs were in the system-organ class (SOC) of Infections and infestations (17%). In this SOC, the most common preferred terms (PTs) were nasopharyngitis (5%), upper respiratory tract infection (2%), urinary tract infection(2%), influenza (2%), and sinusitis (1%). Common local reactions were application site pain and application site erythema. The distribution of TEAEs and frequencies were similar to the findings for the pooled phase 3 trials.

Table 25: Treatment emergent adverse events in **≥1%** of subjects

| | **BPO Cream, 5% n=535** |
|---|---|
| **Subjects with at least 1 TEAE - count subjects and % with data** | **185 (34.6%)** |
| Pooled Upper Respiratory Infections | 49 (9.2%) |
| Urinary tract infection | 9 (1.7%) |
| Influenza | 8 (1.5%) |
| Pooled Gastroenteritis | 7 (1.3%) |
| Application site erythema | 7 (1.3%) |
| Back pain | 7 (1.3%) |
| Application site pain | 7 (1.3%) |
| Hypertension | 6 (1.1%) |
| Cough | 6 (1.1%) |

Reviewer's Table JReview

Phase 2 Trial SGT-BPO1-09

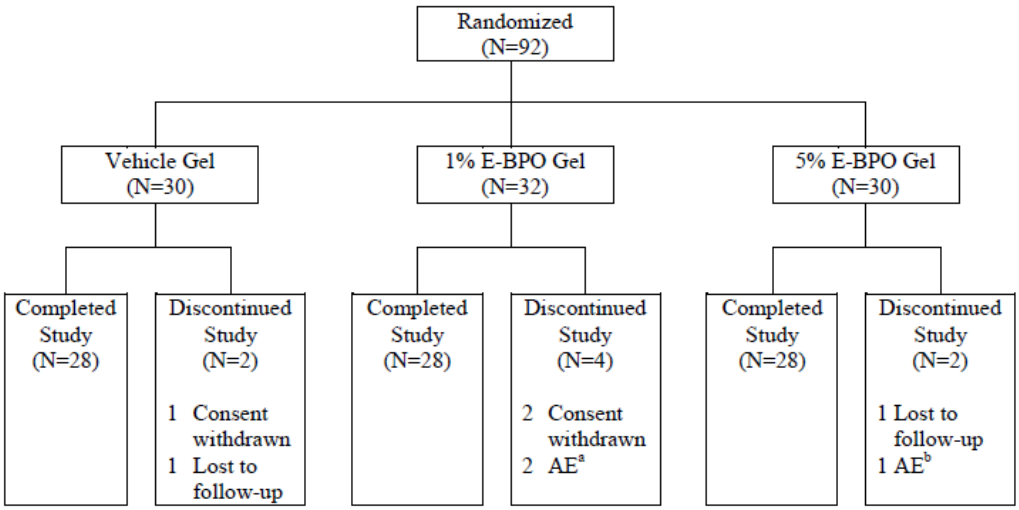
This was a multi-center, randomized, double-blind, vehicle-controlled, 12 week, dose-ranging trial. Eligible subjects had mild, moderate or severe facial rosacea based on the Investigator Global Assessment Scale (IGA) and at least 12 inflammatory papules or pustules. A total of 92 subjects who met the inclusion/exclusion criteria were randomly assigned in a 1:1:1 ratio to 5% BPO gel, 1% BPO gel, or Vehicle gel. Subjects applied the study product once daily for 12 weeks. Assessments of IGA, inflammatory lesion counts, erythema, telangiectasia and local safety (dryness, scaling, pruritus, stinging and burning) were conducted at Screening, Baseline, and Weeks 4, 8, and 12.

The primary efficacy endpoints were:

- Proportion of subjects with the primary measure of success, defined as a 2-grade improvement in the IGA relative to Baseline at Week 12, with the Week 12 IGA of clear or almost clear.
- Change in inflammatory lesion count at Week 12.

Disposition, Demographics, and Baseline Disease Characteristics

A total of 92 subjects were randomized from 10 study sites: 30 subjects to vehicle, 32 subjects to 1% BPO gel, and 30 subjects to 5% BPO gel. Twenty-eight subjects in each treatment group completed the trial (88-93% of the subjects in each treatment group).




[a] Contact dermatitis (08-059); Inflamed cyst (09-021)
[b] Study drug reaction (07-052)

All protocol deviations involved visits outside of the pre-specified window.

The demographic characteristics were comparable across treatment groups. The majority of subjects were female (72.8% [67/92]), not Hispanic/Latino (82.6% [76/92]), and White (97.8% [90/92]) with a mean age of 52 years (range 23 to 82 years.) At Baseline, most subjects had rosacea of moderate severity (74% [68/92]). The remainder of the subjects had rosacea of severe severity (14% [13/92] or mild severity 912% (11/92)]. The mean inflammatory lesion count was 24 (range 12 to 130).

Efficacy

Primary efficacy endpoints at Week 12

- The proportions of subjects with the primary measure of success: 20.0% (6/30) for vehicle gel, 37.5% (12/32) for 1% BPO gel, and 53.3% (16/30) for 5% BPO gel.
- The least squares (LS) mean changes from Baseline in inflammatory lesion counts at Week 12 were -8.8 (95% CI: -15.1, -2.5) for vehicle gel, -21.5 (95% CI: -27.5, - 15.4) for 1% BPO gel, and -14.7 (95% CI: -21.0, -8.4) for 5% BPO gel.

