CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761244Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131311

MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Christopher Dougherty, PhD, MS
Director, Regulatory Affairs, BIPI
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Dr. Dougherty:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 21, 2021. The purpose of the meeting was to discuss the spesolimab development program for preparation of submission of a BLA.

A copy of the official minutes of the meeting/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 Jennifer Harmon, Regulatory Project Manager at 240-402-4880.

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
- Sponsor's Agenda

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: July 21, 2021, 1:30 p.m. – 2:30 P.M. ET
Meeting Location: Teleconference

Application Number: IND 131311
Product Name: spesolimab

Proposed Indication: For the treatment of flares in adult patients with Generalized Pustular Psoriasis (GPP)

Sponsor Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Jennifer Harmon, PharmD

FDA ATTENDEES
Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
Amy Woitach, DO, MS, Clinical Team Leader, DDD
Maryjoy Mejia, MD, Clinical Reviewer, DDD
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Cindy (Liping) Pan, PhD, Senior Staff Fellow, DIIP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Matthew Guerra, PhD, Biometrics Reviewer, DB III
Bazarragchaa Damdinsuren, MD, PhD, Product Quality Team Lead, Office of Biotechnology Products, DBRR IV
Massod Rahimi, PhD, Product Quality Assessor, Office of Product Quality, Division of Biotechnology Review and Research IV
Margaret Kober, RPh, MPA, Acting Chief, Project Management Staff, Division of Regulatory Operations for Dermatology and Dentistry (DRO-DD)
Jennifer Harmon, PharmD, Regulatory Health Project Manager, (DRO-DD)

SPONSOR ATTENDEES
Christopher Dougherty
Mark Lebwohl
Peter Fang
Janine Lamar, PhD, Global Asset Lead Spesolimab

Birgit Gradl, MSc, Dermatology Lead HEOR & Market Access
Sebastian Vulcu, MD, GPV Therapeutic Area Head, Inflammation
Kelly Coble, BS, Drug Metabolism and Pharmacokinetics
Marijo Weinzierl, PhD, CMC Regulatory Affairs
Matthias Arndt, PhD, Drug & Device Lead
Nirali Kotowsky, PhD, Epidemiology Lead
Jason Guercio, MD, Risk Management Physician GPV
Wendy Bischof, MS, Global Regulatory Affairs
Robin Christoforides, MS, US Regulatory Affairs Lead Inflammation
Kathleen Collins, MBA, Vice President, Regulatory Affairs
Jason Guercio, MD, Risk Management Physician GPV
Thomas Seck, MD, Senior Vice President, Medical and Regulatory Affairs
Xiujiang Li, PhD, Senior Clinical Pharmacologist
Kay Tetzlaff, MD, Therapeutic Area Head Medicine
Thomas Bernd Häufel, MD, Lead Risk Management Physician GPV
Christian Thoma, MD, Medical Lead
Hairui, Hua, PhD, Principal Statistician
Susan Wang, PhD Global Head BDS TA Inflammation
Na Hu, PhD, Project Statistician
Michael Shear, MSc, Senior Principal Statistician
Wendelgard Pisternick-Ruf, PhD, Project Medical Writer

1.0 BACKGROUND

The purpose of this meeting is to discuss the development program for spesolimab for preparation of submission of a BLA. FDA sent Preliminary Comments to Boehringer Ingelheim Pharmaceuticals, Inc. on July 16, 2021.

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 Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Regulatory History:

We have had the following meetings/teleconferences with you:

- March 29, 2021 — Emerging Technology Program

- August 5, 2020 — Guidance
- February 6, 2019 — Guidance
- January 29, 2018 — Pre-IND

We have sent the following correspondences:

- June 25, 2021 — Proprietary Name Request Conditionally Acceptable
- April 30, 2021 — Grant Breakthrough Therapy Designation Request
- June 23, 2020 — Advice Letter
- September 7, 2019 — Meeting Request Written Responses
- May 29, 2019 — Advice letter
- April 17, 2019 — Deny-Breakthrough Therapy Designation letter
- February 4, 2019 — Study May Proceed letter

2.0 DISCUSSION

2.1. Clinical/Biostatistics

Introductory Comments:

In this submission, you presented a high-level summary of the safety and efficacy results for your Phase 2 trial (1368-0013). Subjects were enrolled if they had previous or current evidence of systemic symptoms associated with GPP flares. For randomization, subjects had to experience a GPP flare of moderate to severe intensity, defined as a Generalized Pustular Psoriasis Physician's Global Assessment (GPPPGA) total score of ≥ 3, new appearance or worsening of existing pustules, a GPPPGA pustulation subscore of ≥2, and erythema covering ≥5% body surface area (BSA).

