CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215272Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 104601

MEETING MINUTES

Dermavant Science GmbH
Attention: Stacie M. Winter
Director, Global Regulatory Affairs
3300 Paramount Parkway, Suite 150
Morrisville, NC 27560

Dear Ms. Winter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tapinarof cream, 1%.

We also refer to the telecon between representatives of your firm and the FDA on December 21, 2020. The purpose of the meeting was to discuss the content and format for future NDA submission.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Barbara Gould, Chief, Project Management Staff, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Dermavant Science GmbH's Focused Agenda

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: December 21, 2020, 1:30 p.m. – 2:30 p.m.
Meeting Location: Teleconference

Application Number: IND 104601
Product Name: tapinarof cream, 1%

Proposed Indication: For the treatment of plaque psoriasis

Sponsor Name: Dermavant Sciences GmbH
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Barbara Gould

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
David Kettl, MD, FAAP, Clinical Team Leader, DDD
Gary Chiang, MD, Clinical Reviewer, DDD
Sherry Zhou, MD, MSc, Clinical Reviewer, DDD
Barbara Hill, PhD, Pharmacology Supervisor, Division of Pharmacology Toxicology for Immunology and Inflammation (DPT – II)
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Matthew Guerra, PhD, Biometrics Reviewer, DB III
Hamid Shafiei, PhD, Quality Assessment Lead, DNDP II, NDPB V
Jennifer Sykora, PhD, Quality Microbiology Assessor, DMAII/MAB4
Koushik Paul, PhD, Quality Microbiology Assessor, DMAII/MAB4
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Cindy (Liping) Pan, PhD, Senior Staff Fellow, DIIP
Jing (Julie) Ju, PhD, Clinical Outcomes Assessment Reviewer, Division of Clinical Outcome Assessments
(Phil) Phuc Nguyen, MD, Medical Officer, Division of Clinical Compliance Evaluation (DCCE)
Barbara Gould, MBAHCM, Chief, Project Management Staff, Division of Regulatory Operations for Dermatology and Dentistry (DRO – DD)

SPONSOR ATTENDEES

Phil Brown, MD, JD, Chief Medical Officer

Scott Caveney, MD, PhD, Senior Medical Director and Head of PV
Elaine Clark Vice President, Regulatory Affairs and QA
Alan Colborn, PhD Director, Pharmaceutical Development Analytical
Piyush Jain, PhD Director, CMC Product Development
Kimberly McHale, PhD Director, Nonclinical Science
Steve Piscitelli, PharmD Vice President, Clinical Pharmacology & Biometrics
Matt Somerville, MS Director, Biostatistics
Stacie Winter Director, Global Regulatory Affairs

1.0 BACKGROUND

Purpose of meeting:

The purpose of this Pre-NDA meeting is to discuss the content and format of NDA submission targeted for 2nd quarter 2021 for tapinarof cream, 1% for the treatment of plaque psoriasis.

CORONAVIRUS 19 (COVID-19) Clinical Trial Guidance

During the COVID-19 pandemic, ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of trial participants, and modify study conduct accordingly. It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them and that the Agency is appropriately informed of these changes. Refer to the FDA guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Document Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

2.0 DISCUSSION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor affirmed that there will be no submission of additional information within the first 30 after receipt of the NDA.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

Post Meeting:
Following the December 21, 2020 meeting an email was received from Stacie Winter with the following quality question:

Post Meeting CMC Question:
Reference is made to lines 163 to 165 of the preliminary comments, where the Agency stated that 12-month stability data for the 2 gram physical sample could be provided during this timeframe. If the Agency is agreeable, we would like to submit this information withing 30 days of the original submission date.

FDA Response to Post Meeting Question:
The sponsor's request to submit additional stability data within 30 days from original date of submission of the NDA is acceptable.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
    - 12-month stability data for the 2-gram physical sample.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA NUMBER: LATE COMPONENT - QUALITY

2.1. Regulatory

Question 14:
A summary of the development program conducted in support of an NDA for tapinarof cream, 1% is provided in Section 15.4 of this briefing package. A proposed Target Product Profile (TPP) summarizing the desired labeling resulting from this development program is also provided in Appendix 3.
Does the Agency agree that the development program supports the proposed NDA submission?

FDA Response to Question 14:
You have conducted two identical Phase 3 studies of 12 weeks duration, a series of Phase 1 dermal safety studies, a Phase 2 maximal use pharmacokinetics (PK) study, and an ongoing Phase 3 open-label long-term extension study to evaluate safety for an additional 40 weeks of exposure. In addition, you have submitted a pediatric study plan with the study protocol currently under review. As of the October 25, 2020, you suggested approximately 430 subjects have been exposed to the to-be-marketed formulation of tapinarof who have been followed for at least 6 months and approximately 177 exposed subjects who have been followed for 1 year.

