CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

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

Enhanced Pharmacovigilance (EPV) Plan Memorandum

Date:	August 15, 2022
Reviewer:	Kelly Harbourt, PharmD, BCCCP Division of Pharmacovigilance I
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Product Name:	Spevigo (spesolimab-sbzo) Injectable
Subject:	EPV for Guillain Barre Syndrome and Adverse Events in Pregnant Patients
Application Type/Number:	BLA 761244
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2022-650
Task Tracking Tool ID:	2022-263

1 INTRODUCTION

On June 23, 2022, the Division of Dermatology and Dentistry (DDD) requested the Division of Pharmacovigilance (DPV) provide language for postmarketing enhanced pharmacovigilance (EPV) activities for Guillain Barre Syndrome (GBS) with the use of Spevigo (spesolimab-sbzo), Biologics License Applications (BLA) number 761244. On July 29, 2022, DDD requested that DPV provide additional language for EPV for adverse events in pregnant patients, including pregnancy-related outcomes. This language describes how the Applicant, Boehringer Ingelheim Pharmaceuticals, Inc., should conduct the EPV to be requested in the BLA action letter.

2 REGULATORY HISTORY

On October 1, 2021, the Applicant submitted an original application for BLA 761244 for spesolimab-sbzo for the treatment of generalized pustular psoriasis (GPP) flares in adults. Spesolimab is an interleukin-36 receptor antagonist and, if approved, would be the first monoclonal antibody in this class. The recommended dosing regimen is a single 900 mg dose infused over 90 minutes. If GPP flare symptoms persist, a second 900 mg dose may be administered one week later. This BLA was deemed a priority review with priority goal date of June 1, 2022.

Hypersensitivity/Infections

DDD reviewed the safety information submitted with this BLA and identified cases of hypersensitivity, including two cases of drug reaction with eosinophilia and systemic symptoms (DRESS) in spesolimab-treated patients, as well as cases of opportunistic infections. DDD originally consulted DPV on March 23, 2022 for assistance with drafting language for EPV related to the adverse events of special interest (AESIs) of hypersensitivity, including DRESS, and infections. After additional review of this BLA, DDD determined that these AESIs would be included in product labeling in Sections 4 CONTRAINDICATIONS, 5 WARNINGS AND PRECAUTIONS, and 6 ADVERSE REACTIONS. Subsequently, DDD and DPV agreed that routine pharmacovigilance monitoring would be sufficient for these AESIs rather than requesting EPV.

Guillain Barre Syndrome

On April 25, 2022, the Applicant submitted new safety information, including three potential cases of GBS occurring in the clinical development programs for spesolimab and hidradenitis suppurativa, ulcerative colitis, and palmoplantar pustulosis, respectively, which triggered a major amendment and a 3-month extension of the review clock with an updated extended user fee goal date of September 1, 2022. DDD consulted the Division of Neurology (DN1) to assist with review of the GBS cases and to recommend labeling related to GBS. DN1 reviewed the cases submitted by the Applicant and made the following conclusions and recommendations:[1]

- DN1 agreed that two of the three submitted cases described probable GBS. These few cases represent a relatively high frequency of GBS (2/750 vs 2/100,000 per year).
- DN1 did not identify reasonable causal evidence for spesolimab-induced GBS.
- DN1 recommended labeling of GBS in Section 6 ADVERSE REACTIONS rather than in Section 5 WARNINGS AND PRECAUTIONS using the term GBS rather than the

Applicant's proposed language of [redacted] (b) (4)

- DN1 recommended specific MedDRA terms that may assist in identifying cases of GBS (See Section 4).
- DN1 suggested that EPV may increase understanding of this safety signal.

On June 23, 2022, DDD requested via email that DPV recommend language for an EPV regarding cases of GBS with spesolimab use.

Adverse Events in Pregnant Patients

On July 21, 2022, Dr. Mary Kim, clinical reviewer for DDD, discussed the feasibility of the recommended pregnancy registry post-marketing requirement (PMR) with the Division of Pediatrics and Maternal Health (DPMH), the Division of Epidemiology (DEPI), and DPV. She cited the following barriers for the PMR:

- Rarity of the disease (estimates 1 to 9 per million, claims-based data provides an estimated GPP prevalence of 0.9-1 per 10,000 persons in the United States, with an approximate number of individuals with GPP between 29,000-32,000),
- Anticipated approval for use as a flare treatment for GPP under this BLA,
- Variability in frequency of flare/remission periods amongst patients, and
- Difficulty assessing/attributing causality to the drug product in the setting of potential use of other off-label maintenance treatment for stable disease (i.e. methotrexate, acitretin, biologics).

On July 29, 2022, DDD requested the assistance of DPV to recommend language for an EPV regarding reports of adverse events in pregnant patients in order to capture information about pregnancy-related outcomes in patients exposed to spesolimab as an alternative to a PMR.

3 APPLICANT'S PROPOSED LABELING

The Applicant's proposed labeling for Spevigo (spesolimab) injection includes the following language regarding GBS as of June 14, 2022. Labeling negotiations are ongoing at the time of the writing of this memo.

[redacted] (b) (4)

Reviewer's comment: During labeling negotiations with the Applicant, DDD recommended the deletion of Section [redacted] (b) (4) *, and the addition of the following:*

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Clinical Development

Guillain-Barre syndrome

Among 750 subjects exposed to spesolimab-sbzo during clinical development, (b) (4)

4 PROPOSED EPV PLAN

Given the potential serious outcomes associated with GBS, relatively high frequency of GBS cases occurring in spesolimab clinical development programs, and the need for further characterization of this safety signal, DDD requested DPV to assist with drafting an EPV to monitor for GBS with the use of spesolimab. Given the lack of information in pregnant patients in the clinical development program and the rarity of GPP (proposed indication for spesolimab), DDD also requested that DPV assist with language for an EPV to monitor for adverse events in pregnant patients and pregnancy-related outcomes with spesolimab use.

FDA may consider requesting the Applicant to conduct EPV when there are no other feasible or preferred methods (e.g., Sentinel's Active Risk Identification and Analysis (ARIA) system, observational methods, controlled trials, disease or drug registries) to further characterize the identified or potential risk. In these limited cases, an EPV may be used to:

- Further characterize important identified or potential risk(s) from clinical or non-clinical animal data (regardless of expectedness and outcome) by collecting additional data where there are areas of missing information
- Document how specific missing information will be sought using spontaneous reports (passive surveillance efforts)

Typical EPV activities involve one or more of the following three components:

- (Component 1) Using a targeted data collection tool to gather detailed case information specific to the product and AE of interest
- (Component 2) Expeditiously submitting reports of AEs of interest beyond minimum reporting requirements outlined in 21 CFR 314.80, 314.98, and 600.80
- (Component 3) Summarizing and assessing AEs of interest at a frequency and format defined by FDA (e.g., in periodic safety reports or as a separate report)

For the purpose of this consult, DPV proposes EPV activities that include components 2 and 3 to monitor for the occurrence of GBS with spesolimab use and to monitor for adverse events and pregnancy-related outcomes with spesolimab use. As required under 21 CFR 600.80, the Applicant is to report each adverse experience that is both serious and unexpected to the FDA within 15 days from initial receipt of the information by the Applicant (i.e., expedited reporting). As such, cases of labeled SAEs may not be reported to the FDA in an expedited manner.

Under the *Reporting Requirements* section of the BLA action letter for spesolimab, include the following:

We request that for a period of 3 years from the beginning of U.S. marketing of this BLA, you submit all reported occurrences of possible Guillain Barre Syndrome (GBS) with SPEVIGO (spesolimab-sbzo) injection as 15-day expedited reports, and we request that you provide detailed analyses of these reports as part of your required periodic safety reports (i.e., the Periodic Adverse Experience Report [PAER] required under 21 CFR 600.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should include an assessment of the interval and cumulative adverse event reports for all reports of GBS in your post-market safety database; reports from IND, non-IND, and BLA studies; and the medical literature. The summary should include the report narrative or the manufacturer control number if submitted to the FDA Adverse Event Reporting System.

To assist in identifying reports of possible GBS, we are providing a suggested search strategy with the following MedDRA Preferred Terms that may indicate a possible case of GBS: *Acute polyneuropathy; Acute infective polyneuritis; Acute inflammatory demyelinating polyradiculoneuropathy; Cranial nerve disorder; Demyelination; Demyelinating polyneuropathy; Guillain Barre syndrome; Guillain-Barre syndrome; Hyporeflexia; Miller Fisher syndrome; Paralysis ascending; Peripheral sensory neuropathy; Syndrome Guillain-Barre; Subacute inflammatory demyelinating polyneuropathy;* and *Weakness.*

In addition, we request that for a period of 5 years from the beginning of U.S. marketing of this BLA in the U.S., you submit all reported occurrences of possible exposure to SPEVIGO (spesolimab-sbzo) injection in pregnant patients, patients who are lactating, and infants exposed through breastmilk or infants who were exposed while in utero, as 15-day expedited reports, and we request that you provide detailed analyses of these reports as part of your required periodic safety reports (i.e., the Periodic Adverse Experience Report [PAER] required under 21 CFR 600.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should include an assessment of the interval and cumulative adverse event reports for all reports of pregnancy and lactation exposure in your post-market safety database; reports from IND, non-IND, and BLA studies; and the medical literature. The summary should include:

- The report narrative or the manufacturer control number if submitted to the FDA Adverse Event Reporting System
- Total number of cases of each adverse event of interest by time period and cumulative since approval
- Patient and pregnancy outcome
- Infant outcome
- Age (Mean, Range)
- Indication for spesolimab
- Dosage of spesolimab
- Concurrent and past medical history, past surgical history, smoking status
- Concomitant drugs [list all, including prescription and over-the-counter medications (indication, dosage), herbal, and illicit substances]

- Duration exposure to spesolimab for pregnant patient, fetus, or infant
- Action taken with spesolimab
- Dechallenge, Rechallenge information

In addition to the summary and assessment in each periodic report for both GBS and adverse events in pregnant patients, provide the above data, including the respective manufacturer control number for each case, in .xlsx format. Every effort should be made to obtain thorough and complete follow-up of events related to the serious adverse events of interest, including making every effort to obtain results from specialist consults, assessments, or evaluations of patients with any events related to the adverse events of interest. The clinical information collected in this manner will enhance the quality of adverse event reports submitted to FDA and facilitate our assessment of these reports.

5 REFERENCES

1 Foster D. DN Consult Memo, BLA 761244 Spevigo (spesolimab) and GBS. June 16, 2022, DARRTS Ref ID:5001397.

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

/s/

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CONSULTATION FOR THE DIVISION OF DERMATOLOGY AND DENTISTRY

DATE: June 16, 2022

TO: Mary Kim, MD, Division of Dermatology and Dentistry (DDD)

FROM: Dan Foster DO, MPH, MS, Division of Neurology (DN1) medical officer

THROUGH: Laura Jawidzik, MD, DN1 team leader, deputy division director (acting)

SUBJECT: Neurology consult regarding BLA 761244 (spesolimab), requested May 9, 2022

Spesolimab (IND 131311 and BLA 761244) is a new molecular entity (NME) IL-36 inhibitor (recombinant, humanized anti-IL36R IgG1 monoclonal antibody) for generalized pustular psoriasis (GPP). The BLA for this product was submitted October 1, 2021, and is currently under review in DDD. Based on three premarket cases of suspected spesolimab-associated Guillain-Barre Syndrome (GBS) from three non-GPP trials (ulcerative colitis (b) (4) , palmoplantar psoriasis [IND 131311] and hidradenitis suppurativa [IND 131311]), Boehringer Ingelheim Pharmaceuticals (BI) proposes to add the following warning to their company core data sheet:

(b) (4)

Dr. Kim, the DDD clinical reviewer for the spesolimab BLA requested a DN1 consultation regarding the following three issues:

1. Review the GBS case reports ("DDD requests the Division of Neurology review of the cases reported by investigators as Guillain-Barre syndrome")
2. Concurrence with the adequacy of the BI global database search for other GBS cases using MedDRA SMQs GBS (narrow), demyelination (narrow), peripheral neuropathy (narrow)? ("Does the Division of Neurology agree with the Applicant's search terms? If not, would you recommend any additional search terms to the Applicant?")
3. Recommended labeling (b) (4)

Data Reviewed:
Spesolimab Clinical Overview Statement March 29, 2022, including 3 GBS case-reports
Spesolimab IND 131311 DSUR 6 up to September 8, 2021
Spesolimab IND 131311 Medical Officer 30-day Safety Review September 20, 2018
(b) (4)

Drug Background
Spesolimab is a humanized monoclonal antibody directed against the IL-36 receptor. It binds and blocks IL-36 activation and the subsequent dermal inflammation in GPP.

IL-36 is expressed on lung, gut, T-cells, and keratinocytes. IL-36 agonists bind to IL-36 receptor and then activate MyD88, MAPK, and NF-kappaB signaling pathways. These signaling pathways up-regulate target genes for immune cell activation, antigen presentation, pro-inflammatory factor production. IL-36 receptor activation leads to skin inflammation. IL-36 receptor antagonism has the opposite effect.

According to a literature search conducted by this reviewer, IL-36 does not play a direct role in GBS pathophysiology, though one observational study speculates about an indirect role (Zhao, Zhang, & Hui, 2020) (Nyati & Prasad, 2014) (Yuan, Xu, & Liu, 2019) (Soltani, Rahmani, & Reaei, 2019).

