

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217424Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 137015

MEETING MINUTES

Novan, Inc.
Attention: Erin Spence, PhD
Manager, Regulatory Operations
4020 Stirrup Creek Dr, Suite 110
Durham, NC 27703

Dear Dr. Spence:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for berdazimer sodium gel (SB206).

We also refer to the teleconference between representatives of your firm and the FDA on April 4, 2022. The purpose of the meeting was to discuss the content and format of your proposed New Drug Application (NDA).

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

If you have any questions, call Dawn Williams, Regulatory Project Manager at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures: Meeting Minutes
IND 137015 Sponsor pre-NDA preliminary response letter
SB206 Sponsor pre-NDA Facilitation Deck



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 4, 2022, 9:30-10:30 AM
Meeting Location: Teleconference

Application Number: IND 137015
Product Name: berdazimer sodium gel (SB206)

Proposed Indication: molluscum contagiosum (MC)
Sponsor Name: Novan, Inc.

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Shari L. Targum, MD, MPH, FACP, FACC
Meeting Recorder: H. F. Van Horn III, PharmD, MBA

FDA ATTENDEES

Julie G. Beitz, MD, Director, Office of Immunology and Inflammation (OI)

Shari L. Targum, MD, MPH, FACP, FACC, Deputy Director, DDD

David Kettl, MD, FAAP, Clinical Team Leader, DDD

Hamid Tabatabai, MD, Clinical Reviewer, DDD

Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)

Soo Hyeon Shin, PharmD, PhD, Clinical Pharmacology Reviewer, DIIP

Mohamed Alesh, PhD, Biometrics Team Leader, Division of Biometrics III, (DB III)

Marilena Flouri, PhD, Biometrics Reviewer, DB III

Hong Cai, PhD, Chemist, Office of Pharmaceutical Quality, Division of New Drug Products II (DNPD II), Branch IV

H. F. Van Horn III, Pharm D, MBA, Regulatory Health Project Manager, DRO – DD

SPONSOR ATTENDEES

Paula Brown Stafford, MPH, President and Chief Executive Officer

Tomoko Maeda-Chubachi, MD, PhD, MBA, Chief Medical Officer

(b) (4) Principal Biostatistician (Consultant)

(b) (4), Biostatistician Consultant

Cathy White, Vice President, Drug Development Operations

Erin Spence, PhD, Manager, Regulatory Operations

(b) (4) Pharmacology/Toxicology Consultant

Carri Greer, PhD, Chief Technology Officer

(b) (4) Regulatory Affairs Consultant

1.0 BACKGROUND

The Sponsor is developing berdazimer sodium gel (SB206), a (b) (4) nitric oxide (NO) releasing agent indicated for the topical treatment of molluscum contagiosum (MC) in patients (b) (4) of age and older.

The purpose of the meeting is to discuss the proposed format and nonclinical, clinical, and regulatory content of the NDA submission. Furthermore, the Sponsor is seeking FDA's agreement that the content of the NDA and planned analyses for the integrated summaries of safety (ISS) and efficacy (ISE), as well as the clinical datasets (including their format) to be included in the application, are adequate to support filing of the NDA.

A separate Written Responses Only (WRO) has been granted to address Chemistry, Manufacturing and Controls (CMC) content planned for the NDA.

FDA sent Preliminary Comments to Novan, Inc. on March 30, 2022.

2.0 DISCUSSION

2.1. Pharmacology/Toxicology

Question 1:

Does the FDA agree that the completed nonclinical studies described in the briefing package are sufficient and no other nonclinical studies are needed to support the NDA?

FDA Response to Question 1:

We acknowledge that your nonclinical package includes pharmacology studies, pharmacokinetics studies, and toxicology studies including repeat dose oral toxicity studies for up to 13 weeks in rats and dermal toxicity studies for up to 13 weeks in rats or mice and 39 weeks in minipigs, an ICH battery of genotoxicity studies, a dermal carcinogenicity study in mice, an oral subcutaneous fertility study in rats, and oral embryofetal development studies in rats and rabbits to support the safety of your topical drug product. In addition, you have assessed the ocular irritation potential in a Bovine Corneal Opacity and Permeability (BCOP) assay and sensitization potential in guinea pigs.

We also acknowledge that your waiver requests were granted for the conduct of a systemic chronic rodent toxicity study, a pre-and post-natal development study, and a systemic carcinogenicity study based on the lack of significant systemic exposure in the maximal use clinical pharmacokinetics study (NI-MC101). The photo-safety studies waiver request was granted based on the lack of significant absorbance of your product in the 290-700 nm range.

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, submit the Statistical Analysis System (SAS) tumor data sets (tumor.xpt) for this 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 group.	
DTHSACTM	Time in days to death or sacrifice	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 code	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 tumor	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) 3 = Organ/Tissue was not examined	

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.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 10:

Does FDA agree that the proposed pharmacologic class is appropriate (i.e., (b) (4) nitric oxide releasing agent), scientifically valid, and clinically meaningful to HCPs?

