CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214902Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 24, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 214902
Product Name and Strength:	Twyneo (benzoyl peroxide and tretinoin) cream, 3%/0.1%
Applicant/Sponsor Name:	Sol-Gel Technologies Ltd.
OSE RCM #:	2020-2073-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 21, 2021 for Twyneo. Division of Dermatology and Dentistry (DDD) requested that we review the revised container label and carton labeling for Twyneo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel M. Label and Labeling Review for Twyneo (NDA 214902). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 01. RCM No.: 2020-2073.

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/s/

MADHURI R PATEL
06/24/2021 08:41:28 AM

SEVAN H KOLEJIAN
06/24/2021 08:42:58 AM

Clinical Inspection Summary

Date	6/15/2021
From	Christian Shenouda, MD Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Shera Schreiber, M.D., Medical Officer, David Kettl, MD, Clinical Team Leader Strother Dixon, Regulatory Program Manager Division of Dermatology and Dentistry (DDD)
NDA	NDA 214902
Applicant	Sol-Gel Technologies Ltd.
Drug	Benzoyl peroxide and tretinoin cream, 3%/1% (eBPO)
NME	No
Proposed Indications	Treatment of acne vulgaris (acne) in patients nine years of age and older.
Consultation Request Date	November 3, 2020
Summary Goal Date	July 1, 2021
Action Goal Date	July 16, 2021
PDUFA Date	August 1, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator inspections were requested of the pivotal Protocol SGT-65-05: Drs. Lesley Clark-Loeser and Ann Reed. The former was done via onsite inspection, and the latter was conducted via a Remote Regulatory Assessment (RRA) due to the limitations caused by the COVID-19 pandemic. Based on the results of this inspection and RRA, Protocol SGT-65-05 appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

Of note, the initial consult included inspections of Drs. Bruce Katz and Zoe Draelos (both for the pivotal Protocol SGT-65-04). However, the COVID-19 global pandemic has significantly limited OSI's ability to conduct on-site Good Clinical Practice (GCP) inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for additional planned inspections in support of NDA 214902 were reevaluated based on the completed inspection/remote regulatory assessment listed above. Following discussions between OSI and OND, a decision was made that assessment of the application could proceed without these two GCP inspections. However, this means that at this time, we are unable to determine the reliability of the data for Protocol SGT-65-04.

II. BACKGROUND

Benzoyl peroxide (BPO) and tretinoin (ATRA) are two active ingredients with different pharmacological actions that are commonly used for the treatment of acne. Topical retinoids are keratinization inhibitors and benzoyl peroxide is a commonly used topical antibacterial

agent that has been found to be lethal to *P. acnes* as well as other bacteria that may reside on the skin. The investigational product is an encapsulated benzoyl peroxide (E-BPO) and encapsulated tretinoin (E-ATRA) cream, 3%/0.1% (E-BPO/E-ATRA cream, 3%/0.1%) to be used once daily. The sponsor has submitted NDA 214902 to support the use of this investigational product in the treatment of acne vulgaris (acne) in patients nine years of age and older.

Protocols SGT-65-04 and SGT-65-05

Both pivotal studies shared the same clinical design, including inclusion/exclusion criteria, endpoints, and timing of assessments.

Protocol SGT-65-04

Title: "A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris"

Subjects: 424 subjects from 32 U.S sites

Study Initiation and Completion Dates: 12/21/2018 to 20/31/2019

Protocol SGT-65-05

Title: "A Phase 3 Multi-Center, Double-Blind, Randomized, Vehicle-Controlled Study of S6G5T-3 in the Treatment of Acne Vulgaris"

Subjects: 434 subjects from 31 sites U.S. sites

Initiation and Completion Dates: 12/14/2018 to 10/23/2019

Summary

These two studies were multi-center, double-blind, randomized, vehicle-controlled, parallel-group pivotal studies. Subjects were randomized in a 2:1 ratio to receive either E-BPO/ATRA cream, 3%/0.1% or vehicle. Subjects applied the assigned treatment once daily for 12 weeks and used a "pea-size" amount for each area of the face (chin, left cheek, right cheek, nose, left forehead, and right forehead). Following a screening visit, subjects were seen at baseline and then evaluated at Weeks 2, 4, 8 and 12.