According to the most recent Drug Safety Update Report (DSUR 6, 9 September 2020 to 8 September 2021) there have been 747 exposures to spesolimab since the development international birth date on September 9, 2015. The important potential risks listed in the DSUR include the following: infections (serious/severe, opportunistic), systemic hypersensitivity reactions, and malignancy but neither neuropathy nor autoimmune disease. (b) (4)

Indication

Generalized pustular psoriasis (GPP) is a rare monogenic type of psoriasis characterized by widespread pus-filled blisters on a background of red tender skin. This psoriasis subtype (whether familial or sporadic, chronic or relapsing) is caused by a deficiency of IL-36R antagonism and excessive IL-36R activation with subsequent skin inflammation.

While patients with psoriasis have an elevated risk of stroke, epilepsy, multiple sclerosis, migraine, Parkinson's disease, RLS, OSA they are not known to have an elevated risk of GBS (Amanat, Salehi, & Rezael, 2018).

Adverse Effect

Guillain-Barre syndrome describes an immune-mediated polyradiculoneuropathy (Sharizaila, Lehmann, & Kuwabara, 2021). Typically, GBS presents with an antecedent infectious illness is followed by limb weakness that follows an acute monophasic course and reaches a nadir over 2 to 4 weeks. This weakness is symmetric and patients develop hyporeflexia. Supportive studies include spinal fluid, electrodiagnostics, MRI, and anti-ganglioside antibodies. The mean incidence in North America and Europe is 1.1 per 100,000 per year. Incidence increases with age with a peak between 50 and 69.

The Brighton Criteria were created for post-vaccine GBS surveillance. The criteria summarize different levels of diagnostic certainty for based on different amounts of diagnostic information found in case reports. This criteria has been validated for typical presentations of GBS. There are 5 Brighton "levels" of certainty for GBS case reports:

- "level 1" includes the most complete data set among the 5 levels (acute flaccid weakness, consistent electromyogram [EMG] and cerebrospinal fluid [CSF], no alternative). Specifically, for a case report to be considered a "level 1" all 5 of the clinical criteria are met (bilateral weakness, flaccid weakness, decreased reflexes in the weak limbs, monophasic illness pattern, nadir 0.5-28 days after onset), and EMG is consistent with GBS, and CSF has cyto-albuminologic dissociation with protein elevated and pleocytosis <50 cells/microL, and there is an absence of an identified alternative diagnosis
- "level 2" has a little less paraclincal support than "level 1" as it includes EMG or CSF but not both. Specifically, for a case report to be considered "level 2" all 5 of the clinical criteria are met, and EMG or CSF are consistent with GBS, and there is an absence of an identified alternative diagnosis
- "level 3" is based on the clinical picture alone. Specifically, for a case report to be considered "level 3" all 5 of the clinical criteria are met, EMG and CSF are lacking/negative, and there is an absence of an identified alternative diagnosis for weakness

- "level 4" is considered a GBS case report based on fact that the term 'GBS' is the stated diagnosis and alternative diagnoses are lacking though supportive data is not detailed.
- "level 5" is a case report where GBS is excluded due to an alternative diagnosis.

GBS is an umbrella-term that describes a collection of para-infectious acute polyneuropathies:

- classic demyelinating (acute inflammatory demyelinating polyradiculoneuropathy[AIDP])
- axonal (acute motor and sensory axonal neuropathy [AMSAN] or acute motor axonal neuropathy [AMAN])
- pure motor
- pure sensory
- paraparetic
- facial diplegia with distal paresthesia
- pharyngal, cervical, brachial
- GBS with hyperreflexia
- Classic Miller Fisher Syndrome (MFS)
- Acute ophthalmoplegia
- Acute ataxic neuropathy
- Acute ptosis
- Acute mydriasis
- Acute vestibular syndrome

BI's March 29, 2022, Clinical Overview Statement (COS) entitled: "Supporting the update of the Company Core Data Sheet for the treatment of flares in adult patients with GPP (b) (4)

The clinical overview statement included the following three case reports describing GBS associated with spesolimab exposure.

Manufacturer Control Number (MCN) 2022-BI-108847, subject number (b) (6) from Protocol 1368.67 for Hidradenitis Suppurativa (a phase 2, open-label, long-term extension trial of spesolimab in adults with hidradenitis suppurativa):

This AE report involved a 26-year-old French female with a history of obesity, reflux and condyloma, headaches, taking spesolimab for hidradenitis suppurativa. She developed wrist pain September 2021 after approximately 3 months of treatment with the study drug. In November 2021, in addition to wrist pain, her baseline headaches worsened, and she developed generalized weakness with acral paresthesias. She was examined by neurology in November while symptomatic and they found lower extremity areflexia (normal upper extremity reflexes, normal power, normal pain/temperature sensation, no dysmetria, negative Romberg). Her "pan-medullary MRI" was normal. Spesolimab was stopped at this time (patient's perogative). In January after resolution of symptoms, neurology performed an EMG with ultrasound that showed:

> MOTOR NERVES: globally prolonged distal motor latencies with normal conduction velocities and normal amplitudes. Left ulnar motor temporal dispersion. Prolongation of F-wave latencies in median/ulnar/tibial. Absent right peroneal F-wave.
> SENSORY NERVES: "Lengthening of the sensory nerve conduction velocities" of ulnar/median/tibial nerves. Slow median/peroneal/sural sensory conduction velocities. Normal amplitude sensory potentials.
> NEEDLE EXAM: The myogram was normal except for polyphasic motor unit potentials in the left deltoid.
> ULTRASOUND: median nerve swelling at the elbow.
> ELECTRODIAGNOSTIC CONCLUSION: "Electroneuromyogram showed an acute non-length-dependent polyradiculoneuropathy, probably demyelinating and predominantly distal."

This case was assessed by the investigator as drug-related. The sponsor considered this AE (AIDP) to be reasonably causally associated with the study drug based on temporal association and dechallenge. A panel of neurologists determined that this case was not GBS because the time from onset to nadir was too long and the case was confounded by obesity.

REVIEWER COMMENT: This EMG describes a mild generalized acquired demyelinating sensory-motor polyneuropathy in a patient who recently experienced several weeks of acute symmetric limb weakness/paresthesias and lower-extremity hyporeflexia. Other causes for acute flaccid weakness were sought but not found. While some details in the case report are missing, the general picture is consistent with mild GBS, Brighton level 2. It is unclear how obesity confounds this case. The time from onset of GBS symptoms (November) to the time of nadir (at some unspecified point, likely in December based on symptoms having plateaued and then resolved by her EMG appointment in January) is plausibly less than 1 month long, supporting a causative role for spesolimab in this AE. Temporality and de-challenge support possible drug-relatedness. The patient received Comirnaty in May, June and December 2021. Her symptoms began 5 months after the 2nd shot and 1 month before the 3rd. The vaccine type and the timing make vaccine-related GBS unlikely.

MCN 2020-BI-047324, subject number (b) (6) from Protocol 1368.17 (a phase 2, open-label, long-term safety trial in patients with moderate-to-severe ulcerative colitis who have completed previous BI655130 trials).

This AE report involves a 59-year-old, Russian male, with a history of hypertension, chronic cholecystitis, nonalcoholic fatty liver disease, and ulcerative colitis for which he took spesolimab, azathioprine, sulfasalazine, and mesalamine. After 9 months of treatment, the patient presented to the hospital with polyneuropathy and was admitted to the neurology department. His neurology workup diagnosed GBS based on acute symmetric tetraparesis with electrodiagnostic support ("electroencephalography….symmetrical…predominantly motor type…demyelinating nature…"). Upon admission he was coincidentally diagnosed with bilateral polysegmental pneumonia and COVID-19 (he was admitted in August 2021, the same month that Russia approved the 2-dose series Sputnik V, this patient's vaccination status was unreported). The patient died on hospital day 13 from a cerebellar hemorrhage-related tonsillar herniation (a known serious complication of COVID-19 severe acute respiratory syndrome). Assessed as Brighton level 4 GBS by the neurology panel.

REVIEWER COMMENT: Though details are limited, this appears to be a case of GBS (acute weakness, evaluated by a neurologist who considered the history and clinical exam when generating a differential diagnosis). The body of the "electroencephalography" report describes the results of an EMG rather than an EEG. This report suggests the classic AIDP type of GBS. This is likely Brighton Level 2 GBS (clinical picture and paraclinical support for GBS while ruling out other causes). COVID is not known to be a confounder (Caress, Castoro, & Simmons, 2020) (Keddie, Pakpoor, & Mousele, 2021). *Critical illness neuromyopathy has a different temporal and electrodiagnostic profile than is seen in this case. Myelopathy was presumably ruled out on clinical grounds. Tick paralysis affects a younger demographic and presents with bulbar findings. This case lacks the typical features of COVID-related GBS (12 day latency from the onset of COVID symptoms to the onset of GBS symptoms, and facial nerve involvement). The timing of this case and the slow rollout of the Russian vaccine makes it unlikely that this is vaccine-related GBS. Determining that these cases describe likely GBS is easier than determining that this GBS is likely drug-related* (Awong, Dandurand, & Keeys, 1996). *Supporting drug-relatedness are temporality (the AE occurred after drug exposure) and frequency (multiple case reports among a relatively small drug-exposed population). There is a paucity of data regarding strength of association, consistency, dose-response, experimental evidence, pharmacological class (anti-TNF-alpha monoclonal antibodies are thought to cause peripheral demyelination through TNF activity rather than monoclonal structure) or rechallenge. Theoretical plausibility remains an open question (one article suggests an indirect mechanism is possible).*

MCN 2021-BI-102296, subject number (b) (6) from Protocol 1368.24 (a phase 2, open-label, single-arm, long-term trial in patients with palmoplantar pustulosis (PPP) who have completed previous BI spesolimab trials).

This AE report involved a 53-year-old German female with diabetes, alcohol use disorder, neurologist-diagnosed chronic sensorimotor neuropathy, and chronically unsteady gait. After 16 months of treatment with spesolimab for PPP she was hospitalized for acute-on-chronic unsteady gait. They diagnosed GBS and treated her with thiamine/folate while continuing the study drug. She improved 3 weeks after discharge. The neurology panel assessed her as not having GBS based her the time to nadir, confounding by pre-existing neuropathy symptoms/risk factors (diabetes and alcohol), improvement after vitamin administration and physical therapy implying an alternative diagnosis (cofactor deficiency). Treatment with spesolimab continued.

REVIEWER COMMENT: This reviewer agrees with BI that this is not GBS. The time-course in this case (from onset of symptoms and electrodiagnostic abnormalities is over 1 year rather than the more typical 2 weeks) is inconsistent with an acute polyneuropathy. The patient had two competing diagnoses (alcohol and diabetes) with greater prevalence than GBS. She was successfully treated with vitamins rather than IVIG, suggesting cofactor deficiency was a more likely diagnosis than GBS. She was vaccinated with Comirnaty July 2021, 3 months after her 2nd neurologic work up for neuropathy.

BI failed to identify additional cases of peripheral neuropathy in general or GBS in particular from their spesolimab safety database (MedDRA SMQs GBS, Demyelination, Peripheral Neuropathy). The sponsor's literature search failed to identify a basis for IL-36 monoclonal antibody-associated GBS ('GBS and monoclonal antibodies', 'GBS and IL-36 receptor antagonist', 'demyelinating polyneuropathy and monoclonal antibodies', 'demyelinating polyneuropathy and IL-36 receptor antagonist', 'Subacute idiopathic demyelinating polyradiculoneuropathy').

REVIEWER COMMENT:
The sponsor searched their database using the MedDRA term "Guillain-Barre Syndrome" which includes acute infective polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy, Guillain Barre syndrome, Guillain-Barre syndrome, paralysis ascending, syndrome Guillain-Barre. They also used the MedDRA terms "demyelination" and "peripheral neuropathy."

The following terms are relevant to GBS and might increase the sensitivity of the sponsor's search for other cases:

- *"Miller Fisher syndrome" includes Miller Fisher syndrome and Fisher syndrome*
- *"Cranial nerve disorder" includes cranial nerve disorder NOS, cranial nerve lesion NOS, cranial neuropathy NOS, unspecified disorder of cranial nerves*
- *"Acute peripheral neuropathies" includes acute polyneuropathy, acute polyradiculoneuritis and subacute polyneuropathy*
- *"Subacute inflammatory demyelinating polyneuropathy"*
- *"Demyelinating"*
- *"peripheral neuropathies"*
- *"Weakness"*
- *"Hyporeflexia"*

BI concludes that,

> …one of the cases [MCN 2020-BI-047324, subject number (b) (6), the 59-year-old Russian man described above] met Brighton category 4 (i.e., a low diagnostic certainty, with insufficient evidence to meet the case definition). In that case, there was a coincident infection with SARS-CoV-2. The other two cases…were assessed as not GBS. A causal association to spesolimab for any of the reported cases was assessed to be unlikely.

> …in all three cases confounding factors were present. A certain diagnosis of GBS could not be verified in any of these cases. The unspecific symptoms and findings in all three cases may best be referred to as peripheral neuropathy
>
> As based on the data a potential risk of peripheral neuropathy with spesolimab i.v. cannot be ruled out.

REVIEWER COMMENT: This reviewer concludes that there are 2 cases of probable GBS (typical clinical picture, typical paraclinical diagnostic supporting evidence, consideration of alternative diagnosis, all under the direction of neurologists) associated with spesolimab. These few cases when none were expected represent a relatively high frequency of GBS (2/750 vs 2/100,000 per year). Of note, GBS is serious and treatable.