Safety

- No deaths or SAEs were reported during the study.
- Adverse events that led to discontinuation included: application site reaction (5% BPO, related) application site dermatitis (1% BPO, related), and cyst (1% BPO, not related).
- In the 5% BPO gel group, a total of 10 treatment-emergent AEs were reported by 7/30 subjects (23%).The majority of the TEAEs (70% [7/10]) were mild in severity. Two TEAEs were moderate in severity, and one TEAE ("application site reaction") was severe.
- In the 1% BPO gel group, a total of 12 TEAEs were reported by 7/32 subjects (22%). A majority of TEAEs (58% [7/12]) were moderate in severity, and 25% (3/12) were mild in severity. Two TEAEs (two events of "cyst" reported by one subject) were severe. One TEAE

("application site dermatitis") was possibly related to the study product.

- In the vehicle gel group, 16 TEAEs were reported by 11/30 subjects (37%). Half of the TEAEs (50% [8/16]) were moderate in severity, and 44% (7/16) were mild in severity. One treatment-emergent AE ("influenza") was severe. One TEAE was possibly related ("application site reaction") and three TEAEs were probably related ("application site erythema," application site pain," and "application site pruritus".)
- Among subjects with application site irritation, most subjects assessed the severity as mild or moderate. One subject who received the 5% BPO gel experienced severe stinging and burning post-Baseline; no subjects had severe dryness, scaling, or pruritus post-Baseline.
- Across treatment groups, the system organ class in which TEAEs were most frequently reported was "infections and infestations." The most common preferred term (PT) was "nasopharyngitis".
- There were no positive pregnancy tests.

Table 26: Treatment-emergent Adverse Events in Selected Systemic Organ Classes (SOCs)[1]

| | Treatment-emergent Adverse Events | | |
|---|---|---|---|
| **System Organ Class/Preferred Term** | **Vehicle N=30** | **1% BPO Gel N=32** | **5% BPO Gel N=30** |
| Infections and infestations | 7 (23%) | 2 (6%) | 5 (17%) |
| **Bronchitis** | 1 (3%) | 0 (0%) | 0 (0%) |
| **Cystitis** | 0 (0%) | 0 (0%) | 1 (3%) |
| **Fungal infection** | 1 (3%) | 0 (0%) | 0 (0%) |
| **Gastroenteritis** | 1 (3%) | 0 (0%) | 0 (0%) |
| **Influenza** | 1 (3%) | 0 (0%) | 0 (0%) |
| **Nasopharyngitis** | 1 (3%) | 2 (6%) | 3 (10%) |
| **Post procedural infection** | 1 (3%) | 0 (0%) | 0 (0%) |
| **Sinusitis** | 1 (3%) | 0 (0%) | 1 (3%) |
| **Upper respiratory tract infection** | 1 (3%) | 0 (0%) | 0 (0%) |
| Nervous system disorders | 0 (0%) | 2 (6%) | 1 (3%) |
| **Headache** | 0 (0%) | 1 (3%) | 1 (3%) |
| **Migraine** | 0 (0%) | 1 (3%) | 0 (0%) |
| General disorders & Admin Site Con | 2 (7%) | 1 (3%) | 1 (3%) |
| **Application site dermatitis** | 0 (0%) | 1 (3%) | 0 (0%) |
| **Application site erythema** | 1 (3%) | 0 (0%) | 0 (0%) |
| **Application site pain** | 1 (3%) | 0 (0%) | 0 (0%) |
| **Application site pruritus** | 1 (3%) | 0 (0%) | 0 (0%) |
| **Application site reaction** | 1 (3%) | 0 (0%) | 1 (3%) |

Source: Clinical Study Report for SGT-EBPO1-09, adapted from Table 12.2.2.1-1 and 12.2.2.2-1
[1] SOCs in which > one subject reported a TEAE
Admin Site Con=Administration Site Conditions

The Applicant conducted the phase 2 trial using an inadequate IGA scale: the category of "Clear" did not represent the true absence of disease (mild erythema), "Clear" and "Almost clear" were not distinct categories and morphologic descriptors did not clearly specify the level of disease severity. In addition, the Applicant evaluated a formulation/ dosage form (gel vs cream) of their drug product that was not the to-be-marketed formulation. Therefore, the

review team considered this data to be supportive of the findings from the phase 3 trials.

Dermal Safety and Cardiovascular Safety Assessments

The Applicant did not conduct dedicated trials to evaluate dermal safety or cardiovascular safety. The Applicant submitted waivers for the assessment of cardiovascular (CV) safety (thorough QT/QTc) and photo safety (photoallergenicity and phototoxicity). The rationale that the Applicant provided for waiving a thorough QT/QTc study was: the long history of the safe use of BPO in the treatment of acne, absence of CV safety signal in the literature, the GRASE status of BPO and the completed toxicokinetic and repeat dose toxicology studies in Gottingen minipigs with the proposed product showing no increase in the plasma levels of benzoic acid above endogenous levels. The rationale that the Applicant provided for waiving photosafety studies included the following arguments (SDN 7 dated 11/17/2020): 1) the Applicant intends to provide a warning in labeling to instruct patients to avoid unnecessary sun exposure and apply sunscreen per OTC monograph, 2) the UV-VIS spectrum of the drug product and drug substance over the range of 290 to 700 nm showed a molar extinction coefficient (MEC) value below 1,000 L mol-1 cm-1, and 3) a phototoxicity study with BPO cream in New Zealand white rabbits showed negative results (Calvert Study Number 0432LS89.001). These waiver requests were deemed reasonable and granted.