The co-*primary efficacy endpoints* were the mean absolute change in lesion count, including inflammatory and non-inflammatory lesions, from baseline to Week 12 and the proportion of subjects achieving treatment success in Investigator Global Assessment (IGA) from baseline to week 12.

Rationale for Site Selection

The following clinical investigator (CI) site was chosen for inspection using a risk-based approach, including number of enrolled subjects, site efficacy, protocol deviations, and prior inspectional history.

III. INSPECTION RESULTS

1. **Lesley Clark-Loeser**
   8399 West Oakland Park Blvd.
   Sunrise, FL 33351
   Site # 505
   Remote Regulatory Assessment Dates: 5/18/21 (conducted by two ORA investigators)

A Remote Regulatory Assessment (RRA) of this site for Protocol SGT-65-05 was performed in lieu of an onsite inspection. ORA utilized ZoomGov and an online platform (Box.com) to exchange information and communicate with the clinical investigator site.

There were 28 subjects screened at the site, 24 were randomized, and 20 subjects completing the trial. There were 4 discontinuations as follows: Subject # (b) (6) declined further participation after Day 60, and Subject # (b) (6) was lost to follow up (both were assigned to the active product). Subject # (b) (6) was lost to follow up, and Subject # (b) (6) reported work schedule conflicts (both were assigned to the vehicle group).

The RRA included an audit of the available records and study procedures for the 24 randomized subjects which includes: informed consents, protocols, Clinical Investigator's oversight of the study, site training activities and implementation of study procedures, subjects' eligibility, Sub-Investigator's direct involvement, IRB submissions and correspondence, adherence to and documentation of protocol required visits, maintenance of blind, primary efficacy endpoint data, source documents and case report forms, Form FDA 1572s, schedule of assessments, subject discontinuations, adverse and serious adverse event reporting, clinical source data, concomitant medications, protocol deviations, study test article accountability, and sponsor monitoring activities. No concerns were noted.

The co-primary efficacy endpoint data was reviewed for 100% of randomized subjects. There were no discrepancies noted when source data for these endpoints was compared to the sponsor's data line listings. There were no SAEs reported at this site, and no evidence of under-reporting of AEs was noted during the RRA.

2. **Ann Reed**
   1001 NW 13th Street
   Boca Raton, FL 33486
   Site #521
   Inspection Dates: 5/24/2021 – 5/26/2021

At this site for Protocol SGT-65-05, there were 24 subjects screened, 23 randomized, and 20 subjects completed the study. Of the 3 subjects who did not complete the study, Subject # (b) (6) was lost to follow up and Subject # (b) (6) reported work schedule conflicts (both were assigned to the active product); Subject # (b) (6) (assigned to the vehicle group) withdrew due to a planned move abroad.

Records evaluated during the inspection included, but were not limited to, subject medical records and worksheets, informed consent forms, investigational test article accountability records, institutional review board (IRB) approvals, correspondence between the IRB and the clinical investigator (CI), Case Reports Forms (CRFs), and site monitoring correspondence between the monitor and CI. No concerns were noted.

The co-primary efficacy endpoints were verified for all randomized subjects. There were no discrepancies noted when source data for these endpoints was compared to sponsor's data line listings. Although not a discrepancy, during the Screening Visit for Subject # (b) (6), there was no score indicated on the Investigator Global Assessment (IGA), but lesion counts were documented. There were no SAEs reported at this site, and no evidence of under-reporting of adverse events was noted during the inspection.