Of the 83 screened subjects, 53 subjects were randomized in a 2:1 ratio to receive a single dose of spesolimab 900 mg (35 subjects) or placebo (18 subjects) at Day 1. Study product was intravenously (i.v.) administered over a period of 90 minutes. Subjects in both groups who had not received escape medication (standard of care) and had a GPPPGA total score of ≥2 and a GPPPGA pustulation subscore of ≥2) were eligible to receive treatment with an open-label dose of spesolimab 900 mg i.v. on Day 8. After Day 8, rescue treatment with a single i.v. dose of 900 mg spesolimab could be further administered in case of a reoccurrence of a flare [≥2-point increase in both the GPPPGA total score and the pustulation subscore after a previous clinical response to treatment (i.e. a GPPPGA total score of 0 or 1)].

The protocol-specified primary efficacy endpoint was the proportion of subjects with a GPPPGA pustulation score of 0 at Week 1. The key secondary efficacy endpoint was the proportion of subjects with a GPPPGA total score of 0 or 1 at Week 1. The GPPPGA total score was a calculated score obtained by averaging over the three subscores (i.e., erythema, pustules, and scaling/crusting).

You have the following ongoing studies in GPP:

a. Study 1368.27: a randomized, double blind, placebo controlled, Phase 2 dose ranging study to evaluate the efficacy, safety, and tolerability of spesolimab compared to placebo in preventing GPP flares in subjects with a history of GPP

b. Study 1368.25: an open label extension, Phase 2 study for subjects who have completed studies 1368.13 and 1368.27

You propose to submit interim analyses of the data for these studies as part of your BLA submission, as well as part of the Safety Update Report.

Your submission based on data from a Phase 2 trial with a relatively small sample size may not be adequate to make a meaningful assessment of the efficacy and safety and, consequently, the risk/benefit of your product. Additional data from your prevention trial, once complete, would provide additional data for safety evaluation as well as supportive evidence for the efficacy data from your current Phase 2 trial. Refer to FDA Response to Question 6. You indicated that you will submit data from the open-label period of the Phase 2 trial (1368.27). It is difficult, however, to make a judgment about the extent and utility of such data without learning about the number of subjects for whom you intend to submit data and the level of evidence in terms of efficacy and safety without having the data submitted at this stage.

Question 1:
Does the Agency agree that trial 1368-0013 is an adequate and well-controlled trial that can be used as the primary basis for determining whether there is substantial evidence to support the claims of effectiveness of 900 mg spesolimab i.v. for the treatment of flares in adult patients with GPP?

FDA Response to Question 1:
See Introductory Comments. Additionally, there are several characteristics that a trial must meet to be an “adequate” and “well-controlled” trial which include defining clinically appropriate endpoints, adequate powering of the trial using an appropriate estimate of treatment effect, randomization and blinding, and the overall conduct of the trial. Whether the results of the Phase 2 trial provide substantial evidence would depend on whether the trial met its preset objectives, the results are statistically robust with small p-values, the results are consistent across subgroups/“subpopulations,” and the level of support from the secondary endpoints. Therefore, based on the short description of the conduct of the Phase 2 trial and the high level summary of the results for the endpoints, it is difficult to draw conclusions on whether the Phase 2 trial is adequate and well-controlled and its results provide substantial evidence to support the claims of effectiveness of 900 mg spesolimab i.v. for the treatment of flares in adult patients with GPP.

As previously communicated in meeting minutes issued March 16, 2018, and the Study May Proceed letter issued February 4, 2019, we have identified potential issues with your clinical reported outcome (ClinRo) tool, Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA)., Whether your evidence dossier provides sufficient evidence to support GPPPGA will be a review issue.

Provide rationale to support the assumption that subjects with a "first episode of an acute GPP flare of moderate to severe intensity" are experiencing a GPP flare and not acute generalized exanthematous pustulosis (AGEP).