The Applicant addressed the potential of BPO cream, 5% to induce irritation and sensitization by conducting assessments of dryness, scaling, pruritis, stinging and burning during the phase 3 trials. Refer to section 8.2.5.3 of this review for a discussion of the dermal safety findings.

### 8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

As BPO cream, 5% has no quantifiable systemic exposure after cutaneous administration, the proposed product is not expected to promote carcinogenicity. The Applicant did not conduct any dedicated nonclinical or clinical studies to evaluate carcinogenic potential.

In the extension Trial SGT-54-07, single subjects reported the following malignancies: squamous cell carcinoma of the ear and tonsillar cancer. Investigators considered none of the events of malignancy to be related to treatment with BPO cream.

Human Reproduction and Pregnancy

The Applicant did not conduct adequate and well-controlled trials of BPO cream in pregnant or lactating women. The entry criteria for all trials excluded pregnant or lactating female; those who became pregnant discontinued the study product and withdrew from the trial per

protocol. Requirements for sexually active females of childbearing potential (FCBP) [6] who were enrolled in the BPO cream development program included a negative pregnancy test at Baseline and the use of effective forms of contraception, a negative serum pregnancy test at Screening. Investigators withdrew subjects from the trial who became pregnant and, where feasible, followed these subjects until the conclusion of the pregnancy. Animal reproductive studies have not been conducted with EPSOLAY.

All pregnant subjects withdrew from the trials. The events of pregnancy were considered unrelated to the study product. There were no positive pregnancy tests in subjects participating in Trials SGT-EBPO1-09 or SGT-54-02. In phase 3 trial SGT-54-01, two subjects had positive pregnancy tests: a 35- year- old white female (b) (6) on Day 28 and a 42- year- old (b) (6) female on Day 23. Both subjects used abstinence as their method of contraception and had no relevant medical history or concomitant medications. The subject (b) (6) who received vehicle cream had an uncomplicated pregnancy and childbirth and delivered a healthy baby. The subject (b) (6) who received BPO cream was lost to follow up and the outcome of the pregnancy is unknown. In extension Trial SGT-54-07, a 27- year- old white female subject (b) (6) who received BPO cream had a positive pregnancy test on Day 163 and discontinued the trial on Day 178. The subject used Mirena IUD as her method of contraception and had no relevant medical history or concomitant medications. The pregnancy is ongoing with no complications reported to date.

The Applicant submitted a review of the published literature regarding exposures during pregnancy and lactation. According to the Applicant, there is no published literature regarding systemic exposure to BPO after topical application or trials evaluating pregnant females who received BPO products. There are several review articles which discuss the potential risks of the use of topical BPO during pregnancy. Overall, most authors viewed BPO as generally safe during pregnancy due to its rapid metabolism to benzoic acid (Chien 2016; Meredith 2013; Rothman 1988). In view of the prior designation as a "pregnancy Category C" drug, other authors concluded that BPO should only be prescribed during pregnancy if the possible benefit justifies the potential risk (Akhavan 2003; Ives 1992). Similarly, the literature which addresses the use of topical BPO during lactation concluded that it is safe (Pugashetti 2013; Kong 2013.)

Jane Liedtka M.D., Division of Pediatric and Maternal Health (DPMH), evaluated the potential risks of exposure to BPO during pregnancy and lactation and provided recommendations for Section 8 of labeling. DPMH conducted a search of published literature in PubMed and identified no additional relevant publications regarding pregnancy, lactation or fertility. Examination of the key sources of information regarding pregnancy outcomes with drug

[6] FCBP excludes females who were sterilized as a result of the Essure procedure, tubal ligation, bilateral oophorectomy or hysterectomy or post-menopausal for at least 2 years.

exposure indicated no human data (Briggs[7], Reprotox), unknown risk (Micromedex[8]) or small risk that "cannot be excluded" (TERIS[9], Micromedex.) In Hale's Medications and Mother's Milk[10], the author states that "…there are no data on its transfer into human milk. BPO if ingested would be largely destroyed almost instantly by tissue and stomach esterases. It is unlikely that any would be absorbed systemically." See Review by Jane Liedtka M.D., dated January 25, 2021.

Dr. Liedtka provided the following labeling recommendations for Section 8.1 and 8.2.