Labeling Guidance
According to the 2011 Guidance for Industry: *Warnings and precautions, contraindications, and box warning sections of labeling for human prescription drug and biological products – content and format* Section 5 describes serious or clinically significant hazards that have reasonable evidence of causal association (based on reporting frequency, dose-response, consistency with pharmacology/biology, dechallenge/rechallenge).

According to the 2006 Guidance for Industry: *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*, Section 6 describes undesirable drug-associated events for which there is some basis to believe in a causal relationship. This section includes data that has practical importance.

Recommendations
The sponsor proposes the following statement (b) (4)

(b) (4)

Currently, support for this proposal does not meet the standard of reasonable causal evidence for spesolimab-induced GBS. Furthermore, the sponsor's proposed language is vague. (b) (4) This imprecision makes the call for provider vigilance ineffectual. From this reviewer's perspective the sponsor has presented two cases of probable GBS among almost 750 spesolimab-exposed subjects. This may represent a higher frequency than background. It may warrant labeling but there is no other causal evidence beyond temporal association to support placement in Section 5. DN1 proposes that DDD consider the following language for Section 6:

> Among 750 patients exposed to spesolimab during clinical development, two cases of Guillain-Barre syndrome occurred.

Enhanced pharmacovigilance in the post-market setting may also contribute to understanding this safety signal.

References

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Clinical Inspection Summary

Date	4/20/2022
From	Phil Phuc Nguyen, M.D., Medical Officer Karen Bleich, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Acting Branch Chief/ Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Mary Kim M.D., Medical Officer Amy Woitach M.D., Team Lead Kendall Marcus, M.D., Division Director Division of Dermatology and Dentistry
BLA	761244
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc
Drug	Spesolimab
NME	Yes
Therapeutic Classification	Interleukin-36 receptor antagonist
Proposed Indication	Treatment of flares in adult patients with generalized pustular psoriasis (GPP)
Consultation Request Date	1/4/2022
Summary Goal Date	4/22/2022
Action Goal Date	5/18/2022
PDUFA Date	6/1/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Boehringer Ingelheim Pharmaceuticals has submitted data from one phase-2 Study: 1368-0013 to the Agency in support of a Biologics Licensing Application (BLA 761244) for spesolimab as an intravenous treatment of flares in adult patients with generalized pustular psoriasis (GPP).

Two Clinical Investigators, Drs. Bachelez and Turki, were identified for surveillance inspections. Due to the COVID-19 pandemic, travel to Tunisia for the inspection of Dr. Turki was not possible.

Based on the CI inspection conducted by the FDA, the study data generated by the inspected entity appears acceptable in support of this BLA

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II. BACKGROUND

GPP is a rare, severe, and life-threatening variant of psoriasis that is characterized by recurrent, acute onset, widely distributed pustular eruptions on inflamed, erythematous skin. Untreated, GPP can progress to complications including sepsis, acute renal failure, high-output congestive heart failure, and acute respiratory distress syndrome (ARDS). Spesolimab is an interleukin-36 receptor antagonist that modulates the immune response that may treat a GPP flare.

Study 1368-0013

Title: *Effisayil 1: Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity*

Study 1368-0013 is a phase II, multi-center, randomized, placebo-controlled, double-blind, parallel-group, single-dose trial with spesolimab and placebo. Patients who achieved clinical improvement and completed trial 1368-0013 were to be offered to roll over into the open-label extension (OLE) trial 1368-0025 if they met certain inclusion criteria. The follow-up period of trial 1368-0013 was to be 12 to 28 weeks, depending on the timing of the last spesolimab dose in trial 1368-0013, and whether patients continued in the OLE trial.

The protocol specifies the following key endpoints:

- Primary efficacy endpoint: A GPPGA (GPP global assessment) pustulation subscore of 0 indicating no visible pustules, at Week 1
- Key secondary endpoint: A GPPGA total score of 0 or 1 at Week 1

Eligible subjects were to be those aged 18 to 75 years with a diagnosis of GPP based on the consensus diagnostic criteria by the European Rare and Severe Psoriasis Expert Network (ERASPEN). In addition, patients were to be required to have either a GPP Global Assessment (GPPGA) score of 0 or 1; a history of GPP (per ERASPEN criteria above) and previous evidence of fever, asthenia, myalgia, elevated C-Reactive Protein (CRP) levels, or leukocytosis with peripheral blood neutrophilia; or a first episode of acute GPP flare of moderate to severe intensity with evidence of the above findings. Subject's diagnoses were to be confirmed by a central external expert committee.

The study course was to consist of a screening phase up to 35 days, and a treatment phase of 8 weeks. Patients eligible to receive treatment after screening were to be randomized in a 2:1 ratio to receive spesolimab or placebo. All randomized patients were to receive the first dose of study medication (900 mg i.v. spesolimab or placebo) on Day 1 of Week 1. The scheduled primary endpoint visit was to be the Week 1/Day 8 visit. Based on the subsequent treatment response, patients were then to be followed up for 12 to 28 weeks, depending on whether they were also enrolled in the OLE trial.

Per the study report, study 1368-0013 was conducted at 37 sites with screened patients in 12 countries in Europe, North America, North Africa, and Asia. The study lasted from February 20, 2019 to January 5, 2021, with a final Data Base Lock (DBL) on April 1, 2021. 53 subjects were randomized, (35 in spesolimab arm, and 18 in placebo arm), and all randomized subjects were treated. The original protocol and global amendment 1 were dated June 27, 2018, with the latest protocol version 3 dated June 26, 2020.

III. RESULTS (by Site)

FDA Inspections

1. Herve Bachelez M.D.
   Hospital Saint Louis Polyclinique Dermatologique
   1 Avenue Claude Vellefaux Paris, 75010, FRANCE
   Study: 1368-0013
   Site: FRA1
   Dates of Inspection: 28 February, 2022 to 4 March, 2022

   This inspection was conducted on-site. At the time of the inspection, 14 subjects were screened, and 8 enrolled. For all 8 subjects, the entire study file was reviewed and audited against sponsor data for demographic, IP treatment, and lab results.

   Primary and secondary endpoints were verified, specifically: Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) Erythema, GPPGA Pustules at Week 1 (Primary Efficacy), GPPA Scaling/crusting, and GPPA Total Scores at Week 1 (Primary Efficacy), Generalized Pustular Psoriasis Area and Severity Index (GPPASI), Japanese Dermatological Association Generalized Pustular Psoriasis Score (JDA GPP), and concomitant illnesses and medications. Six of eight subjects' photographs of skin lesions were also reviewed. There was no evidence of under-reporting of protocol deviations. The inspection revealed no deficiencies with maintenance of the blind.

   The inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

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OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2021503
NDA#/Referenced IND#:	BLA 761244/IND 131311
Applicant:	Boehringer Ingelheim Pharmaceuticals
Established Name/Trade Name:	spesolimab
Indication:	For the treatment of flares in adult patients with generalized pustular psoriasis ☒Rare Disease/Orphan Designation ☐Pediatrics (>6 years)
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer	Mary Kim
Clinical Team Leader (TL)	Amy Woitach
Regulatory Project Manager:	Jennifer Harmon
COA Reviewer:	Julia Ju, PharmD., PhD.
COA TL:	Selena Daniels, PharmD., PhD.
COA Director:	David Reasner, PhD
Instruments reviewed:	1. Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) ☒ Clinician-reported outcome (ClinRO)

Table of Contents

1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of spesolimab for treatment of flares in adult patients with generalized pustular psoriasis (GPP). The specific targeted clinical outcome assessment (COA)-related labeling claims are related to pustular clearance and improvement in GPP severity, which are derived from a single global, multi-center, double-blind, randomized, placebo-controlled phase 2 study (Study 1368-0013)[1]. To support these claims, the applicant submitted a psychometric report. The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims related to the concept of interest.

The primary efficacy endpoint proposed for labeling is:

- Proportion of subjects with a Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) Pustulation subscore of 0, indicating no visible pustules, at Week 1

The secondary efficacy COA endpoints proposed for labeling are:

- Proportion of subjects with a GPPPGA total score of 0 or 1 at Week 1
- Proportion of subjects with ≥75% reduction in the Generalized Pustular Psoriasis Area and Severity Index (GPPASI 75) at Week 4
- Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4
- Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score at Week 4

The data from Study 1368-0013 demonstrated that spesolimab had statistically significant improvement in the primary and secondary efficacy COA endpoints. However, the subject of this review is related to the GPPPGA-based endpoints per the request of the Review Division.

From a COA perspective, the GPPPGA and its corresponding endpoints should be interpreted with caution due to measurement limitations (e.g., small sample size, limited data on reliability, inadequate anchor scales). The GPPPGA Pustulation subscore could potentially support a labeling claim related to pustular clearance in adults with GPP who have flares, if supported by the clinical trial study design and analysis. However, the GPPPGA total score appears inadequate to support labeling claims because in the sponsor's clinical study, the observed improvement in the GPPGA total score is largely driven by improvement in the GPPGA Pustulation subscore. If this data is included in labeling, it will be important to communicate the variability in response, if applicable, whether expressed graphically or through text; presenting data without point estimates, if applicable; and including any important limitations to the interpretability of the data.

[1] The applicant submitted a marketing application consisting solely of the phase 2 clinical trial data, as well as supportive data.

2. REVIEW CONCLUSIONS

Review Summary
The GPPPGA was reviewed for content validity and other measurement properties (reliability, validity, ability to detect change). The GPPPGA Pustulation subscore could potentially support a labeling claim. However, the GPPPGA total score appears inadequate to support labeling claims because the observed improvement in the GPPGA total score is largely driven by improvement in the GPPGA Pustulation subscore in the sponsor's clinical study.

While the anchor-based analyses are uninterpretable, it is noted that the primary endpoint for Study 1368-0013 is defined as the proportion of subjects with a GPPPGA pustulation subscore of 0, indicating no visible pustules, at Week 1. This endpoint accounts for clinical meaningfulness as the targeted response is complete resolution of signs (i.e., pustular clearance).

Key Issues Identified

Issue 1: Content Validity

- The GPPPGA appears to be content relevant for the target population. Based on qualitative data from patients, pustules appear to be an important and relevant concept to patients with GPP. While patients reported experiencing erythema and scaling/crusting (flaking), they did not rank these concepts as most burdensome.
- The applicant did not conduct qualitative interviews with clinicians. Based on discussion with Clinical, pustules, erythema, and scaling are considered clinically relevant to the target population. However, in the absence of cognitive interviews with clinicians, it is unclear whether the GPPPGA is well-understood and interpreted appropriately across clinicians.

Issue 2: Other Measurement Properties

- It is difficult to fully evaluate the psychometric properties of the GPPPGA due to insufficient sample size.
- There is limited data on the reliability of the GPPPGA. The applicant did not evaluate inter-rater reliability of the GPPPGA.
- Many of the reference measures used for the psychometric analyses were inadequate (e.g., reference measures do not measure similar concepts as the targeted concepts of the GPPPGA).

Issue 3: Data Interpretability

- The small sample size makes it difficult to fully interpret the GPPPGA scores.
- Regarding the clinical meaningfulness of the GPPPGA Pustulation subscore, the sample size and inadequate anchor scales limit the interpretability of the anchor-based analyses. However, it is noted that the primary endpoint for Study 1368-0013 targets complete resolution of signs (i.e., pustular clearance).
- Regarding the GPPPGA total score, the endpoint derivation allows subjects to have a GPPPGA total score of 0 or 1 (clear or almost clear) rather than a target of complete resolution. Examining the item-level data, the Pustulation subscore appears to be driving most of the observed change in the GPPPGA total score (see Descriptive Statistics in Section

5.4.5 of this review). The majority of the participants who had a GPPPGA total score of 1 had at least one sign with mild or greater disease. Based on the limited interpretability of the anchor-based analyses, it is difficult to conclude whether or not the applicant's proposed 1-point reduction (based on 0-4 scale) is a meaningful within-patient score change in the GPPPGA total score. If COA data is included in labeling, it will be important to communicate the variability in response, if applicable, whether expressed graphically or through text, as well as including any important limitations to the interpretability of the data.

Assessment of study endpoints
As noted above, the GPPPGA-based primary endpoint (Proportion of subjects with a GPPPGA Pustulation subscore of 0 at Week 1) assesses clinical benefit via the targeted response of complete resolution of signs; this endpoint appears to adequately support labeling claims. Due to the GPPPGA Pustulation subscore influencing the change in the GPPPGA total score, there is concern that the data from this score may not be communicated in labeling in a way that is accurate, interpretable and not misleading. As such, this endpoint inadequately supports labeling claims.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, sponsors should consider the following:

- Use phase 2 trials to evaluate measurement properties of COAs and accumulate and document evidence to support a definition of clinically meaningful within-patient improvement in COA scores prior to initiating registration studies to the extent possible.
- Identification of concepts should come from patient input (e.g., conducting patient interviews, identifying literature related to previously conducted patient qualitative studies), as well as relevant stakeholders (e.g., clinicians), and be obtained early in drug development (i.e., prior to confirmatory trials).
- Anchor-based methods to identify clinically meaningful within-patient change may be challenging to interpret when sample sizes are small. Therefore, we emphasize the importance of alternative methods such as qualitative research with the target patient population to understand meaningful change, which can be done within the clinical trial aligned with completion of the study (i.e., exit interview study) or outside the clinical trial (i.e., standalone qualitative study).
- When conducting anchor-based analyses, carefully select adequate external anchors to provide direct evidence to interpret meaningful within-patient score changes in COA endpoints (e.g., external anchors that assess the same targeted concept as the COA endpoint).