Your proposed clinical development program appears to support filing for an NDA. Your TPP will be considered as part of the NDA review.

Question 15:
A draft Table of Contents for the proposed NDA is presented in Appendix 4 of this briefing package.

Does the Agency agree with the proposed format and content of the submission?

FDA Response to Question 15:
Your proposed e-CTD format and content outlined in *Appendix 4* appears reasonable for an NDA.

Question 16:
The Applicant proposes to provide the Agency with all references cited in Module 2 of the proposed NDA. All other references cited in Module 1, 3, 4, and 5 as well as references cited in the CSRs will be provided upon request.

Does the Agency agree?

FDA Response to Question 16:
Your NDA submission should be complete at filing. If you have references to be provided, place them in the Appendices of the application. This way, if the reviewer's need the references, they are available without having to request them.

Question 17:
Providing that no safety signals or serious risks are detected after completion of the Phase 3 program, the Applicant considers that post-marketing safety surveillance of tapinarof cream, 1% can be accomplished according to 21 CFR 314.80 in combination with the patient package insert, and does not believe a formal REMS program will be required.

Does the Agency agree?

FDA Response to Question 17:
It is premature to determine whether a REMS program will be required for tapinarof 1% cream for the topical treatment of plaque psoriasis, although it appears unlikely given the information in the briefing document.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 1:
Tapinarof cream, 1% will be packaged into two tube sizes, a 60-g (b) (4) laminate (b) (4) tube as the primary commercial pack and a 2-g aluminum (Al) tube as the physician sample. At time of NDA submission, the applicant anticipates having 24

months of real-time stability data on the 60-g primary commercial pack, but only nine months of real time stability data available on the 2-g physician sample. Based on the excellent stability of tapinarof drug substance and tapinarof cream, 1% in 60-g (b) (4) tubes, along with pharmaceutical development work and stability of tapinarof cream, 1% in 2-g Al tubes, the applicant believes that nine months of real-time data and six months of accelerated data on the 2-g Al tubes is sufficient for submission in the NDA to support an extrapolated shelf-life of (b) (4) months for the physician sample.

Does the Agency agree that the applicant can submit the NDA with nine months real-time stability data, six months of accelerated stability data, and statistical analysis to support an extrapolated shelf-life for the physician sample packaged in 2-g aluminum tubes?

FDA Response to Question 1:
It is acceptable to submit your NDA with nine months of long-tern stability data from 2-g packaging configuration intended for use as the physician samples. However, you should submit additional 3 long-term stability data (total 12 months long-term) within 30 days from the original date of submission of your application.

Question 2:
As described above, at the time of NDA submission, 24 months of real-time stability data will be available for tapinarof cream, 1% in the primary commercial pack (60-gram (b) (4) tubes). Thirty-six months of stability data will become available during NDA review. The applicant would like to amend the NDA early during review with data from the 36-month stability timepoint to support the proposed shelf-life.

Does the Agency agree to allow the applicant to submit stability data from the 36-month timepoint for tapinarof cream, 1% packaged in 60-g (b) (4) tubes no later than at the time of the (b) (4) to the NDA, and that these data can be considered in support of the proposed shelf-life?

FDA Response to Question 2:
No. Any additional stability data that is intended for use in the determination of the expiration dating period (shelf-life) of the drug product should submitted to the application within 30 day from the original date of submission.

Question 3:
The Applicant has developed and validated an in vitro release test (IVRT) to support the NDA. The IVRT method was developed by (b) (4) using a modified Franz Cell system with analysis by LC with UV detection. This method was developed and validated following the guidance provided by the FDA Biopharmaceutics Review Team on August 22, 2019, and consistent with USP <1724>. The specification acceptance criteria range will be based on data generated for pivotal clinical drug product batches and primary registration batches.

Does the Agency have any comments on the in vitro release test (IVRT) development, proposed method, validation data, and/or proposed approach to establishing the acceptance criteria in support of the NDA?

FDA Response to Question 3:
We acknowledged that you have submitted method development and method validation reports for your IVRT method in Appendix 5. We also acknowledged that the typical method parameters are provided in Table 6. However, we could not access the method development/validation reports because it appears that they are password protected. Generally, we make final determination regarding the acceptability of IVRT method and the proposed acceptance criterion during the NDA review. However, we may provide specific feedback regarding IVRT method during IND review, if requested.

Although the method parameters you have evaluated (Table 6) appear acceptable, we could not find any proposed acceptance criterion. Submit appropriate method development/validation reports with a proposed IVRT acceptance criterion as well as supporting IVRT data in your initial NDA submission.