> 8 USE IN SPECIFIC POPULATIONS
>
> 8.1 Pregnancy
>
> Risk Summary
>
> The systemic exposure of benzoyl peroxide is unknown. Based on the published literature, benzoyl peroxide is metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Hence, maternal use is not expected to result in fetal exposure to the drug. Animal reproductive studies have not been conducted with EPSOLAY or benzoyl peroxide.
>
> The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to20%, respectively.
>
> 8.2 Lactation
>
> Risk Summary
>
> There are no data on the presence of benzoyl peroxide in human milk, its effects on the breastfed infant or its effects on milk production. The systemic exposure of benzoyl peroxide is unknown. Based on the published literature, benzoyl peroxide is metabolized to benzoic acid (an endogenous substance), which is eliminated in the urine. Any amount of benzoyl peroxide excreted into human milk by a nursing mother would be expected to be metabolized by tissue and stomach esterases. Therefore,

---

[7] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[8] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 2/19/2020.
[9] Teris - The Teratogen Information System
[10] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing

breastfeeding is not expected to result in exposure of the infant to EPSOLAY. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EPSOLAY and any potential adverse effects on the breastfed child from EPSOLAY or from the underlying maternal condition.

Pediatrics and Assessment of Effects on Growth

The Applicant established the safety and efficacy of BPO cream, 5% for the treatment of inflammatory lesions (papules and pustules) of rosacea in adults. As rosacea is rare in children, the adult population is the relevant population for the indication for which the Applicant seeks approval.

The new indication for the product triggered Pediatric Research Equity Act (PREA) considerations. The Applicant submitted and followed the agreed-upon initial Pediatric Study Plan. The Applicant requested a full waiver of pediatric assessments, since the necessary studies are impossible or highly impracticable because the number of patients is small and those that may be diagnosed with rosacea are geographically dispersed. The Pediatric Review Committee agreed with the Division (Meeting Minutes dated February 23, 2021) that the request for a full waiver of pediatric studies was acceptable as proposed. No pediatric studies are required/ recommended. Refer to Section 8.29 under the heading Pediatrics and Assessment of Effects on Growth for a discussion of the Pediatric Study Plan.

Refer to Section 10 Pediatrics for labeling recommendations for Section 8.4 Pediatric Use.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
BPO cream has low systemic absorption after topical application; therefore, the potential for systemic effects from overdose are limited. There is no available information on overdose with BPO by oral administration.

Drug Abuse Potential/ Withdrawal and Rebound
In view of the mechanism of action and lack of systemic exposure, there is no reason to anticipate any potential for abuse or dependency. The Applicant did not evaluate abuse potential and did not design or conduct trials to evaluate subjects for withdrawal or rebound. There were no data to indicate the occurrence of physical dependency on BPO cream during the clinical trials. Therefore, the review team did not consult with the Controlled Substance Staff.

120-Day Safety Update
Per 21 CFR 314.50(d)(5)(vi)(b), the Applicant submitted a 120- Day Safety Update Report (SUR) (SDN 9 dated December 8, 2020). The review team identified no new safety signals in the SUR. The Applicant stated that additional safety information was available from ongoing phase 1 trial

SGT-54-08, entitled "A Randomized, Double-Blind, Cross-Over, Vehicle Controlled Evaluation of Topical Encapsulated Benzoyl Peroxide on the Skin Microbiome and Skin Biophysical Properties"( Protocol submitted March 11, 2020 to IND 102233.) The objective of the trial was to assess the impacts of BPO cream on the skin microbiome and skin biophysical properties in subjects with moderate to severe rosacea after 8 weeks of treatment with BPO cream or vehicle. To date, of the 40 enrolled subjects, 4 subjects experienced TEAEs which were mild in severity and not related to the study product. One subject experienced a TEAE of "Acute Irritative Dermatitis" which was moderate in severity, related to the study product and led to trial discontinuation. There were no reports of death, SAEs or pregnancies.

### 8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

BPO cream, 5% is not approved or marketed in any jurisdiction. Therefore, this section is not applicable.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the safety data for BPO cream identified no safety signals. The Applicant submitted a review of the literature regarding the safety of off-label use of benzoyl peroxide products in the treatment of rosacea. The published literature which was discussed by the Applicant included two small (< 60 subjects), vehicle -controlled trials (Montes, 1983 and Breneman 2004: Cochrane review, 2015), one active-controlled trial (Ozturkcan, 2004), and a retrospective cohort study using the MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental Database. The Applicant concluded that although local irritation (burning, erythema, edema, dryness, skin tightness, pruritus) was documented in up to 39% of subjects in one trial, no unexpected adverse events were observed.

Thus, there are no safety concerns that are expected to change the favorable benefit/ risk assessment or demonstrate increased risk with administration of BPO cream in the postmarket setting.

### 8.2.11. Integrated Assessment of Safety

The safety profile for BPO cream was adequately characterized during the drug development program. The primary review of safety of the drug product for the treatment of inflammatory lesions of rosacea in adult patients focused on the evaluation of pooled data from phase 3 Trials SGT-54-01 and SGT-54-02. Both phase 3 trials were similar with regard to design, trial population, dosing regimen and key primary and secondary endpoints. Eligible subjects were randomized in a 2:1 ratio to receive either BPO cream or vehicle once daily for 12 weeks.

Treatment with BPO cream was not associated with a risk of death or drug-related SAEs. In the

pooled phase 3 Trials SGT-54-01 and SGT-54-02, two subjects (0.3%) experienced nonfatal serious adverse events (SAEs), one subject in each treatment group. In the BPO group, one subject reported spinal compression fracture (severe); in the vehicle group, one subject reported femur fracture (moderate). Both SAEs were considered to be unrelated to the study product but led to study discontinuation.