FDA Response to Question 10:

The pharmacologic class will be determined during the NDA review. Refer to the *Agency Guidance for Industry and Review Staff Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information*.

See FDA Response to Question 11.

Discussion Question 10 and 11:

The Agency will address the pharmacological class during the review of the NDA.

2.2. Clinical Pharmacology

Question 2a:

Does FDA agree that the data and analyses are sufficient to discharge the risk of QTc prolongation and that no further assessments are needed to support an NDA submission?

FDA Response to Question 2a:

This topic is still under review and a response will be provided in a separate communication.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 2b:

Does FDA agree that no additional clinical pharmacology or pharmacokinetic data on SB206 Gel are needed to support an NDA submission?

FDA Response to Question 2b:

We acknowledge your results of a maximal use pharmacokinetic (PK) study (NI-MC101) which showed low systemic absorption of your product. The need for additional clinical pharmacology studies will be a review issue.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

2.3. Clinical

Question 3:

Does the FDA agree that the local safety data collected to date, which includes patch testing and the evaluation of local skin reactions in all three Phase 3 MC studies, together with the dermal safety studies conducted with SB204 Gel, are adequate to file the NDA and that separate provocative dermal safety studies are unnecessary?

FDA Response to Question 3:

Your plan to submit the results of the active assessment of Local Skin Reactions (LSR)s including patch testing for subjects suspected of developing allergic contact dermatitis in your phase 3 trials, together with supportive safety data from Dermal Safety Studies conducted with SB204 gel in your acne development program, in lieu of conducting provocative Dermal Safety Studies for irritation and sensitization with SB206 gel in subjects with MC appears reasonable to allow for review of local safety.

We agree that clinical photo-safety patch testing studies are unnecessary because significant absorbance of your product in the 290-700 nm range was not demonstrated.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 4:

Does the FDA agree that the anticipated extent of safety follow-up data (for up to 1 year) available at the time of NDA submission and the mock shell are adequate to characterize the potential for permanent local adverse events of SB206 Gel to file the NDA?

FDA Response to Question 4:

You submitted the final clinical study report (CSR) for Trial NI-MC-304 with the study completion date of July 20, 2021, and propose to include a CSR addendum reporting long-term safety for Trials -301/-302/-304 (Table 7 of pre-NDA briefing package).

The final long-term safety data for any subject with an unresolved treatment emergent adverse event (TEAE) (e.g., keloid or hypertrophic scar) for up to 1 year after the last application of study drug should be included at the time of your NDA submission.

However, see the response to question 5 below regarding concerns about the adequacy of safety information to support repeated or extended use.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 5:

Does the FDA agree that the proposed clinical safety package and size of the safety database is sufficient to file and review the NDA submission for the proposed indication?

FDA Response to Question 5:

To date, berdazimer gel has not yet been approved for any indication and the safety data for its use for any indication has not yet been submitted or reviewed by the Agency.

You have not conducted a long-term safety study of SB206 gel, 10.3% for treatment of MC which addresses potential repeat or extended use which is likely in clinical practice. Your proposed NDA safety database for the indication of treatment of MC will include 916 subjects in your phase 3 Trials (NI-MC301/-302/-304) who were treated with berdazimer gel (SB206), 10.3% applied every day (QD) for up to 12 weeks, but does not include any long-term safety data for subjects treated beyond 12 weeks, or in those subjects who required repeat treatment.

We reiterate the following comments from the End-of-Phase 2 (EOP2) meeting of March 6, 2019:

"Because repeated use of your product can be anticipated in patients who do not get complete clearance of all lesions after 12 weeks of treatment, you will need to address long-term safety in sufficient number of relevant subjects to inform safety. For the number of subjects and duration of exposure to the investigational product, you are referred to ICH E1A: guidance for industry: *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment Non-Life-Threatening Conditions and Premarketing Risk Assessment*. Molluscum contagiosum is a benign, self-limited illness which heals without sequelae or adverse cosmetic outcomes in the absence of treatment. A robust safety database will be needed in order to ensure a favorable benefit-risk assessment for this patient population".

The adequacy of the safety data will be a review issue under the NDA.

Discussion:

The Agency pointed out the differences between the acne and MC development programs in terms of the population enrolled and drug product concentration. Although the acne long-term safety data may be supportive, these data do not appear adequate to supplant the need for MC long-term safety data due to differences in concentration

(10.3 % for MC compared to 3.4% for acne) and differences in study population age (greater than or equal to (b) (4) for MC compared to greater than or equal to 9 years for acne). The Agency conveyed the need for sufficient local safety data for the intended population at the dose proposed for marketing.

Post-meeting comment:

The Sponsor inquired about labeling restricting use to a single 12-week treatment course. The Agency advised that the efficacy and safety data might not be adequate to allow for this type of labeling, given the typical standards of care for this condition.

Question 6:

Does the FDA agree that the complete clearance data at each visit is appropriate to include in the label?