Meeting Discussion:
The Agency acknowledged the Sponsor's intent to submit a marketing application consisting solely of the Phase 2 clinical trial (1368-0013) as well as supportive data. While acknowledging that GPP flares can be potentially life-threatening and that GPP is a rare disease, the Agency recommended that the Sponsor include a justification for the target population as well as information supporting how the population will be identified.

The Sponsor submitted additional information to delineate enrolled GPP subjects from subjects with potential AGEP. The Agency acknowledged the Sponsor's additional information.

Question 2:
BI proposes to submit a BLA in Q3/4 2021 based on the compelling results from the adequate and well controlled trial 1368-0013 in GPP flare treatment plus confirmatory evidence for flare treatment from other trials, robust mechanistic evidence of the role of IL-36 in GPP pathophysiology (the MoA), and natural history data on GPP flare. Does the Agency agree with the proposed approach?

FDA Response to Question 2:
See FDA Response to Question 1 and Introductory Comments.

As stated in the response to Question 1, the adequacy of Study 1368.13 to meet substantial evidence requirements will be a review issue. A more robust package would include complete confirmatory data from Study 1368.27.

Meeting Discussion:
The Agency requested that the Sponsor provide data for the individual components of the GPPPGA and to submit analysis results for a multi-component endpoint at Day 8 where each of the individual components of the GPPPGA have a value of zero because such data would help in interpreting the study finding.

2.2. Clinical Pharmacology

Question 3:
Does the Agency agree with the suitability of the bioanalytical methods for spesolimab (Anti-Drug Antibody (ADA), Neutralizing antibody (NAb) and Pharmacokinetic (PK) drug concentration) applied to the clinical trials that will be used for submission?

FDA Response to Question 3:
Based on the assessment of summarized data in the Meeting Package within the scope of this Type B meeting, we agree that the data appears to support the suitability of the immunogenicity assays for detecting and quantitating the binding and neutralizing ADAs in your clinical samples. The adequacy of the validation of the immunogenicity assays will be evaluated as part of the BLA assessment. Address the following points in the BLA submission:

(a) Justify the subject population and number of treatment-naïve samples as well as the number of measurements per sample used for cut-point determinations in assay validations.

(b) Provide assessment on drug tolerance of the assays. The assays should be capable of sensitively detecting ADAs in the presence of spesolimab levels that are expected to be present in serum at the time of patient sampling as measured using the pharmacokinetic (PK) assay.

For additional guidance refer to FDA guidance for industry, *Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019)[1].

The adequacy of bioanalytical method to assess PK drug concentrations will be a review issue. In your initial BLA submission, submit data to support the storage stability of PK samples from the time of collection to analysis and submit incurred sample reanalysis results for review.

Question 4:
BI considers the immunogenicity data package to be included into the Integrated Summary of Immunogenicity (ISI) to be adequate to support the overall assessment of immunogenicity for flare treatment, based on the proposed content of the ISI (including the prospective immunogenicity risk assessment) and preliminary evaluation of immunogenicity data of spesolimab in patients with GPP flares, as shown below. Does the Agency agree?

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA Response to Question 4:
We acknowledge that you plan to provide an Integrated Summary of Immunogenicity (ISI) which summarizes the immunogenicity data of your product obtained from the GPP clinical development program for flare treatment (Trials 1368-0011, 1368-0013, and 1368-0025). We also acknowledge that effect of immunogenicity on PK, efficacy, and safety will be evaluated and the results will be submitted with your BLA submission. Your overall assessment of immunogenicity appears to be reasonable, with the caveat that the adequacy of immunogenicity data will be a review issue and will depend on the bioanalytical methods of immunogenicity assessment applied during your drug development. See FDA Response to Question 3.

Question 5:
Does the Agency agree with BI's position that the potential of spesolimab to cause clinically significant Drug-Drug Interaction (DDI) is low for the treatment of GPP flares, and a clinical DDI evaluation is not necessary for the target indication GPP?

FDA Response to Question 5:
Without clinical evidence, the clinical DDI potential with your product at the proposed dosing regimen in the target patient population(s) cannot be ruled out. However, given the low feasibility of conducting a DDI study in the rare and morbid patient population of GPP, a dedicated DDI study, if deemed necessary, can be conducted after BLA submission. Whether the DDI potential for your product needs to be further assessed in GPP patients will depend on PK results obtained from your planned DDI study in other disease population(s) (i.e., atopic dermatitis) and GPP patients at the proposed dosing regimen. If you plan to use the results of DDI study conducted in a different population to support GPP population, provide a scientific justification in your BLA. See Meeting Preliminary Comments dated 01/26/2018 and 02/01/2019.