A greater proportion of subjects withdrew from the trial due to TEAEs in the BPO group (1.8%) compared with the vehicle group (0.4%). All of the TEAEs which led to discontinuation from the pooled trials were local application site reactions (BPO: pain, pruritus, dermatitis, erythema, edema, discharge; vehicle: papules, erythema) which were related to the study product. None of the subjects provided relevant historical information that would account for those reactions apart from study drug exposure. All of these reactions occurred early in the course of treatment (i.e. within the first 30 days.) Two subjects reported TEAE that were assessed as severe in the BPO group (application site pain and application site erythema.)

In the phase 3 Trials SGT-54-01/ SGT-54-02, a greater proportion of subjects experienced TEAEs in the BPO group (20.3%) compared with the vehicle group (16.7%). After pooling of related terms, the most common TEAEs included upper respiratory tract infection, application site pain, application site pain erythema, application site pruritus and application site edema. The same imbalance between treatment arms was observed for treatment emergent adverse reactions (ARs) as for TEAEs. ARs which occurred in ≥ 1% of subjects in the BPO group and with greater frequency than the vehicle group included application site pain, application site erythema, application site pruritus and application site edema.

Other specific safety considerations included the potential for hypersensitivity reactions, local tolerability and long term safety. No subject who participated in the BPO development program experienced a severe hypersensitivity reaction that was related to the study product. However, there was an imbalance in the proportion of subjects who reported rash.

Investigators explored the association of BPO cream with irritation and contact dermatitis by evaluating the application site for dryness and scaling and documenting the subject assessment of stinging and burning. Most events associated with local tolerability were assessed as mild or moderate in severity and improved from Baseline to Week 12. By Week 12, the most common signs were dryness and itching which were reported as mild in severity by 25% and 24% of subjects, respectively. The only signs or symptoms which were graded as severe by Week 12 were stinging/burning by 1% of subjects.

Examination of long- term effects of BPO cream as administration in Trial SGT-54-07 did not identify any new safety signals or unexpected AEs. The most frequently reported TEAEs were in the system-organ class (SOC) of Infections and infestations (17%). In this SOC, the most common preferred terms (PTs) were nasopharyngitis (5%), upper respiratory tract infection (2%), urinary tract infection(2%), influenza (2%), and sinusitis (1%). Common local reactions were application site pain and application site erythema. The distribution of TEAEs and

frequency were similar to the findings for the pooled phase 3 trials.

The submitted data support the safety of BPO cream for the treatment of inflammatory lesions of rosacea in adult patients. Postmarketing risk management will include professional labeling, and routine pharmacovigilance.

## 8.3. Summary and Conclusions

### 8.3.1. Statistical Issues

There were no major statistical issues affecting the overall conclusions. The treatment effect was generally consistent across trials and endpoints (see Table 9). In addition, there were no substantial differences in efficacy among subgroups (see Figure 1 through Figure 4). In terms of handling missing data, the results were similar irrespective of the method used to impute missing data (see Table 11).

### 8.3.2. Conclusions and Recommendations

To establish the safety and efficacy of EPSOLAY® (benzoyl peroxide) cream, 5% for the treatment of inflammatory lesions of rosacea, the Applicant submitted data from two identically designed, randomized, multicenter, double-blind, vehicle-controlled, parallel-group Phase 3 trials (SGT-54-01 and SGT-54-02). The trials were conducted in subjects 18 years of age and older with moderate to severe rosacea defined as:

- IGA score of 3 (“moderate”) or 4 (“severe”)
- 15 to 70 inflammatory lesions (papules and/or pustules) on the face including those present on the nose
- No more than two nodules (papule or pustule > 5 mm in diameter) on the face

In both trials, subjects were randomized in a 2:1 ratio to receive either BPO cream, 5% or vehicle cream. Subjects applied study product once daily for 12 weeks. Subjects were specified to be evaluated at the following 6 study visits: screening (Day -35 to -1), baseline (Day 1), and Weeks 2, 4, 8, and 12 (end of treatment / end of study).

The protocol specified the following co-primary efficacy endpoints:

- Proportion of subjects achieving IGA success at Week 12, defined as an IGA score of 0 (“clear”) or 1 (“almost clear”) with at least a two-grade reduction from baseline
- Absolute change in inflammatory lesion counts from baseline to Week 12

The protocol specified the following secondary efficacy endpoints:

- Percent change in inflammatory lesion counts from baseline to Week 12
- Absolute change in inflammatory lesion counts from baseline to Week 8
- Proportion of subjects achieving IGA success at Week 8

- Absolute change in inflammatory lesion counts from baseline to Week 4
- Proportion of subjects achieving IGA success at Week 4

For both trials, BPO cream, 5% was statistically superior to vehicle cream on both co-primary efficacy endpoints (p-values < 0.001) and all secondary efficacy endpoints (p-values ≤ 0.009). Refer to Section 8.1.4 for discussion of the results for the co-primary efficacy endpoints and Section 8.1.5 for discussion of the results for the secondary efficacy endpoints.

To define the safety profile of BPO cream, the Applicant evaluated AEs, cutaneous safety assessments (application site dryness and scaling) and local tolerability (application site itching and burning/stinging) at Baseline, Weeks 2, 4, 8 and 12. In addition, investigators recorded findings from brief physical examinations (heart, lung, abdomen) with vital signs (blood pressure, oral temperature, heart rate and respiratory rate) at Baseline and Week 12 and concomitant medications at all visits. The protocols included periodic pregnancy testing and documentation of the outcomes of pregnancies with study product exposure.