Question 4:
The Applicant proposes to perform IVRT testing on the first three commercial batches of tapinarof cream, 1% packaged in 60-g tubes, testing on commercial batch(es) following any manufacturing change requiring notification to the agency per ICH Q12, along with testing of the annual stability commitment batch.

Does the Agency agree with the applicant's systemic approach for IVRT testing?

FDA Response to Question 4:
Your proposal is acceptable provided that you obtain consistent results from the batches tested.

Question 5:
Tapinarof manufacturing and Process Performance Qualification (PPQ) for tapinarof cream, 1% drug product will be performed using the same manufacturing process, equipment, batch size, and facility used for commercial manufacture of tapinarof cream, 1%. PPQ for tapinarof cream, 1% finished drug product is planned for execution prior to completion of commercial-scale validation of tapinarof drug substance. The manufacturing process and equipment utilized for the clinical-scale drug substance used in clinical and registration batches were assessed and it was determined that no significant differences are expected between the clinical-scale and commercial scale drug substance. The PPQ for tapinarof cream, 1% drug product will therefore be manufactured with clinical-scale drug substance. Following commercial-scale drug substance process validation, a confirmatory drug product batch will be produced at the commercially proposed batch size using commercial-scale drug substance.

Does the Agency agree with the applicant's PPQ plan for tapinarof cream, 1% finished drug product using clinical-scale drug substance batches for the drug product validation?

FDA Response to Question 5:
The Agency currently has no immediate concerns regarding the proposed PPQ plan as outlined. We remind you that the FDA does not approve process validation approaches, protocols, or number of specific batches used in process validation studies. The FDA requires that drug manufacturers validate their manufacturing processes [§ 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product. The actual protocols, acceptance criteria and study outcomes (as applicable) will be evaluated during an onsite inspection of the manufacturing facilities. The product design and the suitability of manufacturing processes will be evaluated during the NDA review cycle.

Refer to the guidance for industry *Process Validation: General Principles and Practices* { https://www.fda.gov/media/71021/download } and the guidance for industry for *Container Closure Systems for Packaging Human Drugs and Biologics – Chemistry, Manufacturing, and Controls Documentation* { https://www.fda.gov/media/70788/download } along with the associated Question & Answer document { https://www.fda.gov/media/70794/download }.

Question 6:
The product specification for tapinarof cream, 1% was updated to include globule size, absence of *Burkholderia cepacia* species, and IVRT based on feedback from the Advice letter from the Agency dated August 22, 2019.

Does the Agency agree that the proposed testing attributes meet the expectations for final product specifications for tapinarof cream, 1%?

FDA Response to Question 6:
The proposed drug product specification appears reasonable. However, you should include testing and acceptance criteria for elemental impurities in the drug product specification. If the elemental impurities are controlled through the drug substance specification, you should submit a risk-based assessment in your NDA to omit testing of the drug product for elemental impurities (USP <232/USP <233>, ICH Q3D). The proposed acceptance criteria for microbiological attributes also appear reasonable. However, note that the final acceptability of the manufacturing process, in process control, and method validation will be determined during the review of your NDA.

We acknowledged that the tapinarof cream, 1% is being developed as a multi-use topical treatment and that (b) (4) is performed for at

least one of the primary batches of the drug product at the end of the proposed shelf life. However, the (b) (4) method should be developed based on and/or equivalent toUSP <(b) (4)> . Note that (b) (4) should be performed on product formulated with the (b) (4) listed on the finished product release specification or stability specification (whichever is lower).

Meeting Discussion:
Dermavant is going to provide appropriate information regarding the control of elemental impurities in the drug substance. In addition, they will also provide a risk based assessment that will show that the probability of the presence of elemental impurities in the drug product is very low.

The Sponsor intends to perform (b) (4) at (b) (4) listed on the finished drug product release specification or stability specification. The Sponsor confirmed that this information will be submitted in the NDA.

2.3. Nonclinical

Question 7:
A comprehensive suite of nonclinical pharmacology studies investigating tapinarof's novel mechanism of action have been completed. A detailed package of absorption, distribution, metabolism, and excretion (ADME) and PK data has been generated describing the disposition of tapinarof following repeat administration. The nonclinical safety package is robust and includes an extensive interrogation of safety pharmacology, repeat-dose toxicity following dermal and systemic administration, genotoxicity and carcinogenicity, reproductive and developmental toxicology, and local tolerance.

Does the Agency agree that the proposed nonclinical package is adequate to support the NDA filing?