{See appended electronic signature page}

Christian N. Shenouda, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader,
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CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm. NDA 214902
DDD Review Division /Division Director/Kendall Marcus
DDD Review Division /Project Manager/ Strother Dixon
DDD Review Division/CTL/David Kettl
DDD Review Division/MO/ Shera Schreiber
OOSI/DCCE/ Division Director/ David Burrow
OSI/DCCE/Branch Chief/ Kassa Ayalew
OSI/DCCE/Team Leader/ Phillip Kronstein
OSI/DCCE/GCP Reviewer/ Christian Shenouda
OSI/ GCP Program Analysts/ Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

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06/16/2021 05:13:57 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 25, 2021
To:	H. F. Van Horn III Regulatory Health Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TWYNEO (tretinoin and benzoyl peroxide)
Dosage Form and Route:	cream, for topical use
Application Type/Number:	NDA 214902
Applicant:	Sol-Gel Technologies Ltd.

1 INTRODUCTION

On October 1, 2020, Sol-Gel Technologies Ltd. submitted for the Agency's review an original New Drug Application (NDA) 214902 for TWYNEO (tretinoin and benzoyl peroxide) cream. The proposed indication for TWYNEO (tretinoin and benzoyl peroxide) is for the topical treatment of acne vulgaris in patients 9 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on October 23, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TWYNEO (tretinoin and benzoyl peroxide) cream.

2 MATERIAL REVIEWED

- Draft TWYNEO (tretinoin and benzoyl peroxide) cream PPI received on October 1, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2021.
- Draft TWYNEO (tretinoin and benzoyl peroxide) cream Prescribing Information (PI) received on October 1, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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LAURIE J BUONACCORSI
05/25/2021 08:41:56 AM

BARBARA A FULLER
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LASHAWN M GRIFFITHS
05/25/2021 08:53:18 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 19, 2021

To: Shera Schreiber, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Roselyn Epps, MD, Clinical Reviewer DDD
David Kettl, MD, Clinical Team Leader, DDD
H.F. Van Horn, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for TWYNEO® (tretinoin and benzoyl peroxide) cream, for topical use

NDA: 214902

In response to DDD's consult request dated October 23, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for TWYNEO® (tretinoin and benzoyl peroxide) cream, for topical use (Twyneo).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on May 14, 2021 and we have no comments.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 7, 2021 and we have no comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 1, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 214902
Product Name, Dosage Form, and Strength:	Twyneo (benzoyl peroxide and tretinoin) cream, 3%/0.1%
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sol-Gel Technologies Ltd.
FDA Received Date:	October 1, 2020 and December 21, 2020
OSE RCM #:	2020-2073
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for Twyneo (benzoyl peroxide and tretinoin) cream, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Twyneo prescribing information (PI), Patient Package Insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Patient Package Insert (PPI), container labels and carton labeling. We find the PI and PPI acceptable from a medication error perspective. We note the container labels and carton labeling can be improved for consistency, to facilitate product identification and to prevent drug selection and deteriorated drug errors.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Prescribing Information (PI) and Patient Package Insert (PPI) are acceptable from a medication error perspective. However, the container labels and carton labeling can be improved for consistency, to facilitate product identification and to prevent drug selection and deteriorated drug errors.

4.1 RECOMMENDATIONS FOR THE DIVISION OF DERMATOLOGY AND DENISTRY

A. General Comments

a. We note the use of "[redacted] (b) (4)" in the established name throughout the labels and labeling. We defer to OPQ to determine the establish name for this

product. The OPQ determined establish name should be used throughout the label and labeling. Thus,, if "(b) (4)" is removed from the Prescribing Information and Patient Package Insert, we recommend it also be removed from the container labels and carton labeling.

4.2 RECOMMENDATIONS FOR SOL-GEL TECHNOLOGIES LTD.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. Remove "(b) (4)" from the established name.
2. As currently presented the placement of the graphic "  " in front of the first letter in the proprietary name is prominent. Placement of the graphic in front of the first letter in the proprietary name competes with readability of the proprietary name, which may lead to misinterpretation of the proprietary name as (b) (4). Thus, we recommend moving or removing this graphic.
3. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4) to read "Recommended Dosage: See prescribing information."
4. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
5. Revise the statements "Date received from pharmacy: / / . Discard unused (b) (4) 12 weeks after the date of dispensing." to bold font under storage information on the container labels and carton labeling to increase prominence of this important statement.