The results of these assessments support the safety of BPO cream in the target population with inflammatory rosacea. There were no deaths or drug- related SAEs. There were no serious hypersensitivity reactions during the development of BPO cream. However, postmarketing information from FAERS and the literature included cases with a strong temporal association between BPO application and the development of anaphylaxis with positive dechallenge and rechallenge and angioedema with positive dechallenge. These results support the inclusion of language in labeling to convey the risk of this potential serious adverse reaction. A greater proportion of subjects who received BPO cream experienced adverse reactions at the application site: pain (2%), erythema (2%), pruritus (1%) and edema (1%). The severity of tolerability assessments improved over the course of the trials. In the long-term safety trials, the distribution of TEAEs and frequency were similar to the findings for the pooled phase 3 trials.

The Applicant provided adequate overall exposures to support the conclusion that this benefit /risk analysis is favorable and sufficient for approval of the application.

# 9 Advisory Committee Meeting and Other External Consultations

The FDA conducted no Advisory Committee Meeting regarding this application because the moiety is included in multiple approved combination products for the treatment of acne vulgaris and is well characterized. The safety profile in the target population with rosacea was expected to be similar to the safety profile in the populations for which the moiety is approved. Additionally, there were no novel or complex regulatory issues that required discussion in a public forum.

# 10 Pediatrics

The Applicant established the safety and efficacy of BPO cream, 5% for the treatment of inflammatory lesions (papules and pustules) of rosacea in adults. The adult population is the relevant population for the indication for which the Applicant seeks approval. Rosacea is rare in children.[1,2]

Refer to Section 8.2.9 Pediatrics and Assessment of Effects on Growth for a discussion of the waiver of pediatric assessments.

Per 21 CFR 201.57(c)(9)(iv), labeling recommendations for Section 8.4 Pediatric Use are the following:

8.4 Pediatric Use

(b) (4)

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

Prescribing information

The Applicant submitted proposed Prescribing Information (PI), Patient Information (PPI), container labels and carton labeling for EPSOLAY (benzoyl peroxide) cream, 5%. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, PPI, and the carton/container. These comments are reflected in final labeling. Refer to the OPDP review by Laurie Buonaccorsi PharmD dated February 11, 2021.

Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI, PPI, carton and carton labeling for EPSOLAY and identified areas for improvement. The reviewer recommended that the PI and PPI be revised to prevent wrong technique and wrong dose errors and the PI be revised to facilitate product identification. Additionally, the reviewer recommended that the container labels and carton labeling be revised for consistency, to facilitate product identification and to prevent drug selection and drug errors. (Reviews dated 12/10/2020; 4/7/2021).

The disciplines that provided recommendations regarding PI are tabulated below.

Table 27: Summary of Significant High-Level Labeling Changes

| Section | Location of Reviewer Comments on Proposed Labeling |
|---|---|
| 1 INDICATIONS AND USAGE | Clinical Team Section 1 |
| 2 DOSAGE AND ADMINISTRATION | Product Quality /Clinical Pharmacology Team Section 4.2. 6.3 |
| 3 DOSAGE FORMS AND STRENGTHS | Product Quality Team Section 4.2 |
| 4 CONTRAINDICATIONS | Clinical Team/DPV Section.8.2.5.2 |
| 5 WARNINGS AND PRECAUTIONS | Clinical Team Section 8.2.4; 8.2.5; 8.2.8 |
| 6 ADVERSE REACTIONS | Clinical Team/ DPV Section 8.2.4 |
| 7 DRUG INTERACTIONS | Clinical Pharmacology Team Section 6.3 |
| 8 USE IN SPECIFIC POPULATIONS | Nonclinical Team/ DPMH Section 8.2.9, 18.3.1 |
| 11 DESCRIPTION | Product Quality Team Section 4.2 |
| 12 CLINICAL PHARMACOLOGY | Clinical Pharmacology/ Nonclinical Teams Section 5.3, 5.5, 6.3 |
| 13 NONCLINICAL TOXICOLOGY | Nonclinical Team Section 5.5.2, 5.5.3, 18.31 |
| 14 CLINICAL STUDIES | Statistical Team/ COA Team Section 8.1 |
| 16 HOW SUPPLIED | Product Quality Team Section 4.2 |
| 17 PATIENT COUNSELING INFORMATION | Reflects the data in other sections of labeling, Sections 4, 5, 6 and 14. |

DPV: Division of Pharmacovigilance
COA: Clinical Outcome Assessment
DPMH: Division of Pediatric and Maternal Health

To distinguish their drug from other BPO products, the Applicant sought (b) (4) (b) (4) However, the OPQ reviewer Hamid Shafiei, Ph.D. conveyed the following comment to the Applicant (March 24, 2021), " (b) (4) should be removed from the dosage form throughout the PI (b) (4) (b) (4) (b) (4) refer to section 4.2 of this review, and the Drug Product and Labeling Chapters of the IQA by the Office of Pharmaceutical Quality dated April 7, 2021.