FDA Response to Question 6:

Agreements regarding eventual labeling cannot be made until the supporting data is reviewed under the NDA. Whether results for complete clearance from earlier time points would appear in labeling would be a review issue because this will depend on whether these endpoints were pre-specified and tested following establishing efficacy at the primary time point. However, presentation of descriptive results may be included in the labeling if such results would help in interpreting the clinical trials findings.

Additional Comment:

In the briefing package you provided a summary of the estimand framework for the primary efficacy endpoint (i.e., complete clearance in all MC lesions at Week 12) for the three phase 3 trials, indicating that the population level summary will be the odds ratio between the treatment arms. We recommend that you also assess the population level summary of the difference in response rates (for the primary endpoint) at Week 12 between the treatment arms. Treatment effect as assessed by the difference in the response rates is easier to interpret and, consequently, is preferred for presentation in labeling.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 11:

Does the FDA agree that the proposed indication statement is consistent with Novan's development program (pending review of the application)?

FDA Response to Question 11:

Your proposed pharmacologic classification (b) (4) nitric oxide releasing agent) and indication statement (b) (4) is (b) (4) nitric oxide releasing agent indicated for the topical treatment of molluscum contagiosum in patients (b) (4) of age and older) and other labeling determinations will be review issues to be addressed during

the NDA review cycle following the evaluation of data submitted in support of your proposed labeling claims.

Further discussion regarding the labeled indication can be found in the Agency guidance document *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

(b) (4)

Submit adequate scientific and clinical justification to support the rationale for your labeling proposals,

(b) (4)

(b) (4)

Submit cell culture and in vivo data to support any anticipated labeling claims. If you propose literature to support such claims, include complete literature references.

Discussion:

Refer to Discussion of Question #10.

2.4. Study Data and Statistical Plans

Question 7:

Does the FDA agree with the planned strategy for ISS?

FDA Response to Question 7:

Your plan to include phase 3 Trials NI-MC301/-302/-304 in the ISS appears reasonable. Furthermore, your proposal to present study size-adjusted proportions and study-sized exposure-adjusted incidence rates (along with 95% confidence interval (CI) for the difference between treatment arms) appears reasonable.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 8:

Does the FDA agree with the planned strategy for ISE?

FDA Response to Question 8:

Your proposal to pool the three phase 3 trials for the ISE appears reasonable. We recommend that you additionally present response rates by treatment arm and difference in the response rates between treatment arms (SB206 Gel vs. vehicle) for trials MC301 and MC302 integrated.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 9:

Does FDA agree with the proposed data constructs and format planned for the individual studies and integrated analyses to be included in the NDA?

FDA Response to Question 9:

- a) Forms 1571, 356h and 3397 should be placed in Section 1.1 (Forms). The Proposed eCTD Table of contents for planned NDA submission contains Form 1571, Form 356h, and Form 3397 in Section 1.1.1, 1.1.2 and 1.1.3 respectively.
- b) Form 3674 should be placed in Section 1.1 (Forms). The Proposed eCTD Table of contents for planned NDA submission contains Form 3674 in Section 1.2
- c) Regional Information should be placed in 3.2.R. The Proposed eCTD Table of contents has the Regional Information under 3.2

Refer to the [Comprehensive Table of Contents Headings and Hierarchy](#) Section 1.1 Forms for more details.

From a technical perspective (and not content related), all other sections proposed in the eCTD-NDA Table of Contents are acceptable.

From a technical perspective, your proposed study data format is acceptable.

Your proposal to submit Study Data Tabulation Model (SDTM) and analysis data model (ADaM) formatted datasets for the MC trials is acceptable. Sensitivity analyses for the handling of missing data in the phase 3 trials include a multiple imputation method. Submit the Statistical Analysis System (SAS) code used to implement the proposed multiple imputation methods as well as the SAS code used to analyze the imputed datasets.

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

- a) Each analysis dataset should include treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables, including the center variables (i.e., original and analysis), needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject identification (ID) that permits subjects to be tracked across multiple studies. Further, assign a unique ID to the original site (center) to permit analysis across the phase 3 trials.

- b) 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.

In addition to the electronic datasets, 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).

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

2.5. Regulatory

Question 12:

Is FDA agreeable to this approach and can Module 1.16 be excluded from the pending NDA?

FDA Response to Question 12:

Your plan to omit Sec. 1.16 (Risk Management Plan) of your NDA is reasonable, provided that no safety concern is identified at the time of your NDA submission.

It is unlikely that a risk evaluation and mitigation strategy (REMS) will be required for the safe use of berdazimer as a treatment of molluscum contagiosum based on our review of the summarized information contained in your meeting package. However, the final determination for the necessity of a REMS depends on the overall risk benefit assessment of your application and will be decided after your complete application has been reviewed.

A complete review of the full risk management plan after the NDA is submitted will be necessary to determine whether the proposed approach is acceptable because additional information regarding risks and safe product use may emerge during the review of your application.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 13a:

Does FDA generally agree with omitting the proposed sections of the draft package insert for SB206 Gel?