B. Container Labels

1. Add the route of administration statement "For Topical Use Only" on the principal display panel (PDP), as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Twyneo received on December 21, 2020 from Sol-Gel Technologies Ltd., and the listed drug (LD).

Table 2. Relevant Product Information for Twyneo and the Listed Drug		
Product Name	Twyneo	Retin-A cream (NDA 017340)[a]
Initial Approval Date	N/A	January 26, 1973
Active Ingredient	benzoyl peroxide and tretinoin	tretinoin
Indication	topical treatment of acne vulgaris in patients nine years of age and older	topical application in the treatment of acne vulgaris
Route of Administration	topical	topical
Dosage Form	cream	cream
Strength	3%/0.1%	0.1%
Dose and Frequency	apply a thin layer to the affected areas once daily on clean and dry skin. Avoid contact with the eyes, lips and mucous membranes.	applied once a day, before retiring, to the skin where acne lesions appear, using enough to cover the entire affected area lightly
How Supplied	50-gram pump NDC 79167-301-50, 6-gram pump (professional sample)	RETIN-A Cream NDC Code / RETIN-A Strength/ Form / RETIN-A Qty. 0187-5160-20 / 0.025% Cream / 20 g 0187-5160-45 / 0.025% Cream / 45 g 0187-5162-20 / 0.05% Cream / 20 g 0187-5162-45 / 0.05% Cream / 45 g 0187-5164-20 / 0.1% Cream / 20 g 0187-5164-45 / 0.1% Cream / 45 g
Storage	• Prior to Dispensing: Store TWYNEO Cream	Store below 80°F

[a] Retin-A [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 FEB 24. Available from: https://www.accessdata.fda.gov/spl/data/c52c18fa-2264-4751-bd01-c54ca07ccc9f/c52c18fa-2264-4751-bd01-c54ca07ccc9f.xml.

	between 2ºC to 8°C (36°F to 46°F) until dispensed to the patient. • (b) (4) store TWYNEO Cream at room temperature 20°C to 25°C (68°F to 77°F) for 12 weeks. Discard after 12 weeks. • Do not freeze	
Container Closure	pump	tube

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Twyneo labels and labeling submitted by Sol-Gel Technologies Ltd..

- Container Label received on October 1, 2020
- Carton Labeling received on October 1, 2020
- Professional Sample Container Label received on October 1, 2020
- Prescribing Information and Patient Package Insert (Images not shown) received on December 21, 2020, available from \\CDSESUB1\evsprod\nda214902\0006\m1\us\114-labeling\draft\labeling\pdf-sn0006.pdf

G.2 Label and Labeling Images

Container Labels

(b) (4)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: February 1, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: H. F. Van Horn, RPM
DDD

Subject: IRT Consult to NDA-214902 (SDN001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 11/3/2020 regarding the sponsor's request for substitution of thorough QT study. We reviewed the following materials:

- Sponsor's request for substitution of a thorough QT study (SN0001; link); and
- Sponsor's proposed product label (SN0001; link).

1 IRT Responses

The Sponsor's proposed rationale for not conducting the thorough-QT study appears reasonable. In addition, the submitted safety ECG data do not indicate any unexpected or important effects of Twyneo cream on the QTc interval at the proposed therapeutic dose.

The applicant did not propose QT labeling language in Section 12.2 (Cardiac Electrophysiology, link). For 505(b)(2) regulatory pathway, a standalone thorough QT study is generally not required if the steady-state exposures (Cmax) of the drug from the to-be marketed product at the highest therapeutic dose are not significantly higher than those for marketed product (reference listed drug) and the QT relevant sections of listed drug can be extended to your product label (ICH E14, section 1.3).

Thus, we agree with the applicant's labeling proposal because it is consistent with our labeling practices for which a dedicated QT study is generally not needed (see below for each component) and when one has not been conducted.