Other Prescription Drug Labeling

The Applicant submitted a patient information for EPSOLAY® (benzoyl peroxide) cream, 5%. The Division of Medical Policy Programs (DMPP) and OPDP reviewed and provided comments to ensure consistency with the PI and clarity of the concepts and language of the patient labeling. Refer to the Patient Labeling Review by Jessica Chung, PharmD, MS and Laurie Buonaccorsi, PharmD (dated February 16, 2021).

The final labeling will reflect all recommendations from the team.

## 12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling are not warranted at this time. The benefits of treatment with BPO cream, 5% were demonstrated in adequate and well controlled trials. With limited systemic exposure, the risks are predominantly local site reactions.

## 13 Postmarketing Requirements and Commitment

Based on review of the data in the submission, the review team recommended no clinical postmarketing requirements.

## 14 Division Director (DPT-II) Comments

N/A

## 15 Division Director (OCP) Comments

N/A

## 16 Division Director (Clinical) Comments

I agree with the discipline reviews' conclusion that the Applicant demonstrated sufficient efficacy and a favorable risk/benefit profile for BPO cream, 5% indicated for the topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older. I agree with the recommendation for approval action.

## 17 Office Director (or designated signatory authority) Comments

N/A

# 18 Appendices

## 18.1. References


- Alexis AF et. al. Global epidemiology and clinical spectrum of rosacea, highlighting skin of color: Review and clinical practice experience. J Am Acad Dermatol 2019;80:1722-9
- Breneman D, Savin R, VandePol C, Vamvakias G, Levy S, Leyden J. Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with moderate to severe rosacea. Int J Dermatol. 2004;43(5):381-7.
- Dahl MV, Rosacea: Pathogenesis, clinical features, and diagnosis, UpTo Date, Accessed September 18, 2020.
- Gallo RL, RD Granstein, S Kang, M Mannis, M Steinhoff, J Tan, D Thiboutot, Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee, J Am Acad Dermatol. 2018 Jan;78(1):148-155.
- Minciullo PL, Patafi M, Giannetto L, Ferlazzo B, Trombetta D, Saija A, Gangemi S.J Allergic contact angioedema to benzoyl peroxide. Clin Pharm Ther. 2006 Aug;31(4):385-7. doi: 10.1111/j.1365-2710.2006.00738.x
- Montes LF, Cordero AA, Kriner J, Loder J, Flanagan AD. Topical treatment of acne rosacea with benzoyl peroxide acetone gel. Cutis. 1983;32(2):185-90.
- Shweeb C and Lowenstein EJ. Delayed type hypersensitivity to benzoyl peroxide. JDrugs Dermatol. Mar-Apr 2004; 3(2):197-9
- Two, AM, Wu, W, Gallo, RL, Hata, TR. Rosacea, part I: introduction, categorization, histology, pathogenesis, and risk factors. J Am Acad Dermatol. 2015;72(5):749-758. Journal of the American Academy of Dermatology. 2015, Vol.72(5), p.749-758.
- Two, AM, W Wu, RL Gallo, TR Hata, CME Rosacea: part II. Topical and systemic therapies in the treatment of rosacea. JAAD 2015;72(5):761-770.
- van Zuuren EJ and Fedorowicz Z. Interventions for rosacea: abridged updated Cochrane systematic review including GRADE assessments. First published: 22 June 2015 https://doi.org/10.1111/bjd.13956
- Williamson T, Kamalakar R, Ogbonnaya A, Zagadailov EA, Eaddy M, Kreilick C. Rate of adverse events and healthcare costs associated with the topical treatment of rosacea. Am Health Drug Benefits. 2017;10(3):113-9.


## 18.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant signed the following disclosure statement:

> "I certify that I have not entered into any financial arrangement with the listed clinical investigators …whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

The covered clinical trials as defined in 21 CFR 54.2(e) were Trials SGT-54-01 and SGT-54-02 which provided the primary data to establish effectiveness and safety of this product. (Refer to section Error! Reference source not found. for the trial designs.)

APPEARS THIS WAY ON ORIGINAL

The Applicant adequately disclosed financial interests for clinical investigators.
Covered Clinical SGT-54-01 and SGT-54-02

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: Total of 27 investigators for each trial | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 0<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator 0<br>Sponsor of covered study: Sol-Gel Technologies | | |
| 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) **N/A** |

The investigators participating in the Phase 3 trials (SGT-54-01, SGT-54-02 and SGT-54-07) are listed below.

| SGT-54-01 | SGT-54-02 |
|---|---|
| Alpizar, Sady A. | Amster, Mark |
| Baldwin, Hilary | Badar, Francisco L. |
| Baumann, Leslie S. | Bhatia, Neal D. |
| Cauthen, Ashley Bassford | Davis, Steven A. |
| Desai, Seemal R | Davit, Rajesh Kumar |
| DuBois, Janet C. | Dayan, Steven H. |
| Goldman, Mitchel P. | Dhawan, Sunil S. |
| Herbert, Frances B. | Draelos, Zoe Diana |
| Jackson, Sarah Cenac | Flores, Francisco |
| Kempers, Steven E. | Gold, Michael H. |
| Kerdel, Francisco A. | Haber, Robert S. |
| Lain, Edward L. | Howington, Corinne |
| Heller, Gary Lee. | Knoepp, Theresa Greene |
| Lieberman, Robert D. | Shipp, Dana |
| McKenzie, Mark | Landis, Megan N. |
| Miller, Matthew L. | Malempati, Srikanth |
| Reed, Ann Mazor | Miller, Stephen |
| Rich, Kenneth | Owen, Cindy E. |
| Schilling, Ronald M. | Pointon, Catherine |
| Spann, Candace | Monlux Jr., George W. |
| Stein Gold, Linda | Sadick, Neil S. |
| Weiss, Eduardo | Sligh, Teresa S. |
| Wiltz, Hector | Smith, Stacy R. |
| Ellis, Kimberly | Tu, John H. |
| Yamauchi, Paul Steven | Werschler, William Phillip |
| Feser, Christina L. | Nahm, Walter K. |
| Abreu Ruiz, Mariam E. | Kwong, Pearl |