FDA Response to Question 7:
We acknowledge that your proposed nonclinical package includes safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicology, juvenile animal toxicity, and local tolerance studies with your drug product.

Your proposed nonclinical development program appears reasonable to support an NDA submission. The final determination of the data adequacy to support your NDA application will be made after review of all the submitted nonclinical information.

To enable us to conduct the statistical review of the dermal mouse carcinogenicity study and the subcutaneous rat carcinogenicity study, submit the SAS tumor data sets (tumor.xpt) for each carcinogenicity study to your NDA. Follow the attached standard format for preparing the data.

Table 1: FDA Biostatistics Data Format Sheet

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Type**	**Codes**	**Comments**
STUDYNUM	Study number	char		[3]
ANIMLNUM	Animal number	char		[1,3]
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4,... in ascending order from control. Provide the dosing for each	
DTHSACTM	Time in days to death or	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		[3,4]
TUMORNAM	Tumor name	char		[3,4]
ORGANCOD	Organ/tissue code	char		[3,5]
ORGANNAM	Organ/tissue name	char		[3,5]
DETECTTM	Time in days of detection of	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	[4]
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	[4]
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue)	

[1] Each animal in the study should have at least one record even if it does not have a tumor.

[2] Additional variables, as appropriate, can be added to the bottom of this dataset.

[3] ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

Meeting Discussion:

The sponsor confirmed that they will submit the requested SAS datasets for both carcinogenicity studies in the NDA submission. The Agency thanked the sponsor for this confirmation.

2.4. Clinical Pharmacology

Question 8:
The Applicant acknowledges the previous Agency communication dated August 12, 2019 on the adequacy of the clinical pharmacology package to support an indication in the target patient population. These studies include a series of dermal safety studies in healthy subjects, a maximal use study in subjects with extensive plaque psoriasis, and PK data from a subset of subjects in the pivotal Phase 3 trials. Supportive data from subjects with atopic dermatitis and early studies with previous formulations will also be included. A summary of the completed clinical pharmacology studies is provided herein.

Does the Agency agree that the completed clinical pharmacology studies with tapinarof cream, 1% are adequate to support the NDA filing?

FDA Response to Question 8:
We acknowledge that pharmacokinetics of tapinarof has been characterized in subjects with (b) (4) psoriasis following topical administration of tapinarof cream, 1%. We also acknowledge that the systemic exposure of tapinarof was determined under maximal use conditions in 21 subjects with psoriasis following topical administration of your to-be-marketed formulation (Study DMVT-505-2002). We note that an in vitro drug-drug interaction study for tapinarof as a perpetrator of CYPs and/or drug transporters is completed. Overall, your clinical pharmacology program for the indication of psoriasis appears adequate to support the NDA filing.

In addition, the combination of your nonclinical safety pharmacology studies (with hERG safety margin >30,000) and the clinical QTc assessment in the maximal use study in the subjects with psoriasis would be sufficient to address the risk of QTc prolongation for topical tapinarof cream, 1% in the treatment of psoriasis.

2.5. Clinical/Biostatistics

Question 9:
In accordance with 21 CFR 314.50 (f), the Applicant proposes to provide in the NDA the individual subject case report forms (CRFs) for all subjects who: (i) died during the studies, (ii) experienced serious adverse events (SAE) during the studies, or (iii) discontinued from the studies due to an adverse event (AE). These CRFs will be included in section 16.3 of the respective clinical study reports (CSR), as applicable.

Does the Agency agree with the Applicant's plan for CRF submission in the NDA?

FDA Response to Question 9:
Your proposal for subject case report forms (CRFs) appear reasonable. For ease of review, we recommend you hyperlink relevant CRFs to your ISS discussion.

Question 10:
The long-term extension study, DMVT-505-3003, entitled "A Long-Term, Open-Label, Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream, 1% for the Treatment of Plaque Psoriasis in Adults" remains ongoing. As described in the DMVT-505-3003 study protocol and statistical analysis plan, Dermavant will perform complete analysis of all safety and efficacy parameters on an interim cut of subject data at the time of NDA preparation. The number of subjects included in this data cut will adhere to ICH E1 guidance and will include at least 100 subjects followed for 1 year and at least 300 subjects for 6 months. A full interim CSR will be prepared containing the complete analysis results of all subject data, which will be included with the NDA filing. The final CSR for DMVT-505-3003 with all subject data will be available for inclusion with the 120-day safety update to the NDA.

Does the Agency agree with the submission of the full interim and final CSRs and data for DMVT-505-3003 to the NDA as described?