Tretinoin

The sponsor's maximal use systemic exposure pharmacokinetic study (Study # SGT-65-03) indicates that the exposures (Cmax) of active components and its relevant metabolites (4-keto 13-cis RA, 13-cis RA) following maximal use conditions (once daily for 14 days) were similar between the approved (listed drug; Retin-A Cream, 0.1%) product and test product.

Benzoyl Peroxide

Benzoyl peroxide is a generally recognized as safe and effective (GRASE) active ingredient and is permitted active ingredient (in concentrations of 2.5 to 10%) in OTC topical acne drug products.

2 Background

2.1 Product Information

Sol-Gel Technologies, Ltd. is developing combination of encapsulated benzoyl peroxide and encapsulated tretinoin for the topical treatment of acne vulgaris (age ≥ 9 years). Benzoyl peroxide (MW: 242.23) is an oxidizing agent with bactericidal, keratolytic and anti-inflammatory effects. The sponsor states that the topical tretinoin (MW: 300.44) treatment decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation.

The product is formulated as a cream formulation (Twyneo) containing 3% encapsulated benzoyl peroxide (30 mg/gm) and 0.1% encapsulated tretinoin (1 mg/gm) for local application. The sponsor proposed to apply the cream as a thin layer to the affected areas once daily.

Previously, benzoyl peroxide combinations (up to 5% with other topical agents such as erythromycin, clindamycin, adapalene etc.) are approved for the topical treatment of acne vulgaris. The sponsor highlights that following topical application of benzoyl peroxide results in low systemic exposures and absorbed fraction is converted to benzoic acid and eliminated in the urine. However, the sponsor's clinical development plan did not include any PK specific studies for benzoyl peroxide component.

Benzoyl Peroxide

Pharmacokinetic and metabolism information from the literature also supports the cardiovascular safety of benzoyl peroxide. Benzoyl peroxide is converted in the skin to benzoic acid and hydrogen peroxide. The benzoic acid metabolite is absorbed systemically and is rapidly excreted in urine.

Approximately 5% of topically applied benzoyl peroxide is absorbed through the skin (Nacht et al. 1981). In vitro studies have demonstrated that permeation is both concentration- and time-dependent (Fares et al. 1996), but benzoyl peroxide does not penetrate below the upper layers of the human skin.

Benzoic acid enters the circulation via the blood vessels of the skin and is excreted in the urine as either unchanged benzoate or conjugated with glycine (Life Science Research Office, 1980). In rhesus monkeys, topically applied benzoyl peroxide is excreted in the form of unconjugated benzoic acid with no hippuric acid formed. These experiments in monkeys have shown that no systemic toxic effects were detected due to the lack of accumulation of the drug in body tissues or organs (Gross 2007).

Previously, tretinoin is also approved for the treatment of acne vulgaris and it is available as 0.1% topical cream (Retin-A, NDA-017340 by Valeant, Jan-1973) and other topical formulations including liquid and gel.

The peak concentrations of 1.2 ng/mL of tretinoin (Tmax: NA; Half-life: NA) were observed at steady-state under maximal use condition (adult; Day 14; Study # SGT-65-03). No significant accumulation is expected at steady-state with the proposed therapeutic dose. Similarly, the peak concentrations are expected to be similar across studied age groups (children vs adolescence vs adults; Study # SGT-65-03).

In addition, the sponsor conducted the maximal use systemic exposure (MUSE) pharmacokinetic study (Study # SGT-65-03) evaluating the exposure to tretinoin and its metabolites in subjects with moderate to severe acne under maximal use conditions following single and repeated once daily applications of E-BPO/E-ATRA Cream Versus Retin-A Cream (0.1%, a marketed topical tretinoin product). The sponsor claims that the results (the sum of endogenous Vitamin A-related material plus material from the drug formulation) of the MUSE study established a bridge to support clinical pharmacology of tretinoin in E-BPO/E-ATRA Cream.