Additional Clinical Pharmacology Comments:
In your BLA submission, you should submit exposure response analysis ALT, AST and bilirubin for review.

2.3. Clinical Safety

Question 6:
Does the Agency concur with the strategy to be used for the presentation of safety data in the Summary of Clinical Safety (SCS)/ Integrated Summary of Safety (ISS)?

FDA Response to Question 6:
You state that approximately 401 subjects treated with spesolimab for GPP and other indications will be included in your safety data. Approximately 262 subjects will be exposed to spesolimab for at least 6 months (duration of treatment including residual effect period) and, of those, approximately 55 subjects will have been exposed for at least one year. For subjects with GPP, 57 (of a total of 66) subjects

were scheduled to receive at least one single dose of IV spesolimab 900 mg up to the time of your proposed cut-off for the submission (January 8, 2021).

Your safety database at the time of BLA submission must adequately support your proposed to-be-marketed dose/dosing regimen for spesolimab for the treatment of moderate to severe GPP flare. You are proposing to provide limited safety data in the GPP population. Safety data for spesolimab use in healthy subjects and in development programs for other indications and dose/dosing regimens may provide supportive safety data and will depend on the applicability of the dose, route of administration, and population. Based on the summary provided, in the GPP population there have been at least 2 reported cases of possible Drug reaction with eosinophilia and systemic symptoms (DRESS) with drug-induced liver injury as part of one case and 1 report of torsades de pointes. These safety signals could mandate a need for expansion of the sample size for safety assessments. A balance between the demonstrated benefits and the safety findings/risks will be an important consideration in assessing the adequacy of the overall safety database. We recommend providing additional data from your prevention trial, once complete, for safety evaluation.

Thus far, clinical safety data on spesolimab has been generated and collected across multiple clinical studies in various development programs. In the SCS/ISS, you propose to present all safety data by trial. You do not intend to pool any other studies with your completed GPP Study (1368.13) because of the disparateness of the clinical studies (i.e., differences in indications, study designs, dosing regimen, and route of administration). Provide summary tables describing the number of subjects treated over different durations as well as the number of subjects treated with the to-be-marketed dose. Typically, for a rare disease, a safety database consisting of 1-10% of the existing disease population is preferable for detecting important safety signals (O'Connell and Pariser. Clinical Trial Safety Population Size: Analysis of Drug Approvals for Rare and Common Indications by FDA Center for Drug Evaluation and Research. Exp Opin Orphan Drugs. 2014).

Meeting Discussion:
The Sponsor provided an overview of the safety analysis sets and overall spesolimab exposure that they intend to provide with their submission. The Sponsor also submitted additional information on adverse events noted in the Agency's response. The Agency acknowledged the plan and stated that the adequacy of this safety proposal will be a review issue.

2.4. CTD Module Specific Questions

Question 7:
Does the Agency agree with the organization and proposed content for Module 2.7.1, Summary of Biopharmaceutical Studies and Associated Analytical Methods and Module 2.7.2, Summary of Clinical Pharmacology Studies?

FDA Response to Question 7:
Yes. There are no technical issues. We may, however, request additional information during BLA review.

Question 8:
Does the Agency agree with the general organization and/or proposed content to be included in Module 3 of the BLA?

FDA Response to Question 8:
No. Include summarized CMC information for the surrogate antibody BI 674304 used in the nonclinical studies in section 3.2.S.2.6 or 3.2.R of the BLA. The BLA should include the following:

a) Cell bank stability protocol (in 3.2.S.2.3)

b) Compatibility/in-use stability data (in 3.2.P.2.6 or 3.2.P.8.3)

c) Extractables and leachables assessments and data for product-contacting materials used in the drug substance (DS) and drug product (DP) manufacturing processes (in 3.2.S.2.3 or 3.2.S.2.6 and 3.2.P.2) as well as the container closure systems (in 3.2.S.6 and 3.2.P.2.4).

Meeting Discussion:
The Sponsor provided an explanation for the extent of the information related to the surrogate antibody. The Agency agreed that the high-level summary of the information related to the surrogate antibody appears adequate to support use of this antibody in the toxicology studies. The Agency clarified that items a-c in the FDA Response to Question 8 are applicable to information for spesolimab. The Agency reiterated that the CMC information for the surrogate antibody should be included in Module 3 developmental sections (3.2.S.2.6 or 3.2.R.).