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:
There have been several communications regarding the COAs for this development program, which include the following.

- Meeting Minutes dated March 16, 2018
    - The Agency did not agree with the proposed GPPPGA scoring paradigm (i.e., calculated mean score of erythema, pustulosis, and scaling/crusting) as the

calculated score could be driven by erythema or scaling/crusting and not by pustulosis.
  - Requested morphologic description of each level of pustular severity
  - Requested specific morphologic descriptions of each degree of pustule coalescence to allow easy distinction between grades.
  - Questioned the use of the pustulation subscore to define the population as the severity of pustular lesions is already part of scoring on the GPPPGA.

Reviewer's comment(s): *DCOA was not consulted at this stage. The COA-related comments were provided by Clinical and/or Biostatistics.*

- Study May Proceed letter dated February 4, 2019
  - Reiterated comments related to the GPPPGA (i.e., scoring paradigm, morphologic descriptions) from the Meeting Minutes dated March 16, 2018.
  - Recommended a single GPPPGA scale based on the investigator assessment of the overall disease severity at the time of evaluation (i.e., static, current state investigator global assessment [IGA]).
  - Recommended a photographic guide to be used with the GPPPGA to aid investigators in disease severity assessment and to minimize inter-observer variability.
  - Requested information to support separate assessment of pustules.

Reviewer's comment(s): *DCOA was not consulted at this stage. The COA-related comments were provided by Clinical and/or Biostatistics.*

- Meeting Minutes dated March 12, 2019
  - Reiterated comments related to the GPPPGA (i.e., scoring paradigm, morphologic descriptions, static IGA, photographic guide) from the Meeting Minutes dated March 16, 2018, and Study May Proceed Letter dated February 4, 2019.
  - Acknowledged ongoing qualitative research.
  - Requested final qualitative summary report, including transcripts, once available.

Reviewer's comment(s): *DCOA was consulted at this stage. However, the applicant did not provide sufficient information to fully comment on their COA measurement strategy.*

- Meeting Minutes dated August 19, 2021
  - Reiterated potential issues with GPPPGA.
  - Concluded that the adequacy of the GPPPGA will be a review issue.
  - Requested 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.

Reviewer's comment(s): *DCOA was not consulted at this stage. The COA-related comments were provided by Clinical and/or Biostatistics.*

Previous COA Reviews:

- C2018367_IND 131311_Daniels dated February 9, 2019 [DARRTS Reference ID: 4388492]

Disease Background:
Generalized pustular psoriasis (GPP) is a rare and severe type of psoriasis. It is an autoinflammatory condition with acute, recurrent episodes that are often accompanied by systemic inflammation, which typically necessitates hospitalization. A GPP flare consists of the acute onset of rapidly disseminating painful skin manifestations (including aseptic pustules), which can be accompanied by systemic symptoms, such as high fever and extreme fatigue, as well as acute phase response (with increased C-reactive protein).

Investigational Product:
Spesolimab (BI 655130) intravenous (i.v.) is a humanized antagonistic monoclonal IgG1 antibody that binds to IL-36R and blocks human IL-36α-, IL-36β-, and IL-36γ-induced IL-36R activation, leading to suppressed pro-inflammatory and pro-fibrotic pathways in inflammatory skin diseases.

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Study 1368-0013 are adults (18-75 years) with:

- GPPPGA score of 0 or 1 and a known and documented history of GPP (per ERASPEN criteria) regardless of IL-36RN mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leukocytosis with peripheral blood neutrophilia (above ULN)

OR

- an acute flare of moderate to severe intensity meeting the ERASPEN criteria of GPP with a known and documented history of GPP (per ERASPEN criteria) regardless of IL-36RN mutation status, and in addition with previous evidence of fever, with peripheral blood neutrophilia (above ULN).

OR

- first episode of an acute GPP flare of moderate to severe intensity with evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leukocytosis with peripheral blood neutrophilia (above ULN). For these patients the diagnosis was to be confirmed retrospectively by a central external expert/committee.

A complete list of the inclusion and exclusion criteria is summarized in Section 9.3.1 of the clinical study report for Study 1368-0013.

Reviewer's comment(s): *The study population consisted of 32% men and 68% women. The mean age was 43 (range: 21 to 69) years; 55% of patients were Asian and 45% were Caucasian. Most patients included in the study had a GPPGA pustulation sub score of 3 (43%) or 4 (36%), and patients had a GPPGA total score of 3 (81%) or 4 (19%). 24.5% of patients had been previously treated with biologic therapy for GPP.*

5.2 Clinical Trial Design

Study 1368-0013 is a global, multi-center, randomized, double-blind, placebo-controlled phase 2 trial to evaluate the efficacy, safety, and tolerability of a single intravenous (i.v.) dose of spesolimab in patients with GPP presenting with a flare of moderate to severe intensity.

Patients eligible to receive treatment after screening were randomized; 51 patients (increased from 27 patients with global CTP amendment 1) were required to be randomized in a 2:1 ratio to receive spesolimab or placebo. All randomized patients were to receive the first dose of study medication (900 mg i.v. spesolimab or placebo) on Day 1 of Week 1 (Randomization). Based on the subsequent treatment response, patients were then to be followed up for 12 to 28 weeks.

If the severity and progression of the disease worsened[2] within the first week (Week 1/Days 2-7), the investigator could treat the patient with a standard of care (SoC) treatment of his/her choice (escape medication). If the disease condition was stable, it was recommended to wait until the primary endpoint visit (Week 1/Day 8) before prescribing an escape medication (SoC) since there was an option to administer open-label (OL) spesolimab instead at this time. If escape medication was administered within the first week, the patient was not eligible to receive treatment with a single OL i.v. dose of 900 mg spesolimab on Day 8.

Patients who achieved a clinical improvement to spesolimab and showed no flare symptoms of moderate/severe intensity at Visit 14 or Visit 15 were offered to enter into the open-label extension (OLE) trial 1368-0025, if they had completed this study (Visit 14 or Visit 15) and met the eligibility criteria for the OLE trial.

Refer to Section 9.1 of the clinical study report for Study 1368-0013 for more details regarding the study design.

Reviewer's comment(s): *A total of 53 patients were randomized to receive a single i.v dose of 900 mg spesolimab (n= 35) or placebo (n=18). Patients in either treatment arm who still experienced flare symptoms at Week 1 were eligible to receive a single i.v dose of open-label 900 mg spesolimab, resulting in 12 patients (34%) in the spesolimab arm receiving a second dose of spesolimab and 15 patients (83%) in the placebo arm receiving one dose of spesolimab on Day 8. After Day 8, 6 patients (4 spesolimab arm; 2 placebo arm) received rescue treatment with a single 900 mg dose of i.v spesolimab for reoccurrence of a flare.*

5.3 Endpoint Position, Definition, and Assessment Schedule

The primary and secondary COA efficacy endpoints including the endpoint definition and assessment schedule for Study 1368-0013 is summarized below.

Primary efficacy endpoint:

- Proportion of subjects with a GPPPGA pustulation subscore of 0, indicating no visible pustules, at Week 1

[2] Disease worsening was defined as worsening of clinical status or GPP skin and/or systemic symptoms as defined by the investigator.

Secondary COA Efficacy Endpoints (multiplicity adjusted):

- Proportion of subjects with a GPPPGA total score of 0 or 1 at Week 1
- Proportion of subjects with ≥ 75% reduction in Generalized Pustular Psoriasis Area and Severity Index (GPPASI-75) at Week 4
- Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4
- Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score at Week 4

The GPPPPGA was administered daily at Week 1, Day 8, Day 15, Day 22, and Day 29.

Reviewer's comment(s):
A GPPPGA total score 0 or 1 endpoint was included as a secondary endpoint, in which all subcomponents would need to be ≤2, because patients with severe erythema and scaling would not be expected to achieve a score of almost clear in these components within 1 week. An improvement in all subscores to 0 or 1 would only be expected at later timepoints, such as at 12 weeks.

5.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The applicant has proposed the following specific targeted COA-related labeling claims (in *blue italicized text*):

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Reviewer's comment(s):
Based on discussion with Clinical, data from the GPPASI and patient-reported outcome (PRO) measures will not be labeled as they are not suitable for this drug development program.

This reviewer notes that the interpretation of the analyses after Week 1 is limited as a considerable number of patients had received open-label spesolimab on Day 8, spesolimab rescue medication after Day 8, or escape medication for worsening, insufficient response, or non-response.

5.4.1 Clinical Outcome Assessment Description(s)

Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA)
The GPPPGA is a clinician-reported outcome (ClinRO) instrument designed to assess overall GPP severity based on three components: pustules coalescence, erythema, and scaling/crusting of pustular psoriasis lesions. Each component is rated on a 5-point verbal rating scale, ranging from 0 (clear) to 4 (severe). The recall period is current state. A copy of the instrument (response scale) can be found in Appendix A.

5.4.2 Conceptual Framework(s)
The conceptual framework for the GPPPGA is shown in Table 1 (shown on next page).

Table 1. Conceptual framework of GPPGA

Item/Component	Domain/Subscale	General Concept
Erythema	Erythema	GPP severity
Pustulation	Pustulation	
Scaling/crusting	Scaling/crusting	

5.4.3 Scoring Algorithm

The GPPGA generates single item and total scores. The GPPPGA generates a single item score (i.e., score for a single component) ranging from 0 to 4, with higher scores indicating greater GPP severity. The total score is a composite score ranging from 0 to 4, with lower scores indicating lower severity. The total score is calculated by averaging the three components' ratings. The total score equals 0 if the mean of the three components is 0; equals 1 if $0<\text{mean}<1.5$; equals 2 if $1.5\leq\text{mean}<2.5$; equals 3 if $2.5\leq\text{mean}<3.5$; and equals 4 if mean ≥ 3.5.

5.4.4 Content Validity

The applicant completed the following instrument development activities to evaluate the content validity of the GPPPGA from the patient perspective:

- Concept elicitation (patient advisory boards, focus groups, survey)
- Real world evidence (patient registry)

A summary of the findings for each activity is described below.

Patient Advisory Boards

- Three patient advisory boards were held: a multi-national advisory board (June 2019; n=8 individuals with GPP, n=1 care partner), a Japanese advisory board (June 2020; n=5 individuals with GPP, n=1 care partner), and a multi-national advisory board (September 2020).
- Cutaneous signs reported across the multi-national advisory board (June 2019) and Japanese advisory board (June 2020) include pustules, redness, flaky/peeling skin, inflammation/swelling, and fissures/cracks. Cutaneous symptoms include pain, itching, burning, irritation, dryness/dry skin, discomfort, and soreness.
- Some participants across the multi-national advisory board (June 2019) and Japanese advisory board (June 2020) described systemic signs and symptoms of fever, lymph node swelling, poor sleep, discomfort, general malaise, fatigue, anxiety, and depression.
- Participants in the multi-national advisory board meeting (June 2019) rated pustules, pain, and itch as the top 3 most burdensome signs or symptoms.
- Participants across the multi-national advisory board (June 2019) and Japanese advisory board (June 2020) described impacts as secondary to both the physical symptoms (pain, rash, fever, etc.) and psychological factors (i.e., avoiding activities due to embarrassment of the appearance of skin).
- Participants across the multi-national advisory board (June 2019) and Japanese advisory board (June 2020) also reported a lack of understanding by society that contributed to fear of contagiousness and challenges at work. Socially, participants described experiencing rejection, isolation, and feelings of loneliness (Appendix

- Participants in the Japan advisory board (June 2020) also described a sense of shame living with GPP.
- Participants in the multi-national advisory board (June 2019) reported experiencing flares 2 to 6 times per year, with a duration from 2 to 4 weeks up to 8 months.

Mixed-methods study (focus groups, survey)

- A mixed-methods multi-phase study was conducted to better understand the experiences and perceptions of GPP from patients. In phase 1, virtual focus groups were conducted in nine individuals with GPP. Phase 2 involved a survey in a larger sample of individuals with GPP (n=66) to confirm and expand upon findings in the focus groups. A post-survey virtual focus group was then completed with seven of the individuals that completed the survey to gain a deeper understanding of some of the insights gained in the survey.
- Participants in the focus group (n=9 individuals with GPP) described impacts as secondary to both the physical symptoms (pain, rash, fever, etc.) and psychological factors (i.e., avoiding activities due to embarrassment of the appearance of skin).
- Participants in the focus group described GPP at its worst as significant pain, discomfort, and multiple physical, social, and emotional impacts.
- Participants in the focus group described flares as a cycle of pain, itch, and pustules when their disease worsens.
- The survey demonstrated that 'more pain overall,' 'pain,' 'more pustules,' 'increased pain in hands, arms, feet or toes,' and 'itching' were ranked as the most burdensome symptoms during periods of disease worsening.
- The survey confirmed the physical, emotional, and social impacts identified in the global and Japan advisory board. More than half of participants reported fear, worry, and anxiety about worsening GPP.
- More than 70% of survey respondents reported moderate to severe impacts on the ability to exercise or engage in physical activity, complete errands, attend important life events, complete household chores, socialize, be intimate with a partner or spouse, and wear shoes during periods of flare.
- The majority of survey respondents reported flares >/=2 times per year (n=57, 87%), with some experiencing flares as frequently as 4-5 times annually (n=13, 20%), or >6 times annually (n=17, 26%).
- More than three-quarters of survey respondents (n=50, 77%) reported they expect "some symptoms" even when their GPP is "under control."
- Survey respondents also reported impacts during periods between flares. The most commonly reported moderate to severe impacts between periods of disease worsening included the ability to exercise or engage in physical activity (n=29, 44%) and attend important life events.