FDA Response to Question 13a:

You should provide data in support of the rationale for your plan to omit the following sections from your proposed label at the time of the NDA submission:

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- i. Boxed Warning
- ii. Sections 7 (Drug Interactions)
- iii. Section 9 (Drug Abuse and Dependence)

The determination for omission of certain sections in the final label will be made during labeling discussions following your NDA submission and review.

Discussion:

The Agency recommended that the Sponsor submit their rationale regarding these sections in the application, which will be reviewed after NDA submission.

Question 13b:

Does FDA agree, pending a review of the data, that the proposed package insert provides adequate information (as supported by the SB206 Gel development program) to inform Healthcare practitioners of the safety and effectiveness of SB206 Gel?

FDA Response to Question 13b:

The content of labeling and the adequacy of the data which support it will be reviewed during the NDA review cycle.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 13c:

Does FDA have any other recommendations at this time regarding the *format* of the proposed draft package insert?

FDA Response to Question 13c:

Not at this time. Initial comments regarding format of the labeling may be included in the 74-day letter if the application is filed. Consideration of specific elements of labeling will be communicated following review of supporting data in your application and labeling comments will be further communicated during the review.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 14a:

Given that the NDA will be submitted electronically, does FDA agree that a field copy of Module 3 sent to the local FDA field office is unnecessary?

FDA Response to Question 14a:

We agree that a field copy of Module 3 need not be sent to the local FDA field office. A copy of your letter notifying the District office of the eCTD submission is required to be included in section 1.3.2.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

Question 14b:

Novan welcomes FDA's feedback regarding the proposed NDA index structure, hierarchy, and format.

FDA Response to Question 14b:

See FDA Response to Question 9.

Discussion:

The sponsor accepted FDA's response, no discussion occurred.

3.0 ADMINISTRATIVE COMMENTS:

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 17, 2022, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.¹

¹ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>
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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*.² 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.³

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 Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

² 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>.

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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- 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 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

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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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁶

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁷

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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 356h⁸ and the guidance for industry, *Identification of Manufacturing Establishments in*

⁸ <https://www.fda.gov/media/84223/download>
 U.S. Food and Drug Administration
 Silver Spring, MD 20993
www.fda.gov

*Applications Submitted to CBER and CDER Questions and Answers*⁹. 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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹⁰

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ATTACHMENTS AND HANDOUTS

- IND 137015 Sponsor pre-NDA preliminary response letter
- SB206 Sponsor pre-NDA Facilitation Deck

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

¹⁰ <https://www.fda.gov/media/85061/download>

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/

SHARI L TARGUM
04/20/2022 03:01:45 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 137015

MEETING MINUTES

Novan, Inc.
Attention: Emily N. de León, MSCR, PMP
Senior Director, Regulatory Operations
4105 Hopson Road
Morrisville, NC 27560

Dear Ms. de León:

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

We also refer to the meeting between representatives of your firm and the FDA on March 6, 2019. The purpose of the meeting was to discuss the development program for berdazimer sodium gel.

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 Dawn Williams, Regulatory Project Manager at (301) 796-5376.

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: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: March 6, 2019; 11:00am
Meeting Location: FDA White Oak Campus; Building 21; Room 1539

Application Number: IND 137015
Product Name: berdazimer sodium gel
Proposed Indication: For the treatment of molluscum contagiosum
Sponsor Name: Novan, Inc.

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Kendall Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Tatiana Oussova, MD, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Hamid Tabatabai, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
Dawn Williams, BSN, Regulatory Project Manager
Mohamed Alosch, PhD, Biostatistics Team Leader, Division of Biostatistics III (DB III)
Rebecca Hager, PhD, Biostatistics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCP III)
Jihye Ahn, Clinical Pharmacology Reviewer, DCP III
Hamid Shafiei, PhD, Acting Quality Assessment Lead, DNDP II, NDPB V
Paresma Patel, PhD, Product Quality Reviewer, NDPB II

SPONSOR ATTENDEES

Emily N. de León, MSCR, PMP, Senior Director, Regulatory Affairs
Tomoko Chubachi, MD, PhD, Vice President of Medical Dermatology
Paula Brown Stafford, MPH, President and Chief Operating Officer
Elizabeth Messersmith, PhD, Chief Development Officer
Carri Geer, PhD, PhD, Chief Technology Officer and Senior Vice President, Pharmaceutical Development

(b) (4)

David Hebert, PhD, Biometrics

1.0 BACKGROUND

Regulatory Correspondence History:

We have sent the following correspondences:

- August 29, 2018 Pediatric Study Plan- Initial Agreement
- July 27, 2018 Pediatric Study Plan- Written Response
- February 8, 2018 Study May Proceed

2. DISCUSSION

2.1. Regulatory

Question 1:

Does the Agency agree with the proposed label claim for SB206: treatment of molluscum contagiosum?

FDA Response to Question 1:

The proposed indication appears reasonable based on our understanding of the treatment effects of your drug product at the current stage of development. The precise language for labeling will be considered during the review of the NDA.