Tretinoin

Tretinoin, retinol and isotretinoin are among the metabolites of Vitamin A and occur endogenously. After topical application of 2 grams/day of 0.025% tretinoin gel to four normal male subjects for 14 days, there was a non-significant increase of 13% in tretinoin plasma concentrations above endogenous pre-dose levels, which was less than the statistically significant diurnal variations (Buchan et al. 1994). Because of the diurnal, endogenous nature of tretinoin and its dependency on diet, it would be extremely difficult, if not impossible, to design a clinical study to test the effects of topical tretinoin on QT/QTc prolongation.

In A Phase 1b, Multicenter, Open-Label, Parallel-Group, Maximal Use Systemic Exposure (MUSE) Study to Evaluate the Pharmacokinetics, Safety and Tolerability of E-BPO/E-ATRA Cream Compared to Retin-A® 0.1% in Subjects with Moderate to Severe Acne Vulgaris (Study CSR SGT-65-03), PK parameters of tretinoin and its metabolites (all-trans 4-keto retinoic acid, 9-cis retinoic acid, 4-keto 13-cis retinoic acid, and 13-cis retinoic acid) were determined after once a day topical application for 14 days of E-BPO/E-ATRA Cream versus the Listed Drug (Retin-A 0.1% Cream) for subjects ages 12 and up.

In this study, the Day 2 and Day 14 plasma concentrations (trough) of tretinoin and its metabolites were also determined after a once a day application of E-BPO/E-ATRA Cream for subjects ages 9 and up. The study results demonstrate that overall, the assessment of the relative bioavailability using the unpaired t-test or ANOVA different age groups, the PK parameters (Cmax and AUC) were not significantly different when comparing E-BPO/E-ATRA Cream with Retin-A® as shown in Figures 5 through 15 provided in Study SGT-65-03 ($p > 0.05$). Based on the 90% confidence interval (CI) approach, many of the values of the confidence interval for Cmax and AUC of tretinoin and the metabolites in adults and adolescents demonstrated equivalence for E-BPO/E-ATRA Cream and Retin-A®, but not all.

There were no appreciable differences in mean changes in heart rate after 14 days of treatment. Over this same period, the mean changes in RR interval, PR interval, QRS duration, QT interval, and QTcF (QT interval using the Fridericia's correction formula) interval were comparable between the treatment groups. Both the Investigator's and Cardiologist's evaluation noted that

there was no major shift in overall interpretation of the ECG from Baseline to Day 17. Most subjects had normal ECG interpretation at both time points, except for 2 subjects from the Retin-A Cream, 0.1% group who had an abnormal ECG after a normal screening ECG was recorded at Baseline. These results were not clinically significant.

Overall, in the cases where the bioequivalence criteria were not met, the exposure following the application of E-BPO/E-ATRA Cream was lower than the exposure following the application of Retin-A®. Furthermore, the study demonstrated that based on the assessment of the relative bioavailability using the unpaired t-test or ANOVA among the different age groups, the PK parameters (Cmax and AUC) were not significantly different following E-BPO/E-ATRA Cream or Retin-A® with the exception for a significant difference observed in exposure between adults and adolescents treated with Retin-A® for 14 days.

Table: Clinical Pharmacology Studies Conducted with E-BPO/E-ATRA Cream, 3%/0.1% - Summary of the MUSE Pharmacokinetic Study