Patient Registry

- A retrospective analysis of the Corrona registry evaluated clinical and patient-reported outcomes in individuals with GPP (n=60) and palmoplantar pustulosis (PPP) (n=64) relative to those with plaque psoriasis (n=4,894).

- Patients with GPP had consistently higher mean itch, pain, and fatigue visual analog scale (VAS) scores relative to those with plaque psoriasis (itch - 48 vs. 35; fatigue 43 vs. 30; pain 33 vs. 22), as well as higher patient global assessment of severity scores (46 vs. 36).
- GPP patients (n=60) reported lower quality of life and experienced greater impairment in the workplace and in activities of daily living. Based on the Work Productivity and Activity Impairment (WPAI) questionnaire, GPP patients had higher presenteeism (% impairment while working; 29 vs. 13), and % daily life activities impaired (32 vs. 17) than patients with plaque patients.

Reviewer's comment(s): *The findings from the described activities demonstrate that patients experience erythema, pustules, and scaling/crusting (flaking). However, pustules, pain, and itch appear to be the most important and relevant concepts in GPP. Overall, the pustule component of the GPPPGA, which supports the primary endpoint, appears to be content relevant for the target population. There is a lack of clinician input in the submitted qualitative data. As such, it is unclear whether the GPPPGA is well-understood and interpreted appropriately across clinicians. Based on discussion with the Clinical, the components of the GPPPGA are considered clinically relevant.*

5.4.5 Other Measurement Properties

The applicant evaluated the psychometric properties of the GPPPGA using data from Study 1368-0013.

A summary of the psychometric findings from Study 1368-0013 is provided. For more details on the methodology and results of these analyses, refer to the Section 5 of the Psychometric Analysis Report ("Assess Validity, Reliability, and Responder Definition for Key Clinician-reported Outcome Endpoints Used in GPP BI Clinical Trial 1368-0013: GPPPGA and GPPASI"). Note that the results from these psychometric analyses should be cautiously interpreted due to the small sample size.

Descriptive statistics

- Fifty-three participants were enrolled in the study and had baseline GPPPGA data.
- The majority of the sample were female (67.9%) and were Asian (54.7%) and White (45.3%) with a mean age of 43.0 years (standard deviation [SD]: 10.9).
- The median scores for GPPPGA at baseline (Day 1) were:
    - Pustulation subscore: 3.0
    - Erythema subscore: 3.0
    - Scaling/crusting: 3.0
    - Total score: 3.0
- 13.2-35.8% of clinicians endorsed the highest severe category responses at baseline across the GPPPGA components (i.e., clinicians rating patients as severe).

  Reviewer's comment(s): *Due to the inclusion criteria (inclusion of participants with an acute flare of moderate to severe intensity OR first episode of an acute GPP flare of moderate to severe intensity), participants were expected to be rated with higher severe category responses.*

- Appendix C presents the GPPPGA total scores and subscores at the baseline and Day 8 visits for all participants.

Unidimensionality

- For the confirmatory factor analysis (CFA),
  - At Week 1, the Comparative Fit Index (CFI) and Standardized Root Mean Square Residual (SRMR) estimates for both constrained and unconstrained models were ≥0.90 threshold for CFI and <0.1 for SRMR. The Root Mean Square Error of Approximation (RMSEA) values for both models were <0.08). Regarding the individual factor loadings, the constrained model showed factor loadings of 0.708, 0.893, and 0.893, for 'erythema', 'pustules', and 'scaling/crusting' items, respectively. For the unconstrained model, the factor loadings were 0.708, 0.896, and 0.889, for 'erythema', 'pustules', and 'scaling/crusting' items, respectively.

  - At Week 2, the factor loadings for the 'erythema', 'pustules', and 'scaling/crusting' items ranged from 0.800 to 0.852 for the constrained model and from 0.808 to 0.878 for the unconstrained model.

Reviewer's comment(s):
This reviewer notes that the applicant indicated in their psychometric analysis report that "for simple models, such as the single factor model proposed here, the RMSEA may not accurately reflect model fit. The RMSEA statistic can be inflated for simple models with few degrees of freedom, thereby giving the impression of poor fit. In this case, and if other fit statistics suggest an acceptable fit, the RMSEA criteria can be softened. Finally, small sample size may limit the assessment of the fit statistics and a rule of thumb is that an adequately specified model contains 10 ratings per model parameter."

Based on the selected model and the small sample size, it is difficult to interpret the findings from the CFA.

Reliability

- For assessment of internal consistency reliability (GPPPGA total score), Cronbach's α coefficient was 0.21 at baseline, 0.81 at Week 1, and 0.64 at Week 4.

- For assessment of test-retest reliability[3], the intra-class correlation coefficients (ICCs) for the GPPPGA Pustulation subscore ranged from 0.83 to 1.0 for the analysis population defined by JDA GPP Part A and 0.54 -0.78 for the analysis population defined by JDA GPP Part B. The ICCs for the GPPPGA total score ranged from 0.70 to 0.97 for the analysis population defined by JDA GPP Part A and 0.31 to 0.74 for the analysis population defined by JDA GPP Part B.

[3] Stability was defined as (1) All subjects who had the same Japanese Dermatological Association (JDA) GPP Severity Index Part A assessment of skin symptoms score at specified time periods (Day 3 to Day 4, Week 1/Day 8 to Day 15, Day 15 to Day 22, and Day 22 to Week 4/Day 29) and (2) All subjects who had the same JDA GPP Severity Index Part B assessment of systemic symptoms score at specified time periods (Day 3 to Day 4, Week 1/Day 8 to Day 15, Day 15 to Day 22, and Day 22 to Week 4/Day 29).

Reviewer's comment(s):
Per the applicant, assessment of test-retest reliability was uninterpretable using data from baseline. As such, this time point was replaced with the following time periods: Day 3 to Day 4, Week 1/Day 8 to Day 15, Day 15 to Day 22, and Day 22 to Week 4/Day 29.

In general, the ICCs were within acceptable and within reasonable range for the analysis population defined by JDA GPP Severity Index Part A which was based on skin symptoms. There were mixed results for the analysis population defined by the JDA GPP Severity Index Part B which was based on systemic symptoms.

Convergent Validity

- For assessment of convergent validity:
    - Moderate correlations were observed between the GPPPGA Pustulation subscore and patient-reported symptom and health status assessments, such as the EuroQol Five Dimension Five Level (EQ-5D-5L) Pain/Discomfort scale (r= 0.47), EQ-5D VAS (r= 0.47), Dermatology Life Quality Index (DLQI) total Score (r= 0.33), DLQI Item 1 (r= 0.45), DLQI Item 2 (r= 0.30) at Week 1. Moderate correlations were also observed between the GPPPGA Pustule subscore and clinician-reported assessment, such as the Clinician Global Impression-Improvement (CGI-I, r=0.48) at Week 1.
    - A moderate correlation was observed between the GPPGA Pustulation subscore and DLQI Item 1 (r=0.36) at Week 4, but all other correlations with the other assessments were weak.
    - Moderate correlations were observed between the GPPGA total score and patient-reported symptom and health status assessments, such as the EQ-VAS (r=-0.47,), DLQI total score (r=0.33), EQ-5D-5L Pain/Discomfort item (r= 0.47), DLQI Item 1 (r=0.45), DLQI Item 2 (r=0.30), and CGI-I (r=0.48) at Week 1.
    - Moderate correlations were observed between the GPPGA total score and patient-reported and clinician-reported assessments, such as the EQ-VAS (r=-0.33,), DLQI total score (r=0.47), EQ-5D-5L Pain/Discomfort item (r= 0.48), DLQI Item 1 (r=0.46), DLQI Item 2 (r=0.32), and CGI-I (r=-0.32) at Week 4.

Reviewer's comment(s):
The applicant noted the following: "The CGI-I findings are less supportive, but more likely due to issues with it as anchor, which need to be looked at with more criticism as multifactorial effect can significantly impact the CGI-I at Week 4. CGI-I was the only measure used to assess change in the trial, and investigators tend to include information unrelated to efficacy in their CGI ratings, which may affect the assessment as the timepoint of interest is longer. In addition, CGI-I at Week 4 was possibly impacted by other factors such as investigators' subjectivity, patients' personal perception, comparison not to baseline but to previous visit, becoming accustomed with previous status, and recall/memory problem."

This reviewer acknowledges the applicant's rationale for the findings from the CGI-I. This reviewer notes that the other reference measures are also questionable as none of

the concepts are similar to the concepts of the GPPPGA. None of the reference measures assess pustules, erythema, or scaling/crusting, which are the components of the GPPPGA or, more generally, the signs of GPP.

Known Groups Validity

- For assessment of known groups validity:
  - The mean GPPGA Pustulation subscores observed across the DLQI, JDA GPP Severity Index, CGI-I subgroups showed a positive trend with the higher severity anchor group having higher GPPGA Pustulation subscores at Week 1. The results from the mean scores of two reference measures (JDA GPP Part A Erythema area and JDA GPP Part A Edema area) were not statistically significant at Week 1.
  - The mean GPPGA Pustulation subscores observed across the DLQI, JDA GPP Severity Index, CGI-I subgroups did not show a clear trend at Week 4; the pattern of the scores were inconsistent across the reference subgroups. At Week 4, the results were not statistically significant in most reference measures. Only mean scores of two reference categories showed significant results: the JDA GPP Part A Erythema area with pustules, 2-category and JDA GPP Part A Edema area, 2-category.
    The mean GPPGA total scores observed across the DLQI, JDA GPP Severity Index, CGI-I subgroups showed a positive trend with the higher severity anchor group having higher GPPGA total scores at Weeks 1 and 4. The results was not significant for the JDA GPP Part A Erythema area, 2-category subgroup. Results from Week 4 showed significant difference between the mean GPPGA total score in most reference measures (exception was CGI-I and JDA GPP Severity Index).

Reviewer's comment(s):
The results for the known groups validity analysis are difficult to interpret due to the small sample size. Further, the reference measures used may be inadequate. For example, the DLQI has intrinsic limitations as it generates a total score combining multiple concepts of signs, symptoms, and impacts. Additionally, it is unclear whether the cutoffs for the CGI-I, EQ-5D-5L Pain/Discomfort scale, EQ-5D VAS represents clinically distinct groups. The minimum sample size of 30 per group is generally recommended for these analyses. The sample size was below 30 per group in most instances.

Responsiveness

- For assessment of responsiveness, the LS mean change scores of the GPPPGA Pustulation subscore ranged from -1.66 to -2.46 as anchored to the CGI-I scores from "much improved" to "very much improved," respectively at Week 1.
- For assessment of responsiveness, the LS mean change scores of the GPPPGA total score ranged from -1.08 to -1.50 as anchored to the CGI-I scores from "much improved" to "very much improved," respectively at Week 1.
- For assessment of responsiveness, the LS mean change scores of the GPPPGA Pustulation subscore ranged from -2.87to -2.88 as anchored to the CGI-I scores from "much improved" to "very much improved," respectively at Week 4.
- For assessment of responsiveness, the LS mean change scores of the GPPPGA total score ranged from -2.11 to -1.98 as anchored to the CGI-I scores from "much improved" to "very much improved," respectively at Week 1.

- For assessment of responsiveness, the LS mean change scores of the GPPPGA Pustulation subscore was -2.11 as anchored to a 2-category change on the EQ-5D-5L Pain/Discomfort subscale score at Week 1.
- For assessment of responsiveness, the LS mean change scores of the GPPPGA total score was -1.34 as anchored to a 2-category change on the EQ-5D-5L Pain/Discomfort subscale score at Week 1.
- For assessment of responsiveness, the LS mean change scores of the GPPPGA Pustulation subscore was -2.24 as anchored to a 2-category change on the DLQI Item 1 score at Week 1.
- For assessment of responsiveness, the LS mean change scores of the GPPPGA total score was -1.56 as anchored to a 2-category change on the DLQI Item 1 score at Week 1.

Reviewer's comment(s):
The results for the responsiveness analysis are difficult to interpret due to the small sample size. Further, most of the reference measures appear inadequate. For example, the concepts of the DLQI item 1 and EQ-5D-5L Pain/Discomfort scale are misaligned to the GPPPGA Pustulation subscore and total score. The minimum sample size of 30 per group is generally recommended for these analyses. The sample size was below 30 per group in most instances. Further the distribution across the subgroups were not equal.

5.4.6 Interpretation of Meaningful Within-Patient Score Changes

The applicant performed the following analyses to support the proposed threshold(s) for meaningful within-patient score change in the GPPPGA Pustulation subscore and total score:

- Anchor-based analyses
  - Distribution of change on the target COAs by change on anchors
  - Anchor-based empirical cumulative distribution function and probability density function curves
- Distribution-based analyses

The applicant proposed the following thresholds for meaningful within-patient score change for each target COA:

- GPPPGA Pustulation subscore: The applicant proposed a 2-point reduction (based on 0-4 scale) to be a meaningful within-patient score change in the GPPPGA Pustulation subscore.
- GPPPGA total score: The applicant proposed a 1-point reduction (based on 0-4 scale) to be a meaningful within-patient score change in the GPPPGA total score.