Question 2:

Does the Agency agree that the proposed safety database, consisting of the projected subject exposure in the proposed SB206 program, including Phase 3 for MC (approximately 500 subjects), the subjects exposed to SB206 in the Phase 2 study NI-WA201 for EGW/PAW (79 subjects), and (over 2000 subjects) with acne exposed to berdazimer sodium in the SB204 development program, is sufficient to support overall safety database for filing a NDA for SB206 for the treatment of molluscum contagiosum?

FDA Response to Question 2:

Your development program will have to demonstrate the safety and efficacy of your drug product for the indication of treatment of MC. You note the number of subjects exposed to berdazimer sodium gel (NVN1000 and hydrogel) include the following:

- In two planned phase 3 trials (NI-MC 301, -302), approximately 308 subjects will be exposed to SB206, 12% gel QD for up to 12 weeks.
- In trial NI-MC201, 95 subjects (≥ 2 years of age) were exposed to SB 206, 12 % gel QD (48) or BID (47) . (Table 17, briefing package).
(Additional 95 subjects were exposed to SB206 at 4% or 8% BID for 12 weeks).
- 30 adult subjects with EGW/PAW in trial NI-WA201 were exposed to SB206, 12% gel QD for 12 weeks. (Additional 51 subjects were exposed to SB206 at 4% QD, 4% BID, or 8% QD for 12 weeks).

- > 2000 subjects with acne exposed to berdazimer sodium gel at different strengths, application frequencies, or durations.

Subjects exposed to berdazimer sodium gel at strengths, frequencies, and durations other than the intended to-be-marketed regimen (SB206, 12% gel QD x 12 weeks) may provide supportive evidence of safety but will not address the 12% concentration or the population likely to use your product.

Your product has not been approved for any indication to date and any safety experience has not been critically reviewed. While your acne trials may have included 2000 subjects, the concentration was one third that proposed for the MC trials. Additionally, the development programs for acne and EGW did not include any exposures to young children which is the population most likely to use your proposed product. We recommend that your development program and Pediatric Study Plan address all relevant pediatric age groups. Additional subjects are recommended in your MC development program to assess safety and this number will likely exceed the number needed to demonstrate efficacy.

Subjects who clear during the trial should be followed for a longer period to ensure durability of clearance (recurrence of lesions) and to assess safety. Assessments should include longer term cosmetic outcomes (6- 12 months after treatment) for the treated MC lesions (e.g., development of keloids or scarring) for these benign, self-limited lesions. Evaluations of safety and efficacy should be conducted by trained blinded assessors. Assessments by parents/guardians may not be reliable.

Because repeated use of your product can be anticipated in patients who do not get complete clearance of all lesions after 12 weeks of treatment, you will need to address long-term safety in sufficient number of relevant subjects to inform safety.

For the number of subjects and duration of exposure to the investigational product, you are referred to ICH E1A: guidance for industry: *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment Non-Life-Threatening Conditions and Premarketing Risk Assessment*. Molluscum contagiosum is a benign, self-limited illness which heals without sequelae or adverse cosmetic outcomes in the absence of treatment. A robust safety database will be needed in order to ensure a favorable benefit-risk assessment for this patient population.

Provocative evaluations of dermal safety are recommended for your product, including assessments for irritation and sensitization.

Meeting Discussion:

The Sponsor proposed extending the follow-up to 12 weeks beyond the treatment period. The Agency noted that the proposal sounded reasonable, but encouraged the sponsor to include a greater number of subjects (500-600 subjects) for this concentration. The Agency recommended submitting the entire safety database regardless of the concentration. The follow-up period may need to be longer than the proposed 12 weeks to fully assess the

potential for scarring or poor wound healing. Adverse events should be followed until resolution.

2.2. Chemistry, Manufacturing, and Controls

Question 3:

Does the Agency agree that the CMC information for berdazimer sodium drug substance, including methods and specifications, is adequate to support the proposed SB206 Phase 3 clinical studies?

FDA Response to Question 3:

Adequate information has not been provided in the briefing package to determine the adequacy of the Phase 3 drug substance CMC information for berdazimer sodium drug substance. The final determination will be made at the time of submission of the updated CMC data to the cross-referenced IND (b) (4). At the time of submission, clarify the drug substance batches intended for use in Phase 3 studies under this IND. Additionally, provide the following information in the CMC amendment:

- Differences in manufacture process, manufacture equipment, scale, in-process controls, and control of starting materials from Phase 2
- Comparison of impurity profiles, including an evaluation of potentially mutagenic impurities, elemental impurities, and residual solvents.
- Any differences in drug substance physical properties due to manufacture process changes.
- Updated drug substance specifications and acceptance criteria with adequate justifications for proposed changes.
- Current analytical methods and method validation data.
- Updated drug substance batch release and available stability data for Phase 2 and Phase 3 batches
- When available, comparability of drug product manufactured with drug substance manufactured using the Phase 3 process.

Question 4:

Does the Agency agree that the available drug substance stability data are adequate to initiate the proposed Phase 3 studies?