Study ID (Study Phase) Study Period	Primary Objective(s) of the Study	Study Design	Dosing Regimen/ Treatment Duration	Subjects[a] M/F (Age Groups) Centers (Location)	E-BPO/E-ATRA Cream, 3%/0.1%			Retin-A Cream, 0.1%	
					Children 9 to < 12 years	Adolescents 12 to < 18 years	Adults ≥ 18 years	Adolescents 12 to < 18 years	Adults ≥ 18 years
SGT-65-03 (Phase 1b) Study Period 27 Jun 2019 to 04 Nov 2019	To determine the tretinoin and metabolite plasma concentrations and systemic exposure following single and repeat applications of E-BPO/E-ATRA Cream, 3%/0.1%[b] and Retin-A Cream, 0.1%	Multicenter, open-label, randomized, parallel-group, active-controlled, maximal use systemic exposure study	Once daily for 2 weeks (14 days)	62 subjects with acne 32M/30F E-BPO/ E-ATRA Cream, 3%/0.1% (35 total including 12 adults, 15 adolescents, and 8 children[c]) Retin-A Cream, 0.1% (27 total including 12 adults and 15 adolescents) 2 (US) Study Centers	Predose Tretinoin (ng/mL)				
					0.928 ± 0.307	0.958 ± 0.210	1.12 ± 0.200	0.907 ± 0.193	0.998 ± 0.229
					Day 1 C_{max} Tretinoin[d] (ng/mL)				
					1.09 ± 0.156	1.06 ± 0.199	1.22 ± 0.207	1.10 ± 0.161	1.18 ± 0.188
					Day 1 AUC_{0-24} Tretinoin[d] (h•ng/mL)				
					21.3 ± 4.27	22.2 ± 4.69	25.0 ± 4.76	21.3 ± 2.93	24.0 ± 4.21
					Day 14 C_{max} Tretinoin[d] (ng/mL)				
					1.07 ± 0.169	1.11 ± 0.199	1.19 ± 0.221	1.07 ± 0.150	1.31 ± 0.198
					Day 14 AUC_{0-24} Tretinoin[d] (h•ng/mL) -				
					21.3 ± 3.00	23.1 ± 4.21	24.2 ± 4.23	21.3 ± 3.97	25.0 ± 4.04

MUSE: maximal use systemic exposure study
$AUC_{(0-24)}$: area under the plasma concentration time curve from time of administration to 24 hours, calculated by linear trapezoidal rule
C_{max}: maximum (observed) plasma concentration
a The demographics are based on the safety population.
b The study drug was referred to as either S6G5T-3 or E-BPO/E-ATRA Cream, 3%/0.1% . These terms are synonymous.
c In children (9 to < 12 years), PK parameters were determined after the first and following 14 days of once daily applications of E-BPO/ BPO/E-ATRA Cream only.
d When the PK parameters for the metabolites 4-keto 13-cis retinoic acid and 13-cis retinoic acid were analyzed, comparable results following a single and 14 days of topical applications of E-BPO/E-ATRA Cream and Retin-A Cream, 0.1% among all age groups were observed. PK analyses revealed that the 4-keto 13-cis retinoic acid PK exposure was approximately 2 times higher than that of the parent compound, and the 13-cis retinoic acid PK exposure was similar to that of the parent compound following treatment with E-BPO/E-ATRA Cream or Retin-A, 0.1%. Note: None of the plasma samples had measurable concentrations of 9-cis retinoic acid or all trans 4-keto retinoic acid except for 3 subjects who had ≤ 2 quantifiable PK samples for the metabolite all-trans 4-keto retinoic acid; hence no PK analysis was performed for the two metabolites.

No formal clinical drug interaction studies or special population (renal impairment or hepatic impairment) have been conducted by the sponsor.

2.2 Sponsor's Position related to the Question

The sponsor claims that the both components of the cream (i.e., benzoyl peroxide and tretinoin) are previously approved and their exposures (Cmax,ss) at the highest therapeutic dose are not expected to be significantly higher than those for marketed product (reference listed drug).

Sol-Gel asserts that, based on the documented clinical history of topical use of both benzoyl peroxide and tretinoin in humans, with no noted cardiovascular safety signals, there is negligible risk of any cardiac adverse events, including QT prolongation, after topical administration of E-BPO/E-ATRA Cream for the treatment of acne.

Benzoyl peroxide (dose range from 2.5 to 10%) is a generally recognized as safe and effective (GRASE) and is an active ingredient that has been on the market for decades for the over-the-counter (OTC) topical treatment of acne. From the final benzoyl peroxide OTC monograph, the safety of benzoyl peroxide was established after a review of studies on genotoxicity, tumor promotion with chemical/ultraviolet initiation, animal carcinogenicity, photocarcinogenicity, as well as related epidemiological data.