FDA Response to Question 10:
The 120-day safety update should include only safety data for subjects that have been accounted for in your initial NDA filing. Your proposal to submit a full interim CSR to the NDA filing is reasonable. At the time of NDA filing, you should specify the number of subjects the 120-day safety update will include. You may submit the final CSR with the 120-day safety update; however, it should contain no new subjects to the safety population previously presented.

Question 11:
The Applicant intends to submit study datasets in accordance with the current Study Data Tabulation Model (SDTM) implementation guide, version 1.4. Details of the proposed dataset submission plan are provided in Appendix 1.

Does the Agency agree with the proposed dataset submission plan?

FDA Response to Question 11:
We agree with your proposal to submit Clinical Data Interchange Standards Consortium (CDISC) compliant Study Data Tabulation Model (SDTM) datasets. According to your Study Data Standardization Plan, it appears that you plan to submit Analysis Data Model (ADaM) datasets for only your Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS). In your NDA, submit ADaM datasets for your Phase 2 and Phase 3 trials in subjects with plaque psoriasis.

For the analysis datasets, we have the following general comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. If any subjects were enrolled in more than

one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

The primary method for handling missing efficacy data in your Phase 3 trials is the Multiple Imputation (MI) approach. Submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze these datasets. The SAS code should be self-contained and executable with the datasets submitted in the NDA.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan (SAP), all protocol and SAP amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Meeting Discussion:
The Sponsor proposed to submit ADaM datasets for the phase 2 and phase 3 trials that they conducted and were conducted by GlaxoSmithKline (GSK). The Agency stated that the Sponsor's proposal appears reasonable.

Question 12:
The Applicant acknowledges the Agency advice letter dated September 1, 2020. Please note the effects of COVID-19 were assessed per our statistical analysis plans submitted on June 5, 2020 via SN 0109; containing an additional sensitivity analysis of the primary efficacy endpoint in the pivotal studies (DMVT-505-3001 and 3002) as well as summaries of individual visits affected by COVID-19. These data are summarized in the CSR, per Agency guidance.

The Applicant experienced minimal impact of COVID-19 when completing the Phase 3 pivotal studies. No subjects were diagnosed with COVID-19 and over 92% of available subjects completed in clinic visits at the primary efficacy endpoint visit (Week 12).

The Applicant considers these additional analyses as described in the study statistical analysis plans adequately address the impact of COVID-19 on our Phase 3 pivotal studies.

Does the Agency agree?

FDA Response to Question 12:
It is difficult to provide detailed comments without knowing the extent of the impact of the COVID-19 pandemic on your clinical trials. For each trial, clarify the number of

subjects whose visits were impacted by COVID-19 (i.e., the number of subjects who have missing data by week/visit and the number of subjects who have virtual assessments by week/visit).

The SAP specifies only one additional sensitivity analysis for COVID-19 (i.e., "an additional sensitivity analysis of the primary endpoint will be added in the ITT population based on OC only and excluding any virtual PGA assessments at Week 12"). We recommend including an analysis based on the ITT population (i.e., all randomized subjects) where subjects with virtual assessments are considered missing and imputed along with the other missing data (e.g., subjects who discontinued the trial and subjects who have missing data due to COVID-19) using the prespecified primary imputation approach (i.e., multiple imputation).

Your dataset should include all subjects enrolled in the clinical trials, including those whose visits were impacted by the COVID-19 pandemic. In your analysis datasets, include a flag that identifies the visits that are missing due to the COVID-19 pandemic along with the reasons for missing the visits (e.g., center closed, patient decision, etc.) when applicable. In addition, include a flag that identifies the visits where virtual assessments were performed.

Question 13:
As suggested in the Agency advice letter dated September 1, 2020, the Applicant will conduct a tipping point analysis of the primary efficacy endpoint in the pivotal studies (DMVT-505-3001 and 3002) and intends to include the results within the overall construct of the Integrated Summary of Efficacy (ISE). The ISE will include a section describing the additional FDA-suggested analyses, methods, and results.

Does the Agency agree with the Applicant that the results of the tipping point analysis referenced in the September 1, 2020 Advice letter can be incorporated within the ISE?

FDA Response to Question 13:
Your proposal to include the tipping point analysis in the ISE is acceptable.

Additional Comment:
You included the SAP for the ISE. We reiterate the comment from the written responses (dated October 9, 2020) that due to its unique treatment assignment structure/regimen and potentially different treatment population, we do not see the utility of (b) (4) with the pivotal Phase 3 trials (DMVT-505-3001 and DMVT-505-3002) for the ISE.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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that there will be no submission of additional information within the first 30 after receipt of the NDA.