FDA Response to Question 4:

The proposed stability protocol and available drug substance stability data appear reasonable to initiate Phase 3 studies. We note that multiple container closure configurations are currently on stability testing under IND (b) (4). As development proceeds, we remind you that formal stability studies should be conducted with the drug substance container closure intended for commercial storage and distribution. We refer you to the following guidance for industry ICH Q1A(R2) *Stability Testing of New Drug Substances and Products*.

Question 5:

Does the Agency agree that the available supportive drug product stability data and specifications are adequate to initiate the proposed Phase 3 studies?

FDA Response to Question 5:

Yes, we agree. The drug product specification and supportive stability data provided are considered sufficient to initiate Phase 3 clinical studies.

2.3. Nonclinical

Question 6:

Does the Agency agree that the completed dermal nonclinical studies for berdazimer sodium and SB204 are adequate to support the proposed Phase 3 clinical studies for SB206 for the treatment of molluscum contagiosum?

FDA Response to Question 6:

Yes. We agree that the completed dermal nonclinical studies for berdazimer sodium, SB206 and SB204 are adequate to support the proposed phase 3 clinical studies for SB206 for the treatment of molluscum contagiosum.

Question 7:

Does the Agency agree that the completed dermal nonclinical studies for berdazimer sodium and SB204 are adequate to support NDA filing for SB206 for the treatment of molluscum contagiosum?

FDA Response to Question 7:

Yes. We agree that the completed dermal nonclinical studies for berdazimer sodium, SB206 and SB204 are adequate to support the NDA filing for SB206 for the treatment of molluscum contagiosum.

Question 8:

Since no quantifiable systemic clinical exposure was observed for SB204 and SB206, does the Agency agree that the completed nonclinical studies are adequate to support the proposed Phase 3 studies for SB206 for the treatment of molluscum contagiosum?

FDA Response to Question 8:

We agree that if Agency review determines no quantifiable or negligible systemic clinical exposure is observed during the maximal use systemic exposure study conducted with SB206 Gel that the completed nonclinical studies are adequate to support the proposed phase 3 studies for SB206 for the treatment of molluscum contagiosum.

See the response to question 11 regarding your maximal use PK study.

Question 9:

Since no quantifiable systemic exposure was observed for SB204 and SB206, does the Agency agree that the completed nonclinical studies are adequate to support the NDA filing for SB206 for the treatment of mollusum contagiosum?

FDA Response to Question 9:

We agree that if Agency review determines no quantifiable or negligible systemic clinical exposure is observed during the maximal use systemic exposure study conducted with SB206 Gel that the completed nonclinical studies are adequate to support the NDA filing for SB206 for the treatment of mollusum contagiosum.

Question 10:

Does the Agency agree with the approach of requesting a waiver for pre- and post-natal development and systemic rat carcinogenicity studies?

FDA Response to Question 10:

Yes. We agree with your proposed approach of requesting a waiver for conduct of both the pre- and post-natal development and systemic rat carcinogenicity studies based on no quantifiable or negligible systemic clinical exposure under maximal clinical use conditions of SB206 Gel. In addition, submit a waiver request for conduct of the systemic chronic rodent toxicity study.

Additional Nonclinical comment:

Submit the UVA-UVB-vis absorbance spectrum for SB206 Gel. If there is no significant absorbance in the 290-700 nm range, then conduct of the a nonclinical phototoxicity study is not needed for SB206 Gel as outlined in the ICH S10 guidance *Photosafety Evaluation of Pharmaceuticals*.

2.4. Clinical Pharmacology

Question 11:

Does the Agency agree that the current clinical pharmacology package, with no quantifiable clinical exposure from SB206 as well as SB204, is sufficient to support the NDA filing for SB206 in mollusum contagiosum?

FDA Response to Question 11:

No, we do not agree. We recommend you conduct a maximal use pharmacokinetic (PK) study in patients with mollusum contagiosum. We note that you collected PK samples at a single time point in your Phase 2 study (NI-MC201). This is not sufficient for PK assessment of your product. Furthermore, the study results from study NI-AC101 (maximal use study in subjects with acne vulgaris) would not support the bioavailability (BA) requirement for the proposed product (SB206), as the formulation, indication, and study population are different. Information on designing a maximal use PK study is provided below.

The purpose of a maximal use PK study is to assess systemic safety by completely characterizing the PK of parent and metabolites at steady state. It is conducted by obtaining adequate number of PK samples following administration of your to-be-marketed formulation. This study should be conducted in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. The idea is to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- Frequency of dosing
- Duration of dosing
- Use of highest proposed strength
- Total involved surface area to be treated at one time
- Amount applied per square centimeter
- Method of application/site preparation
- Sensitive and validated analytical method

The study itself could be a standalone trial in Phase 2 or could be a sub-group of subjects in a larger Phase 3 trial. Either approach is acceptable. Should a standalone approach be used, you should take steps to ensure that the target patient population (age, gender, race, etc.) is properly represented in your maximal use PK study. Additional information on maximal use study can be found in a publication by Bashaw et al [*Ther Innov Regul Sci*. 2015 Jan; 49(1):108-115].