Reviewer's comment(s): *These thresholds were based on triangulation of the results from anchor-based and distribution-based methods.*

Anchor-based analyses
Table 2 (shown on next page) summarizes the anchors utilized by the applicant and their corresponding target COA. Copies of the anchor scales are in Appendix B.

Table 2. Summary of proposed anchor scales for GPPPGA Pustulation subscore and total score

Targeted COAs (concept)	Anchors (concept)	Anchor response scale	Recall period (target/anchor)	Assessment schedule (target/anchor)
GPPPGA Pustulation subscore (Pustulation severity) and total score (GPP severity)	DLQI Item 1 (degree of itch, soreness, pain, sting)	4-point scale: Very much, A lot, A little, Not at all	Current state/Previous week	daily at Week 1, Day 8, Day 15, Day 22, and Day 29
	EQ-5D-5L Pain/Discomfort subscale (pain severity)	5-point scale: No pain or discomfort, Slight pain or discomfort, Moderate pain or discomfort, Severe pain or discomfort, Extreme pain or discomfort	Current state/ Today	daily at Week 1, Day 8, Day 15, Day 22, and Day 29
	EQ-5D VAS (health)	0-100 VAS: Best health, Worst health	Current state/Today	daily at Week 1, Day 8, Day 15, Day 22, and Day 29
	CGI-I as per JDA Severity Index (GPP severity)			daily starting at Day 2 at Week 1, Day 8, Day 15, Day 22, and Day 29

Reviewer's comment(s):
The selected anchor scales have the following limitations, which impacts interpretability of the results from the anchor-based analyses:

- *The concepts measured in the DLQI item 1 (itchy, sore, painful, stingy) are not aligned with the concept of the GPPPGA Pustulation subscore or total score (Pustulation severity/GPP severity). Similarly, the concept measured in the EQ-5D-5L Pain/Discomfort subscale (pain or discomfort) and EQ-5D VAS (health) is not aligned with the concept of the GPPPGA Pustulation subscore or total score (Pustulation severity/GPP severity). We generally recommend that an anchor scale measures the same concept (i.e., the aspect of the disease specified in the endpoint, as opposed to global status of the disease) of the target instrument to the extent possible to provide the most direct evidence.*
- *The recall period of the DLQI Item 1 ("last week") does not align with the assessment time period of the prespecified GPPPGA endpoint (current state). We generally recommend that the anchor scale's recall period should be consistent with the assessment time period of the prespecified endpoint to the extent possible.*

A summary of the anchor-based analyses is described below. However, the results from these analyses should be cautiously interpreted due to the small sample size.

- For the GPPPGA Pustulation subscore, results from baseline to Week 1 change score assessments showed combined anchor-based estimates between -2.30 and -2.11 and combined 95% CI estimates between -2.81 and -1.66.
- For the GPPPGA total score, results from baseline to Week 1change score assessments indicate anchor-based estimates between -1.56 and -1.34, and 95% CI estimates between -1.93 and -1.03.

Distribution-based analyses

A summary of the distribution-based analyses is described below.

- For the GPPPGA Pustulation subscore, calculation of half SD resulted in 0.72 points. Calculation results with 0.25 SD and 0.33 SD were 0.36 and 0.48 points, respectively. Calculation of 1 SEM resulted in 0.82 points for the Day 3 to Week 1/Day 8 changes.
- For the GPPPGA total score, calculation of half SD resulted in 0.37 points. Calculation results with 0.25 SD and 0.33 SD were 0.19 and 0.25 points, respectively. Calculation of 1 SEM resulted in 0.46 points for the Day 3 to Week 1/Day 8 changes.

Reviewer's comment(s):

While anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in COA endpoints, interpretation of the anchor-based analyses for the GPPPGA Pustulation subscore and total score is difficult given the small sample size of the study. The applicant also provided anchor-based empirical cumulative distribution function (eCDF) and probability density function (PDF) curves, but they are difficult to interpret due to the small sample size.

In addition to anchor-based methods, the applicant conducted distribution-based analyses. However, distribution-based methods (e.g., effect sizes, certain proportions of the standard deviation and/or standard error of measurement) are only considered supportive to anchor-based methods.

While this reviewer cannot interpret the anchor-based analyses, it is noted that the primary endpoint for Study 1368-0013 is defined as the proportion of subjects with a GPPPGA pustulation subscore of 0, indicating no visible pustules, at Week 1. This endpoint accounts for clinical meaningfulness as the targeted response is complete resolution of signs (i.e., pustular clearance).

The GPPPGA-based secondary endpoint (GPPPGA total score) derivation allows subjects to have a GPPPGA total score of 0 or 1 (clear or almost clear) rather than a target of complete resolution at Week 1. Because the GPPPGA total score is a composite score, there was concern as to whether select components were overly influencing the observed score change. As such, an information request was submitted by the Biostatistics reviewer. Based on the item-level analyses, the Pustulation subscore appears to be driving most of the observed change (see Descriptive Statistics in Section 5.4.5 of this review). Further, based on discussion with the Biostatistics reviewer, most of the subjects with a GPPPGA total score of 1 have at least one sign with mild or greater disease. Therefore, based on these considerations, it is difficult to conclude whether or not the applicant's proposed 1-point reduction (based on 0-4 scale) is a

meaningful within-patient score change in the GPPPGA total score. See Appendix C for GPPPGA total scores and subscores at baseline and Day 8 for all subjects.

6. APPENDICES

Appendix A Generalized Pustular Psoriasis Physician's Global Assessment (GPPPGA)
Appendix B Copies of Anchor scales

- Appendix B.1 Dermatology Life Quality Index (DLQI) Item 1
- Appendix B.2 EuroQoL Five Dimension-Five Level (EQ-5D-5L) Pain/Discomfort subscale
- Appendix B.3 EQ-5D-5L Visual Analog Scale (VAS)
- Appendix B.4 CGI-I

Appendix C GPPPGA total scores and subscores at baseline and Day 8 (All subjects)

Appendix A: GPPPGA

Pustules	
☐ 0 = Clear:	No visible pustules
☐ 1 = Almost Clear:	Low density occasional small discrete (non coalescent) pustules
☐ 2 = Mild:	Moderate density grouped discrete small pustules (non coalescent)
☐ 3 = Moderate:	High density pustules with some coalescence
☐ 4 = Severe:	Very high density pustules with pustular lakes
Erythema	
☐ 0 = Clear:	Normal or postinflammatory hyperpigmentation
☐ 1 = Almost Clear:	Faint, diffuse pink or slight red
☐ 2 = Mild:	Light red
☐ 3 = Moderate:	Bright red
☐ 4 = Severe:	Deep fiery red
Scaling/crusting	
☐ 0 = Clear:	No scaling and no crusting
☐ 1 = Almost Clear:	Superficial focal scaling or crusting restricted to periphery of lesions
☐ 2 = Mild:	Predominantly fine scaling or crusting
☐ 3 = Moderate:	Moderate scaling or crusting covering most or all of lesions
☐ 4 = Severe:	Severe scaling or crusting covering most or all lesions

PGA Score for GPP

0 = If mean=0 for all three components
1 = If 0 < mean <1.5
2 = If (1.5 <= mean <2.5)
3 = If 2.5 <= mean <3.5
4 = If mean >=3.5

Appendix B: Copies of Anchor Scales

Appendix B.1: Dermatology Life Quality Index (DLQI) Item 1

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score: ☐

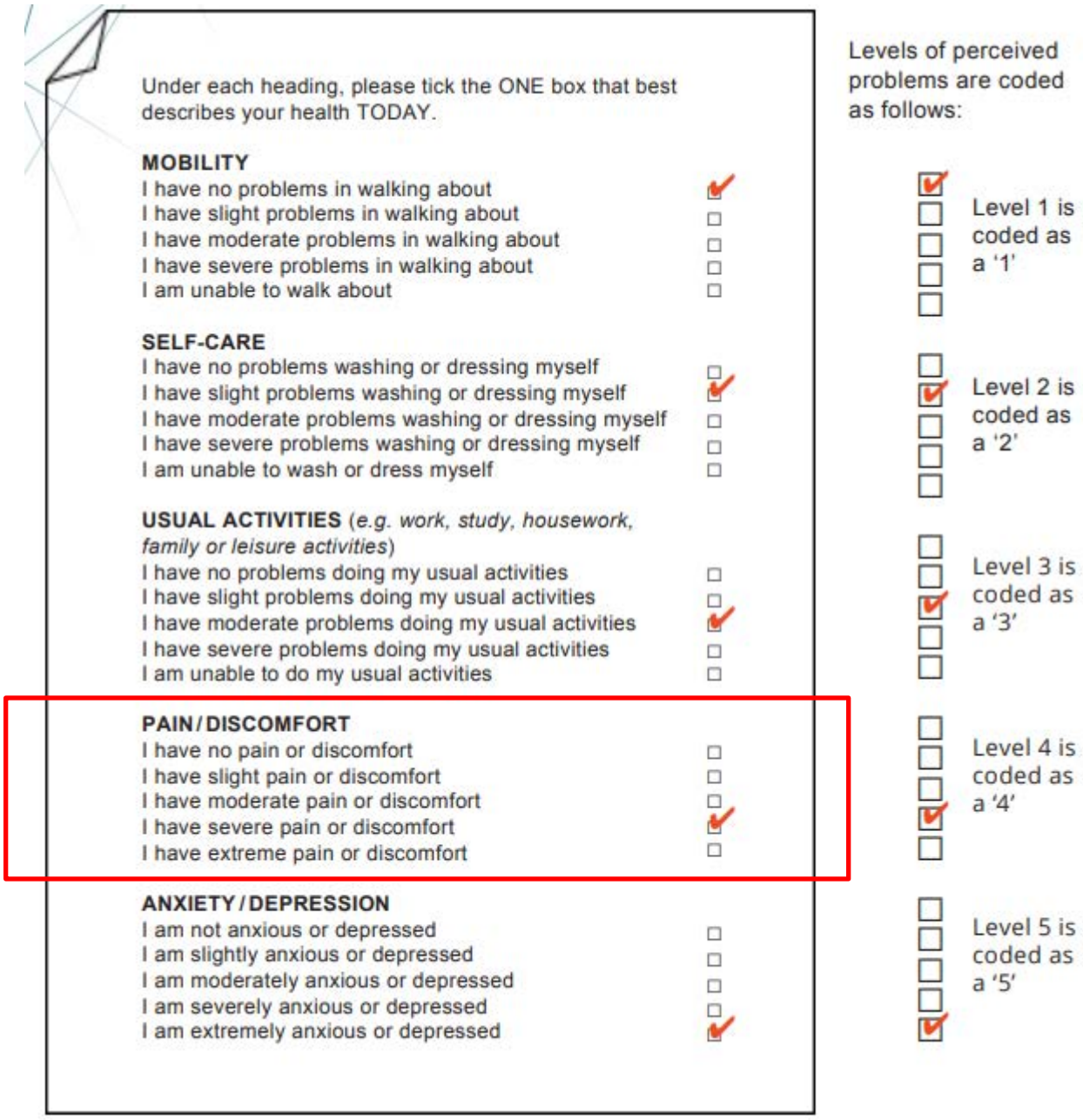
Name: Diagnosis:

Address:

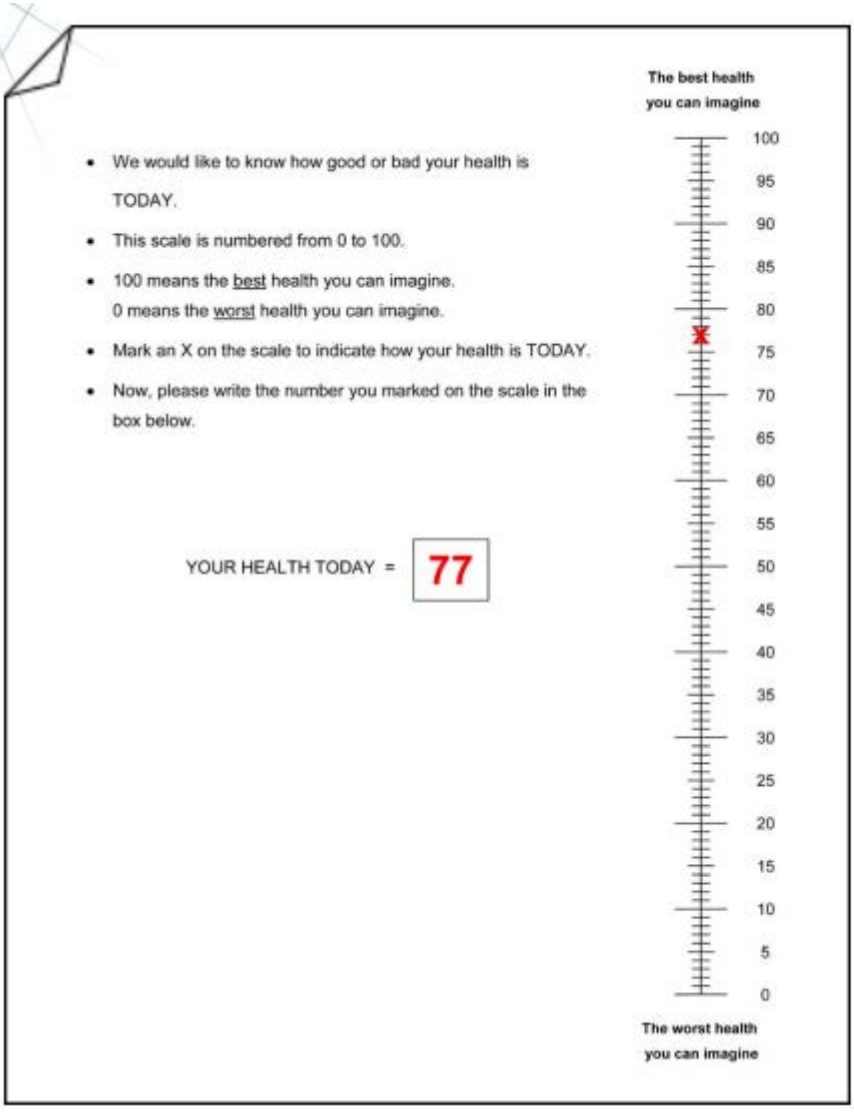
The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