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FDA Response to Post Meeting Question:
The sponsor's request to submit additional stability data within 30 days from original date of submission of the NDA is acceptable.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
    - 12-month stability data for the 2-gram physical sample.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length,

randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

4.0 Sponsor's Agenda

- Sponsor's Focused Agenda
    - Question 12: Lines 456-460 and 462-476 Clinical/Biostats
    - Question 11: Lines 405 to 435 Biostats
    - Question 10: Lines 390-395 Clinical
    - Question 7: Lines 312-327 Nonclinical
    - Question 6: Lines 272-275 and 280-286 CMC

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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

/s/

KENDALL A MARCUS
03/08/2021 08:42:16 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104601

MEETING MINUTES

GlaxoSmithKline Intellectual Property Development Ltd. England
Attention: Laurie E. Harris Bliga
Manager Global Regulatory Affairs
20 TW Alexander Drive, PO Box 14910
Research Triangle Park, NC 27709

Dear Ms. Bliga:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK2894512 cream.

We also refer to the meeting between representatives of your firm and the FDA on January 11, 2016. The purpose of the meeting was to discuss the development program for GSK2894512 cream.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Pinky Patel, Regulatory Health Project Manager at (301) 796-7475.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: January 11, 2017 at 11 a.m. ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland, 20903

Application Number: IND 104601
Product Name: GSK2894512 cream
Indication: For the topical treatment of (b) (4) psoriasis
Sponsor Name: GlaxoSmithKline Intellectual Property Development Ltd. England

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Pinky Patel

FDA ATTENDEES
Julie Beitz, MD, Director, Office of Drug Evaluation III (ODE III)
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Nancy Xu, MD, Associate Director for Labeling, DDDP
Kettl David, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Melissa Reyes, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Hae-Young Ahn, PhD, Deputy Director, Division of Clinical Pharmacology (DCP) III
Chinmay Shukla, PhD, Acting Clinical Pharmacology Lead, DCP III
Yanhui Lu, PhD, Clinical Pharmacology Reviewer, DCP III
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biostatistics (DB) III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Marilena Flouri, PhD, Biostatistics Reviewer, DB III
Selena Daniels, PharmD, MS, Reviewer, Clinical Outcome Assessments (COA) Staff
Ebony Dashiell-Aje, PhD, Reviewer, COA Staff
Paul Phillips, MS, Lead Regulatory Health Project Manager, DDDP
Pinky Patel, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
John Kraus, MD, PhD, Medicine Development Leader, GSK2894512

Melissa Green, MS, MBA, Global Regulatory Lead, Dermatology
Tomoko Chubachi, MD, PhD, MBA, Project Physician Leader, GSK2894512
Jay Getsy, DMD, DO, Senior Medical Director, Dermatology
Johnny Peppers, PhD, Clinical Development Scientist
Jonathan Haddad, MPH, Director, Statistics
Sterling Wu, PhD, Manager, Statistics
Li Ye, MS, Manager, Statistics
Mark Desiato, Vice President, Global Regulatory Affairs

1.0 BACKGROUND

Purpose of meeting was to discuss the development program for GSK2894512.

2.0 DISCUSSION

Pharmacology/Toxicology

Question 1:
Does the Agency agree that the nonclinical program (Section 10.2) conducted to date and studies ongoing and planned are sufficient to support initiation of the Phase III clinical studies, and to support approval of the NDA for (b) (4) psoriasis?

FDA Response:
Your currently available nonclinical studies appear acceptable to support the proposed Phase 3 clinical studies **except** (b) (4). Clinical studies should be supported by suitable nonclinical data from repeat-dose toxicology studies in which the animals were dosed on at least as many consecutive days as would patients in the proposed clinical trial. See the ICH M3(R2) document for detailed information concerning the appropriate duration of the repeat-dose toxicology data needed to support a given clinical study. There are currently no long-term nonclinical studies available to support (b) (4) long-term clinical studies with durations of up to 52 weeks. Your nonclinical program appears acceptable to support the NDA submission.

Clinical/ Biostatistics/ Clinical Pharmacology

Question 2:
Does the Agency agree that the GSK2894512 cream strength of 1% and application frequency of once daily is appropriate for evaluation in all Phase III studies for (b) (4) adult psoriasis?

FDA Response:
While your proposed dose/dosing regimen may prove to be appropriate for your Phase 3 program, we note that your dose finding studies are still ongoing and data through the proposed primary efficacy time point has not been presented.