Question 9:
BI intends to include the establishments used for cell bank manufacture and testing, drug substance manufacture, drug product manufacture, release testing, stability testing, storage of stability samples, secondary packaging and labelling of the drug product, and warehouse storage of the drug substance and drug product in the BLA, in sections 3.2.S.2.1 and 3.2.P.3.1 reflecting the commercial manufacturing chain. Additionally, BI intends to include separate 3.2.S.2.1 and 3.2.S.P.3.1 documents for the development sites, reflecting the manufacturing chain pertaining to the clinical trial supplies for the studies to be included in the BLA. The sites described for the clinical trial supplies will cover the establishments used for cell bank manufacture and testing, drug substance manufacture, drug product manufacture, release testing, stability testing, storage of stability samples, secondary packaging and labelling of

the drug product, and warehouse storage of the drug substance and drug product sites described above. Does the Agency agree?

FDA Response to Question 9:
The described separate documents for commercial and development DS and DP manufacturing sites in the BLA sections 3.2.S.2.1 and 3.2.P.3.1 are acceptable. In addition, identify all tests conducted at each in-process, DS, and DP testing site in 3.2.S.2.1 and 3.2.P.3.1.

Question 10:
Does the Agency agree with the number and the selection of the executed batch records for the BLA submission?

FDA Response to Question 10:
Your proposal to submit one executed batch record from one batch of DS and its corresponding DP manufactured at the commercial manufacturing facilities is reasonable. In addition, submit up-to-date master/blank batch records that will be used for DS and DP commercial manufacturing.

Meeting Discussion:
The Sponsor and the Agency agreed that the master batch records will be submitted within 60 days of the BLA submission.

Question 11:
BI would like to submit additional stability data to support a (b) (4) month shelf life for spesolimab (b) (4) mg/mL drug substance during the review period in order to obtain approval for a shelf life of (b) (4) months. Does the Agency agree?

FDA Response to Question 11:
We will request one simple stability data update for the same DS and DP batches provided in the original BLA around month 7 for a standard review and month 4 for a priority review application to assess up-to-date data from on-going stability studies and assign appropriate dating periods for the materials. The proposed shelf-life should be based on available real-time stability data from at multiple batches manufactured with the proposed commercial manufacturing process or a process considered fully representative of the commercial manufacturing process.

Question 12:
Does the Agency agree with the general organization and/or proposed content of nonclinical information to be included in the BLA?

FDA Response to Question 12:
The general organization and the proposed content of nonclinical information to be included in the BLA appear reasonable. Include your updated carcinogenicity assessment for spesolimab in the initial BLA submission.

Question 13:
Does the Agency agree with the general organization and/or proposed content of clinical information to be included in the BLA?

FDA Response to Question 12 and 13:
There are no technical issues with Modules 4 and 5.

Refer to the Comprehensive Table of Contents Headings and Hierarchy and the M4 Organization of the Common Technical Document for Registration of Pharmaceuticals for Human Use Guidance for Industry for more details on each module/section referred in the FDA Response.

From a technical perspective (not content related), all other sections proposed in the eCTD-IND Table of Contents are acceptable (includes Modules 2, 3, 4, and 5). Whether the content will be sufficient, will be a review issue.

Question 14:
Does the Agency concur with the planned strategy for the reporting and presentation of efficacy in the integrated summary of efficacy (ISE)/summary of clinical efficacy (SCE)?

FDA Response to Question 14:
It is difficult to provide comments without first finding out whether data from the open-label periods would provide support for the Phase 2 trial (1368-0013). See Introductory Comments.

Question 15:
Does the Agency agree with the proposed content of Modules 2.7.4 (see Appendix 13) and 5.3.5., and that these modules together satisfy the requirement for an Integrated Summary of Safety (ISS)?

FDA Response to Question 15:
Your proposal to split the ISS across Module 2 and Module 5, with the narrative portions located in Module 2.7.4 (Summary of Clinical Safety, SCS), and the appendices, including tables, figures, and datasets located in Module 5, as part of the clinical trial report, appears acceptable. Also, refer to response to Question 6.