We recommend you record the amount of formulation used by each subject and ensure that there are sufficient number of subjects within the lowest age range. In addition to assessing the systemic levels of hydrolyzed N methylaminopropyl-trimethoxysilane (hMAP3), you should also assess methemoglobin levels and nitrate levels. You could propose surveillance PK sampling timepoints in the younger subjects and this should be based on prior experience in the older cohort.

We recommend you submit a protocol with sufficient time for the Agency to review before initiating this study.

Meeting Discussion:

The sponsor agreed to conduct an open label maximal use study in parallel with Phase 3. The Agency responded that this is a reasonable approach.

Question 12:

Does the Agency agree that, considering the previous SB204 tQT study results demonstrating no meaningful change in QT interval and given there is no quantifiable clinical exposure in subjects treated with SB206 12%, no further evaluation of QTc prolongation is needed for the NDA filing for SB206 for molluscum contagiosum?

FDA Response to Question 12:

It is premature to provide a response at this time without reviewing the results of your maximal use PK study in subjects with molluscum contagiosum. See FDA response to Question 11. Generally, evaluation of QTc prolongation could be waived if your systemic exposure under maximal use conditions is sub-nanomolar and in vitro hERG assay shows no signal. If you desire to seek a waiver for QTc assessment, you will need to submit an official waiver request for review.

2.5. Clinical/Biostatistics

Question 13:

Novan does not plan to conduct additional sensitization and irritation studies in support of the NDA filing with SB206. Does the Agency agree?

FDA Response to Question 13:

No, we do not agree. You will need to evaluate the dermal safety of your product. This can be done by active assessment for local adverse reactions (contact irritancy, contact allergenicity) in your clinical trials. Additionally, if your product absorbs UV light at relevant wavelengths, you will need to address the potential for phototoxicity and photoallergenicity.

Submit the absorption spectrum data for your drug product (SB 206, 12% Gel) for review by the Agency. Phototoxicity and Photoallergenicity trials can be waived if your drug product does not absorb light between 290 and 700 nm. The initial consideration for assessment of photoreactive potential is whether a compound absorbs photons at any wavelength between 290 and 700 nm. A compound that does not have a molar extinction coefficient (MEC) greater than 1000 L mol⁻¹ cm⁻¹ at any wavelength between 290 and 700 nm is not considered to be sufficiently photoreactive to result in direct phototoxicity. See the ICH guidance: S10 *Photosafety Evaluation of Pharmaceuticals*.

Meeting Discussion:

The Agency recommended performing active assessment during the clinical trials for allergenicity and dermal irritation. The Sponsor would perform patch testing with those patients that have sign of sensitization to confirm the diagnosis. Dermal safety studies conducted for the acne indication may be provided as supportive data.

Question 14:

For the Phase 3 program, the proposed primary endpoint is the proportion of subjects ≥ 2 years of age who achieve complete clearance of all molluscum lesions at or before Week 12. Does the Agency agree that this endpoint is appropriate and sufficient to form the basis of a NDA filing?

FDA Response to Question 14:

The primary endpoint of complete clearance of mollusca at week 12 is acceptable.

Molluscum contagiosum is a benign, self-limited illness which heals without sequelae or adverse cosmetic outcomes in the absence of treatment. Your clinical trials will need to

assess the performance of your product in clinical situations likely to occur in clinical practice. Your clinical trials, as described in your Pediatric Study Plan, will need to address all relevant populations. (b) (4)

While exclusion of periocular lesion treatment is acceptable, all lesions in the perioral and genital area should be considered treatable. Treatment of only lesions on the trunk for children under two years of age would not be acceptable. Treatment on the limbs should be included. This exclusion may be considered for infants, who are less than one year of age by definition, if supported by adequate rationale and/or clinical experience. Clarify the risks of oral intake of your proposed topical product which could justify such an exclusion.

Secondary endpoints based on partial clearance of mollusca lesions are not considered clinically meaningful and would not be accepted for labeling claims.

We have the following additional comments based on the short protocol provided in the briefing document. Additional comments will be provided upon submission of a complete protocol.

- Include subjects with active atopic dermatitis (AD) in trials. (b) (4)
(b) (4) we recommend that subjects with all molluscum lesion types (inflamed or un-inflamed) be included in the trial.
- (b) (4); all lesions outside the peri-ocular area should be treated.
- Subjects will not be able to discern the difference between local adverse reactions and the predicted inflammatory response to treatment, which you would not consider as an adverse event. It is unclear how the investigators will attribute local skin reactions to either categories of adverse drug reactions or the "beginning of the end (BOTE)" signs "(BOTE signs are not considered Adverse Events (TEAE) by investigators) for MC lesions."
- Include assessment of local skin reactions (LSRs) and scarring by investigators at all clinic visits. Include an additional clinic visit at Day 2 (24-hours after the first drug application) for assessment of LSRs.
As currently proposed, the investigator will assess the application site and reports a LSR and associated symptoms as an Adverse Event only in the event that a subject reports a score of (b) (4) for subject tolerability assessment score at any visit.
- We do not agree with your proposed (b) (4) at all clinic visits according to the following scale:

(b) (4)

Source: Protocol Synopsis NI-MC301, p. 86 of EOP2 Briefing Package.