You provided an 8-week interim analysis of your Phase 2 dose-ranging studies (203121 and 203120) and limited Week 12 data, the Agency has the following comments concerning your Phase 2 data:

- **Psoriasis Phase 2 Study (203120):**
  - Your PGA results at Week 8 (using the LOCF data) showed that the lowest dose of GSK2894512 cream 0.5% QD had the highest response rates (46%) followed by the highest dose of GSK2894512 cream 1% BID (38%), then 1% QD (29%), and 0.5% BID (29%).
  - Your PASI 75 results at Week 8 showed that the highest dose of GSK2894512 cream 1% BID had the highest response rate (52%) followed by the 1% QD (41%), 0.5% BID (41%), and 0.5% QD (39%). However, your limited data at Week 12 showed a different trend in that the GSK2894512 cream 0.5% BID had the highest response rate (57%) followed by 0.5% QD (50%), 1% QD (44%), then 1% BID (33%).
  - Your PASI 50 results at Week 8 and Week 12 were not consistent with the findings of the PASI 75. Your PASI 50 results showed that the GSK2894512 cream QD doses (i.e., 1%, 0.5%) generally had higher response rates than those of the BID doses.

- **AD Phase 2 Study (203121)**

(b) (4)

Given the lack of consistency in efficacy trend across the treatment doses for the different endpoints, time points (Week 8 vs. Week 12) (b) (4), it would be difficult to concur with your selection of GSK2894512 cream 1% QD for future trials. You are encouraged to select the dose(s) for your Phase 3 trials based on data for the same time point that you plan to assess efficacy (i.e., Week 12) as selecting a dose based on extrapolation of efficacy results of Week 8 for Week 12 might not be supported by your interim Phase 2 results.

Meeting Discussion:
The sponsor stated that they are currently evaluating preliminary 12 week data, which they think support their initial selection of the dose based on the 8 week data.

Question 3:

Does the Agency agree that the overall planned Phase III program would support the following (b) (4)?

- (b) (4)
- US: GSK2894512 1% cream is indicated for the topical treatment of plaque psoriasis

FDA Response:
Generally, data from two adequate and well controlled trials are recommended to support an indication. Specifically, you will need to conduct two adequate and well-controlled trials (b) (4) to support an indication for psoriasis. The most expedient way to demonstrate the efficacy of your product would be to compare it to a vehicle control. If you also wish to compare the efficacy of your product to other products, the trial designs will be more complex. (b) (4) See additional comments in response to Question 6.

Question 4:
Does the Agency agree that the treatment duration of 12 weeks is appropriate in the pivotal Phase III studies to support the proposed indications?

FDA Response:
The optimal treatment duration for your topical product should be captured in your Phase 2 dose-ranging studies. See above discussion in Question 2 regarding the adequacy of your Phase 2 dose-ranging studies. A complete analysis of your Phase 2 studies will be critical in determining the optimal dose and duration of treatment for GSK2894512 in (b) (4) plaque psoriasis, (b) (4).

Question 5:
Does the Agency agree that the primary and key secondary efficacy endpoints are appropriate and support NDA approval?

FDA Response:
Your proposed primary endpoint of the proportion of subjects with PGA (or (b) (4)) of 0 or 1 along with a minimum of 2-grade improvement at Week 12, and the secondary endpoint of the proportion of subjects with ≥ 75% improvement in (b) (4) (or PASI) from baseline to Week 12 are acceptable. You will need to seek agreement with the Agency on the proposed PGA and (b) (4) scales prior to initiation of your clinical trials.

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Question 9:
Does the Agency agree that (b) (4)

FDA Response:
Withdrawal and retreatment should be evaluated in the Phase 3 clinical trials to determine duration of effect and response to retreatment. Whether this information supports the long term safety of your product is a review issue.

Question 10:
Does the Agency agree that the anticipated size and duration of exposure of the safety database will be sufficient to file an NDA for (b) (4) psoriasis?

FDA Response:
Your clinical development program, as described in the briefing package, would be acceptable to satisfy ICH E1A for long-term use safety database.

Question 11:
Does the Agency agree that the planned Phase III program appropriately assesses safety and efficacy in the pediatric patient population?

FDA Response:
Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. Supporting information in the PSP would typically include incidence and prevalence information for the relevant pediatric populations who have the conditions that you plan to study to justify an eventual labeled indication.

Your proposed iPSP will need to address (b) (4) plaque psoriasis down to at least 4 years of age (see etanercept label). As previously discussed in Question 3, (b) (4)

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

(b) (4)

Question 12:
Does the Agency agree with the proposed (b) (4) in the pivotal Phase III clinical studies?

FDA Response:
Your proposal appears reasonable, provided that the endpoints are in agreement with the Agency.

Question 13:
Dose the Agency agree with proposed (b) (4) ?

FDA Response:
See response to Question 6.

Question 14:
Does the Agency agree with the proposed method for handling missing data for the primary and key secondary endpoints in the (b) (4) pivotal Phase III clinical studies?