Question 16:
Does the Agency agree with our proposals for inclusion of patient narratives (PNs) and Case Report Forms (CRFs)?

FDA Response to Question 16:
Your proposal appears generally reasonable.

In the narratives, include the date and study day in the discussion relating to the event(s) e.g. “The event happened on xx/yy/2020 (study day zz). Also include how the onset of the event relates to exposure (number of doses and date of occurrence relative to most recent dose).

Additionally, report intensity of adverse events per Common Terminology Criteria for Adverse Events (CTCAE) version 6, instead of the Rheumatology Common Toxicity Criteria (RCTC) version 2.

For any reported adverse event of suspected drug induced liver injury (DILI), provide the following information:

Narrative, table and graphic formatting for patients with suspected DILI

1. Narratives: Patient narratives should follow a chronologic order of events and clinical data. They should be written or edited by physicians or other medical personnel skilled in differential diagnosis and history writing. The narratives should include the following information:

    a) Age, sex, race/ethnicity

    b) Indication for investigational product (IP)

    c) Dose and exposure by dates & study day of IP

    d) Medical history & concomitant medications, including start and stop dates
    e) Treatment emergent liver or DILI related symptoms and course (e.g. jaundice, pruritus, rash, abdominal pain, nausea, vomiting, fatigue, altered mental status)

    f) Details on any hospitalizations and treatments given for the liver injury

    g) All follow-up data available including laboratory values and clinical course

    h) Site investigator opinion on cause of liver injury

    i) Evaluation testing for other causes of liver injury. These data may be included in tabular form. (See example Table 2).

Table 2:

Test	**Test done after injury onset**	**Date, study day done and result**
Hepatitis A IgM antibody	{Yes**//**No}	
Hepatitis B surface antigen	{Yes**//**No}	

Hepatitis B anti-HB core IgM antibody	{Yes//No}	
Hepatitis C antibody	{Yes//No}	
Hepatitis C RNA	{Yes//No}	
Hepatitis E IgM antibody	{Yes//No}	
ANA (anti-nuclear antibody)	{Yes//No}	
ASMA (anti-smooth muscle antibody)	{Yes//No}	
Immunoglobulin G (IgG) level	{Yes//No}	
CMV (cytomegalovirus) antibody IgM	{Yes//No}	
EBV (Epstein Barr Virus) heterophile antibody	{Yes//No}	
EBV capsid antibody IgM	{Yes//No}	
EBV early antigen IgG	{Yes//No}	
Abdominal or liver ultrasound	{Yes//No}	
Abdominal CT scan	{Yes//No}	
Abdominal MRI scan	{Yes//No}	
MRCP or MRC (magnetic resonance cholangiopancreatography or MR cholangiography)	{Yes//No}	
Cholangiogram (ERCP or percutaneous)	{Yes//No}	
Liver histology	{Yes//No}	

2. Liver Related Laboratory Data

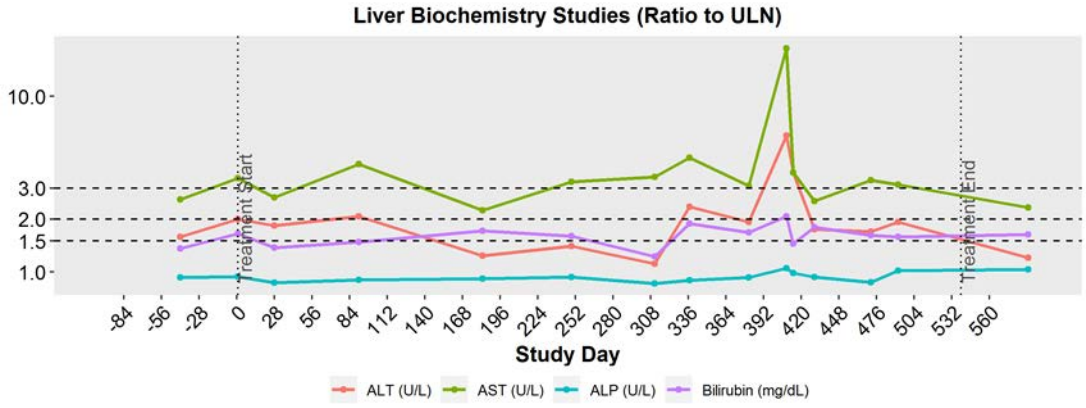
   a. Tabular: For each patient, provide ALT, AST, ALP, GGT total bilirubin (TB), direct bilirubin (DB), CPK and LDH over time and in tabular fashion (See example Table 3):