| SGT-54-07 | |
|---|---|
| Alpizar, Sady A. | Amster, Mark |
| Baldwin, Hilary | Badar, Francisco L. |
| Baumann, Leslie S. | Bhatia, Neal D. |
| Cauthen, Ashley Bassford | Davis, Steven A. |
| Desai, Seemal R | Davit, Rajesh Kumar |
| DuBois, Janet C. | Dayan, Steven H. |
| Reiman, Lionel M., MD | Dhawan, Sunil S. |
| Jackson, Sarah Cenac | Draelos, Zoe Diana |
| Kempers, Steven E. | Flores, Francisco |
| Kerdel, Francisco A. | Gold, Michael H. |
| Lain, Edward L. | Haber, Robert S. |
| Heller, Gary Lee. | Knoepp, Theresa Greene |
| Lieberman, Robert D. | Shipp, Dana |
| McKenzie, Mark | Landis, Megan N. |
| Miller, Matthew L. | Malempati, Srikanth |
| Reed, Ann Mazor | Miller, Stephen |
| Rich, Kenneth | Owen, Cindy E. |
| Schilling, Ronald M. | Pointon, Catherine |
| Spann, Candace | Monlux Jr., George W. |
| Stein Gold, Linda | Sadick, Neil S. |
| Weiss, Eduardo | Sligh, Teresa S. |
| Wiltz, Hector | Smith, Stacy R. |
| Ellis, Kimberly | Tu, John H. |
| Yamauchi, Paul Steven | Werschler, William Phillip |
| Feser, Christina L. | Nahm, Walter K. |
| Abreu Ruiz, Mariam E. | |

## 18.3. Nonclinical Pharmacology/Toxicology

### 18.3.1. Nonclinical labeling

Recommended changes to nonclinical information in sections 8.1, 12.1, and 13.1 of the applicant's proposed labeling are provided below. There is no established pharmacologic class (EPC) for benzoyl peroxide. Therefore, the first sentence in the Highlights section of labeling under the Indications and Usage section is acceptable since it does not contain an EPC. The photocarcinogenicity study results contained in section 13.1 were deleted because it has been determined that this study does not predict human risk per the ICH M3(R2) guidance document. Reviewer recommended deletions and additions are indicated by ~~strikethrough~~ and underlined text, respectively.

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

**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/

---

HOWARD F VAN HORN III
04/20/2022 11:13:59 AM

BARBARA A HILL
04/20/2022 11:17:10 AM

CHINMAY SHUKLA
04/20/2022 12:23:01 PM

MATTHEW W GUERRA
04/20/2022 12:25:45 PM

MOHAMED A ALOSH
04/20/2022 02:04:57 PM

HAMID R SHAFIEI
04/20/2022 03:22:29 PM

MELINDA L MCCORD
04/21/2022 01:17:29 PM

GORDANA DIGLISIC
04/21/2022 01:45:05 PM

TATIANA OUSSOVA
04/22/2022 12:28:38 AM

# Clinical Outcome Assessment Review Memorandum

| | |
|---|---|
| **From** | Parima Ghafoori, PharmD<br>Clinical Outcome Assessment (COA) Reviewer<br>Division of Clinical Outcome Assessment (DCOA)<br><br>Selena Daniels, PharmD, MS<br>COA Team Leader<br>DCOA |
| **To** | Division of Dermatology and Dentistry |
| **COA tracking number** | C2020349 |
| **NDA/IND#** | NDA 214510/ IND102233 |
| **Drug Sponsor:** | Sol-Gel Technologies Ltd. |
| **Indication:** | Treatment of inflammatory lesions of rosacea in adults 18 years of age and older<br><br>Please check all that apply:<br>☐ Rare Disease/Orphan Designation<br>☐ Pediatric |
| **PDUFA Goal Date:** | April 26, 2021 |
| **Instrument(s) reviewed:** | (b) (4) |

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by Division of Dermatology and Dentistry (DDD) on July 22, 2020 (DARRTS Reference ID: 4652828) for NDA 214510.

In this submission, the applicant is seeking approval of S5G4T-1 for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. The sponsor proposes specific targeted clinical outcome assessment (COA)-related labeling claims from two multicenter, randomized, double blind, vehicle-controlled phase 3 clinical trials (Studies SGT-54-01 and -02). (b) (4)

(b) (4)

3 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

---

**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/

---

SELENA R DANIELS
01/25/2021 04:12:59 PM

ELEKTRA J PAPADOPOULOS
01/25/2021 04:14:57 PM