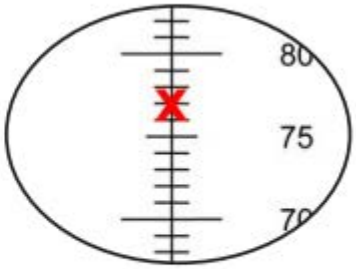
1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	

Appendix B.2: EQ-5D-5L Pain/Discomfort subscale



Appendix B.3: EQ-5D-5L VAS





For example,
the response above
should be coded as 77

Appendix B.4 CGI-I

Category	Change in modified JDA severity index total score for GPP	and/or	Category description
Very much improved	Reduction by 3 or >points	or	Clear or almost clear of signs of GPP
Much improved	Reduction by 1 or 2 points	or	At least one of the following: • Area of erythema with pustules (%) reduced by ≤30% or • Clinically meaningful improvement in at least 2 other components of the modified JDA severity index for GPP (area of erythema, area of edema, fever, WBC, CRP, Alb)
Minimally improved	0 points (no change)	and	At least one of the following: • Area of erythema with pustules (%) reduced by ≤20% or • Clinically meaningful improvement in at least 1 other component of the modified JDA severity index for GPP (area of erythema, area of edema, fever, WBC, CRP, Alb)
No change	0 points (no change)	and	Not meeting the other criteria of "minimally improved"
Worsened	≥ + 1 point	-	Not applicable

Abbreviations: Alb, albumin; CRP, C-reactive protein; GPP, General pustular psoriasis; JDA, Japanese Dermatology Association; WBC, White blood cells.

Appendix C. GPPPGA total scores and subscores at baseline and Day 8 (All subjects)

		Baseline GPPPGA				Day 8 GPPPGA				Applicant's	
Subject ID	TRT01P	Pustules	Erythema	Scaling	Average	Pustules	Erythema	Scaling	Average	GPPPGA 0/1	Comment
(b) (6)	Speso 900 mg IV SD	2	3	3	2.67	0	1	1	0.67	1	
	Placebo	4	3	3	3.33	1	0	1	0.67	1	
	Placebo	2	4	3	3.00	0	2	1	1.00	1	
	Speso 900 mg IV SD	3	3	2	2.67	0	2	1	1.00	1	
	Speso 900 mg IV SD	3	3	2	2.67	0	2	1	1.00	1	
	Speso 900 mg IV SD	3	3	3	3.00	0	1	2	1.00	1	
	Speso 900 mg IV SD	4	3	3	3.33	0	2	1	1.00	1	
	Speso 900 mg IV SD	3	3	2	2.67	0	2	1	1.00	1	
	Speso 900 mg IV SD	4	4	3	3.67	0	1	2	1.00	1	
	Speso 900 mg IV SD	4	3	3	3.33	0	1	2	1.00	1	
	Speso 900 mg IV SD	4	4	4	4.00	0	2	2	1.33	1	
	Speso 900 mg IV SD	2	3	4	3.00	0	2	2	1.33	1	
	Speso 900 mg IV SD	4	3	2	3.00	0	2	2	1.33	1	
	Speso 900 mg IV SD	3	3	3	3.00	0	2	2	1.33	1	
	Speso 900 mg IV SD	2	3	3	2.67	0	1	3	1.33	1	
	Speso 900 mg IV SD	3	3	4	3.33	0	1	3	1.33	1	
	Speso 900 mg IV SD	4	3	2	3.00	0	3	1	1.33	1	
	Speso 900 mg IV SD	3	4	2	3.00	0	3	2	1.67	0	
	Placebo	3	3	2	2.67	2	2	2	2.00	0	
	Speso 900 mg IV SD	3	3	3	3.00	0	3	3	2.00	0	
	Speso 900 mg IV SD	4	4	3	3.67	0	3	3	2.00	0	
	Placebo	3	3	3	3.00	2	3	2	2.33	0	
	Speso 900 mg IV SD	3	3	2	2.67	2	3	2	2.33	0	
	Speso 900 mg IV SD	2	4	2	2.67	0	4	3	2.33	0	
	Speso 900 mg IV SD	3	3	3	3.00	1	3	3	2.33	0	
	Speso 900 mg IV SD	2	4	4	3.33	2	3	2	2.33	0	
	Placebo	3	3	3	3.00	2	3	3	2.67	0	
	Speso 900 mg IV SD	2	4	2	2.67	2	4	2	2.67	0	
	Speso 900 mg IV SD	3	3	2	2.67	2	3	3	2.67	0	
	Placebo	4	4	3	3.67	2	4	2	2.67	0	
	Placebo	3	3	3	3.00	2	3	3	2.67	0	
	Placebo	4	3	3	3.33	3	2	4	3.00	0	
	Placebo	2	3	3	2.67	3	3	3	3.00	0	
	Placebo	2	4	3	3.00	2	4	3	3.00	0	
	Speso 900 mg IV SD	4	3	3	3.33	3	3	3	3.00	0	
	Speso 900 mg IV SD	4	4	3	3.67	2	4	3	3.00	0	
	Placebo	3	3	3	3.00	3	3	3	3.00	0	
	Placebo	3	2	3	2.67	3	3	3	3.00	0	
	Speso 900 mg IV SD	4	4	2	3.33	3	4	3	3.33	0	
	Placebo	2	3	3	2.67	3	4	3	3.33	0	
	Placebo	3	3	3	3.00	4	3	3	3.33	0	
	Placebo	4	4	3	3.67	4	3	3	3.33	0	
	Speso 900 mg IV SD	3	4	3	3.33	3	4	3	3.33	0	
	Placebo	2	3	3	2.67	3	3	4	3.33	0	
	Speso 900 mg IV SD	3	4	4	3.67	3	4	4	3.67	0	
	Speso 900 mg IV SD	4	3	2	3.00	4	3	4	3.67	0	
	Speso 900 mg IV SD	4	4	3	3.67	4	4	3	3.67	0	
	Speso 900 mg IV SD	4	4	4	4.00	4	4	4	4.00	0	
	Placebo	4	4	4	4.00	4	4	4	4.00	0	
	Speso 900 mg IV SD	3	3	3	3.00	9999	9999	9999	9999	0	Discontinued
	Speso 900 mg IV SD	3	3	3	3.00	9999	9999	9999	9999	0	Rescue SOC before Day 8
	Placebo	4	3	2	3.00	9999	9999	9999	9999	0	Rescue SOC before Day 8
	Speso 900 mg IV SD	3	3	2	2.67	9999	9999	9999	9999	0	Rescue SOC before Day 8

Note: Applicant's GPPPGA 0/1 column is an indicator variable (1 = yes, 0 = no)

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

PATIENT LABELING REVIEW

Date:	March 29, 2022
To:	Jennifer Harmon, PharmD Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Reviewer Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	SPEVIGO (spesolimab-xxxx)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761244
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.

1 INTRODUCTION

On October 1, 2021, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761244 for SPEVIGO (spesolimab-xxxx) injection. The proposed indication for SPEVIGO (spesolimab-xxxx) injection is for the treatment of flares in adult patients with generalized pustular psoriasis.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on November 5, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for SPEVIGO (spesolimab-xxxx) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft SPEVIGO (spesolimab-xxxx) injection MG received on October 1, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 17, 2022.
- Draft SPEVIGO (spesolimab-xxxx) injection Prescribing Information (PI) received on October 1, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 17, 2022.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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RUTH I MAYROSH
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LAURIE J BUONACCORSI
03/29/2022 02:14:47 PM

BARBARA A FULLER
03/29/2022 02:44:31 PM

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

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

Memorandum

Date: March 28, 2022

To: Mary Kim, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Jennifer Harmon, Regulatory Project Manager, DDD

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

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments SPEVIGO™(spesolimab-xxxx) injection, for intraveneous use

BLA: 761244

In response to DDD's consult request dated November 5, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for SPEVIGO™(spesolimab-xxxx) injection, for intraveneous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on March 16, 2022, and our comments are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DDD on March 17, 2022, and we have no comments.

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

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LAURIE J BUONACCORSI
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Brief Memorandum

Date: March 2, 2022 **Date consulted:** January 31, 2022

From: Jean Limpert, MD Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dentistry (DDD)

Drug: SPEVIGO (spesolimab) injection, for intravenous use

BLA: 761244

Applicant: Boehringer Ingelheim Pharmaceuticals Inc.

Subject: Input for Pregnancy Labeling and Postmarketing Requirements (PMR)

Proposed Indication: Treatment of flares in adult patients with Generalized Pustular Psoriasis (GPP)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for BLA 761244
- DPMH consult request dated January 31, 2022, DARRTS Reference ID 4930018

Consult Question: In section 8.1 Pregnancy in the proposed PI, the applicant proposes the statement, (b) (4)

1. Does DPMH agree with the applicant's proposed statement, (b) (4)
2. If not, a follow-up question would be DPMH's recommendation regarding the utility and feasibility of a post-marketing pregnancy registry or recommendations on other methods to collect post-marketing safety information pregnancy given the rarity of the disease.

INTRODUCTION AND BACKGROUND

On September 30, 2021, Boehringer Ingelheim Pharmaceuticals, Inc., submitted an original 351(a) BLA for priority review for Spesolimab for the treatment of flares in adults with GPP. On January 31, 2022, DDD consulted DPMH to assist with the two questions noted above.

Regulatory History

- FDA granted orphan drug designation for the treatment of GPP on October 3, 2018, and breakthrough therapy designation on April 30, 2021.
- There are no interleukin 36 (IL-36) receptor antagonists currently approved in the US. Spesolimab is also being investigated in phase II clinical trials as a treatment for inflammatory bowel disease, palmoplantar pustulosis (PPP), and atopic dermatitis.

GPP and Pregnancy

- GPP is a rare, auto-inflammatory, episodic, dermatologic condition. GPP is considered a severe form of pustular psoriasis. The prevalence is not known due to its rarity and lack of standardized methodologies for diagnosis. Flares may be triggered by pregnancy, menstruation, infection, stress, and various drugs. Flares are thought to result from dysregulation of the IL-36 signaling cascade which leads to excess production of inflammatory cytokines.[1] Flares are clinically characterized by the sudden onset of large areas of painful, non-infectious pustules. In severe cases, which may be life-threatening, patients may experience fever and systemic inflammation that may necessitate hospitalization[2] as complications can include sepsis and organ failure. Mortality rates are between 2 and 16%.[3,4]

[1] Marrakchi, S., Puig, L. Pathophysiology of Generalized Pustular Psoriasis. *Am J Clin Dermatol* **23,** 13–19 (2022). https://doi.org/10.1007/s40257-021-00655-y.
[2] Zheng M, Jullien D, Eyerich K. The Prevalence and Disease Characteristics of Generalized Pustular Psoriasis. Am J Clin Dermatol. 2022 Jan;23(Suppl 1):5-12. doi: 10.1007/s40257-021-00664-x. Epub 2022 Jan 21.
[3] Bachelez, Hervé. "Trial of Spesolimab for Generalized Pustular Psoriasis." *The New England journal of medicine.* 385, no. 26 (2021): 2431–2440.

- Pustular psoriasis of pregnancy, also referred to impetigo herpetiformis, is currently considered a variant of GPP that occurs during pregnancy or is triggered by pregnancy. It most commonly presents in the third trimester but may also occur earlier in pregnancy.[5] Recurrences with subsequent pregnancies are frequent, and sometimes occur with greater severity.[6,7] Complications during pregnancy include placental insufficiency and electrolyte abnormalities. Severe disease may lead to stillbirth, neonatal death, fetal abnormalities, and maternal death.[8] A case report of severe impetigo herpetiformis in the second trimester of pregnancy described the need for termination of the pregnancy due to severe symptoms despite corticosteroids, immunosuppressants, and phototherapy.[9]
- There are currently no approved treatments for GPP in the United States. Treatments used during pregnancy include systemic corticosteroids, cyclosporine, infliximab, narrow-band ultraviolet B radiation, granulocyte and monocyte adsorption apheresis, and systemic antibiotics.[10] While methotrexate and retinoids are used to treat non-pregnant patients with GPP, their use is contraindicated during pregnancy.
- There are approved treatments for GPP outside of the United States. In Japan, TNF-alpha inhibitors (adalimumab, infliximab), IL-17 inhibitors (secukinumab, brodalumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab) are approved for the treatment of individuals with GPP who have had an inadequate response to conventional therapy.