Table 3:

Visit Date	Study Day	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	TB (mg/dL)	DB (mg/dL)	CPK (U/L)	LDH (U/L)

   b. Graphic: For each patient, provide an ALT, AST, ALP, total bilirubin line graph as multiples of ULN over time with IP exposure included in the graph (See example Figure 1)

Figure 1:



Abbreviations:
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CPK: creatinine phosphokinase
DB: direct bilirubin
DILI: drug-induced liver injury
GGT: gamma-glutamyl transferase
IP: investigational product
LDH: lactate dehydrogenase
TB: total bilirubin

Meeting Discussion:
The Sponsor informed the Agency that trials conducted with spesolimab thus far have used Rheumatology Common Toxicity Criteria (RCTC) version 2 as the classification system for AE (adverse event) intensity. The Sponsor proposed to provide data insofar as possible incorporating CTCAE (Common Terminology Criteria for Adverse Events) version 5 classification for laboratory data. The Agency agreed with this proposal.

Question 17:
Does the Agency agree with the proposed timing and content of the Safety Update Report (SUR) for BLA submission?

FDA Response to Question 17:
Your application was granted Breakthrough Therapy Designation and may be appropriate for Priority Review. If Priority Review designation is granted, your

proposal to provide the SUR within 90 days of the BLA submission appears reasonable. Whether the content will be adequate will be a review issue.

Question 18:
Does the FDA agree with the information outlined in the Electronic Submission Plan (ESP) in Appendix 15?

FDA Response to Question 18:
From a technical standpoint, the information outlined in the ESP in Appendix 15 is acceptable.

In general, Clinical Data Interchange Standards Consortium (CDISC) compliant Study Data Tabulation Model (SDTM) and Analysis Data Model (AdaM) datasets are acceptable. For the analysis datasets, we have the following general comments:

1. 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.

2. The analysis dataset documentation (Define.xml) should include adequate 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 and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

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).

In addition, include the following in Module 5:

1. reference ranges for all laboratory values in the data listings where those laboratory values are presented

2. in the presentation of laboratory data, “flag” all laboratory values and vital signs that are outside of the reference ranges

3. tables of raw incidence rates of adverse events at ≥1% by treatment group as well as the exposure-adjusted rates (in patient-years) by treatment group.

Question 19:
Does the Agency agree that the provided patient experience data is relevant and will be sufficient and overall supportive of the evaluation of benefit risk for the treatment of GPP?

FDA Response to Question 19:
We agree that patient experience data are important and necessary to assess benefit/risk for the treatment of GPP flares. As previously stated within meeting minutes issued 3/12/2019, your final qualitative summary report, including transcripts, will aid in determining if the proposed clinical outcome assessments are fit-for-purpose in the context of your drug development program (i.e., appropriate for its intended use; validly and reliably measures concepts that are both clinically relevant and important to patients; and data can be communicated in labeling in a way that is accurate, interpretable and not misleading). Whether this data will be sufficient, will be a review issue.

2.5. Regulatory

Question 20:
Does the Agency agree that the proposed patient population, submission timeframe and duration of the proposed EAP are acceptable?

FDA Response to Question 20:
You are proposing to submit your EAP protocol in Q3 of 2021. Your protocol is intended to treat patients 18-75 years of age with up to 2 doses of 900 mg iv of spesolimab (1 week apart) for a non-life-threatening GPP flare (new or worsening of widespread eruption of sterile macroscopically visible pustules, with or without systemic inflammation).

As stated above, it is difficult to draw conclusions on whether your completed Phase 2 trial (1368.13) is adequate and well-controlled and its results provide substantial evidence to support the claims of safety and effectiveness in the treatment of GPP. As such, this uncertainty would preclude expanded access of spesolimab outside a controlled clinical trial setting for the requested use in non-life-threatening GPP where alternative therapies are available.

Question 21 a & b:
Provided that the Agency supports the proposed approach to submit a BLA application based on the randomized Phase II Clinical Trial 1368-0013; BI foresees further questions may need to be discussed. Given the granted Breakthrough Therapy Designation status for spesolimab in GPP, BI would propose to have additional phone/email interactions to discuss specific administrative topics regarding the BLA submission rather than formal meetings.

a) Does the Agency support BI's proposal for further interactions?

b) Can the Agency summarize and advise the overall future meeting and interaction possibilities which Breakthrough Therapy designation offers?