Topical tretinoin as a treatment for acne has also been on the market for decades and is available in a wide range of dosages up to 1%. Furthermore, tretinoin is a naturally occurring metabolite of Vitamin A, and is present endogenously.

2.3 Nonclinical Cardiac Safety

Refer to the sponsor's non-clinical overview (m2.4).

A 13-week dermal toxicity study followed by a 4-week recovery period using male and female Göttingen minipigs (n = 6/sex/group) was conducted using E-BPO/E-ATRA Cream, 6%/0.1% (Study No. 1256-012). Additional groups included an untreated control, placebo control, E-ATRA, 1.0% alone and E-BPO, 6% alone. The study included a toxicokinetic evaluation that utilized validated bioanalytical methods to detect benzoyl peroxide absorption (measured as benzoic acid) and tretinoin absorption (measured as all-trans 4-keto-retinoic acid, 4-keto-13-cis retinoic acid, 13-cis-retinoic acid and all-trans retinoic acid). The concentrations of benzoic acid, 13-cis-retinoic acid, 4-keto-13-cis-retinoic acid, all-trans retinoic acid and all-trans-4-keto retinoic acid were below the lower limits of quantitation in most samples. There were insufficient measurable concentrations to be able to calculate toxicokinetic parameters. The lower limit of quantitation was 1 ng/mL for each of the retinoic acid congeners and 48.2 ng/mL for benzoic acid (reaction by-product/metabolite of benzoyl peroxide). It was concluded that there was negligible systemic exposure to benzoic acid and retinoic acid congeners after twice daily application of 15 mg/kg benzoyl peroxide/0.25 mg/kg tretinoin in the E-BPO/E-ATRA Cream. Due to the lack of systemic exposure, no further pharmacokinetic or metabolism studies were conducted.

In the 7-day non-GLP dermal tolerability study [(b) (4) Study No. 1161-001 (cross reference is made to NDA (b) (4) Module 4.2.3.2)], one male and one female Gottingen minipig were administered E-BPO Cream once per day on four separate 25 cm2 sites at concentrations of 0%, 5%, 7% and 10%. No irritation, clinical signs, body weight or gross pathology changes were noted at any concentration. A GLP-compliant 13-week dermal toxicity study [(b) (4) Study No. 1161-002 (cross reference is made to NDA (b) (4) Module 4.2.3.2)] was conducted in Gottingen minipigs (n = 4/sex/group) using four groups: untreated control, Vehicle (placebo), E-BPO Cream, 5% (clinical concentration), and E-BPO Cream, 10% (maximum feasible concentration). Materials were applied once per day to a 200 cm2 application site (10 x 20 cm) at a rate of 2 mg/cm2 (or 400 mg of formulation per application) and standard toxicological parameters were assessed, including toxicokinetics. Parameters evaluated included clinical signs, dermal irritation, body weight, ophthalmoscopy, electrocardiography, clinical pathology, gross pathology, organ weights and histopathology. No evidence of systemic toxicity was observed at any dose and mild irritation was reported in some animals treated with the 5% and 10% formulations, which resolved after approximately 5 weeks. No increase in plasma levels of benzoic acid above endogenous or background levels was observed with either the 5% or 10% formulations. The no-observed-adverse-effect-level (NOAEL) was 10%.

2.4 Clinical Cardiac Safety

Refer to the sponsor's summary of clinical safety (m2.7.4).

In the Phase 2 study (SGT-65-02), the safety and efficacy of E-BPO/E-ATRA Cream was established in a 12-Week dose range study vs. single ingredient formulations (E-BPO Cream, 3%; E-ATRA Cream, 0.1%; E-ATRA Cream, 0.05%) and Vehicle Cream.

In this study, blood tests and electrocardiogram (ECG) monitoring were performed. There were no apparent differences in mean changes from baseline to Week 8 and 12 in any of the hematological and clinical chemistry test results among the six treatment groups. There were no clinically significant abnormalities in ECGs in the study.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov.

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/

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