Drug Characteristics[11]

- *Drug class*: Spesolimab, an IL-36 receptor antagonist, is a humanized monoclonal IgG1 antibody (mAb) against human IL-36R produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.
- *Mechanism of Action*: Inhibits IL-36 signaling by binding to the IL36 receptor which prevents subsequent activation of IL-36 receptor by cognate ligands (IL-36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways. While spesolimab is thought to reduce immune cell-mediated

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[4] Choon SE, Navarini AA, Pinter A. Clinical Course and Characteristics of Generalized Pustular Psoriasis. Am J Clin Dermatol. 2022 Jan;23(Suppl 1):21-29. doi: 10.1007/s40257-021-00654-z. Epub 2022 Jan 21.
[5] https://www.uptodate.com/contents/dermatoses-of-pregnancy?sectionName=PUSTULAR%20PSORIASIS%20OF%20PREGNANCY&search=generalized%20pustular%20psoriasis&topicRef=89271&anchor=H52&source=see_link#H52
[6] Genovese G, Moltrasio C, Cassano N, Maronese CA, Vena GA, Marzano AV. Pustular Psoriasis: From Pathophysiology to Treatment. Biomedicines. 2021 Nov 23;9(12):1746.
[7] Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2014;53(6):676–684.
[8] Zheng M, Jullien D, Eyerich K. The Prevalence and Disease Characteristics of Generalized Pustular Psoriasis. Am J Clin Dermatol. 2022 Jan;23(Suppl 1):5-12. doi: 10.1007/s40257-021-00664-x. Epub 2022 Jan 21
[9] Yao, Xinjing. "A Case of Impetigo Herpetiformis in Which Termination of Pregnancy Was Required." *The Journal of international medical research.* 48.7 (2020): -. Web.
[10] Genovese G, Moltrasio C, Cassano N, Maronese CA, Vena GA, Marzano AV. Pustular Psoriasis: From Pathophysiology to Treatment. Biomedicines. 2021 Nov 23;9(12):1746.
[11] Draft PI for BLA 721244, accessed February 24, 2022.

inflammation and interrupt the inflammatory response driving cytokine production, the precise mechanism linking reduced IL-36 activity and the treatment of flares of GPP is unclear.[12]

- *Molecular weight*: 146 kilo Daltons
- *Half-life*: 26 days
- *Dosage form*: 450 mg/7.5 mL (60 mg/mL) solution in a single-dose vial
- *Dosing*: Administered as a single 900 mg by intravenous infusion over 90 minutes. If flare symptoms persist, may administer an additional 900 mg dose one week after the initial dose.

DATA REVIEW

Nonclinical Experience

Embryo-fetal development (EFD) and pre- and postnatal development (PPND) toxicity studies were performed in mice using a surrogate mouse specific IL36R antagonist monoclonal antibody. In the EFD study, the surrogate was administered intravenously at doses up to 50 mg/kg to pregnant female mice twice weekly during the period of organogenesis. The surrogate was not associated with embryofetal lethality or fetal malformations. In the PPND study, the surrogate was administered intravenously at doses up to 50 mg/kg to pregnant female mice twice weekly from gestation day 6 through lactation day 18. There were no maternal effects observed. There were no treatment-related effects observed on postnatal developmental, neurobehavioral, or reproductive performance of offspring.

Reviewer comment: DPMH reached out to the Pharmacology/Toxicology for additional information. The EFD and PPND studies were conducted in mice with a mouse-specific surrogate antibody because spesolimab it is not active in animals. Therefore, calculations for multiples of exposure for spesolimab is not appropriate.

Clinical Experience

Pregnant women were excluded from clinical trials. Three pregnancies following maternal exposure to spesolimab occurred across clinical trials for GPP and non-GPP indications as noted below. One pregnancy resulted in miscarriage (first trimester exposure), one pregnancy had an unknown outcome (unknown trimester of exposure), and one pregnancy resulted in healthy infant (unknown trimester of exposure).[13] Additional details are below.

[12] Applicant's submission for BLA 761244, Clinical Overview, page 9.
[13] Safety Update report for Spesolimab dated December 15, 2021, page 33.

Table 1: Reviewer's Table: Pregnancies Reported in Clinical Trials[14]

Trial information	Spesolimab dose/duration	Trimester of exposure	Maternal history; concomitant medications	Pregnancy outcome
Trial 1368-0032 (Atopic Dermatitis)	Not reported[15]	First trimester	20-year-old with atopic dermatitis and baseline trichomoniasis, medical marijuana intake	Miscarriage at 12 weeks
Trial 1368-0016 (PPP)	High dose spesolimab for 41 weeks;[16] duration during pregnancy not reported	Not reported	30-year-old; other information not reported	Healthy infant
Trial 1368-0027 (GPP)	Not reported[17]	Not reported	Not reported	Not reported

Reviewer comment: Key details regarding the dose of spesolimab, route of administration, and duration of exposure during pregnancy were not reported. However, based on the clinical trial information, the dose and routes of administration in each of the above trials differ from the dosing proposed for Spevigo.

Review of Literature

Applicant's Review of Literature

The applicant conducted a literature search and did not identify any publications relevant to spesolimab and pregnancy.

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex,[18] TERIS,[19] REPROTOX[20] and *Drugs in Pregnancy and Lactation*[21] to find relevant articles related to the use of spesolimab during pregnancy. Search terms included "spesolimab" AND "pregnancy,"

[14] Information from Safety Update report for Spesolimab dated December 15, 2021, page 33.
[15] Summary of Clinical Safety, page 14, Overview of trials with spesolimab in patients with other disease describes dose regimen in trial as spesolimab 600 mg q4w (4x)
[16] Summary of Clinical Safety, page 14, Overview of trials with spesolimab in patients with other disease describes the high dose regimen as spesolimab 600 qw (5x), 600 q4w (3x), then 600 q4w (9x)
[17] Summary of Clinical Safety, page 13, describes the study as a dose-finding study, route of administration for spesolimab as subcutaneous administration with intravenous infusion as rescue treatment over duration of 48 weeks
[18] https://www.micromedexsolutions.com, accessed 2/25/2022
[19] Truven Health Analytics information. TERIS, accessed 2/25/2022.
[20] Truven Health Analytics information. REPROTOX, accessed 2/25/2022.
[21] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 2/25/2022.

"pregnant woman," "congenital malformations," "stillbirth," and "spontaneous abortion." No relevant articles were identified.

DISCUSSION/CONCLUSIONS

1. **Does DPMH agree with the applicant's proposed statement,** (b) (4) [redacted]

   DPMH does not agree with inclusion of this statement as a precautionary statement because the available nonclinical data and lack of clinical data do not provide evidence to make this recommendation. The animal data have not identified adverse embryofetal developmental effects and there are no pregnancy data regarding spesolimab exposure at the proposed dosing regimen for Spevigo. The three reports of pregnancy in the clinical trials for spesolimab contain incomplete information and cannot assist to identify any safety concerns for use during pregnancy. Since there are no approved therapies for GPP, and it is potentially life-threatening for both the mother and fetus, it is critical for pregnant patients to have access to an effective treatment absent a clearly identified risk that would potentially alter the risk benefit for use during pregnancy.

2. **If not, a follow-up question would be DPMH's recommendations regarding the utility and feasibility of a post-marketing pregnancy registry or recommendations on other methods to collect post-marketing safety information pregnancy given the rarity of the disease.**

   Given the anticipated use of spesolimab in females of reproductive potential and pregnant women in this rare disease population, DPMH recommends collecting postmarketing information to assess maternal and fetal outcomes in patients with GPP who become pregnant while undergoing treatment. The three cases of exposure during pregnancy contain incomplete information about spesolimab exposure and the pregnancy outcomes, and indicate that pharmacovigilance alone would be a suboptimal means of data collection.

   Since GPP is a rare disease, DPMH recommends a post-marketing requirement for a Descriptive Pregnancy Safety Study (DPSS) to collect prospective and retrospective data in women exposed to spesolimab during pregnancy. The applicant would be required to use a structured approach to collect data via targeted questionnaires throughout pregnancy and up to one year postpartum. The applicant would have to obtain follow-up information on all spesolimab-exposed pregnancies of which they become aware. The reader is referred to the FDA Draft Guidance for Industry Postapproval Pregnancy Safety Studies, published May 2019, for further details.[22]

[22] https://www.fda.gov/media/124746/download

RECOMMENDATIONS

1. DPMH recommends the following language for the pregnancy PMR:
   Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to SPEVIGO (spesolimab) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

2. DPMH recommends including contact information about the DPSS in labeling subsection 8.1 Pregnancy, under the Risk Summary subheading, and in section 17.

   Example language is provided below:[23]

   SECTION 8 USE IN SPECIFIC POPULATIONS
   Subsection 8.1 Pregnancy
   Risk Summary

   Place the following information at the end of the Risk Summary

   There is a pregnancy safety study for SPEVIGO. If SPEVIGO is administered during pregnancy, health care providers should report SPEVIGO exposure by calling [insert phone number] or [insert webpage].

   17 PATIENT COUNSELING INFORMATION
   Pregnancy
   Advise patients that there is a pregnancy safety study that monitors pregnancy outcomes in women exposed to SPEVIGO during pregnancy, and they can be enrolled by calling [insert phone number] or [insert webpage]. *[see Use in Specific Populations (8.1)]*.

3. DPMH is available to provide assistance with labeling to comply with PLLR.

[23] https://fda.sharepoint.com/sites/insideFDA-CDER-OND/SiteAssets/Forms/AllItems.aspx?id=%2Fsites%2FinsideFDA-CDER-OND%2FSiteAssets%2FSitePages%2FDivision-of-Pediatrics-and-Maternal-Health--DPMH-%2FCurrent PLLR practices- For CDER Reviewers Final Version April 2021%2Epdf&parent=%2Fsites%2FinsideFDA-CDER-OND%2FSiteAssets%2FSitePages%2FDivision-of-Pediatrics-and-Maternal-Health--DPMH-

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03/02/2022 02:36:55 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	January 27, 2022
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761244
Product Name, Dosage Form, and Strength:	Spevigo (spesolimab-xxxx)[a] injection, 450 mg/7.5 mL (60 ml/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
FDA Received Date:	January 3, 2022
OSE RCM #:	2021-1960
DMEPA 1 Safety Evaluator:	Madhuri R. Patel
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

[a] The nonproprietary name for this BLA has not yet been determined; therefore, the placeholder "spesolimab-xxxx" is used throughout this review to refer to the non-proprietary name for this product and not intended to be included in the final labels and labeling.

1 REASON FOR REVIEW

As part of the approval process for Spevigo (spesolimab-xxxx) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Spevigo Prescribing Information (PI), Medication Guide (MG), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Medication Guide (MG), container labels, and carton labeling. We note that the labels and labeling can be improved to facilitate product identification and to prevent wrong dose and deteriorated drug errors.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed label and labeling can be improved and we provided recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. Prescribing Information

1. Highlights and Dosage and Administration

a. We recommend revising "(2 x 450 mg/7.5 mL vials)" to read "(two vials of 450 mg/7.5 mL)" for clarity.

2. How Supplied/Storage and Handling Section

    a. We note the Dosage and Administration section contains the following information, not found in the How Supplied/Storage and Handling section, container label, carton labeling: "If not administered immediately, store the diluted solution under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours. Protect from light." We defer to DDD on if this information needs to be included in Section 16 of the PI.

4.2 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

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

A. Container Labels

1. We encourage replacing the (b) (4) with the national drug code (NDC) to the container labels as per 21 CFR 201.2.

2. Revise and bold the statement "Store in refrigerated at 2°C to 8°C (36°F to 46°F)" We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

B. Carton Labeling

1. We recommend adding "per vial" next to the "450 mg/7.5 mL (60 mg/mL)" strength in the colored box. Additionally, we recommend placing the statement "Contents: contains TWO – 450 mg/7.5 mL single-dose vials" on one line, instead of splitting into two lines.

2. Revise and bold the statement "Must be refrigerated, store at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light." We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Spevigo received on January 3, 2022 from Boehringer Ingelheim Pharmaceuticals, Inc..

Table 2. Relevant Product Information for Spevigo	
Initial Approval Date	N/A
Nonproprietary Name	spesolimab-xxxx
Indication	treatment of flares in adult patients with generalized pustular psoriasis (GPP)
Route of Administration	intravenous infusion
Dosage Form	injection
Strength	450 mg/7.5 mL (60 ml/mL)
Dose and Frequency	single dose of 900 mg (2 x 450 mg/7.5 mL vials) administered as an intravenous infusion over 90 minutes. Must be diluted before use. If flare symptoms persist, an additional intravenous 900 mg dose may be administered 1 week after the initial dose
How Supplied	NDC Number 0597-0035-10: Each carton contains two single-dose 450 mg/7.5 mL (60 mg/mL) glass vials
Storage	store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Prior to use, unopened TRADENAME vials may be stored at room temperature, 20°C to 25°C (68°F to 77°F), for up to 24 hours in the original carton to protect from light
Container Closure	glass vial

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Spevigo labels and labeling submitted by Boehringer Ingelheim Pharmaceuticals, Inc..

- Container label received on January 3, 2022
- Carton labeling received on January 3, 2022
- Prescribing Information and Medication Guide (Images not shown) received on January 3, 2022, available from \\CDSESUB1\evsprod\bla761244\0012\m1\us\proposed.doc

G.2 Label and Labeling Images

Container labeling

(b) (4)

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

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MADHURI R PATEL
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SEVAN H KOLEJIAN
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