FDA Response to Question 21a:
We are agreeable to use other communications outside the formal meetings (i.e., teleconferences, information requests, and emails) to discuss certain specific administrative topics. The appropriate point of contact is always the project manager.

FDA Response to Question 21b:
We refer you to the guidances for industry, *Formal Meetings Between the FDA and Sponsors of Applicants of PDUFA Products*, *Expedited Programs for Serious Conditions – Drugs and Biologics* and MAPP 6025.6 Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics for additional detail on meetings and FDA interactions relating to Breakthrough Therapy Designated drug development programs.

Question 22:
Reference is made to a request for clarification submitted to IND 131311 in SEQ 0063, dated March 17, 2020 pertaining to the assessment of ECG -related findings. Can the Agency provide any comments to the referenced submission?

FDA Response to Question 22:
Yes, we agree that a detailed categorical outlier analysis is not needed and the assessment of ECG related findings as part of the general adverse event assessment in the ongoing and planned clinical trials is sufficient.

Additional Product Quality Comments:

1. To facilitate our review of the DS and DP manufacturing processes for spesolimab, provide the information for process parameters and in-process controls, as applicable, in the following tabular format. Provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to section 3.2.R or to applicable sections 3.2.S.2.6/3.2.P.2.

Process Parameter/ Operating Parameter/ In-Process Control	Proven Acceptable Range/ Control Limits/ Targets[1] for Commercial Manufacturing Process	Criticality Classification[2]	Characterized Range/ Control Limits/ Targets[1] tested in Process Development Studies	Manufactured Range/ Control Limits used for Clinical Study Lots	Manufactured Range/ Control Limits used in Process Validation	Justification of the Proposed Commercial Acceptable Range[3]	Comment [4]

[1]As applicable.
[2]For example, critical process parameter, key process parameter, non-critical process parameter, as described in Module 3.

[3]This could be a brief verbal description and/or links to the appropriate section of the eCTD.
[4]Optional.

The requested summary information will not substitute for detailed information and adequate data from process characterization and process validation studies in sections 3.2.S.2.5, 3.2.S.2.6, 3.2.P.2 and 3.2.P.3.5 to support the commercial manufacturing process.

2. To facilitate our review of the control strategy for spesolimab, provide information for quality attributes and process- and product-related impurities for the DS and DP in the following tabular format. The tables should summarize information from Module 3 and may be submitted either to section 3.2.R or to applicable sections 3.2.S.2.6/3.2.P.2.

Quality Attributes and Process- and Product-Related Impurities for DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method(s)[4]	Proposed Control Strategy[5]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1]For example, critical quality attribute or non-critical quality attribute.
[2]What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.
[3]What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.
[4]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[5]List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.
[6]This could be a brief verbal description and/or links to the appropriate section of the eCTD.
[7]Optional.

3. In the addition to the method validation reports, include the SOPs for the DS and DP release and stability tests in section 3.2.R of the BLA.

The recommended long-term storage condition of spesolimab DS is at (b) (4)C. Our current thinking regarding post-approval annual stability studies (under protocol in section 3.2.S.7.2) for frozen materials is that the identification of unexpected changes in product quality, as one of the main reasons to perform annual stability testing throughout the product life-cycle, is better supported through the use of stability studies on materials stored under a non-frozen condition. In preparation for your marketing application and to cumulate adequate data to support the post-approval annual stability program, incorporate studies in which DS is held under appropriate non-frozen conditions. Assess quality attributes based on your understanding of the molecule for enough duration (e.g., the currently performed (b) (4) months at (b) (4)C) to note trends. Include the non-frozen condition in DS post-approval annual stability protocol in section 3.2.S.7.2 of the BLA.

Meeting Discussion Regarding PREA Requirements:

The Sponsor asked the Agency to confirm that being granted orphan designation for the

same indication as their planned BLA submission would preclude their having to submit an iPSP. The Agency confirmed that the Sponsor's understanding is correct.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- 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.

- 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.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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[2] and Pregnancy and Lactation Labeling Final Rule[3] 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 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.

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ATTACHMENTS AND HANDOUTS

26 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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
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