(b) (4)

Meeting Discussion:

The Sponsor has not noted any inadvertent oral ingestion to date, and would like to study older subject initially in a staged approach. The Agency inquired whether there had been any investigation regarding the potential harms of oral ingestion. The Sponsor proposed to review more limited applications in the first five subjects under age 2. The Agency inquired whether these would be excluded from efficacy results. The Agency noted that the Pediatric Review Committee may have further recommendations regarding dosage administration techniques regarding younger subjects.

The sponsor would like to forego a Day 2 assessment and instead perform a 30-minute post-dose assessment which they think is more accurate and useful. The Agency responded that telephone assessment on Day 2 would be sufficient.

(b) (4)

The Sponsor noted that the commercial packaging will be 2 aluminum tubes where equal amounts of (b) (4) active product and hydrogel will be dispensed (b) (4) and mixed at that time and then applied to the affected area. This packaging will be used for Phase 3 studies. The Agency noted that this was not fully described in the briefing document.

The Agency noted that the human factors study will be needed to support the 2-tube dispensing proposal. The sponsor is not pursuing a dual chamber pump at this concentration.

Question 15:

Novan believes the key secondary endpoints are clinically relevant and, if shown to be statistically significant using the proposed hierarchical testing strategy, should be included in the proposed product labeling. Does the Agency agree?

FDA Response to Question 15:

See above discussion.

The meeting package states that the “familywise error rate with respect to the primary endpoint and key secondary endpoints will be strongly controlled at the $\alpha=0.05$ level using a stepdown testing strategy.” From the guidance for industry: *Multiple Endpoints in Clinical Trials*, “In a step-down procedure, one calculates the p-values from all tests to be considered at one time and starts hypothesis testing with the smallest p-value (i.e., statistically the most robust endpoint test) and then steps down to the next smallest p-value (i.e., the next most robust endpoint test), and so on.” However, the meeting package further describes a fixed-sequence method where endpoints are tested in a pre-specified order. Both methods are reasonable for controlling the overall Type I error rate, but the protocol and SAP should specify a single method.

Question 16:

For the primary analysis of the primary efficacy endpoint, it is proposed that subjects who discontinue the study before Week 12 will be treated as failures (non-responders). Does the Agency agree that this methodology is appropriate?

FDA Response to Question 16:

The synopsis specifies that only subjects who achieve complete clearance at Week 12 will be counted as responders for the primary analysis, and all other subjects will be reported as failures. This proposal is reasonable. The protocol should specify sensitivity analyses that utilize alternative assumptions from those of this primary method to ensure that efficacy results are not driven by the method of handling missing data. We recommend conducting a tipping point analysis to explore the space of plausible missing data assumptions.

Question 17:

Does the Agency agree that the power for each study is appropriate to support the NDA filing?

FDA Response to Question 17:

The power calculations appear reasonable for explorations of efficacy given the results of the Phase 2 trials. However, the size of the safety population proposed is inadequate for the population or primarily young children which is the focus of the trials. See discussion above.

Additional comments

- Clarify how subjects with MC lesions who are enrolled from the same household will be handled in the randomization and analysis.
- Randomization for the Phase 3 trials is planned to be stratified by site, age (<2 years vs. ≥ 2), and the number of lesions at baseline (3-18 vs. 19-70). You should prioritize the factors used for stratification to the ones most relevant to efficacy so there are not too many strata. We note your explanation of the proposed cut point for the baseline lesion count strata from the submission dated 3/2/2018 that “(b) (4)
(b) (4)
(b) (4)
however, we recommend examining your Phase 2 data to evaluate whether the treatment effect differed based on baseline lesion count. With a total planned sample size of approximately 300 subjects, randomization is expected to balance baseline lesion counts across the treatment groups without the need to stratify randomization based on an arbitrary cut point.
- To maintain the integrity of the trial and reduce the chance of bias, we recommend pre-specifying the criteria for inclusion in the per protocol (PP) population in the protocol.
- The synopsis states that the results for the primary endpoint will be presented as the odds ratio between SB206 12% and vehicle gel along with the associated 95% confidence interval. Note that for labeling, the proportion of subjects with complete clearance of MC lesions in each treatment arm will be reported for ease in interpreting the study findings. The proposed logistic regression model adjusts for the age groups of 2 to <18 years vs. ≥ 18 years with a group for ≤ 2 years added when those subjects are being analyzed. Clarify why you do not propose to stratify randomization by all 3 age groups. Generally, the analysis should follow the randomization, and stratification should be planned so that a sufficient number of subjects is expected to be enrolled in each stratum to aid in the analysis and interpretation of study findings.

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 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 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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format--- Standardized Study Data (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The [FDA Study Data Technical Conformance Guide](#) (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the [FDA Study Data Standards Resources](#) web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

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.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf>) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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
03/06/2019 02:02:12 PM