FDA Response:

You proposed to use the Intent to Treat (ITT) population for the statistical analysis of the primary and key secondary endpoints; however, you did not provide the definition of ITT in your "summaries".

(b) (4)

Question 15:
Does the Agency agree that the maximum-use PK (MUPK) study plan outlined is sufficient for (b) (4) psoriasis (b) (4)?

FDA Response:
We acknowledge that you are conducting Phase 2 studies from which you will obtain sparse pharmacokinetic (PK) samples (b) (4) in subjects with psoriasis. (b) . We have the following comments:

- We do not agree with your proposal of (b) (4)
- In the maximal use PK trials, we recommend that you characterize the PK of your to-be-marketed formulation following the first dose application and at steady state.
- For the maximal use PK trial(s), we recommend that you do not set the upper limit of disease involved BSA that will be treated, unless such limitation is justified due to any safety concerns. Rather, we recommend for example:
  a. (b) (4)
  b. (b) (4), you should enroll subjects with ≥ 20% BSA involved in adults and ≥ 10% BSA involved in subjects 6-17 years of age
- You should characterize systemic exposure of the parent drug and all major metabolites under the maximal use conditions.
- You should also estimate the maximum dose of the formulation that would be applied in the maximal use PK trial.

We recommend that you submit protocols to the Agency for comments prior to initiating your maximal use PK trials in adults and pediatrics.

Additional Comments:
We note that in your completed PK study (Study 201851), the systemic exposure of GSK2894512 on Day 21 were lower compared to those observed on Day 1 in subjects with AD. Provide a scientific justification to support this decrease in exposure. Also clarify if you assessed attainment of steady state in this study.

Meeting Discussion:
The Sponsor inquired whether it would be acceptable to conduct maximal use PK trials in (b) (4). The Agency responded that the maximal use PK trials in both adult and pediatric subjects should be conducted (b) (4) as described in the response to Question 15. The PK sampling design in pediatric subjects may be sparse based on the PK results from the adults.

The Sponsor stated that the reduced systemic drug exposure on Day 21 in the completed PK study (Study 201851) could have been due to improvement of the disease over time. The Agency reiterated the need for steady state PK assessment of the drug product under maximal conditions.

Corrigendum:
(b) (4)

Question 16:
Does the Agency agree that a formal TQT study is not required?

FDA Response:
It is premature to determine whether a formal TQT study is required at this time. A waiver of thorough QT study may be submitted for review if results from maximal use PK trials show that maximum plasma concentrations of parent drug and metabolites are below 1 nM and there are no positive signals from in vitro hERG experiments. The PK data should include those covering the target age population as systemic exposure may be higher in younger subjects.

Question 17:
a. Does the Agency agree with the proposed package of dermal safety studies?
b. Does the Agency agree with conducting all dermal safety studies in healthy volunteers?
c. An irritation study was conducted in healthy Japanese volunteers with the to-be-marketed formulation. Is this study acceptable for the registration package?

FDA Response:
Generally, recommended topical safety studies are cumulative irritancy (not less than 30 evaluable subjects), contact sensitization (not less than 200 evaluable subjects), photoallergenicity (not less than 50 evaluable subjects), and phototoxicity (not less than 30 evaluable subjects). These studies should be conducted with the final to-be-marketed formulation and are often conducted in parallel with phase 3 studies.

Dermal safety studies are typically conducted in healthy volunteers.

No details are provided in the briefing document for the studies listed in table 7 on page 33, so we are unable to comment on the acceptability of the studies for the NDA submission, particularly with respect to application frequency, amounts and acceptability of controls.

Question 18:
Does the Agency agree that (b) (4) healthy volunteers is an acceptable number to investigate contact sensitization?

FDA Response:
No. As previously advised at the May 6, 2009 pre-IND meeting, contact sensitization studies should enroll not less than 200 evaluable subjects.

Question 19:
Does the Agency agree that the proposed clinical pharmacology studies are sufficient to support approval of the NDA for GSK2894512 cream for (b) (4) psoriasis (b) (4) in the intended patient populations?

FDA Response:
No, we do not agree. You should conduct (b) (4) maximal use PK trials in subjects with psoriasis (b) (4). Furthermore, you should address the potential for drug interactions during development. For further information, you are referred to draft guidance for industry, *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*. See response to Question 15.

Additional Comments:

1. Clinical outcome assessments will need to be culturally adapted and adequately translated for all intended study populations for use in multinational trials. You may refer to the ISPOR principles for the translation and cultural validation process (https://www.ispor.org/workpaper/research_practices/PROtranslation_adaptation.pdf) for further guidance.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of

Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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/s/

KENDALL A MARCUS
01/13/2017